THE FUNCTION OF A TEACHING HOSPITAL*

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relationship between teaching hospital and ersity is an old one In most cities the teaching ital is older than the university, and in some of them ably London) medical schools attached to hospitals dated the university and were later incorporated Yet most of these hospitals, at the time they were t, did not differ much from non teaching hospitals ther in structure, staffing or administration From we may deduce that, if they felt that their service to community differed from that of other hospitals, difference in function must have been very limited evidence received by the Royal Commission on the ersity of London (1913) leaves no doubt that it was act restricted to the acceptance of students as entices to learn the practical handling of the sick the physicians and surgeons to the hospital This is, and always must be an important function of hing hospitals for on it depends the practical ruction of general practitioners and specialists who the basis of any health service, organised or ganised And it was enough for the dark ages of icine, when familiarity with the natural history of ase, and with the lives of ordinary and extra ordinary made up the whole armamentarium of the practising or But it has become increasingly inadequate over last two centuries, because of the growth of natural ice

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atural science, in essence, is a method by which the al sequence of events may be traced and identified an be, and is being, applied to the whole field of ral phenomena, beginning with the physical sciences, eeding to the biological sciences, then to the clinical ices, and more recently to the social sciences To scientist himself the purpose of science is to acquire ledge *for its own sake*, *to the community at large* usefulness of science depends on applying knowledge on, to the control of natural phenomena in the ests of man himself This distinction between the isition and the use of knowledge is to my mind the er distinction between pure and applied science ould seem self evident that knowledge must be ired before it can be used

appreciation of this is essential if the true function e teaching or university hospital is to be understood it is the function of the universities to acquire ledge, to impart that knowledge, and to teach the ods of acquiring it, and it is the function of the h service to use that knowledge in the prevention cure of disease The teaching or university hospital has a unique function in marrying these two points iew It alone can, should, and must provide the point for the acquisition of new knowledge concerning disease, for teaching how that knowledge can be and for pioneering the use of that knowledge in the ention and cure of disease To quote the words of William Osler, uttered half a century ago on the ect of the Johns Hopkins Hospital

> the type of school I have always felt the Hospital ld be and which we tried to make it—a place of refuge he sick poor of the city—a place where the best that is n is taught to a group of the best students—a place e new thought is materialized in research—a school where men are encouraged to base the art upon the science of medicine—a fountain to which teachers in every subject would come for inspiration—a place with a hearty welcome to every practitioner who seeks help—a consulting centre for the whole country in cases of obscurity We must convince the authorities that the subjects of clinical work come directly within the sphere of the university and that certain hospitals must be adapted to meet the demands of the scientific study of disease and the scientific training of students "

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What does a university or teaching hospital need if it is to fulfil its central purpose? Its most important need is undoubtedly that its board of governors, administration, and staff should be united in recognition of their opportunity and in determination to realise it Secondly, it needs a medical staff skilled in the several disciplines which constitute the practice of medicine Some if not all, should also be skilled in scientific method, and able to devote a substantial part of their time to the acquisition of new knowledge and its application to the problems of the sick, and some should have such close *contact with other scientific* disciplines that they can use in their own work the methods and knowledge so gained It needs adequate inpatient and outpatient facilities for the treatment of the sick for the investigation of disease and for the teaching of students Finally it needs laboratories where those who are trying to advance knowledge may work, for the advances of technology have equipped us with techniques and machines that now enable us to get an answer to questions which have hitherto defied analysis

Judged by these standards, and indeed by contemporary practice as I have seen it in the United States, Canada Scandinavia, and Western Germany, most of our teaching hospitals in Britain are woefully inadequate The new building in Sheffield is a sign that we are moving in the right direction, but not all cities are as fortunate as is Sheffield I want to examine, therefore, some of the reasons that have impeded or are impeding progress

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One of the obvious reasons is money This may be important in the future, but it was relatively unimportant in the past, had the will been there, the means could have been found Without any doubt the most important reason has been the prevalence of two opinions (1) that the advancement of clinical science is incompatible with the treatment of the sick, and (2) that all advances in medical science come from the preclinical laboratories, and that the clinical sciences are unnecessary to the advancement of medicine Neither of these opinions are rational and like most irrational opinions they are based on mistrust and fear The first has been held by the less enlightened consultant physicians and surgeons who fear that university departments menace the prestige which was once their monopoly in clinical subjects The other has been held by non clinical scientists who fear that the growth of clinical science will compete for the support available for scientific research I have no doubt that these attitudes of mind are being overcome, and they are being overcome in the only possible way, by the growth of mutual respect between colleagues with a common purpose—the relief of human suffering

But although these attitudes of mind, are dying they are by no means dead, and I know of nothing so mischievous to our common purpose Three examples will perhaps illustrate why I feel so strongly on this subject

When I was a student I was vividly impressed by the tragedy of two patients—a wood-worker who had driven a nail into his hand two days before he came to hospital with a grossly inflamed hand, and who died the next day of septicæmia, and a nurse whom I helped to hang the Christmas decorations and who died three days later

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m an address given on the occasion of the opening of the w university building at the Sheffield Royal Infirmary

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of a cavernous sinus thrombosis following a boil on her lip Their deaths were not attributable to any lack of skill or attention but solely to lack of knowledge They would not have occurred today thanks to penicillin, discovered and developed by Fleming, Florey, and Chain, working severally in the laboratories of St Mary's Hospital and Oxford University

Again when I was a student, patients with pernicious anæmia invariably died Today they do not die, thanks to the discovery by Minot and Murphy, working in the Thorndike laboratories of the Boston City Hospital, of the efficacy of liver, whose active substance has recently been identified and characterised by brilliant work of chemists and physicists

Finally, one of the commonest disabilities of middle-aged women in my student days was iron-deficiency anæmia This was then invariably and quite unsuccessfully treated with a mixture containing 7 grams of iron and ammonium citrate and 2 minims of liquor arsenicalis, a preparation which was demonstrably inactive It was only later, thanks to clinical experimentation, that it was found that much larger doses of iron were needed, and nowadays such are among the most grateful of our patients

These examples show that good doctoring and good nursing are not enough Knowledge, too, is needed, and knowledge is most easily and certainly won by the scientific method And while history shows abundantly that the key information may come from any discipline—from departments of medicine, surgery, pathology, physiology, pharmacology, biochemistry, and even the so-called basic sciences—knowledge tends to advance over a broad front, and it will not advance if the important disciplines concerning disease in man are neglected Thus the services of the teaching hospital are not only services to the individual patients, they are services to humanity as a whole

Although professional jealousy is the greatest hindrance to the development of the teaching hospital, an important misconception plays a part It relates to experiment To some minds experiment in medicine has come to mean something immoral or unethical which is inflicted on the individual patient against his own interests This is not so May I remind you of the nature of an experiment It is the alteration of preferably, one, or sometimes more than one, factor, and the observation of its effect All treatment is in fact in the nature of an experiment If we take a sick patient and we alter his diet, or his way of life, or give him a drug, or perform a surgical operation, we are, in the scientific sense, performing an experiment Most doctors, however, are not interested in the result, or have not sufficient time to assess the results properly It is the peculiar function of university departments of medicine, surgery, obstetrics, and therapeutics that they shall have the scientific training so to devise their treatment, and that they shall have enough leisure so to observe and assess its results, that new knowledge shall result Thus will their patients reap greater benefits and all mankind shall profit

Let us, for example, contrast the knowledge gained about the efficacy of the new antituberculous drugs with that gained about sympathectomy in hypertension By means of careful design and observation, it became abundantly clear, from the first patients treated in this country, how far and in what conditions streptomycin, p aminosalicylic acid, and isoniazid would help patients with pulmonary tuberculosis As a result the sick of the country as a whole got the maximum benefit from these drugs as soon as possible Not a single life or a single day of illness was unavoidably wasted Contrast sympathectomy for hypertension, an operation performed on thousands of patients, but without plan, so that now, some twenty years after its introduction, we still do not know how much it increases expectation of life in any but the most severe forms of hypertension is contrast between the results of a well planned and a badly planned experiment provides one of the eloquent pleas for the place of the university medicine

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One final word The success or failure of the service of the future depends on its esprit de The spirit of the health service depends more spirit of our teaching hospitals than on any other the teaching hospitals set the standard and they the men Now it seems to me very important we are to get the best out of our teaching hc we should spare no effort to recruit the best men, to permanent staff No man who has had a long as I have, in staff recruitment can be happy wi present system in which men are appointed to posts for life, and the filling of staff vacancies at t hospitals depends too largely on the accidents of and deaths The Scandinavian system, in which move from smaller to larger hospitals and teaching hospitals seems to me better In the first it gives the teaching hospitals an opportunity of the best, for these men have proved themselves in field Secondly it provides an incentive to excel, for general excellence is rewarded Finally, I doubt if good for most men to remain in precisely the same for thirty five years, particularly when the unc of private practice has been removed This is not a point of outstanding importance, but e in a service demands attention to such details

CAROTICO-VERTEBRAL STENOSIS

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The recognition of the frequency and sig of occlusion of the cervical portion of the carotid has been a major advance in the study of ce vascular disease Atheroma in this site has been forward as a reasonable pathological explanation the many cases of cerebral infarction which have known to occur without occlusion of the intra vessels Indeed, the clinical study of patients in the carotid artery has been occluded in the neck led to the recognition of various clinical syndr which are described in full in the writings of (1951, 1954), Cloake (1951), Symonds (1955), and others

Our personal experience, like that of others, has that occlusion of the carotid artery may be present out symptoms, signs, or infarction of the brain, it may be the basis of a clinical picture identical every way with thrombosis of the middle artery, and, finally, that it may be present when clinical picture is one of a steadily progressive cranial lesion presenting perhaps with dementia, mittent sensory and motor phenomena, or visual turbance—a picture often indistinguishable from caused by a cerebral tumour

It is difficult, however, to accept that such a clinical spectrum should depend solely on of one or even both carotid arteries For this rea seemed logical to investigate the major col channels—the vertebral arteries and the circle of W in cases of carotid-artery occlusion in an effort to an explanation for some of the discrepancies between clinical and the pathological pictures

We have previously reported (Hutchinson and Yates 1956) the results of an investigation into the incidence of atheroma of the vertebral artery in its cervical portion a segment of the artery rarely examined routinely at necropsy. We found that stenosis and occlusion due to atheroma in this part of the vertebral artery might be responsible for a characteristic pattern of infarction of the cerebrum and cerebellum. It seemed also that these changes in the vertebral artery, often accompanying atheroma of the carotid artery, might play an integral rôle in certain of the syndromes previously attributed to occlusion of the carotid artery alone.

Further study has confirmed us in this view. Indeed the association of vertebral and carotid atheroma is so common that we suggest that the term "caroticovertebral stenosis" gives the correct emphasis to the part played in disease by atheroma of the four major arteries in the neck which supply the brain (the internal carotid and vertebral arteries) and to the site of the vascular lesion in many cases of cerebral infarction.

Another aspect of vertebral-artery stenosis and one of some importance is that such stenosis alone may be responsible for infarction of the brain without either occlusion of the intracranial vessels or disease of the carotid arteries. We present here observations on these aspects of cerebrovascular disease.

Technique

To examine the cerebrovascular tree thoroughly, the brain was injected at necropsy with radio-opaque gelatin through the carotid and vertebral arteries at a pressure approximating to the systolic blood-pressure during life. The brain was then removed in the routine manner and fixed in formalin. In the first 38 patients in the series the vertebral artery was then dissected from the vertebral canal, but we found this method too laborious and time consuming for routine use; at the last 35 necropsies the cervical spine was removed with the carotid and the vertebral arteries in situ. Later the carotid artery was examined, the spinal cord removed from the cervical vertebræ, and the spine decalcified in 6% nitric acid. The vertebral artery could then be dissected from the vertebral canal with ease and examined at all points in its course.

ANALYSIS OF 22 CASES WITH CEREBRAL INFARCTION

Case no.	Site of infarction	Occlusion of appropriate intracranial vessel	Internal carotid artery Rt	Internal carotid artery Lt	Vertebral artery Rt	Vertebral artery Lt
1	Rt frontoparietal	Middle and anterior cerebral (rt)	◓	◓	○	○
2	Lt parietal	Middle cerebral (lt)	○	○	◦	◦
3	Lt frontal, lt parietal rt parietal	0	●	●	●	●
4	Rt parietal rt occipital	Middle and posterior cerebral (rt)	○	○	○	○
5	Lt frontoparietal rt parietal	Middle and common anterior (lt) 0	○	●	○	●
6	Lt occipital	Posterior cerebral (lt)	○	○	◦	◦
7	Rt parietal rt insula lt capsule	Middle cerebral (rt)* 0	●	●	•	•
8	Rt occipital rt inferior cerebellar	0	◓	○	•	◦
9	Lt parietal lt inferior cerebellar	0	◓	●	◦	◓
10	Lt and rt basal ganglia (old cysts) rt superior cerebellar	0	◓	◓	•	◓
11	Lt frontoparietal lt superior cerebellar	0	●	●	●	●
12	Rt capsule and basal ganglia bilateral cerebellar (sup. and inf.)	0	◓	◓	◓	●
13	Lt parieto occipital bilateral superior cerebellar	Middle cerebral (lt)* 0	○	●	●	◦
14	Lt parietal rt basal ganglia bilateral superior cerebellar	0	◓	●	◓	•
15	Rt parietal lt inf. cerebellar	0	◓	◓	•	●
16	Rt frontoparietal, rt superior cerebellar	Middle and anterior cerebral (rt)* 0	●	●	○	○
17	Lt parietal pons	0	●	●	○	●
18	Bilateral superior cerebellar pons bilateral occipital	0	○	○	●	•
19	Lt parietal	0	◓	●	◓	●
20	Rt inferior cerebellum	Posterior inferior cerebellar (rt)	◓	◓	●	◓
21	Pons	Basilar	◓	◓	●	•
22	Rt int. capsule	0	●	◓	◓	○

* Extension of thrombus from internal carotid artery.

On the right a cross section depicting the degree of stenosis or occlusion at the worst point of the four major vessels in each case given. All the vessels are represented as of the same diameter except where striking and significant discrepancy was found.

Review of Pathological and Clinical Material

The observations presented are based on the study of 33 patients who came to necropsy as a result of a cerebrovascular lesion or whose clinical history suggested such an event in the past

Significant stenosis of the lumen of carotid and of vertebral arteries was often found, by "significant" we mean diminution of the lumen by at least half In 40 of the cases examined there was either significant stenosis or occlusion of one or more of the major vessels in the neck Of these, 10 had lesions of the carotid artery alone, and 7 of the vertebral artery alone, in 23 cases (more than half the total) the lesions involved both the carotid and the vertebral arteries

The pathological basis for the stenosis was always atheroma, with the occasional addition of either old or recent thrombosis A not uncommon finding was hæmorrhage into the base of the plaques of atheroma Although some of these hæmorrhages were small, others, by dissecting the base of the plaque, had obviously caused further sudden narrowing of the lumen of the artery Atheroma was particularly common at the origin of the vertebral artery from the subclavian artery and often extended up the vessel for some distance, otherwise there was no typical site for the atheroma in the course of the artery through the vertebral canal Atheroma was least common in the short intracranial segment of the artery, it was not unusual to find severe atheroma of the cervical portion of the vertebral and carotid arteries when the intracranial vessels were either free from disease or showed only minimal changes The carotid artery was often affected by atheroma just at or above the cervical bifurcation, the atheroma extending for a short distance up the artery Often the artery was free from atheroma above this site The details of the distribution of the pathological change in the carotid artery were similar to those reported by Samuel (1956)

In our series there were 22 cases of cerebral infarction (see table) Many had more than one infarct The total number of separate infarcts in the 22 cases was 47, of these, 29 were cerebral, 15 cerebellar, and 3 in the brain-stem In 16 of the 22 cases infarction was present without occlusion of an appropriate intracerebral vessel In 10 the following intracerebral vessels were occluded the anterior cerebral (2), middle cerebral (8), posterior cerebral (2), basilor (1), and posterior inferior cerebellar (1) In 3 cases the intracerebral occlusion was caused by extension of thrombus from the internal carotid artery We wish to draw attention to the frequency of multiple infarctions not only in the cerebrum but also in the cerebellum, and to the fact that in only 1 of the 15 cerebellar infarcts was the cerebellar artery supplying the infarcted area occluded

Finally, the spinal cord was examined in 35 cases, and in none was there either macroscopical or microscopical evidence of infarction

Since we are concerned to show what we believe to be the effects on the brain of either occlusion or stenosis of one or more vessels in the neck, we have grouped the material as follows (1) disease of the vertebral artery alone, (2) disease of the carotid artery alone, and (3) disease of both the carotid and the vertebral arteries —"carotico-vertebral stenosis"

(1) *Disease of Vertebral Artery*

In 7 patients the atheroma was confined to the cervical portion of the vertebral artery In 2 of these patients stenosis was the cause of infarction of the brain In both cases the infarction was confined to the territory ultimately dependent on the vertebral artery the brain-stem, the cerebellum, and the occipital lobe

Case 18 —A man, aged 47, had been in excellent health until, four months before death, he first complained of tingling in his right arm and right leg The tingling occurred in short

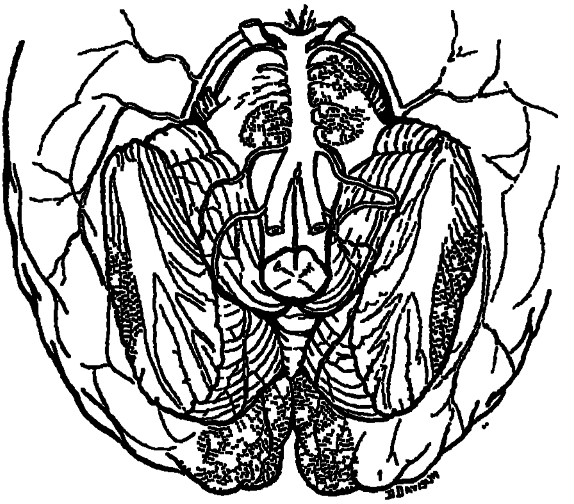

Fig 1—Case 18 distribution of infarcts

attacks, lasting a few minutes only, and was appreciat along the whole of the arm and the leg On occasion attacks were accompanied by a feeling of heaviness in t affected limbs, but the duration was so short that there no real disability, and he continued at his work Six day before death he suddenly became ill and complained persistent heaviness and weakness of both legs Next da he was very unsteady in walking From this time onwa he had difficulty in reading print On the evening of the second day a sudden attack of "jumping" of the right arm and right leg lasted for five minutes and was followed next morning by a similar attack in the left limbs Unlike the attack of -the night before, this attack was followed by persistent weakness From this time onwards the patient's relations noted a steady deterioration in his condition, with increasing weakness of all his limbs

On admission the patient lay quietly in the bed unable to move his head or his limbs and unable to speak or to swallow That he was fully conscious was shown by the fact that he moved his eyes fully in all directions in response to verbal requests His jaw, tongue, and palate were almost completely immobile His limbs were flaccid and powerless; his reflexes were not unduly brisk, his abdominal reflexes were absent and his plantar responses extensor Sensation was difficult to assess with any degree of accuracy, but it could be shown that pain sense was absent below his clavicles No useful information was obtained on his fields of vision The signs and their anatomical implication indicated thrombosis of the vertebral and basilar arteries The patient passed quietly into coma and died on the sixth day of the terminal illness Tracheotomy only temporarily relieved his respiratory distress

Necropsy Findings

The body was that of a well-nourished man of middle age The tracheotomy wound appeared healthy, though the trachea and main bronchi were acutely inflamed Both lungs showed active bronchopneumonia The coronary arteries were somewhat atheromatous but nowhere severely stenosed All the other organs of the body were essentially normal

The carotid arteries were normal throughout their course The intracranial vessels were normal except the left vertebral artery which had a plaque of atheroma, about 1 cm from its penetration of the dura, narrowing the lumen by a third The posterior communicating arteries were patent and of normal size The right vertebral artery was twice the size of the left It was occluded by organised thrombus extending from its point of entry into the vertebral canal opposite the sixth cervical vertebra to the level of the atlas

The brain (fig 1) showed bilateral infarction of the occipital lobes On the right side a single and fairly recent infarct extended from the calcarine region to the inferior surface of the lobe and to the posterior hippocampal fusiform, and inferior temporal gyri There were two distinct infarcts on the left side, one (a few weeks old) involved much of the cuneate gyrus, and the other was fairly recent and lay at the occipital pole in the lingual gyrus There was bilateral recent infarction of the cerebellum Both infarcts involved cerebellar foliæ rather than deep white matter and occupied an area about 2 cm in diameter in the centre of the upper surface of each hemisphere In the brain stem recent infarction involved the caudal half of the pons It did not involve the region beneath the floor of the fourth ventricle and was most extensive on the left side The cervical portion of the spinal cord was normal

Case 8 —A man aged 82 was admitted to hospital after a car accident Two months earlier he had fractured his right humerus but apart from this he was well until the recent accident He had been unconscious for only a few moments at the time of the accident and on admission to hospital the only physical sign of injury was a shallow abrasion of the skin over the right occiput Radiography of the skull however, showed a linear fracture of the left temporo parietal region The patient remained well for the next seventeen days and then suddenly complained of pain in the chest and intense dyspnœa Bronchopneumonia was diagnosed, but there was no response to treatment and he died suddenly three days later Unfortunately a detailed neurological examination was not made before he died

Necropsy Findings

The body was that of a poorly nourished old man showing no bruising or other evidence of trauma A linear fracture of the skull extended from the occiput to the right temporal bone, but the underlying dura was not torn Apart from terminal bronchopneumonia the organs of the body were not significantly abnormal There was no evidence of cardiac infarction

The right internal carotid artery was slightly narrowed by a plaque of atheroma just above its sinus, the left was normal The right vertebral artery was occluded at its origin from the subclavian artery, the smaller left vertebral artery was patent The intracranial cerebral arteries were all free from atheroma The posterior communicating arteries were patent but very small

The brain showed bilateral atrophy of the frontal gyri with thickening of the overlying arachnoid There were small recent petechial hæmorrhages in the arachnoid at the junction of the territories of the left middle and posterior cerebral arteries, typical of those seen at the borders of infarcted territory There was recent infarction of the medial and inferior parts of the right occipital lobe, there was an infarct of similar age in the right cerebellar hemisphere in the territories of both the anterior and the posterior inferior cerebellar arteries

In both case 18 and case 8 there was a considerable discrepancy in size between the vertebral arteries (a common anatomical variation), in both cases the larger artery was occluded by disease In case 18 the smaller left vertebral artery was partially stenosed by atheroma, and in case 8 the posterior communicating arteries were small and presumably incapable of sustaining a collateral circulation In both cases the terminal infarction appears to have come on spontaneously, the head injury in case 8 did not appear to have produced any significant cerebral trauma and could not be held responsible for the final fatal episode

(2) *Disease of Carotid Artery*

In 10 of our series the carotid was the site of either stenosis or occlusion without affecting the vertebral arteries at any point in their course In only 2 (cases 1 and 16) was infarction of the brain present That the vertebral arteries can maintain a precarious cerebral circulation in some patients is shown by the following example of long standing bilateral occlusion of the internal carotid arteries

Case 16 —A woman, aged 69, was admitted to hospital having been found unconscious in a gas filled room The only previous history of cerebral disease was that, for several weeks past, the patient had been noted by her relations to be rather forgetful When she recovered from coma next day, left hemiplegia was present, which persisted until she died six weeks later Death followed bronchopneumonia and the effects of prolonged sepsis from extensive bedsores

Necropsy Findings

The body was that of a wasted old woman with extensive decubitus ulceration of the sacral region There were extensive old pericardial adhesions but the heart was normal The coronary arteries were atheromatous but nowhere occluded Both lungs were involved by active bronchopneumonia The kidneys were irregularly shrunken (80 and 90 g) and showed the changes of chronic pyelonephritis The left internal jugular vein was blocked by newly formed thrombus

The left internal carotid artery was occluded in the neck by old organised thrombus at a point just above the sinus, the remainder of the artery being free from atheroma and thrombosis The right carotid artery was almost occluded in its intracranial portion, a small channel less than 1 mm in diameter remaining The atheroma responsible for this narrowing extended into the right middle and anterior cerebral arteries, which were occluded by thrombus for about 1 cm The circle of Willis was normal, except the right posterior communicating artery whose lumen was considerably diminished by atheroma The cerebral arteries on the left side were normal The basilar and the vertebral arteries throughout their length were patent and free from atheroma

The left cerebral hemisphere was normal The right showed infarction of part of the frontal and parietal lobes of the lateral part of the head of the caudate nucleus, and of the anterior half of the corpus callosum These infarcts dated probably from the time of onset of hemiplegia six weeks before death The temporal and occipital lobes were normal There was infarction of cerebellar foliæ in the territory of the right superior cerebellar artery (fig 2) The brain stem was normal

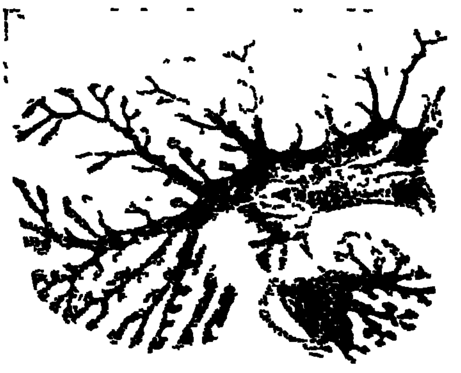

Fig 2—Case 16 section of cerebellum showing infarction of foliæ in territory of superior cerebellar artery

(3) *Disease of Carotid and Vertebral Arteries (Carotico-vertebral Stenosis)*

Atheroma of both the carotid and the vertebral arteries in the neck was present in 23 of the cases In 8 of them it is clear, from a study of the clinical history and the pathological material, that a combination of stenosis of both the carotid and the vertebral arteries was the vital factor in the production of the clinical picture For this reason we suggest the term "carotico vertebral stenosis," which emphasises to the full the underlying vascular disease

Both the clinical histories and the pathological examinations in these 8 patients allow of subdivision into two groups (1) 4 patients in whom the illness was sudden and fatal showed infarction of both the cerebral and the cerebellar hemispheres, and in 3 of the patients the infarction was precipitated by generalised circulatory failure, and (2) 4 patients had a clinical history of steadily progressive cerebral disease (3 of them required the aid of additional radiological techniques to exclude the diagnosis of a cerebral tumour, and in all 4 the findings in the carotid and the vertebral arteries were remarkably similar)

The findings in the first group of patients have been described in full elsewhere (Hutchinson and Yates 1956), therefore we repeat here only the essential clinical and pathological details These 4 patients (3 females and 1 male) all showed stenosis or occlusion of the carotid and the vertebral arteries in their cervical course In 1 of the patients the disease in the vertebral arteries was unilateral but had almost completely occluded the lumen of the right vertebral artery, which in this particular instance was nearly twice the size of the left—illustrating again the occasional importance that discrepancy in size between the two vertebral arteries may assume when disease develops. Three of the patients had no previous history whatever suggesting cerebral arteriosclerosis, and each died in coma developing in circumstances which led to circulatory failure. Stokes Adams attacks, carbon monoxide poisoning, and operative hypotension were the precipitating factors in the 3 cases. In the 4th patient symptoms due to intracranial infarction came on suddenly and apparently spontaneously. The necropsy findings in these 4 patients were identical in basic pattern. In each were found an infarct of one cerebral hemisphere and infarction (bilateral in 3 patients) of the cerebellum. The area infarcted in each case was either in or adjacent to the territory supplied by the superior cerebellar arteries in the cerebellum. In no case was the infarct associated with either occlusion or significant narrowing of the cerebellar or the basilar or the intracranial portion of the vertebral arteries. In all 4 cases the brain stem, though no doubt the site of terminal ischæmia, was free from frank infarction.

The 4 patients of the second group are considered together because their history was one of progressive cerebral disease. Though other patients in the series showed a comparable severity of stenosis in the vessels of the neck, the clinical history and opportunity for personal investigation were not adequate in these to allow of any detailed interpretation. The findings in 2 of the 4 patients were as follows.

Case 3.—A man, aged 70, complained throughout the summer of 1955, of constantly feeling tired and off colour. In September, 1955, his relations noted that he was a little forgetful, but the symptoms were so slight that they were put down to his advancing years. He remained in this state until April, 1956, when he was suddenly taken ill while on holiday. At this time he was confused and disoriented and showed distinct dysphasia. In addition to this there was an increase of the reflexes in the right arm and leg and a right lower facial weakness. Both plantar responses were extensor. He was admitted to hospital at this time.

On admission his cerebrospinal fluid (C.S.F.) was normal both in composition and pressure. Electroencephalography showed no evidence of a focal disturbance. Angiography of the left carotid artery revealed an occlusion just above the origin of the internal carotid artery. After this the clinical picture was most unusual. Although he was not apparently aware of his surroundings he constantly rotated to the left in bed, which movement persisted until his death six days later. Since it was still not certain that the underlying lesion was neither a subdural hæmatoma nor an infiltrating glioma, burr holes were made, and the underlying brain was seen to be infarcted.

Necropsy Findings

The body was that of an obese man. Apart from the brain and vessels in the neck there were no significant pathological changes. The aorta and coronary arteries were moderately atheromatous.

Of the cerebral vessels (fig. 3) the internal carotid arteries were both occluded by atheroma and thrombus. On the left side the lesion was old and organised; on the right it was recent. The left vertebral artery was narrowed to a thin slit for its first 2 cm. The lumen of the right vertebral artery was narrowed to half by an atheromatous plaque for 1 cm from its origin. Throughout the rest of their course these arteries were normal. The intracranial vessels (except the left middle cerebral artery, where there was a plaque 1.5 cm long which narrowed the lumen by half) were free from atheroma.

The left cerebral hemisphere was infarcted in two areas: (1) the posterior half of the middle and inferior frontal gyri involving the cortex and the gyral white matter; and (2) an area of 3 cm by 2 cm in the parietal lobe similarly involving cortex and gyral white matter. On the right side there were also two areas of infarction, but here both were in the parietal lobe, the more posterior extending to the junction of t parietal and the occipital lobes. The cerebellum and t brain stem were normal.

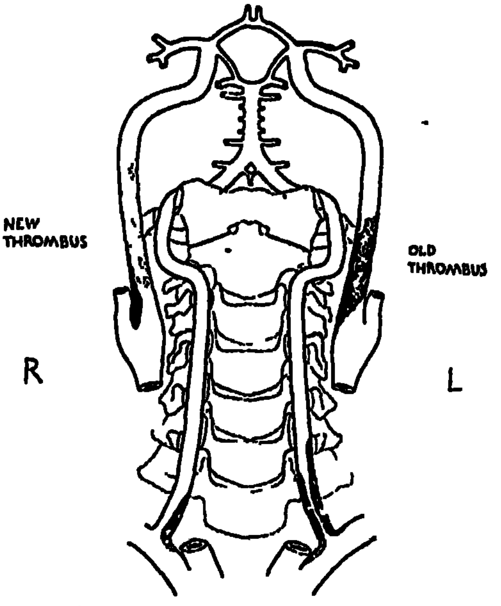

Fig 3—Case 3: sites of atheromatous stenosis and thrombotic occlusi

Case 10.—A man, aged 65, had been subject to twe months' progressive deterioration in memory and intellect power, as a result of which he had to retire from his job year before his retirement was due. From the onset of the symptoms his speech was slurred. Six months later developed symptoms due to prostatic obstruction but, becau of his mental state and severe old standing bronchitis, w not operated on. His dementia progressed over the ne six months, after which he was admitted to hospital f investigation.

On admission he had blood pressure 200/100 mm H prostate moderately enlarged, and blood urea level 120 m per 100 ml. He was confused and disoriented, and his spee was slurred. His reflexes were increased in all four limb and both plantar responses were extensor. Radiograph of his chest and skull and examination of his C.S.F. we normal. *He remained demented and died three weeks lat* from bronchopneumonia.

Necropsy Findings

The body was that of a thin emaciated old man. The hea weighed 350 g., the left ventricle being hypertrophied. Th coronary arteries were much stenosed by atheroma, but n myocardial infarction had taken place. Both kidneys we small (70 and 50 g.) owing to chronic pyelonephritis secondar to benign hypertrophy of the prostate. The other organ were not significantly abnormal.

The internal carotid arteries were severely atheromatou at their sinuses; both were narrowed by half at this point. Elsewhere in these vessels only slight atheroma was present. The right vertebral artery was occluded at a point 1 cm abov its origin; the left, which was the larger, was severel stenosed for the first 5 cm of its course. The intracrani vessels were free from disease.

The brain showed a small infarct at the posterior end of the left inferior frontal gyrus. The basal ganglia of both side contained several small old cysts, the result of earlier ischæmi An infarct, partly cystic, was found in the white matter of the right cerebellar hemisphere medial to and above the dentate nucleus. There was patchy necrosis of many cerebellar folia in the territory of the right superior cerebellar artery.

Discussion

Certain points arising from the pathology of these cases require consideration.

The common occurrence of infarction of the brain without occlusion of the intracranial vessels only confirms the observations of many previous workers. It is worth emphasising, however, that in no case of cerebral infarction in this series—where both the carotid and the vertebral arteries were examined throughout their length—was there any difficulty in providing a reasonable pathological interpretation for both the clinical phenomena and the distribution of infarction.

We were surprised by the frequency of infarcts in the hind-brain, particularly in the cerebellum. One reason for this finding was, we feel, the practice of fixing the brain in formalin before it was examined, thus making the softened areas of non-hæmorrhagic infarction easier to detect in the hardened brain.

In most of the cases we have described the infarct did not involve the "classical" sites such as the territory of the posterior inferior cerebellar artery. (Only 2 of 18 infarcts of the hind-brain were of this type: in both of these cases the vertebral artery was atheromatous throughout its cervical course.) The territory of the superior cerebellar artery near the point of junction with the territory of the posterior inferior cerebellar artery was the commonest site for these infarcts. Theoretically it is this area and the distal areas of the occipital lobes which may be expected to suffer if the vertebral circulation fails. These areas, in terms of distance from the source of supply, are the counterparts of the distal territory of the middle cerebral artery in which we found infarction when the carotid arteries were occluded in the neck.

Within the territory of the middle cerebral arteries we observed that the infarction was often incomplete and that areas of necrosis lay adjacent to areas of relatively normal tissue within the affected area. This patchy distribution of infarction where the site of the occlusion was proximal to the local vessel was no doubt an expression of the inadequacy, in the final stages, of the collateral blood supply.

Examination of the vertebral artery in its cervical course, by revealing either occlusion or stenosis, provided the pathological basis for those hind-brain infarcts which occurred without occlusion of the cerebellar vessels within the skull. In 4 of the cases the infarction was bilateral and approximately symmetrical within the cerebellum; in 3 others the infarct was unilateral. In addition infarction of the occipital lobes was present in 2 cases. In all these patients severe disease of the vertebral arteries in the neck was demonstrable, but in only 1 of them could the state of the cervical segment be deduced from the appearance of the intracranial portions of the artery. The midline structures—the pons, the medulla, and the spinal cord—escaped damage where the occlusions of the vertebral arteries were in the neck. It is a tribute to the efficiency of the circle of Willis as a collateral channel that it can maintain the blood-supply to the midline vital centres—in these circumstances an efficiency on which survival depends. In only 1 of these patients was the pons infarcted, and none of the 35 cervical cords was affected—surely surprising in the case of the cervical cord, where both vertebral arteries, the immediate source of supply in health, were often diseased or stenosed. No doubt the cord and brain stem were the site of ischæmia in the terminal stages in many cases.

The circle of Willis is not always adequate to maintain the blood supply to the hind-brain when the vertebral arteries are diseased. The necropsy findings in cases 18 and 8 show conclusively that the brain may become infarcted as a result of occlusion of the vertebral arteries when the carotid arteries and the circle of Willis are patent and healthy. The clinical history of case 18 is of considerable interest because the intermittent sensory and motor symptoms, spread over six months, were in many ways similar to the episodic history sometimes observed in patients thought to have occlusion of the carotid arteries. Very probably in this patient the site of production of the symptoms was either the brain-stem or the cervical cord. This may be the case in other patients where similar complaints have been attributed to occlusion of the carotid artery alone. Our material shows that many such patients have also stenosis or occlusion of the vertebral arteries in their cervical portions.

Atheroma affected the carotid arteries alone in 10 patients. In no case of unilateral involvement did cerebral infarction follow: in all the cases the vertebral arteries were patent. Moreover in case 16 at necropsy there was clear evidence of long-standing bilateral disease of the carotid arteries, and the only symptom noted by her relations before the terminal episode was occasional loss of memory. The final infarction was precipitated by accidental exposure to carbon monoxide. The pathological findings in this patient are of considerable interest. Despite the patent vertebral arteries there was infarction of the cerebellum in the territory of the superior cerebellar artery in addition to the infarct of the cerebrum. The posterior communicating artery on the same side was almost completely occluded by atheroma. The escape of the tegmentum and the cerebellum in cases of basilar thrombosis has been explained after the work of Critchley and Schuster (1933) and Biemond (1951) by the collateral circulation through the posterior communicating and the posterior cerebral arteries. The findings in case 16 not only support this explanation but also suggest that the territory of the superior cerebellar artery may partly depend on the carotid circulation even in health.

In our series the commonest condition of the major vessels of the neck was for all to be affected by atheroma, as we found in 23 cases. In 4 of the cases which were fully studied the clinical history was one of slowly progressive cerebral disease. Although in 2 patients there was a history of intermittent episodes no single feature of the clinical history pointed clearly to the diagnosis of vascular disease alone. In 3 patients it was necessary to resort to special radiographic techniques to establish the diagnosis. In the 4 cases the pathological findings were essentially the same—i.e., a severe stenosis caused by atheroma of all four major vessels in the neck. In contrast the intracranial vessels were in each case free from atheroma, although in 2 of the cases the final infarction of the cerebrum was associated with extension of the thrombus from the carotid artery into the middle cerebral artery.

Therefore we feel that this clinical picture should be regarded as an expression of progressive diminution of the total cerebral blood-flow owing to stenosis of the cervical portions of the major vessels to the brain. For this reason we suggest the term "carotico-vertebral stenosis" for these cases; to call them examples of internal-carotid occlusion places undue emphasis on the part played by occlusion of a single artery in the production of the symptoms.

A gradual diminution of the cerebral blood-flow alone cannot reasonably be held to explain the episodes of sensory and motor dysfunction which may be a feature of the clinical history. The common occurrence of small hæmorrhages in the walls of the carotid artery, within the plaques of atheroma, has already been noted (Yates 1954). We have suggested elsewhere (Hutchinson and Yates 1956) that the sudden development of one of these hæmorrhages in the coat of the artery may be a factor in initiating these transient episodes. Other factors—e.g., variations in the blood-pressure—may also play a part in disturbing the precarious balance of the already impaired cerebral blood-flow.

A sudden fall in the blood-pressure was almost certainly responsible for the development of terminal infarction in a further group of 4 cases. In 3 of them massive widespread infarction of the cerebrum and the cerebellum followed stenosis of the carotid and vertebral arteries associated with circulatory failure. Probably these patients, since they were free from any clinical sign of cerebrovascular disease, would later have presented a clinical picture of what we have designated "carotico-vertebral stenosis" They emphasise one of the dangers of hypotension in the aged

Finally, we feel that the recognition of the atheroma confined to the extracranial portions of the major vessels of the brain has more than a theoretical interest Since the intracranial vessels may well be normal or, at the most, the site of a minimal atheroma, surgical replacement of one or other of the vessels in the neck would be useful and logical That surgery may successfully accomplish this is shown by the case reported by Eastcott et al (1954) Such an advance offers hope that the early diagnosis of patients in this group may lead to progress in the treatment of the patient with "cerebral arteriosclerosis"

Summary

The cerebrovascular tree, including the whole length of the vertebral and carotid arteries, was examined in 83 patients considered to have died of cerebrovascular disease

In these arteries occlusion or severe atheromatous stenosis of the cervical segments was common

A clinical syndrome and a pattern of infarction are reported where the vertebral arteries alone were diseased

Stenosis of the cervical portion of the vertebral arteries plays an important part in the clinical picture previously attributed to occlusion of the internal carotid arteries The term "carotico-vertebral stenosis" is suggested as a more appropriate title for this syndrome

A surprising severity of disease of the extracranial, in contrast to the intracranial, cerebral arteries was noted in many patients The hope is expressed that, by the early clinical recognition of such cases, surgical replacement of diseased segments of the internal carotid arteries might, by improving the total blood-flow to the brain, prove useful

We wish to thank Prof A C P Campbell and Dr Fergus R Ferguson for their helpful criticism, Miss D Davison and Mr E G Smith for drawings of specimens, Mr W Beech, Miss R Davidson, and Mr G Lamb for technical assistance, and Mr R T Johnson and Dr G E Smyth for the clinical details of case 3

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We have preached the sermon of simplicity so long that we have tended to ignore the fault into which we have been drawn of stripping the language clean to a degree that nothing shows, in spots, but the bones Case records are made to read like telegrams, and into the intercellular substance of our modern more or less technical writing, even as in the pronouncements of politics, where it matters less abbreviations trickle from the moving fountain pen like water dribbling from a leaky faucet It implies a degree of presumptuousness on the part of the author, an expectation that because a certain combination of initials means something to him it must mean the same to all The scientific culture of the day seems to be impelled by a sense of urgency in the delivery of its messages but one need scarcely recognize in it the urgency that must have inspired the abbreviations used by the hieroglyphic author of a former day trying to get a short article off to his editor by the afternoon bullock cart Verbosity is a fault but so is cryptogrammic abbreviation Midway lies clear and incisive language, confusing neither by the use of unnecessary words nor by the omission or mutilation of necessary ones"—Dr JOSEPH GARLAND, *Int Rec Med*

TREATMENT OF ACUTE SORE THRO WITH PENICILLIN

A CONTROLLED TRIAL IN YOUNG SOLDIERS

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ACUTE sore throat is one of the most common plaints in medical practice today Although short it is important because serious disease such as rheumat fever or acute nephritis may follow streptococcal infections of the throat Under Service conditions in the United Kingdom cases of acute sore throat fever are usually admitted to hospital instead being treated in barracks Since, in civilian prac such patients are treated at home, a unique oppor arises in military hospitals for the study of t complaint

Exudative pharyngitis is often regarded as being caused by the hæmolytic streptococcus without bact logical confirmation and is consequently treated with penicillin, other antibiotics, or sulphonamides In many such cases, however, no streptococci are found by bacteriological examination (Commission on Acute Respiratory Diseases 1944), so there is no specific need for penicillin Furthermore there is the risk of inducing penicillin sensitivity, and the work of Brown (1948, 1956) indicates that this is not negligible

We have conducted a controlled therapeutic trial to see whether it is reasonable to exhibit penicillin routinely to all patients with acute pyrexial sore throat without previous bacteriological identification of the infecting organism We describe here the effect of four days' treatment with intramuscular penicillin on the clinical course and complications of acute sore throat, on the subsequent increase of streptococcal antibody in the serum, and on the convalescent carrier rate of β-hæmolytic streptococci

Material

Between March and May, 1955, and September and December, 1955, 352 patients with infection of the upper respiratory tract were admitted to the Cambridge Military Hospital, Aldershot This is the expected numb and indicates endemic disease Almost all of these patients were National Servicemen, aged 18–21, undergoing military training Our cases were derived from these according to the following clinical criteria

(1) The primary complaint was sore throat

(2) Pyrexia was present (100 3°F on any one occasion o 99 3°F on two or more occasions within twenty four hours)

(3) Admission was within seventy two hours of the onse of sore throat

(4) There was no clinical evidence of more generalise disease of which sore throat may only have been a coinciden feature (e g, glandular fever)

So that the investigation should be as uniform a possible, the clinical and pathological investigations were made entirely by us The patients' signs and symptoms were assessed clinically every morning on a special chart Each patient was asked whether or not his throat fel sore, and his answer was recorded The degree of rednes and the amount of tissue swelling seen in the throa

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I—COMPARISON OF TREATMENT GROUPS AT START OF PENICILLIN THERAPY

—	Streptococcal		Non streptococcal	
	Non specific treatment (40 cases)	Penicillin treatment (42 cases)	Non specific treatment (19 cases)	Penicillin treatment (20 cases)
Mean duration of sore throat before admission (days)	1.5	1.3	2.2	1.6
Mean initial temperature (°F)	101.6	101.8	100.8	100.6
Mean initial white-cell count (per c mm)	14,100	14,000	13,170	11,100
Percentage of cases with exudate	79	79	60	[illegible]
Percentage of cases with tonsillectomy	7	13	21	10
Percentage of patients aged 17–21 yr	80	82	[illegible]	[illegible]

(abnormal injection) the presence or absence of faucial or pharyngeal exudate, and the size of the cervical lymph nodes were likewise recorded in a crudely quantitative way. These daily assessments continued until the patient was discharged from hospital. The oral temperature was recorded twice a day at standard times. A swab from fauces and pharynx was obtained under direct vision by one of us on each day that the patient was retained in hospital, except Sundays. The swabs were immediately inoculated on to two plain horse blood agar plates, one of which was incubated anaerobically. In addition the swab was inoculated on to a gentian violet blood agar plate and on to Hoyle's medium. The various bacterial colonies were assessed quantitatively after overnight culture. Total and differential white cell counts were made at noon on the first, third, and fifth days after admission.

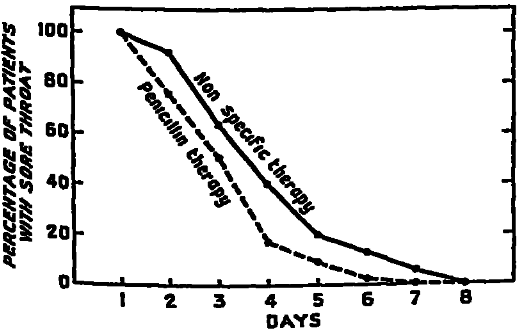

Fig 1—Effect of penicillin on duration of subjective soreness of throat in streptococcal cases

The patients were recalled three or four weeks after discharge, when they were questioned about recurrence of sore throat and about any symptoms suggesting either rheumatic fever or acute nephritis. A throat swab and a specimen of serum were obtained. Antistreptolysin O titres of the acute and convalescent sera were estimated in most cases by Dr R M Fry, of the Public Health Laboratory, Cambridge. A Paul Bunnell screening test was made on each specimen of serum. When Lancefield group A streptococci were recovered from the throat after three days' treatment with penicillin, the sensitivity of the organism to penicillin was tested.

Treatment.—A special ward was set aside for treating these patients only. Whether or not the patient received penicillin was governed by predetermined labelling of his allotted bed. The choice of bed for any particular patient was determined by administrative factors beyond our control, and the physician making the clinical assessments was usually unaware of the treatment. Patients receiving penicillin were given a combination of procaine penicillin 300,000 units and crystalline penicillin 100,000 units ('Seclopen' 1 ml) twice daily for four days, irrespective of clinical progress. Both groups received aspirin gargles at six hour intervals (mistura acidi acetylsalicylici *B P C* 1/2 fl oz). All the patients were treated in bed until their temperature had been normal for twenty-four hours.

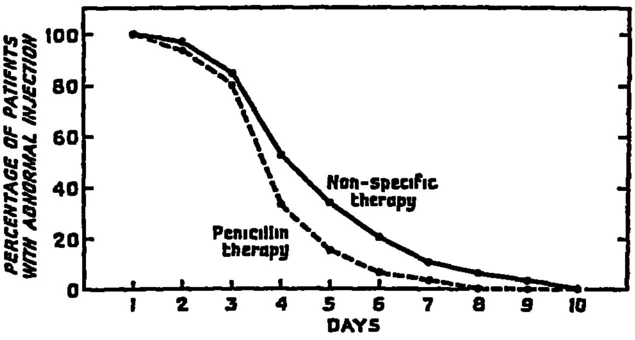

Fig 2—Effect of penicillin on duration of injection (œdema + redness) of throat in streptococcal cases

Results

121 consecutive patients satisfying the criteria described above were admitted to the trial.

For purposes of analysis they were divided retrospectively into two groups according to the bacterial flora of the throat.

(1) Those showing a predominant (60 cases) or a light (22 cases) growth of Lancefield group A streptococci on initial culture.

(2) Those from whom group-A streptococci were not isolated (39 cases). In 9 of these cases a light growth of hæmolytic streptococci not belonging to Lancefield group A was obtained, the remaining 30 showed a normal bacterial flora.

These two subdivisions will be referred to as the streptococcal and non-streptococcal groups, but we emphasise that the distinction depends entirely on whether or not group-A streptococci were isolated on initial culture. We do not mean to imply that streptococci were necessarily responsible for the illness.

Each of these groups was further subdivided according to whether or not penicillin was given, the division being

TABLE II—MEAN DURATION OF SPECIFIED CLINICAL FEATURES AFTER ADMISSION IN PATIENTS WITH AND WITHOUT LANCEFIELD GROUP-A STREPTOCOCCI IN THROAT

—	Streptococcal			Non streptococcal		
	Mean difference (days)	Standard error	Statistical significance	Mean difference (days)	Standard error	Statistical significance
Duration of sore throat	0.81	±0.32	Significant	0.42	±0.31	Not significant
Duration of pyrexia	0.95	±0.28	Highly significant	0.21	±0.43	Not significant
Duration of abnormal injection	0.98	±0.39	Significant	1.30	±0.66	Not significant

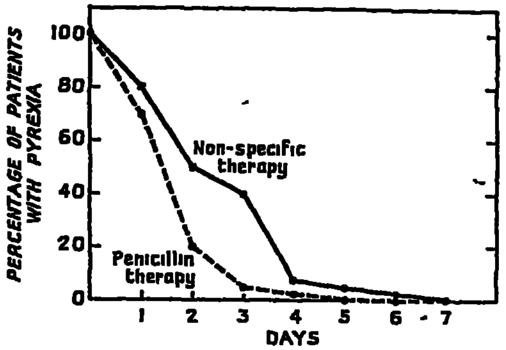

Fig 3—Effect of penicillin on duration of pyrexia in streptococcal cases

governed by random selection as described above In this way it was possible to assess the effect of penicillin in cases with and cases without a growth of group A streptococci on initial culture

Comparison of Treatment Groups—In table I specified clinical features are compared between the treatment groups It will be seen that the streptococcal cases on admission were reasonably uniform, whereas fairly large differences due to chance arose between the non streptococcal treatment groups

Duration of "Soreness" of Throat—The answers received in the streptococcal group are summarised in fig 1 The shorter duration of sore throat in those given penicillin is statistically significant, this is shown in table II The difference between the two treatment groups in the non streptococcal cases is not significant

Duration of Abnormal Injection of Throat—The results in the streptococcal group are given in fig 2, which shows that penicillin reduced the duration of abnormal injection of the throat in those harbouring streptococci The difference between the two treatment groups in the non-streptococcal cases is not significant (table II)

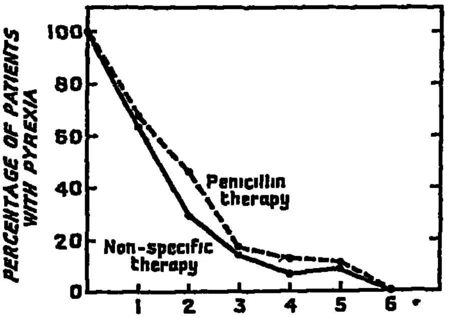

Fig 4—Effect of penicillin on duration of pyrexia in non streptococcal cases

Duration of Pyrexia—The results (figs 3 and 4) show quite clearly that penicillin reduces the duration of pyrexia by about twenty-four hours in those with group-A streptococci in the throat, whereas it has no effect in the absence of these organisms

Duration of Leucocytosis—Fig 5 shows the effect of penicillin on the duration of leucocytosis (11,000 or more white cells per c mm) in the streptococcal group It will be seen that 50% of those receiving only aspirin gargles still had abnormal counts on the third day, compared with 15% of those receiving penicillin Owing to the small numbers no definite statement can be made about the non streptococcal cases, but, at least, this gross difference on the third day was not seen

Antistreptolysin O Titre—The results are summarised in table III Surprisingly only 5 cases (16 7%) from the untreated streptococcal group showed a significant rise Only 1 case from the streptococcal group treated with penicillin showed a similar rise

Acute and Convalescent Carrier rate of Group A Streptococci—Fig 6 shows the proportion of patients from whom group A streptococci were isolated in hospital and during convalescence It will be seen that a four day course of intramuscular penicillin in adequate dosage did not eradicate the hæmolytic streptococcus from the throat in all the cases By the ninth day (four days after the end of penicillin therapy) 40% of the patients treated with penicillin produced group A streptococci, and during convalescence (three or four weeks later) there was no difference between the two treatment groups A penicillin sensitivity test was done in those cases showing a growth of the organism on the third day after admission and in no case were resistant strains of group A streptococci found

Complications Following Admission—There was one mild recurrence of sore throat after discharge from hospital among the streptococcal cases treated with penicillin No other complications developed after admission in any of the four groups, and there was no case of acute nephritis, acute rheumatism, or chorea

Discussion

Since the classical description by Felty and Hodges (1923) the syndrome of sore throat, pyrexia, faucial exudate, and painful lymphadenopathy is commonly regarded as being of streptococcal origin In practice, owing to the difficulties and delay in obtaining bacteriological confirmation of a diagnosis of streptococcal sore throat, many cases are treated with antibiotics or with sulphonamides on the basis of clinical diagnosis alone, but the possibility of accurately diagnosing streptococcal sore throat clinically has been disputed

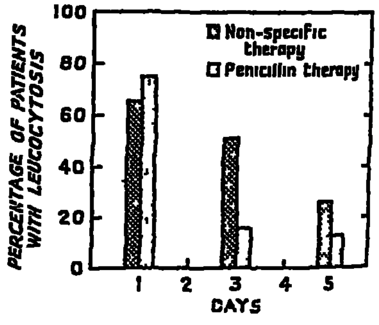

Fig 5—Effect of penicillin on duration of leucocytosis (11,000 or more white cells per c mm) in streptococcal cases

Rantz et al (1946) found that they could predict with an accuracy of 70% whether or not streptococci would be recovered from a throat swab, and the work of Breese and Disney (1954) supports this

On the other hand, in this country Landsman et al (1951) Bishop et al (1952), and Chapple et al (1956) could not separate streptococcal and non streptococcal varieties of acute sore throat

We too have found the diagnosis difficult, and, like the Commission on Acute Respiratory Diseases (1944, 1945, 1947), observed many cases of sore throat and pyrexia of abrupt onset with dysphagia and pharyngeal

TABLE III—EFFECT OF PENICILLIN ON INCREASE OF STREPTOCOCCAL ANTIBODY (ANTISTREPTOLYSIN O) AMONG STREPTOCOCCAL AND AMONG NON STREPTOCOCCAL CASES

	No of cases			
	Streptococcal		Non streptococcal	
	Non specific treatment	Penicillin treatment	Non specific treatment	Penicillin treatment
2 tube increase	5 (16 7%)	1 (3 3%)	1	0
1 tube increase	5	13	[illegible]	2
No increase or decrease	20	16	11	11

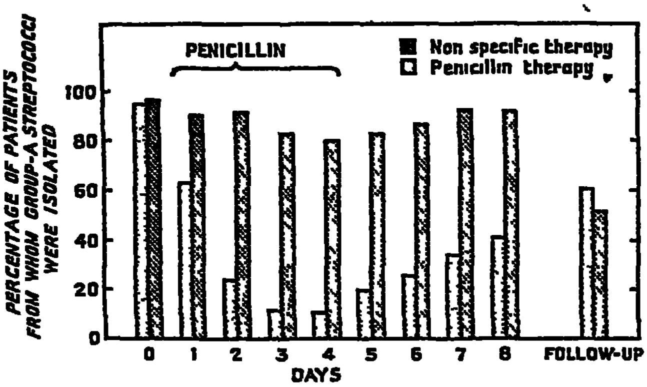

Fig 6—Effect of penicillin on proportion of patients from whom group-A streptococci were isolated on successive days after admission and at follow up three to four weeks later

exudate from which streptococci could not be isolated although repeated attempts were made to do so

Because of this difficulty in confidently diagnosing streptococcal sore throat without bacteriological aid we decided that it would be useful if all cases of acute sore throat satisfying our criteria (see above) were included in the trial In this way it is possible to compare the effect of penicillin therapy in those with and those without pathogenic streptococci in the throat

Intramuscular penicillin, rather than oral antibiotics and sulphonamides was chosen for assessment because (1) it is commonly used in practice for this complaint, and (2) it is generally regarded as the most efficient form of therapy for streptococcal sore throat (Denny et al 1953)

Streptococci were isolated from 82 (66%) of the 121 cases in the trial We must emphasise, however, that the so called streptococcal and non streptococcal groups are not ætiologically homogeneous, and that, even in those cases from which a predominant growth of group-A streptococci was isolated, the streptococcus could not be implicated with certainty as the cause of the initial illness (Commission on Acute Respiratory Diseases 1944, 1947) Nevertheless the results seem to justify this somewhat arbitrary and broad division into streptococcal and non streptococcal cases on the basis of bacteriological findings

The effect of penicillin on the symptoms and signs of the acute disease corresponds to the findings of Denny et al (1953), who were also studying young men, and of Bennike et al (1951), who investigated patients in all age-groups Like ours, both these series were treated in hospital

We find that the most striking effect of penicillin among those from whom hæmolytic streptococci were isolated was the reduction in duration of pyrexia and of leucocytosis (figs 3 and 5) This agrees with our clinical impression that the patients treated with penicillin felt better more quickly The duration of sore throat was also shortened, but, like the reduction in œdema and injection, the effect was not so great (figs 1 and 2) Owing to the small size of the sample no definite statement can be made about the non-streptococcal cases The fact, however, that there was no difference in the duration of pyrexia between the two non-streptococcal treatment groups suggests that penicillin therapy is unlikely to affect an acute sore throat unless streptococci are isolated

As regards the convalescent carrier-rate of group-A streptococci, our findings seem to differ from those of Denny et al (1953), who found a 10% convalescent carrier rate after a five-day course of intramuscular penicillin Their results refer to streptococci of the same type as those isolated during the acute illness Even lower figures were obtained by Bennike et al (1951) after a six day course of penicillin Our findings are based on a four-day course of penicillin, which was followed by a convalescent carrier-rate of group-A streptococci practically identical with that of the untreated group Wannamaker et al (1953) found that a ten day course of intramuscular penicillin was the only reliable way of eliminating streptococci from the throat

The real importance of acute sore throat is the risk of subsequent rheumatic fever or of acute nephritis Rammelkamp et al (1952), studying the effect of *epidemic* exudative tonsillitis in young airmen found that if typable group-A streptococci were isolated, the risk of subsequently developing rheumatic fever was about 3% Our experience, in this country, of more than 300 soldiers of a similar age with *endemic* exudative tonsillitis from whom group-A streptococci were grown, suggests that the risk of developing an initial attack of rheumatic fever is less than 1%, even in the absence of antibiotic treatment (unpublished)

Catanzaro et al (1954) have shown that rheumatic fever is not prevented unless the hæmolytic streptococcus is eradicated from the throat, whatever the increase of streptococcal antibody in the serum Therefore, if penicillin is being used as a prophylactic against rheumatic fever, a four-day course is of doubtful value

Therefore intramuscular penicillin will only be useful in cases of acute sore throat with pyrexia if hæmolytic streptococci are present A four day course will shorten the duration of symptoms by about twenty-four hours No other beneficial effect can be expected, and the risk of inducing drug sensitivity must be carefully considered

Summary

A controlled trial to assess the effect of a four-day course of intramuscular penicillin in acute sore throat with pyrexia is described

Penicillin reduced the duration of the illness by about twenty four hours only if Lancefield group A streptococci were isolated

Although penicillin suppressed a rise in antistreptolysin-O titre (which took place in a sixth of the cases not treated with penicillin), a four-day course of penicillin did not affect the convalescent carrier-rate of hæmolytic streptococci

We are indebted to Prof R Cruickshank for his constant advice and encouragement and to Colonel W R C Spicer and Lieutenant Colonel J A G Carmichael, whose interest and coöperation made the investigation possible Our results were analysed with the help of Mr D T Beeston, B SC, of the Army Medical Directorate (Statistics)

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PAIN IN THE LOWER LIMB AFTER SYMPATHECTOMY

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SINCE Royle (1924) described the technique of lumbar sympathectomy for spastic conditions, and made the incidental observation that the limbs became warm when deprived of their sympathetic supply, the operation has come to occupy an established place in the treatment of certain vascular disorders of the lower limb

Lumbar sympathectomy has been shown to have the following beneficial results

(1) Reduction of vasomotor tone, leading to increased blood-flow, especially to the skin and foot This may be effective in increasing the collateral circulation in obliterative arterial disease, in improving the skin nutrition in an ischæmic limb, so that ischæmic ulceration may heal, and in reducing the vasospastic component of certain peripheral vascular diseases (particularly those associated with Raynaud's phenomenon)

(2) A decrease in response to injurious environmental factors such as cold Thus the operation is effective in severe cryopathies—e g, conditions such as chronic pernio or erythrocyanosis frigida

(3) Elimination of sweating, especially of the foot In this way severe hyperhidrosis can be relieved

(4) Improvement in some patients with otherwise intractable causalgia There is no agreement as to how this result is produced

Certain complications have also been described (Ross 1935) These include troublesome dryness of the skin in the area affected by the operation, excessive sweating above it, and pain In this paper we describe the clinical features of the pain together with the results of studies made on a small series of cases, and discuss its possible cause

Investigation

The cases of post sympathectomy pain examined comprise those seen in the twelve months preceding May, 1956, in the surgical professorial unit of St Thomas's Hospital During that year 51 lumbar sympathectomies were carried out in 42 patients by members of the surgical unit Pain after operation was observed in 9 extremities (7 patients)

In each case the operation was performed through an anterolateral extraperitoneal incision and removal of the gangliohated trunk was confirmed by histological *section* The aim of the operation was to excise the paravertebral trunk from the sides of the second to the fourth lumbar vertebræ

Clinical Features of Post sympathectomy Pain

The clinical features were remarkably similar in each of the 7 patients The most constant feature was a *latent period* until the tenth to the seventeenth postoperative day, *when the pain appeared By this time the patients* had all been discharged from hospital The onset was sudden, the pain becoming severe and unremitting in some cases, and always worst at night In each case the pain had an identical *distribution to the anterior* parts of the thigh down to the knee, and corresponding quite closely to the distribution of the first and second lumbar dermatomes

The pain was associated with marked hyperæsthesia, and relief was not obtained with aspirin and codeine In 2 cases pethidine had to be given Some patients had sleepless nights for as long as three weeks, after which the pain usually began to abate

Physical examination revealed hyperæsthesia to light touch in the affected areas, with *cool, moist skin,* but with no sensory loss or other evidence of somatic nerve damage

Spontaneous remission occurred in all cases but 1 1 patient whose pain was very severe had relief over night after seventeen days With the others the pain subsided more gradually, taking from ten to sixteen weeks to disappear In 1 patient the pain is still present, though less severe, after five and a half months

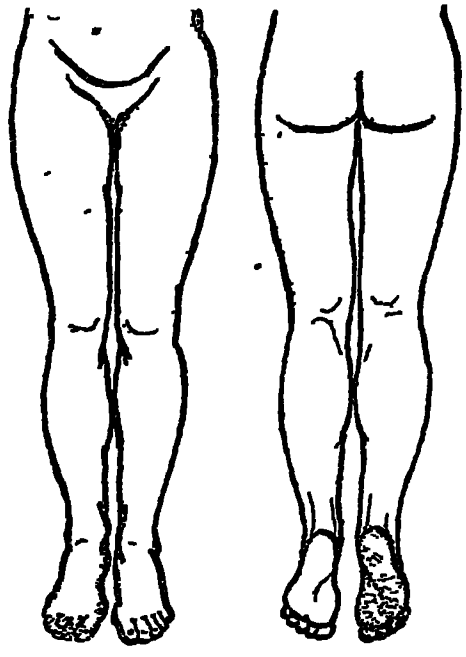

Fig 1—Skin-resistance pattern *after left lumbar sympathectomy* The darkest areas are those of lowest resistance (highest sudomotor activity)

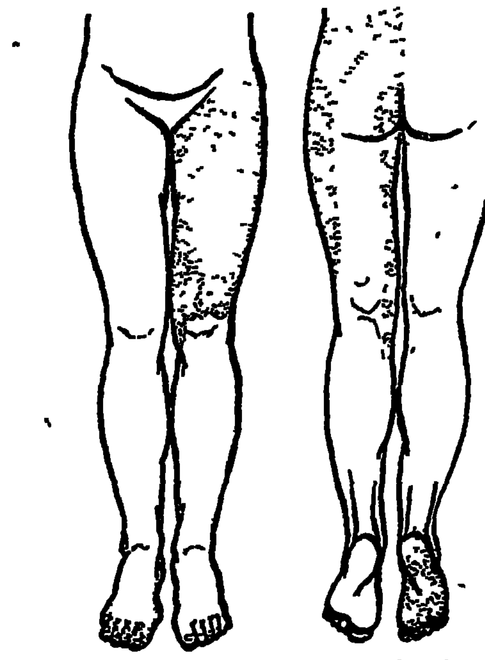

Fig 2—Skin-resistance pattern in a patient with post-sympathectomy pain Note the increased sudomotor activity over the area where the pain is felt.

SKIN RESISTANCE READINGS OVER THIGH

—	Thigh (Dermohmeter units)	Foot (in shaded area)
Normal	5–15 (10)	25–50 (40)
Lumbar sympathectomy (no pain)	5–25 (12)	0
Post sympathectomy pain	25–30 (30 approx)	0

This gives the range of values with the approximate average in each group in parentheses 1 of the 6 sensitivities was always selected to give a maximum deflection on the normal foot

Thus the duration of the pain may be summarised as follows

(1) Onset after a latent period of ten to seventeen days

(2) Spontaneous remission (occasionally with dramatic suddenness) after ten to sixteen weeks

Sudomotor Activity

The technique of measurement of the electrical resistance of the skin, developed by Richter (1947 et seq) was used to study these patients Richter and others have shown that the electrical resistance of the skin depends upon sweat gland activity and not on vasomotor or other physiological changes A puncture in the skin or an abrasion reduces the resistance almost to zero This test was selected as those which depend on bloodflow are subject to variable factors other than sympathetic activity, and cannot give information about the segmental distribution of sympathetic denervation

A small portable dermohmeter was used which is similar to the modification of Richter's apparatus described by Jasper and Robb (1945) It consists of a microammeter range 1 to 50 (with a deflecting needle to prevent overload) connected to nine 1½-volt batteries arranged in series, with a rotary switch providing six sensitivities The switch can be adjusted to obtain a large scale deflection of the meter in areas of normal sudomotor activity This was found to permit clear demarcation of the denervated zones without the use of a specially warmed environment to induce sweating

Skin-resistance measurements were carried out on all of the patients with post-sympathectomy pain except the first, and to establish a basis for comparison with these and other recorded patterns of skin resistance following sympathectomy, measurements were recorded from 19 normal limbs and from 16 limbs of patients who had undergone lumbar sympathectomy at times varying from several days to eleven years before, and who had not suffered the typical pain

Normal limbs —The pattern of skin resistance in the normal lower limb (figs 1 and 2, right leg) was found to be as described by Richter and others, with maximal readings (indicating lowest resistance) on the sole of the foot, especially the toes where sudomotor activity is greatest

Sympathectomised limbs without pain —The usual pattern following lumbar sympathectomy is shown in fig 1 (left leg) where the areas shaded darkest represent zones of greatest sudomotor activity In the unshaded areas this is zero In each case except 1 in which denervation appeared to be complete, sudomotor activity was found to persist in the anterior part of the thigh in the area coinciding with the first two lumbar dermatomes In 2 instances, readings slightly higher than those on the normal side suggest slight increase in sweating in this zone

The residual area of sudomotor activity following lumbar sympathectomy was noticed by Richter (1947) Ray and Console (1948) found the same residual-area in every one of a series of "total" sympathectomies, from the stellate ganglion to the sacral trunk They found that it was abolished after rhizotomy of the anterior roots of T12, L1 and L2, and described a technique combining this rhizotomy with lumbar ganglionectomy, which was said to produce complete sympathetic denervation without demonstrable motor weakness in the limb

A possible explanation for this phenomenon of residual sympathetic activity following lumbar sympathectomy has been provided by Kuntz (1950) who showed in anatomical dissections the presence of accessory ganglia in the anterior nerve roots of the upper lumbar segments, thus providing a pathway that by-passes the paravertebral trunk These accessory ganglia had previously been described by Wrete (1934) and Skoog (1947)

Sympathectomised limbs with pain —In the 8 limbs examined with post sympathectomy pain, *considerably increased sweating was discovered in the area of distribution of the pain*, compared to the normal side and compared to the sympathectomised but pain-free limb (fig 2) We could find no previous reference to this observation

Discussion

Post sympathectomy pain is a distinct entity—not to be confused with wound pain or with persistence of pain which was present before operation Although it is well known scant reference to it can be found in the English literature

Cohen (1953), referring to it as an "all too common complaint," describes as characteristic features the onset about the tenth postoperative day, worsening at night, with hyperæsthesia of the thigh and clearing within three to six weeks, "occasionally lasting months" Ross (1935) mentions it briefly, and Martin et al (1956) state that "the cause is not clear but it occurs in about 12% of cases"

Several possible reasons for this pain have been suggested (Simeone 1956) including

(1) Traction on the lumbar roots (Cohen)

(2) Degeneration of sympathetic nerve fibres causing root irritation

(3) Traumatic neuritis of the genito femoral nerve which lies close to the sympathetic trunk

(4) The presence of afferent fibres from the limb in the sympathetic trunk causing referred pain

None of these explanations seem adequate for the pain seen in our small group of patients The following factors appear to be significant

(1) The syndrome seems to be peculiar to the operation of sympathectomy, and is not seen after other operations in which somatic nerves may be injured

(2) The pain is constantly distributed to the front of the thigh in the first two lumbar dermatomes

(3) Residual sympathetic activity is always found in this area after a lumbar sympathectomy This is possibly due to the presence of accessory sympathetic ganglia, which occur even in cases without pain, in the anterior roots of L1 mainly but also in T12 and L2

(4) Greatly increased sympathetic activity in this area when it is the site of pain has been demonstrated in our observations

Other writers (Ross 1935, Grimson et al 1949) have referred to active sweating in other areas following sympathectomy, which may be an attempt to compensate for partial loss of sudomotor activity This is not always seen, and its relation to the increased sweating we have found in this small group with pain is a matter for conjecture

Summary

The clinical features of post-sympathectomy pain following lumbar sympathectomy are described

The results of studies carried out on 9 limbs with such pain following 51 lumbar sympathectomies are described

The new observation has been made that sudomotor activity is considerably increased over the area in the thigh where the pain is felt

We should like to acknowledge the interest and assistance of Prof J B Kinmonth and all the other members of the surgical unit at St Thomas's Hospital in this investigation

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CONGENITAL HYPERTHYROIDISM

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Congenital hyperthyroidism is rare, and all the reported cases have been the offspring of mothers who were thyrotoxic during pregnancy or had been treated for hyperthyroidism within a few years previously (White 1912, Margetts 1950, Fischer 1951, Jirsová and Brychnac 1953, Koerner 1954, Skelton and Gans 1955)

Juvenile hyperthyroidism is also uncommon Symptoms may date from the first few months of life and persist for many years (Ellis 1935) Koerner in 1954 was able to find only ten reports of hyperthyroidism in infants under 1 year of age, and McClintock et al (1956) had only one child below the age of 3 years in their own series Cattell (1949) found that, of all cases of Graves's disease, only about 1% occurred in children of 13 years or less

We report here a further case of true congenital hyperthyroidism, once again the offspring of a mother with thyroid disease

Case-report

The child's mother a woman of 25, had three normal children, the third being born in February, 1954 At the end of the same year she developed symptoms of hyperthyroidism—tiredness nervousness and irritability sweating, hunger, loss of weight prominence of her eyes and enlargement of her thyroid gland Partial thyroidectomy was performed in February, 1955 She apparently made a satisfactory recovery and for about 9 months, felt well without any of the symptoms which had previously troubled her

Her child a boy was born on Jan 19, 1956 The mother was 'only fairly well' during her pregnancy and felt that her eyes had again become prominent She became emotional and nervous but denied many of the symptoms of which she had previously complained

The infant was delivered at home by a midwife two weeks prematurely and weighed at birth 6 lb The midwife noted that the baby was limp and cyanosed and had bulging eyes He improved slowly, and about 6 hours later sucked vigorously when put to the breast Thereafter he was always hungry requiring 2 hourly feeding , but as the doctor did not wish the mother to breast-feed him, he was given 'Ostermilk no 1' It was estimated that in the second week of life he was receiving nearly 70 calories per lb of body-weight daily Despite this he did not sleep at night He was never jaundiced, but his mother noticed that his skin was very red and marked easily His bowels moved six to eight times daily, the motions being greenish On the day before admission his mother noted for the first time that he was easily startled and 'always moving" She also thought that his eyes were rather wide and staring He sweated freely His family doctor referred him to the Royal Hospital for Sick Children, Edinburgh on Feb 11 because of enlargement of his thyroid gland and failure to gain weight

Condition on Admission

The baby was very thin (weight 6 lb 1 oz) There was marked bilateral lid retraction and a suggestion of proptosis (figs 1 and 2) The skin was warm and moist, and dermatographia was easily demonstrated He was very alert and hyperactive, with increased muscle tone and an exaggerated response to noise and other stimuli He had a pulse rate of 176 His systolic blood pressure was 75 mm Hg (flush method) His thyroid was diffusely enlarged, but no vascular bruit was heard on auscultation over the gland Systematic examination was otherwise negative , in particular there was no cardiac murmur—or any evidence of jaundice, splenomegaly, or hepatomegaly

Investigations

Hæmoglobin 13·3 g per 100 ml White cells 13,500 per c.mm Urine normal Radiographs of chest and skull within normal limits *Radiographs of wrists showed epiphyseal* centres consistent with the baby's stated age Tryptic activity was present in the stools Electrocardiography revealed sinus tachycardia The serum bilirubin level was 0·8 mg per 100 ml , and the serum-cholesterol 140 mg per 100 ml The glucose tolerance curve was flat, the maximum rise being only 15 mg per 100 ml

A radioactive iodine test of the child's thyroid function was performed, using a dose of 1·6 µC of ^{131}I Urine was collected, through Paul's tubing attached to the penis, for 48 hours without loss In the first 24 hours 12·5% of the administered dose was excreted, and 1·2% was excreted in the 24–48 hour *period The uptake of iodine* by the thyroid gland appeared, by direct measurement to be about 90% of the dose after 24 hours

Treatment and progress—The baby was fed 3 hourly but remained hyperactive and extremely hungry He continued *to receive about 70 calories per lb* of body weight daily His

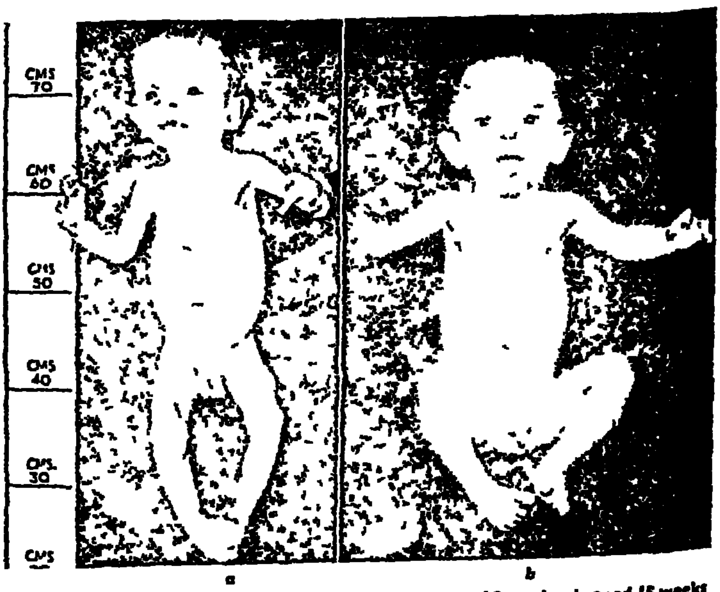

Fig 1—Infant with congenital hyperthyroidism *a*, aged 3 weeks , *b*, aged 15 weeks

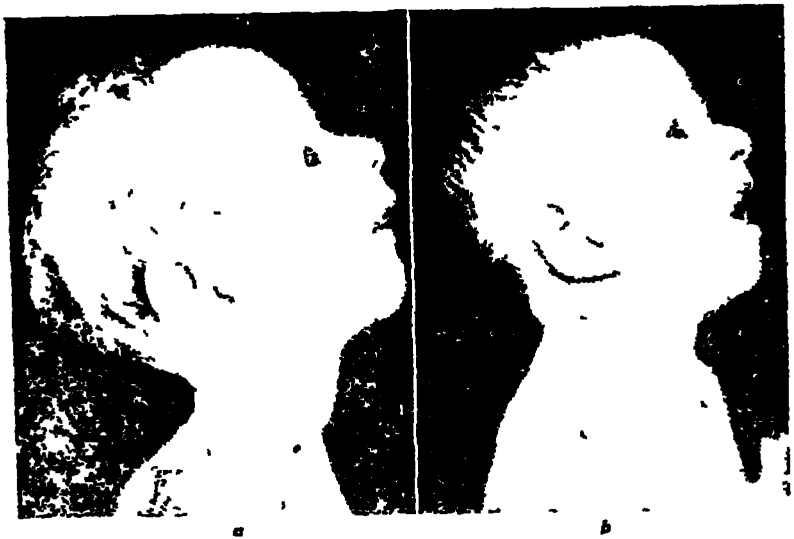

Fig. 2.—Same baby as in fig. 1. a, aged 3 weeks, with goitre and congenital hyperthyroidism. b, aged 15 weeks without goitre.

stools were loose, green, and very frequent, and in his first week in hospital his weight did not increase.

Treatment was begun on Feb. 17 with carbimazole 5 mg. and potassium iodide 30 mg. daily, and in 10 days he gained 1 lb. in weight. The administration of iodine was then stopped but that of carbimazole was continued in a dosage of 1.25 mg. daily until April 3. This quantity was then given on alternate days until April 17, when all treatment was stopped. As a result of treatment he became less restless and hyperkinetic, his pulse rate settled to about 126–134, and he produced one or two formed yellow stools daily. He was discharged from hospital on Feb. 28, weighing 7 lb. 10 oz., a gain of 1 lb. 9 oz. since the start of treatment.

His immediate progress thereafter was not entirely satisfactory, partly owing to maternal incompetence. He required readmission to hospital on March 6 for a week because of severe infection of his upper respiratory tract and a perianal abscess. He was seen regularly afterwards and improved considerably. On April 30 he weighed 9 lb. 8 oz., seemed contented and slept well, and his pulse and stools were normal. His thyroid gland was no longer clinically enlarged, and his subsequent progress and development were perfectly normal (figs. 1 and 2).

On June 12 he had been started satisfactorily on mixed feeding, weighed 12 lb. 6 oz., had normal motions and a pulse rate of 110. He appeared to be an active, bright, normal baby.

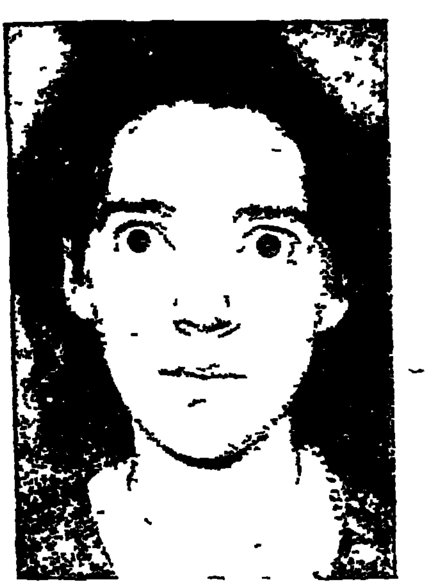

Fig. 3—Exophthalmos in mother of infant with congenital hyperthyroidism.

A month after the birth the mother weighed 9 st.—about 10 lb. less than before the pregnancy. She stated that she had become restless and irritable during the pregnancy, and these symptoms had persisted. Her appetite was good, but she did not regain her normal weight, sweated excessively, and was sure that her eyes had become more prominent. They had felt itchy and weepy, especially in the mornings. She thought that her thyroid gland had begun to enlarge again beneath her operation scar. On examination she was agitated and restless. Her hands were hot, moist, and tremulous, but her pulse rate was only 84. She had striking bilateral exophthalmos and lid retraction (fig. 3) and small nodular thyroid swellings below her scar. Clinically she gave the impression of being moderately thyrotoxic. A radioactive iodine test of her thyroid function was carried out in the out-patient department, but unfortunately one urine sample was accidentally discarded, the sample being passed $6^1/_2$ hours after the dose was given. Excluding this sample, her 48-hour urinary excretion of iodine was only 5.1%, and her protein bound plasma activity after 48 hours was 1.8% of the dose per litre of plasma.

She was subsequently satisfactorily treated with carbimazole.

Discussion

The development of hyperthyroidism in this infant, whose mother had undergone partial thyroidectomy for exophthalmic goitre 11 months before his birth, is yet another example of probable transplacental transmission of maternal thyrotrophic hormone. Congenital hyperthyroidism has only been described in cases where the mother has been thyrotoxic or has had treatment for such a condition. It is often assumed, not necessarily correctly, that exophthalmic goitre is due to overproduction of thyrotrophic hormone (T.S.H.) and to the pituitary's becoming unresponsive to the inhibitory effect of increasing concentrations of thyroid hormone. In such circumstances one would expect that, after operation, the serum-T.S.H. levels would rise because of the continued production of T.S.H., which had previously been inactivated by the thyroid tissue. Certainly such evidence as there is, in the absence of generally applicable assays of T.S.H., suggests that there is such a rise following operations, and Rundle (1945) demonstrated the steady progression of exophthalmos during the first postoperative year. The patient with congenital hyperthyroidism recorded by Koerner (1954) was the offspring of a mother with inadequately treated post-thyroidectomy hypothyroidism, and in such patients Rawson and Starr (1938) and Gilliland and Strudwick (1956) have demonstrated by far the highest detectable serum-T.S.H. levels.

Nikitovitch and Knobil (1955) have suggested that maternal T.S.H. cannot pass the placenta; if this were true in cases of congenital hyperthyroidism, hyperplasia of the thyroid gland in the infant could only be due to overproduction of the infant's endogenous T.S.H. This may happen when the thyrotoxic mother is treated with anti-thyroid drugs, because Freiesleben and Kjerulf-Jensen (1947) have shown that, in rats, thiouracil compounds are transmitted to the fœtus through the placenta. In such circumstances the infant's production of thyroid hormone is inhibited, and it may be born goitrous or even slightly hypothyroid. This, however, seldom happens unless the mother is herself rendered hypothyroid, and no thyrotoxic infant has been born to such a woman, although the mother of the child with congenital hyperthyroidism reported by Fischer (1951) received propylthiouracil towards the end of her pregnancy.

Toxicity in the infant cannot be due to transplacental transmission of maternal thyroid hormone because such toxicity would not be associated with hyperplasia of the infant's thyroid gland. In any case, congenital hyperthyroidism has been reported when the mother has been hypothyroid (Koerner 1954).

Our patient's mother was moderately thyrotoxic, both clinically and on the basis of her metabolism of radioactive iodine. The mothers of the patients reported by White (1912), Margetts (1950), and Fischer (1951) were also thought to be thyrotoxic during pregnancy. Our patient's mother and the mothers of the patients described by Skelton and Gans (1955) had severe exophthalmos, and all of the reported cases of congenital hyperthyroidism have had exophthalmos In view of the accumulating evidence that there is a separate pituitary factor capable of producing exophthalmos, it is of interest that Keynes (1952) reported the birth of a baby with congenital exophthalmos but no evidence of thyrotoxicosis to a mother who had had a thyroidectomy for hyperthyroidism a year previously and developed progressive exophthalmos after the operation

The present baby was undoubtedly thyrotoxic by all clinical criteria, and the result of the radioactive iodine studies showed that, in such a child, iodine metabolism is essentially the same as is observed in the thyrotoxic adult Van Middlesworth (1954) has studied the uptake of radioactive iodine in healthy newborn babies, and in his experience the 24-hour uptake of radioactive iodine by the thyroid gland exceeded 90% in two out of seven children tested on the third day of life He suggests a physiological hyperthyroidism in the newborn infant, because uptakes in his other infants were also greater than are usually observed in normal adults

If the disease is, as we believe, due to transplacental transmission of maternal T S H , it should be self limiting in duration after birth Most of the published cases have in fact been benign, although the patient described by White (1912) died, as did both those of Skelton and Gans (1955) Koerner's (1954) patient was very ill, as were several others , but it appears that, if the hyperthyroidism can be controlled for a few weeks, natural remission will take place For that reason we treated our patient with iodide to overcome the immediate effects of the thyrotoxicosis, and with carbimazole to render him reasonably normal until natural remission occurred Progress as a result of this treatment was entirely satisfactory We believe this was a causal relationship, although there might have been clinical remission even in the absence of treatment

The management of congenital hyperthyroidism is distinct from that of hyperthyroidism developing later in childhood In the congenital case the stimulus that initiates the production of toxicity is derived from the mother, and the condition can be regarded as benign In the later cases, however, the problems are similar to those of adult hyperthyroidism, it being essential to continue treatment with an anti thyroid drug for at least 18 months, and there is, as in adults, a tendency to subsequent relapse possibly necessitating partial thyroidectomy

Summary

A case of congenital hyperthyroidism is reported in the infant son of a woman who had had a partial thyroidectomy for exophthalmic goitre eleven months previously

There was evidence that both mother and infant were thyrotoxic, the infant showing the characteristic features of the disorder, including a goitre, tachycardia, lid retraction, hyperkinesis, restlessness, diarrhœa, and a ravenous appetite, with failure to gain weight

The child was treated with iodide for 10 days and with carbimazole until the age of 3 months Striking clinical improvement coincided with the onset of treatment After treatment was stopped his subsequent progress was satisfactory and normal

It is believed that congenital hyperthyroidism is due to transplacental passage of maternal thyrotrophic hormone and that the resulting hyperthyroidism in the infant is normally self limiting

We are grateful to Dr D N Nicholson under whose care this patient was treated for his interest and to Sister Jean Wood for her skill and help in the collection of the infant s urine One of us (A G M) is in receipt of an expenses grant from the Secretary of State for Scotland through the Advisory Committee on Medical Research

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NEURONE SELECTION IN RELIEF OF PAIN

FURTHER EXPERIENCES WITH INTRATHECAL INJECTIONS

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In heavy conveying solvents, phenol or silver nitrate can be injected intrathecally so that they flow over a series of posterior-root ganglia to relieve pain in cancer The solvents used are glycerin or ' Myodil ' (ethyl iodo phenylundecylate) Propylene glycol was abandoned as dangerous (Maykut and Ryan 1953) Since my last paper (Maher 1955) and after experience with over 125 cases, improvements in technique have been evolved for example, (*a*) I no longer use heavy cinchocaine hydrochloride (' Nupercaine ') before the phenol injection, (*b*) the dose and strength of the agents used have been better adjusted , and (*c*) injections are now given in the epidural and subdural layers, as well as below the arachnoid With reasonable care, the method is safe and some 90 punctures have been carried out in the cervical region alone

Solutions Used

Phenol alone (1 in 20).—1 g of phenol crystals is quickly weighed and placed in a dry sterile 30 ml bottle A sterile rubber cap is applied 20 ml of sterile glycerin or myodil is injected through the cap to give a 1 in 20 solution Smaller amounts can be prepared proportionately and the solution will keep for two weeks Weaker solutions do not afford permanent relief, and stronger solutions may cause unwanted effects (table I)

Phenol with silver nitrate.—Gr $2^1/_2$ (0 16 g) of silver nitrate are weighed and placed in a sterile 30 ml bottle A sterile cap is fitted 8 ml of sterile distilled water is injected through the cap When the phenol has dissolved, 1 ml of this solution is added to 24 ml of phenol solution (1 in 25) in glycerin 1 ml of this mixture, which contains gr $^1/_{80}$ (0 75 mg) of silver nitrate, is the usual dose If stored in the dark the solution will keep for three weeks

TABLE I—EFFECTS OF DIFFERENT STRENGTHS OF SOLUTION WHEN INJECTED INTRATHECALLY

Grade of change	Phenol in glycerin or myodil (1 ml)	Relief	Cutaneous analgesia	Cutaneous anæsthesia	Proprioceptive sensation	Motor function
I	1 in 30	Immediate not permanent	Nil	Nil	No effect	No effect
II	1 in 20	Permanent	Usually nil	Nil	No effect	No effect
III	1 in 15	Permanent	Definite	Scattered	Variable	No effect
IV	1 in 10	Permanent	Severe	Severe	Impairment of limb	

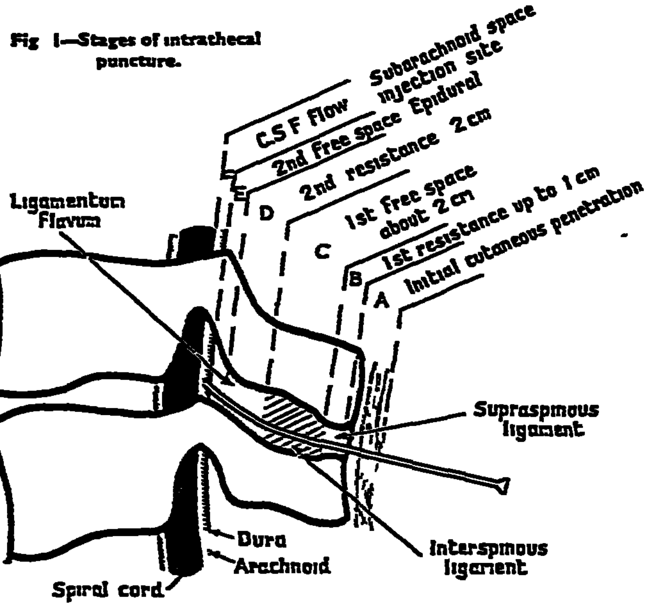

Fig 1—Stages of intrathecal puncture.

Local anæsthetic.—Cinchocaine hydrochloride was at first used as a safety measure before the phenol was injected, but it was found to be unnecessary Without cinchocaine, the immediate approximates more closely to the final result When there has been no previous anæsthesia, it is certain that any relief of pain is due to the phenol. It is also possible to assess the effects of different strengths of phenol.

Subarachnoid Injections

TECHNIQUE

Spinal Puncture

The patient is seated upright If possible it is preferable to puncture at one segment higher than the involved neurones so that the agent flows caudally The epidural space is easily located by gauging the resistance to the needle and repeatedly injecting procaine The theca is then penetrated The following stages are illustrated in fig 1

(A) Procaine (2% solution) is injected subcutaneously using a fine needle (26 gauge ½ in.)

(B) Further infiltration is made into the interspinous ligament and beyond The lumbar-puncture needle (Howard Jones type 21 gauge 3½ in) is then entered at rather less than 90 to the skin the shank being lower than the point It must enter the interspinous ligament at the peak of the interspinous ridge

(C) It passes easily for about 2 cm., procaine is injected continuously and flows freely

(D) A gripping resistance is felt and the needle can be safely pushed forwards for as long as this continues As it proceeds progressively less procaine can be injected—a sign of probable success

(E) The needle suddenly seems to ride over a ridge and the procaine flows freely in the epidural space

(F) It is then advanced 2 mm without the stylet cerebrospinal fluid (C.S.F.) will flow and the stylet is replaced

Position for Injection

Position I (for lumbar and high sacral injection)—The patient is laid on the painful side in the lateral lumbar-puncture position and rotated slightly backwards with a very slight downward slope of the spine towards the sacrum

Position II (for S4–5 segments)—He remains vertical during the injection at L5–S1 interspace

Trial Injection of Phenol

This is made when the pain is at a maximum to ensure that all the affected roots are reached To reach roots at the lumbar level the injection is made at the L1–2 or L4–5 interspace using position I 1 ml of phenol (1 in 20 in glycerin or myodil) is the standard dose First 0 5 ml is injected Pain should diminish and the remaining 0 5 ml is immediately injected The slope of the spine is increased as much as is necessary *to relieve all the pain*

To reach roots at the dorsal and cervical levels 3–3 5 ml of phenol (1 in 20 in myodil) is used Using position I, the injection is made at C3–4 interspace (for occipital pain) or C5–6 interspace (for brachial-plexus pain) The position of each 1-ml. dose is confirmed radiologically. Using position II for the sacral segments 1 5 ml of the solution is given in the L5–S1 interspace The limbs should be rested for three days afterwards

Total relief for five days indicates that no further injection is needed in that area

Supplementary Injections

For permanent relief, the initial pain-relieving injection must be followed usually after five days, by injections in other areas covering all adjacent predictable pain patterns 1 ml of the phenol solution covers about 4 to 6 segments at a session By further injections at different adjacent levels, using 1 ml for each it is possible to denude a patient of all pain fibres bilaterally below umbilical level without cutaneous sensory change or severe side-effects Fig 2 illustrates the usual injection range for pelvic cancer and for sarcoma of the lower limb, which usually involves injection at D12–L1 and L3–L4. For cancer of the rectum these segments are used after a vertical injection in position II has been allowed to gravitate to the tip of the dural sac for the lowest sacral and coccygeal elements This may cause temporary retention of urine For cervical- or brachial-plexus segments, one injection of 3 5 ml. of phenol (1 in 20 in myodil) is sufficient

When the initial phenol injections do not give adequate relief the phenol and silver-nitrate solution can be used at resistant sites after a few days. It is of particular value in cancer in the pelvis primary or secondary.

Side-effects

Before and after injection morphine is given if necessary, and if there is severe pain it may be relieved by

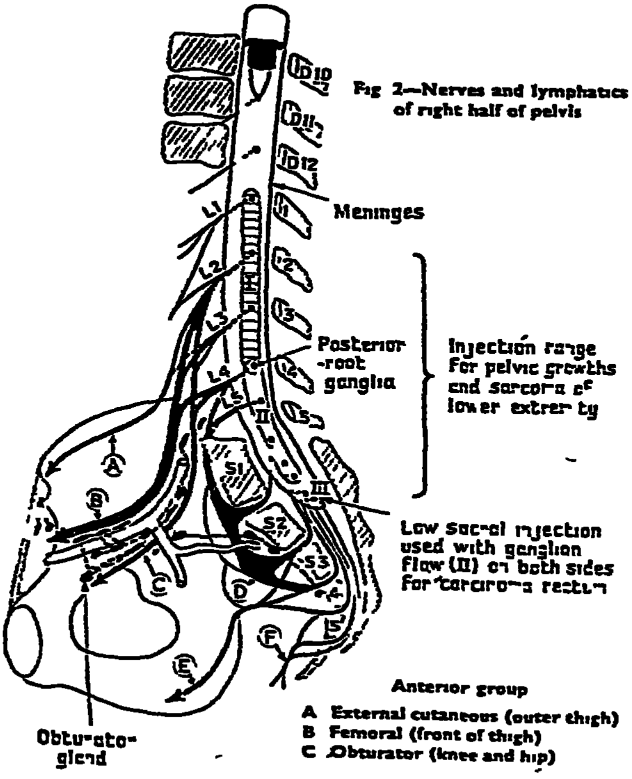
D10
D11
D12
Meninges
L1
L2
L3
L4
L5
Posterior -root ganglia
Injection range for pelvic growths and sarcoma of lower extremity
S1
S2
S3
S4
S5
II
III
A
B
C
D
E
F
Low sacral injection used with ganglion flow (II) on both sides for carcinoma rectum
Obturator gland

Fig 2—Nerves and lymphatics of right half of pelvis

Anterior group
A External cutaneous (outer thigh)
B Femoral (front of thigh)
C Obturator (knee and hip)

Posterior group D Sciatic E Pudendal F Coccygeal

0 3 ml of cinchocaine hydrochloride injected through the needle There are often attacks of pain or lightning pains for a week before relief is felt In 2 cases injection of silver nitrate (gr $^1/_{20}$) was followed by a meningitis (800 cells per c mm in the C S F) There were no after-effects, however, and relief lasted for over a year

Variations

Because the solution tends to accumulate below L1, the dosage of phenol solution (1 in 20) has to be limited to 1 ml Above this vulnerable stretch, the dose can be increased, and curiously the cervical region can take at least 3 5 ml of phenol solution (1 in 20) Possibly this is due to longer and narrower root pockets in this region

Increased strength (up to 1 in 15) can be used above *the L1 level A strength of 1 in 10 seems* to give cutaneous anæsthesia, bedsores, and muscular impairment Although this is not cord damage, it is functionally equivalent to it

The effect of sterile water, added to 1 ml of phenol solution (1 in 20), varies with the amount added 0 1 or 0 2 ml enhances the effect, and 0 3 ml *leads to effects* of grade III or IV (table I) Equal parts of water and phenol in 2 extreme cases diffused to the cord, producing profound anæsthesia, and, after a few days, loss of power Dry phenol in the conveying agent never affected the cord even on direct application

RESULTS

I have now treated 106 patients with severe pain by these methods Most of them experienced relief but in 33 of them the pain returned in a few hours Necropsy was done in 17 of these failures, and there was gross metastasis in the spine of all of them Fig 3 shows carcinoma cells in the posterior root ganglion in one of these 3 further patients who got no immediate relief showed no motor or sensory change whatever, even with phenol 1 in 10 the spinal canal at necropsy was found completely occluded by growth

In the failures, therefore, immediate relief suggests action only on the fibres of the posterior root (nerve-fibre block) Absorption of phenol in the fibres must be very rapid because no extension of cutaneous sensory change occurs on tilting the spine further a few minutes after the injection I infer that in successful cases, phenol affords permanent relief only by selection of the smaller cells of the posterior root ganglia (nerve cell block) If these cells are sheltered from the phenol by areas of carcinoma, permanent relief cannot be expected

There is further evidence to suggest such sheltering

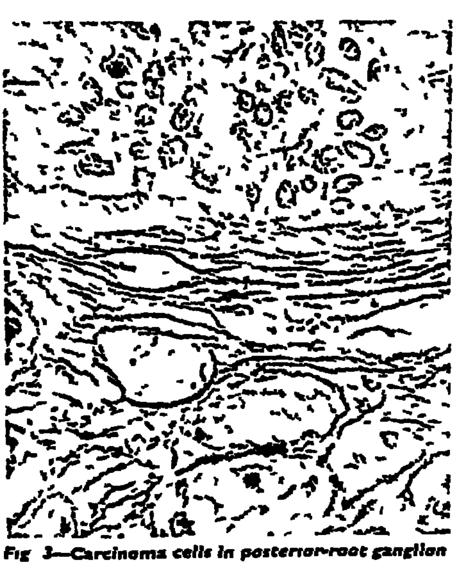

Fig 3—Carcinoma cells in posterior-root ganglion

(1) With pelvic cancer, injection for the femoral components alone often gave total relief When this had lasted for some weeks, a so-called "return of pain" was often now felt in the sciatic group of dermatomes (L4,5, S1 2 3) (fig 2) If phenol was injected dually, total relief continued in 1 case lasting for a year afterwards Both femoral and sciatic nerves were involved simultaneously in 16 cases, of these only 3 were relieved The failures had relief only *in the recently invaded nerve group* This suggests that there had been long-standing perineural spread to the ganglia along the femoral elements with more recent impingement on the sciatic group, or vice versa

(2) In cases resistant after injection, the total pain area was often reduced to one or two points Further phenol injection even at 1 in 10 strength made no difference to these points

(3) The length of nerve between the growth and the cord influenced the results All cases of sarcoma of the lower limb were totally relieved, even at a late stage Here, however, there is a different form of spread Of 16 cases of pulmonary cancer, only 6 were relieved here pain often begins when the growth leaves the lung border adjacent to the vertebral column, and having only 2 cm to travel, the growth rapidly invades the ganglia and the pain becomes intractable Horner's syndrome is a sign that metastases are involving the roots, cordotomy is indicated In 1 such patient pain was reduced, by injection, to an intractable ulnar distribution corresponding *to the roots involved in* Horner's syndrome By contrast, carcinoma in the pelvis has a comparable perineural travel length of some 16 cm Of 14 cases of carcinoma of the rectum, 10 were successful, with uterine cancer, 19 out of 28 patients were relieved

TABLE II—RELATION OF DURATION OF PAIN TO RELIEF

Duration of pain (months)	No of patients	No relieved	No unrelieved
Less than 1	11	10	1
1–3	29	23	6
4–12	42	25	17
Over 12	24	11	13
Total	106	69	37

Since infiltration of a ganglion takes time to develop it was decided to regroup cases according to how long *they had had pain and to* compare the results attained (table II) Within limitations imposed by the rate of extension of the growth and the distance it must travel, the prospects for relief depend largely on the duration of the pain before injection The outlook seems independent of the stage of the growth and of the intensity of the pain *The chance of relief seems best when pain has* been present for less than a month, especially in lung cancer, with its relatively short distance from the root ganglia

Of 26 cases of pelvic cancer not relieved by phenol alone, 15 were relieved by the injection of phenol with silver nitrate at lumbar level Injection was usually made at the same interspace as the previous unsuccessful phenol injection Injection in the dorsal region in 4 cases relieved pain permanently in gastric and renal cancer For cervical and upper dorsal sites it was unsuccessful and considered unsafe

In contrast to phenol, silver nitrate, at whatever strength, merely selected pain neurones without causing disability Increase in strength increased meningeal reaction Silver nitrate tended to "fix" a temporary phenol effect to make it permanent, and it became possible to employ phenol 1 in 25 with gr $^1/_{80}$ silver nitrate in 1 ml of vehicle Recently this has been added to myodil and used as an initial injection

Other Methods

Extra-arachnoid injections were most often used in the cervical region A Howard Jones needle (18 gauge $3^1/_2$ in) with a short bevel point is used, with the patient in position I Careful local anæsthesia using 2% procaine up to the epidural space (E in fig 1) is necessary Then the needle is carefully pushed forwards to prod the dura This gives a sharp sensation After the needle has been rotated through 180°, 1 ml of phenol solution (1 in 20 in myodil) is injected *Its position is confirmed radio*

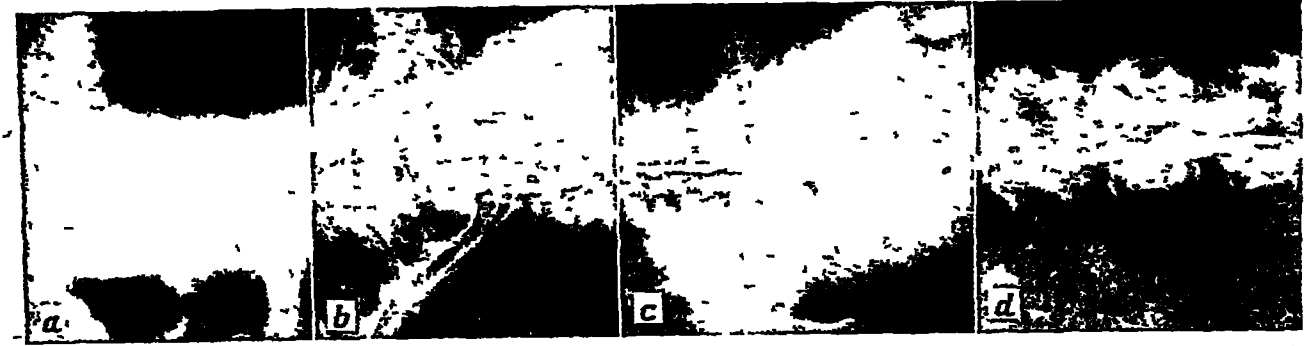

Fig 4—Injection at different thecal layers (a) epidural injection taking the segmental shape of the spinal canal, (b) subdural injection with root travel into the brachial plexus, (c) intrathecal injection (' oil-in the-water-bath ' appearance) (d) " double-line ' block of both intra- and extra-arachnoid injection

logically (fig 4*b* shows bilateral flow towards the root exits) 2–3 ml of the agent is then injected, followed by a further radiograph

Phenol in myodil subdurally has the following effects

(1) It runs bilaterally in a cephalic direction towards the roots on each side, although the patient lies in position I

(2) It tends to divide into portions opposite the root exits

(3) It travels along the nerve roots, mostly on the ' downward ' side In doing so it would tend to surround the ganglia thereby overcoming the effect of sheltering

The subdural space was reached in 7 cases and excellent relief was obtained in all of them

By combining subarachnoid with subdural or even epidural injections (double-line block), there should be more certainty of reaching all sides of the ganglia Here subdural injection of 2–3 ml of phenol solution (1 in 20 in myodil) is followed by further advance of the needle through the arachnoid where 1 ml of the same agent could be injected intrathecally at lumbar level or 3 ml at cervical level Fig 4*d* illustrates double line block with the meningeal lining showing as an interval

Non-malignant Conditions

Since there is no sheltering by tumour tissue, relief would be expected in non-malignant conditions treated by subarachnoid injection But inpatients with arthritis and scoliosis, an irregular spinal canal and osteophytes often make injections hazardous 3 patients with spondylitis showed relief and better movement Of 12 arthritic patients 4 were relieved but 8 developed acute exacerbations with generalised pains even after small doses Intrathecal injection is therefore usually contra indicated for arthritis

1 patient with post herpetic neuralgia was completely relieved Severe and continuous flexor spasms in a case of hemiplegia ceased permanently after injection, with improved movement of the leg Dr Peter Nathan, of the National Hospital for Nervous Diseases, alleviated 3 further cases of flexor spasms by this method Subdural and epidural injections of 1 ml of phenol solution (1 in 20 in myodil) give good relief in 2 or 3 cases and seem a safer measure for non malignant conditions

Conclusions and Discussion

The chance of successfully relieving the pain of cancer varies directly with the distance of the growth from the ganglia and indirectly with the duration of the pain

In an outpatient department where a cancer patient attends when his pain begins, it is easy to deal with it then and there using a phenol trial injection at the required level One or two successive injections at weekly intervals will cover neighbouring segments and prolong the relief by forestalling further extension of the growth If the pain is resistant phenol with silver nitrate should be used after admission to hospital The addition of subdural injections may further improve the chances of relief A Pain Relief Centre has been set up in this area to encourage early treatment

Better agents may be found in the future and the principle of neurone selection using gravitational flow may find a wider use But for cancer, unless they are done early, such procedures will continue to have the same doubtful reputation for haphazard results For pain from non-malignant causes extra arachnoid methods are probably safer

Summary

A technique for arachnoid puncture at all spinal levels has been evolved for the relief of severe pain With 1 ml of a 1 in 20 solution of phenol pain fibres only were affected, and there was no cutaneous sensory change, extensive areas on both sides can be treated

Success was more likely when the pain was of relatively recent onset Further pain-forestalling injections in adjacent segments were necessary for permanent relief

Resistant pain may be partly due to ' sheltering " of nerve cells from the phenol solution by areas of growth in the posterior-root ganglia Phenol with silver nitrate afforded relief in a number of cases resistant to phenol alone

Subdural injection may prove useful in conditions other than cancer Subarachnoid injection of phenol is useful for flexor spasm, but is not recommended for arthritis

My great thanks are extended to Dr Ralston Paterson Dr E C Easson Dr and Mrs J Starkie, Dr Helen Russell, Mrs M Laycock Mr F Inston and Mr A B Miller, M P S I should also like to thank Sir Geoffrey Jefferson F R S, Mr R T Johnson and Dr Reginald Reid, of the neurosurgical department, Manchester Royal Infirmary, for their help

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" The Public Health Service is composed of two separate but related parts. On the one hand there is the House-keeping Service—providing ambulances nurses, inspectors and the other health and welfare services for the community that can best be done in a communal fashion On the other hand there is another more important duty that is being neglected, namely, long term enquiry The sort of investigation and action which a hundred years ago was made with assurance of profitable result, is no longer available to us Progress will be halting and hesitant and difficult to achieve We are, however, passing through one of the great social experiments and we are not taking note of where we are going, nor of the results of our efforts, for all our social experiments will bring bad as well as good results *Noise hurry* long life, new techniques good and hardful, accompany our progress and we accept them with an alarming complacency The preoccupation of the Department for the chores is leaving little time for enquiry, and young men with an enquiring mind are not entering the service Never was patient social research so needed, and probably never so revealing ' —Dr LLEWELLYN ROBERTS, medical officer of health for Sheffield, in his report for 1955

HOMOZYGOUS HÆMOGLOBIN-E DISEASE IN INDONESIA

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SINCE the discovery of hæmoglobin E in 1954 by Itano et al (1954) in a family of partly Indian origin and simultaneously by Chernoff et al (1954) in the Siamese, this abnormal pigment has been observed in Veddas from Ceylon (Graff et al 1954), in Indonesians (Lie Injo Luan Eng 1955a), and in Burmese (Lehmann et al 1956)

Three conditions associated with this abnormal pigment have been recognised the hæmoglobin E trait, which is the heterozygous form for the gene of this abnormal hæmoglobin, pure hæmoglobin E disease, representing the homozygous state, and hæmoglobin E/thalassæmia disease, representing the double heterozygous state for the hæmoglobin-E and the thalassæmia genes

Six cases of pure hæmoglobin E disease have been reported from Thailand (Chernoff et al 1956) and two in Burmese (Lehmann et al 1956), but in no case was it possible to study both parents to prove the homozygosity of the condition

We report here three cases of pure hæmoglobin E disease in Indonesians In two of the three cases both parents were carriers of hæmoglobin E

Methods

All pipettes and counting chambers used for hæmatological determinations carried the certificate of the U S National Bureau of Standards Observations were made in duplicate Fœtal hæmoglobin in the blood was estimated by the method of alkali denaturation described by Singer et al (1951) For normal adults 2% alkali-resistant hæmoglobin of the total amount of hæmoglobin was taken as the upper limit of normal (Singer et al 1951, Lie Injo Luan Eng 1955b)

Hæmoglobin was analysed by paper electrophoresis according to the method described by Smith and Conley (1953) with veronal buffer pH 8 6 and ionic strength 0 05 and phosphate buffer pH 6 5 ionic strength 0 1 Serum-bilirubin and urobilin and urobilinogen in the urine were examined in the laboratory of the Central General Hospital, Djakarta

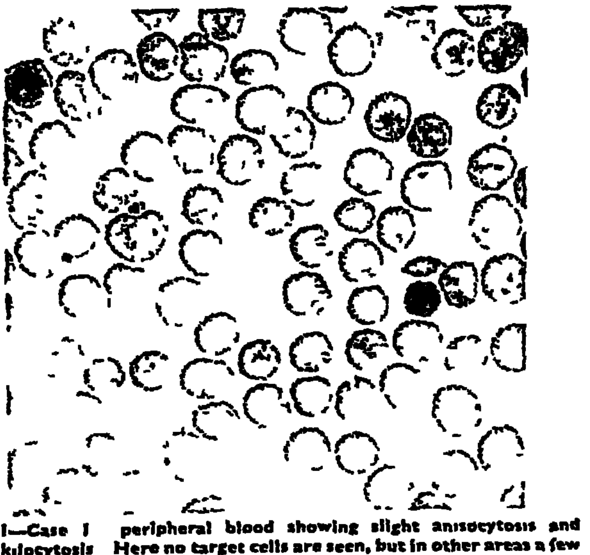

Fig 1—Case 1 peripheral blood showing slight anisocytosis and poikilocytosis Here no target cells are seen, but in other areas a few target cells were found (× 837)

Case-reports

Case 1—A girl, aged 9 years, was examined only because, during a survey on pathological hæmoglobins in the wards of the Central General Hospital in Djakarta her mother, who was being treated for chronic bronchitis was found to be a carrier of hæmoglobin E trait The whole family was therefore examined, and it was found that case 1 the eldest child had pure hæmoglobin E in her blood, and her father was a carrier of hæmoglobin E trait The family came from Padang in Sumatra So far as they knew they were pure Indonesian. The girl did not feel ill but, according to her mother, she was not strong, was easily fatigued, and had always looked somewhat pale She had never had icterus

Physical examination on Jan 31, 1956 showed that she was in good nutritional state and did not look ill but seemed slightly anæmic Her lymph nodes were not enlarged heart and lungs were normal, and spleen and liver both slightly enlarged, firm, and not tender No other physical abnormalities were noticed

Radiography of her skull, long bones, metacarpals and metatarsals, thorax, vertebræ, and pelvis did not show any abnormality Her lungs and heart were also normal on radiography

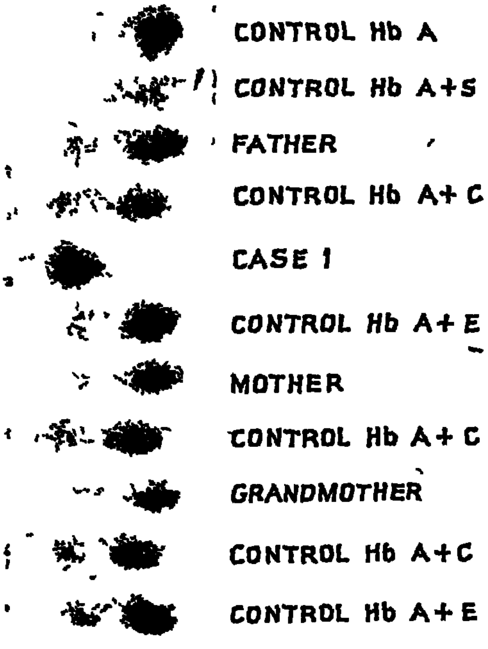

Fig 2—Paper electrophoresis at pH 8 6 of hæmoglobin of case 1, her parents and her grandmother compared with controls

Laboratory findings—Hæmatological data are summarised in table I There was slight erythrocytosis and microcytosis The mean corpuscular hæmoglobin concentration (M C H C) however, was normal The changes in the peripheral blood were not obvious (see fig 1) There were only slight poikilocytosis and anisocytosis No normoblasts were seen There were no Howell Jolly bodies and no rings of Cabot, but there were a fair number of cells with basophil stippling Only a few target cells were seen There was also a slight reticulocytosis A sickling test with 2% sodium metabisulphite was negative No malarial parasites were observed The resistance of the erythrocytes to hypotonic saline solution was increased The amount of alkali resistant hæmoglobin was found not to be increased Paper electrophoresis of the hæmoglobin at pH 8 6 showed only one type of hæmoglobin having a mobility which seemed to be similar to that of hæmoglobin C However since both parents were found to carry hæmoglobin E with a mobility higher than that of hæmoglobin C, it was expected that the child had hæmoglobin E and not hæmoglobin C Indeed at pH 6 5 the mobility was found to be definitely less than that of hæmoglobin C When the child's hæmoglobin was mixed with normal hæmoglobin so that the relative concentrations of the abnormal and the normal component were about the same as in a trait carrier the abnormal component had the same mobility at pH 8 6 as that of

TABLE I—LABORATORY FINDINGS IN CASE 1 AND FAMILY

—	Case 1	Mother	Father	Sister	Brother	Grandmother
Age when examined	9 yr	45 yr	50 yr	3 yr	13 mos	70 yr
Hb (g per 100 ml)	10 9	11 6	14 4	11 9	10 2	11 9
Red cells (millions per c mm.)	5 69	4 55	5 29	4 63	6 06	4 80
Packed cell volume (%)	33 5	37 0	42 5	38 0	34 0	39 0
Mean corp volume (cµ)	58 9	81 3	80 3	82 1	56 1	81 3
Mean corp hæmoglobin (µµg)	19 2	25 5	27 2	25 1	16 8	24 8
Mean corp hæmoglobin conc (%)	32 5	31 4	33 9	31 3	30 0	30 5
White cells (per c mm)	5400	8900	7100	5800	17 000	8800
Differential count of white cells	Eosinophilia	Eosinophilia	Normal	Eosinophilia	Normal	Normal
Reticulocytes (%)	2 7	0 2	0 4	0 4	1 0	0 9
Poikilo anisocytosis	±	—	—	—	+	—
Basophil stippling	+	—	—	—	—	—
Target cells	A few	Very rare	Very rare	Very rare	A few	Very rare
* Saline fragility initial at	0 40 %	0 40 %	0 40 %	0 40 %	0 40 %	0 40 %
complete at	0 20 %	0 28 %	0 24 %	0 28 %	0 20 %	0 32 %
Hijmans van den Bergh reaction direct/indirect	Not increased	Not increased	Not increased	Not increased	Not increased	Not increased
Alkali resistant hæmoglobin (% of total)	1 3	1 1	1 0	0 8	1 7	1 0
Hæmoglobin analysis	E	A + E	A + E	A	A + E	A + E
Urobilinuria	+	—	—	—	—	—
Spleen enlargement	±	—	—	—	—	—
Liver enlargement	+	—	—	—	—	—
Malaria	—	—	—	—	—	—

* Control determinations of the osmotic saline fragility in normal persons showed initial hæmolysis at 0 44–0 40 % (mostly at 0 44 %) complete hæmolysis at 0 32–0 28 % (mostly at 0 32 %)

hæmoglobin E and was slightly faster than hæmoglobin C It was therefore evident that the child had pure hæmoglobin E (see fig 2) The serum bilirubin level was not raised The urine contained urobilin and urobilinogen but no bilirubin or albumin In the fæces a few eggs of *Ascaris lumbricoides* were found but no other parasites or other abnormalities Bone marrow puncture was unfortunately not allowed

Progress—After three weeks' iron therapy there was no hæmatological improvement The amount of alkali resistant hæmoglobin was again found not to be increased

Family

The mother, aged 45, had chronic bronchitis, was very thin, and looked ill Her heart was normal, her spleen and liver were not enlarged The laboratory findings are summarised in table I

The father, aged 50, was healthy, no abnormalities being found on physical examination His spleen and liver were not enlarged The laboratory findings are summarised in table I He was a carrier of hæmoglobin E trait

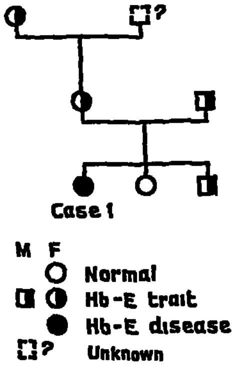

Fig 3—Pedigree of case 1

The second child, a girl aged 3 years, was not ill On physical examination no abnormality was found except slight rhinitis Her spleen and liver were not enlarged The laboratory data are summarised in table I The hæmatological findings were within the normal range for her age except for eosinophilia Her hæmoglobin was of the normal type

The youngest child, a boy of 13 months, was dystrophic and had influenza, diarrhœa, and bronchitis His spleen and liver were not enlarged The laboratory findings are listed in table I He was found to be a carrier of hæmoglobin E trait

The grandmother of case 1 was aged 70 and healthy On physical examination no abnormalities were found Her spleen and liver were not enlarged She was a carrier of hæmoglobin E trait (fig 2 and table I) Other laboratory findings are also listed in table I

The pedigree of this family is shown in fig 3

Case 2 —An Indonesian soldier, aged 36, from the island of Timor was registered as a regular donor at the Blood Transfusion Service of the Red Cross in Djakarta When he gave 500 ml of blood on May 9, 1956, a small amount was taken for routine survey of pathological hæmoglobins, and his erythrocytes were found to contain pure hæmoglobin E We studied him further on July 7, 1956 He said that he was quite healthy, was very seldom ill and did his heavy job without any complaint He had never had anæmia or icterus He was married and had two healthy children

On physical examination he was in a good nutritional state and not anæmic There was not the slightest icterus His lymph nodes were not enlarged, his lungs and heart were normal, and his liver was not enlarged, but his spleen was just palpable one finger breadth below the costal margin, firm, and not tender

Radiography of his skull, long bones, metacarpals and metatarsals, thorax, vertebræ, and pelvis did not reveal any abnormality

Laboratory findings on July 23, 1956, are listed in table II There was microcytosis but no anæmia The M C H C was normal The peripheral blood showed only slight anisocytosis but there were numerous target cells (fig 4) Red cells with basophil stippling were present The number of reticulocytes was not increased The numbers of leucocytes and of thrombocytes were normal A sickling test with 2% sodium metabisulphite was negative No malarial parasites were found The resistance of the red cells to hypotonic saline solution was increased The serum bilirubin level was not raised Electrophoresis showed only hæmoglobin E (fig 5) The percentage of alkali resistant hæmoglobin was within normal limits The urine did not show any abnormality

Family

On Sept 14, 1956, the parents of case 2 could not be examined, but we examined his wife and two children

The wife did not feel ill She was two months pregnant On physical examination no abnormalities were found The laboratory findings are shown in table II She was a carrier of hæmoglobin-E trait

The elder child, a girl aged 3 years, had pure hæmoglobin-E disease (see case 3)

The second child, a boy aged 1 year, had rhinitis and was very often ill with pyrexia He had had dysentery of undetermined ætiology two months before examination On physical examination he was found to be somewhat dystrophic The

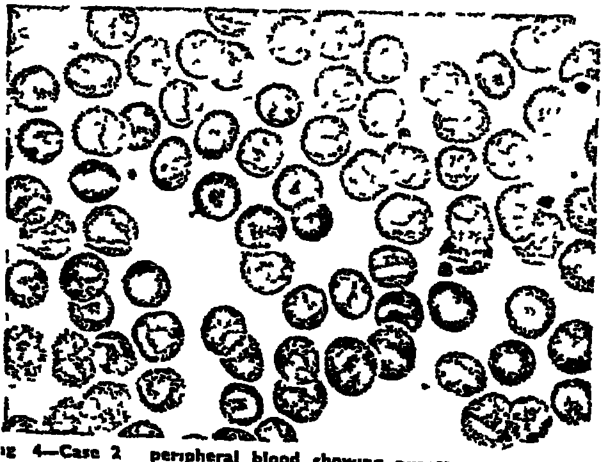

Fig 4—Case 2 peripheral blood showing numerous target cells (× 837)

TABLE II—LABORATORY FINDINGS IN CASES 2 AND 3 AND FAMILY

	Case 2	Wife	Case 3 (daughter)	Son
Age when examined (yr)	36	21	3	1
Hb (g per 100 ml)	14 5	13 5	13 0	10 9
Red cells (millions per c mm)	6 57	5 15	6 20	4 91
Packed cell volume (%)	42 5	41 0	39 0	35 0
Mean corp volume (cμ)	64 7	79 6	62 9	71 3
Mean corp hæmoglobin (μμg)	22 1	26 2	21 0	22 2
Mean corp hæmoglobin conc (%)	34 1	32 9	33 3	31 1
White cells (per c mm)	6300	10,000	7700	7250
Differential count of white cells	Normal	Normal	Normal	Slight eosinophilia
Reticulocytes (%)	1 3	0 2	0 6	0 8
Poikilo anisocytosis	+	+	+	+
Basophil stippling	+	−	−	−
Target cells	Numerous	Very rare	Moderate	Very rare
Saline fragility initial at	0 40	0 44	0 40	0 44%
complete at	0 20	0 32	0 24	0 24%
Hijmans van den Bergh reaction direct/indirect	Not increased	Not increased		Not increased
Alkali resistant hæmoglobin (% of total)	1 5	0 6	6 0	1 8
Hæmoglobin analysis	E	A + E	E	A + F
Urobilinuria	−	−	−	
Spleen enlargement	+	−	−	−
Liver enlargement	−	−	−	−
Malaria	−	−	−	−

laboratory findings are shown in table II In his fæces no abnormalities were found He was a carrier of hæmoglobin E trait

Case 3 —A girl, aged 3 years, daughter of case 2, was healthy She was in a good nutritional state and very seldom ill On physical examination no abnormalities were found Her spleen and liver were not enlarged Her heart and lungs were also normal The laboratory findings are shown in table II Her hæmoglobin was within normal limits for her age There was a clear microcytosis of the erythrocytes The mean *corpuscular hæmoglobin was normal* The peripheral blood showed slight anisocytosis Target cells were present but not so numerous as in her father's blood Basophil stippled cells *were not found The number of reticulocytes was not increased* A sickling test with 2% sodium metabisulphite was negative No malarial parasites were found The resistance of the erythrocytes to hypotonic saline solution was increased Electrophoresis of the hæmoglobin revealed hæmoglobin E and a trace of fœtal hæmoglobin The amount of alkali resistant hæmoglobin was 6% of the total amount No abnormalities were found in the urine The fæces contained a few eggs of *Trichocephalus dispar*, no other parasites

Discussion

It is not strictly permissible to describe a person as homozygous for a gene responsible for an abnormal hæmoglobin unless the diagnosis by electrophoresis has been confirmed by a study of his family (Lehmann et al 1956, Chernoff et al 1956) It is known that the laboratory findings in sickle cell/thalassæmia disease may be indistinguishable from those found in homozygous sickle cell disease Analogous to this, certain cases of hæmoglobin-E/thalassæmia *disease indistinguishable from* homozygous hæmoglobin-E disease might also be found In such cases only study of the family would be conclusive

In none of the few cases of pure hæmoglobin E disease published up to now were both parents studied Therefore the *homozygosity of the cases was not entirely* proved

In all three of our cases the diagnosis by electrophoresis was pure hæmoglobin-E disease In case 1 the diagnosis was confirmed by a *family study, both parents being* carriers of hæmoglobin-E trait, and no thalassæmia factor being found in this family

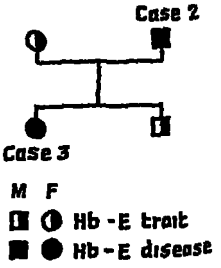

Fig 6—Pedigree of cases 2 and 3

The parents of case 2 were not examined, in case 3 both parents were carriers of hæmoglobin E, but a thalassæmia factor in the father could not be entirely ruled out

As one of us (Lie-Injo Luan Eng 1956) has pointed out, in comparing hæmoglobin types one should compare *them in similar* conditions The pure form of a hæmoglobin type should not be compared with the trait form, because this can lead to a wrong conclusion (fig 2) This is especially important when one has to differentiate two hæmoglobin types showing *only* a slight difference in mobility—e g, hæmoglobin E and hæmoglobin C at pH 8 6 If one compares the mobility of the hæmoglobin of case *1 with hæmoglobin C found in the control* trait hæmoglobin C (fig 2), the wrong conclusion could be reached that the hæmoglobin found in case 1 was hæmoglobin C However, both parents and the grandmother of case 1, who were trait carriers of the abnormal hæmoglobin had a pathologic component in their hæmoglobin with exactly the same mobility as that of hæmoglobin E being slightly greater than that of hæmoglobin C However, *the relative mobilities seen on paper* electrophoresis are not entirely constant, owing to factors which we do not yet understand Small differences are therefore difficult to assess and one must repeat the procedure several times before one can be sure of the constancy of the differences in relative mobility on paper electrophoresis Electrophoresis at an acid pH will help in making an accurate diagnosis This has been pointed out by H A Itano (personal communication) Also at pH

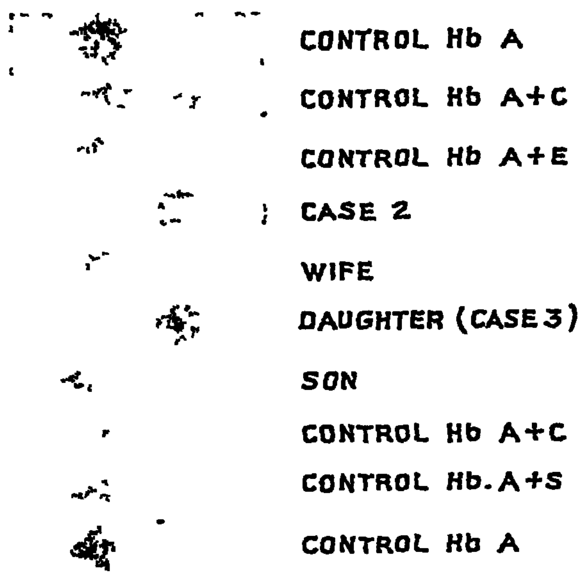

Fig 5—Paper electrophoresis at pH 8 6 of hæmoglobin of case 2 case 3, and family

6·5 one should compare hæmoglobin solutions under similar conditions. We found that, at this pH, the pure form of hæmoglobin E seems to have a mobility slightly greater than that of hæmoglobin E found in the trait condition. Study by open-boundary electrophoresis is more accurate, but this method is available only in a few laboratories and is impracticable for the mass survey.

The clinical picture in case 1 resembled that described in the cases of Chernoff et al. (1956). She complained of easy fatigability and tiredness; her spleen and liver were slightly enlarged, and she had slight anæmia. Case 2 resembled the cases described by Lehmann et al. (1956). He was entirely healthy and led a very active life without any complaint. His spleen was only just palpable. There was not the slightest anæmia. Case 3 also was healthy and had no anæmia. In all our cases the blood showed microcytosis and the M.C.H.C. was normal. The resistance of the erythrocytes to hypotonic saline solution was increased. In all three cases there was no clear evidence of increased hæmolysis. In cases 1 and 2 the amount of fœtal hæmoglobin was not increased. In all the published cases the amount of alkali-resistant hæmoglobin was slightly increased, ranging from 2% to 6·4% of the total amount of hæmoglobin (Chernoff et al. 1956, Lehmann et al. 1956). Case 1 had only a few target cells in her peripheral blood. Other workers have always found numerous target cells in the peripheral blood of cases of pure hæmoglobin-E disease.

The two other conditions associated with hæmoglobin E in the blood are the trait hæmoglobin E and hæmoglobin-E/thalassæmia disease. In a study of 15 families it was found by one of us (Lie-Injo Luan Eng 1956) that the heredity of hæmoglobin E fits the theory that this gene is transmitted as a mendelian dominant factor, and that this gene is an allele of the gene for normal hæmoglobin. Carriers of the trait are heterozygous for the gene for hæmoglobin E. They are clinically asymptomatic. But hæmatological study of 36 carriers of hæmoglobin-E trait by Chernoff et al. (1956) and of 44 by Lie-Injo Luan Eng (1956) revealed that many of the trait carriers showed slight microcytosis of the erythrocytes, and that the resistance of the red blood cells to hypotonic saline solution was sometimes increased.

The gene for hæmoglobin E has been found in many countries in South East Asia and plays an important rôle in this part of the world. The distribution of hæmoglobin E in Asia has been discussed by Lehmann et al. (1956). In a survey of about 4000 samples of blood from different islands in Indonesia hæmoglobin E was found on all the islands examined (Lie-Injo Luan Eng 1956). On the island of Java the approximate incidence is 3%. On the island of Madura, however, the incidence is much higher—about 17% (Lie-Injo Luan Eng unpublished).

Hæmoglobin-E/thalassæmia disease has been described especially by Chernoff et al. (1956) and by Lie-Injo Luan Eng (1956). Both clinical and laboratory findings were very variable. Different hæmoglobin patterns—namely, E + F, E + A, and E + A + F—were found by Lie-Injo Luan Eng (1956). The syndrome was very like that found in Cooley's anæmia.

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CUSHING'S SYNDROME WITH CARCINOMA OF BRONCHUS

AND WITH FEATURES SUGGESTING CARCINOID TUMOUR

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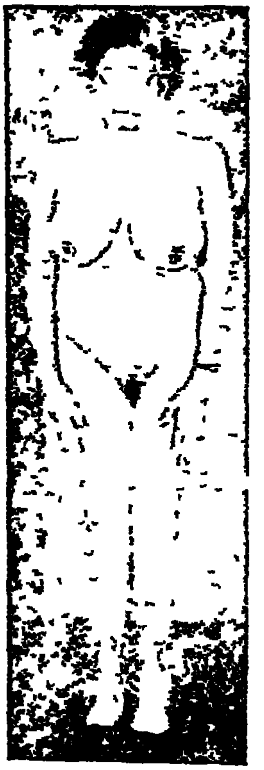
Cushing's syndrome is usually associated with hyperplasia, hyperfunction, or tumours of the adrenal cortex whose secretions are responsible for the clinical and metabolic features of the disease. A few cases, however, have been described in association with carcinoma of the bronchus, pancreas, or thymus (Thorne 1952), cerebral lesions (Zondek 1923), diseases of the liver (Bongiovanni and Eisenmenger 1951), and tumours of the ovaries. The relation between the syndrome and these lesions is not understood. The patient whose case we report here suffered from Cushing's syndrome and a carcinoma of the bronchus, and showed other unusual features which suggested the presence of a functioning carcinoid tumour.

Case-report



A woman, aged 55, was first seen by one of us (A. S. R.) at the Lagan Valley Hospital, in September, 1955, complaining of pustular spots on the legs and arms, and growth of hair on the face. Her menstrual periods had ceased 2 years previously and there were no past illnesses. Her mother had had diabetes mellitus, but there was no indication that this might have been due to Cushing's syndrome. She had a stout body and thin limbs, and there were pads of fat in the supraclavicular triangles, axillæ, groins, and cervicodorsal region. There were no red striæ on the skin, but 3 weeks later one appeared on the abdomen and after another 10 weeks there were several. The blood-pressure at this time varied between 155/80 and 175/90 mm. Hg.

She was regarded as an early case of Cushing's syndrome and admitted to the Royal Victoria Hospital, Belfast, on Jan. 6, 1956. In addition to the previous complaints she mentioned diarrhœa and swelling of the ankles, and said that her hair had become darker and had been falling out for 6 months. On questioning she said that her face had become fatter in the past few months and that she was a little short of breath on exertion.

On examination (see figure) the face was rounded, the cheek had a cyanosed flush, and there was moderate hair growth on the upper lip, sides of face, and chin. An acneiform rash was present over the limbs and abdomen and there were several purple striæ on the abdomen. There was marked thoracolumbar kyphosis and the blood-pressure was 170/100 mm. Hg. Dullness and decreased air entry were found at the base of the right lung. The liver was enlarged three finger breadths below the costal margin it felt hard but was neither nodular nor tender There was no ascites, and the clitoris was not enlarged

Investigations

In September, 1955, X ray films of the pituitary fossa and intravenous pyelography were normal, and there was normal density of the thoracic spine The 17 ketosteroid excretion was 5 6 mg in 24 hours, in December it was 1 8 mg

In January, 1956, the patient had heavy glycosuria but no ketonuria X-ray films of abdomen and excretion urography were normal, as were films of the skull and the rest of the skeleton Films of the chest showed a large rounded mass projecting from the hilum of the right lung and compressing the right main bronchus Tomograms and bronchoscopy (Mr H M Stevenson) suggested a bronchogenic cyst We assumed that this mass was responsible for the chest signs but had no other significance A barium meal revealed a small ulcer in the region of the pyloric antrum Presacral insufflation of oxygen and tomography showed adrenal shadows of normal size and shape The blood sugar was 153 mg per 100 ml *in the fasting state, and rose to 344 mg 2 hours after ingestion* of 50 g of glucose The peripheral blood picture was normal The serum potassium was 2 m eq per litre, and the serum bicarbonate 37 m eq The hypokalæmia was sufficient to produce T wave changes in the electrocardiogram Liver-function tests revealed an alkaline phosphatase of 23 King-Armstrong units and serum bilirubin of 1 3 mg per 100 ml, but the thymol turbidity and zinc sulphate flocculation tests were normal A 6 day corticotrophin stimulation test (Prunty 1956) gave a normal resting value and rise for 17-ketosteroids The resting level of 17 ketogenic steroid excretion was normal, but no rise occurred after corticotrophin

Finally, peritoneoscopy (R B W) showed that the liver was largely replaced by bluish nodules of tumour Biopsy showed these to be anaplastic carcinoma, the source of which could not be identified

Progress

In the month after admission a few purpuric spots appeared on the trunk and the diarrhœa subsided On the night of Feb 4, she suddenly developed acute dyspnœa and retrosternal pain There was bronchospasm and generalised moist sounds were heard throughout both lungs The temperature was 104 5 F and the pulse irregular, the rate varying from 120 to 160 per min A myocardial infarct seemed the probable explanation of what was thought to be acute left ventricular failure, but next morning her dyspnœa and bronchospasm had disappeared and an electrocardiogram yielded no evidence of infarction The purpuric rash on her abdomen became more profuse Her temperature remained at about 105°F for the next 2 weeks 2 days after this attack her diarrhœa returned, and it remained severe for 3 weeks She passed 7–10 watery stools daily without blood or mucus Ascites developed very rapidly over the next few days but then gradually subsided Her abdominal striæ became less marked

Urine taken 3 days after this attack contained 5 hydroxy indole acetic acid (5 H I A A) identified by paper chromatography (Prof D C Harrison) The amount was greater than normal but less than is usual with a functioning carcinoid tumour After intravenous injection of 10 ml of 10% alcohol another specimen of urine showed a slightly greater amount of 5 H I A A On questioning the patient again, we found that she had noticed flushing attacks for 2 months before admission These attacks involved her whole body, lasted about a minute and came on after meals During her stay in hospital however there were no attacks of flushing *These findings suggested the presence of a functioning carcinoid tumour* but there was no clinical evidence of pulmonary or tricuspid stenosis Cardiac catheterisation was attempted but was unsuccessful

She continued to have attacks of dyspnœa at night although never as severe as the first, but otherwise she seemed to be improving and getting stronger However she died on April 8 after a few hours coma

Post mortem Examination

A spherical tumour 4 cm *in diameter was found at the* hilum of the right lung *The* bronchus and pulmonary artery were in close relationship but were not involved On section the tumour was *unencapsulated and fleshy in consistence* There were a few hæmorrhagic areas No other tumour was found in the lungs

The liver was much enlarged and contained numerous metastatic tumour nodules (diameter 3 mm to 3 cm) many with hæmorrhages There were tumour deposits in the lymph nodes of the porta hepatis and the para aortic region

In spite of a careful search no tumour deposits were found elsewhere In the heart, no endocardial thickening was evident, and the valve cusps were everywhere thin The endocrine glands appeared normal

Microscopy —The tumour in the lung was a carcinoma. *The cells ranged from the rather small ovoid cell seen in the* so called oat cell carcinomas to more definite polyhedral epithelial cells with more copious cytoplasm In the liver these latter cell types formed the bulk of the metastases, and in some areas definite, though rudimentary, glands were found

Sections of the pituitary and adrenals showed no lesions Crooke's hyaline change was absent in the basophils of the anterior lobe

Discussion

This case has two features of interest first, the co existence of Cushing's syndrome and bronchial carcinoma, and secondly, the presence of symptoms and signs suggesting a malignant carcinoid tumour

Only three cases of Cushing's syndrome associated with bronchial carcinoma have been reported previously (Brown 1928, *one case*, Thorne *1952, two cases)* In all of these the tumour was an oat cell carcinoma The pituitary was normal in one, enlarged in one, and the site of metastases in the third The adrenal cortices were normal in one and hyperplastic in two The livers of *two were extensively involved by metastases, and* that of the third showed central congestion and necrosis of the lobules

In our patient, as in Thorne's two cases, the liver was extensively invaded However, the brain, pituitary, and adrenals were normal This was an unexpected finding since in all the reported cases of Cushing's syndrome associated with carcinoma of the thymus or pancreas, and in two of the three described above with carcinoma of the bronchus, the adrenal glands were hyperplastic In the absence of adrenal hyperplasia the features of Cushing's syndrome in our patient are difficult to explain They might be attributed to failure of a heavily infiltrated liver *to inactivate* the adrenal cortical hormones, but if this were so, one would expect to see Cushing's syndrome more often in severe liver disease Moreover, the patient described by Brown had all the features of Cushing's syndrome but no metastatic involvement of the liver by the bronchial carcinoma There is no evidence that bronchial carcinomas are hormonally active, although Jepson (1956) has reported a case without features of *Cushing's syndrome in which the 17 ketogenic* steroid excretion was extremely high

In our patient, a few weeks before her death, the abdominal striæ became less prominent and the purpura and acneiform skin rash disappeared The case may therefore have been one of "transient Cushing's syndrome" (Zondek 1923), resulting from hypothalamic dysfunction (Zondek and Leszynsky 1956) A raised *intracranial pressure may be associated with* Cushing's syndrome, as in cases of meningioma in the region of the cervical cord (Heimbecker 1944) or cerebellar astrocytoma (Crispell and Parson 1952) The syndrome may disappear after the intracranial hypertension has been relieved The prolonged hyperpyrexia in our patient was another feature which might have been caused by hypothalamic dysfunction There is, however, no direct *evidence for this hypothesis*

The syndrome associated with malignant carcinoid tumour (argentaffinoma)—namely, flushing attacks diarrhœa asthma right sided valvular heart *lesions, and* hepatomegaly—is becoming well known, but cases exhibiting some or all of these features have been reported with carcinoma of various organs in the absence of a carcinoid tumour (Arnett and Long 1931, Cassidy

1931, 1934, Weber 1943, Rosenbaum et al 1953) However, carcinoid tumours are often associated with carcinoma in other parts of the body (Pearson and Fitzgerald 1949, McKusick 1956), and a carcinoid may have been overlooked in some of the patients with symptoms suggestive of its presence In our case a careful search was made at necropsy, but no carcinoid tumour was found

Estimation of 5-HIAA (a metabolite of 5-hydroxytryptamine) in the urine is now generally regarded as the most useful test for the presence of a carcinoid tumour and is thought to be specific Two cases of carcinoma, however, have been reported (one of the breast and one of the larynx) (Clerc Bory et al 1954) in which urinary chromatograms showed abnormally large amounts of 5HIAA It was not stated whether the livers were involved by tumour or not In a small series of cases of gastro-intestinal carcinoma with liver metastases (Snow et al 1955), a slightly raised excretion of 5-HIAA was reported, but the levels were much lower than those found in cases of malignant carcinoid by the same authors In another series of cases of carcinoma with metastases in the liver the urinary excretion of 5HIAA was normal (Haverback et al 1956)

In our patient, a slight excess of 5HIAA was found in the urine The liver was extensively infiltrated by metastases from a bronchial carcinoma, but no carcinoid tumour was discovered We conclude therefore that increased urinary excretion of 5-HIAA may occur with malignant tumours other than carcinoid

Summary

The case is reported of a woman of 55 with a carcinoma of the bronchus She presented the clinical features of transient Cushing's syndrome and had some symptoms suggestive of a carcinoid tumour There was a slight excess of 5HIAA in the urine, but a carcinoid tumour was not found at necropsy

We are grateful to Prof J H Biggart for his advice on the pathological findings, to Prof D C Harrison for the estimation of 5HIAA, to Mr H M Stevenson for the bronchoscopy, and to Mr R G Wood for the photograph

ADDENDUM

Since this article was submitted, Boyland et al (1956) have reported the detection of small amounts of 5HIAA in the urine of patients with carcinoma of bronchus and other sites, following the ingestion of 2 g of *l* tryptophan In these patients significant amounts of 5HIAA were not apparently found unless tryptophan had been ingested, although this is not definitely stated in every case

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UTERINE MYOMA AS A HEREDITARY DISEASE

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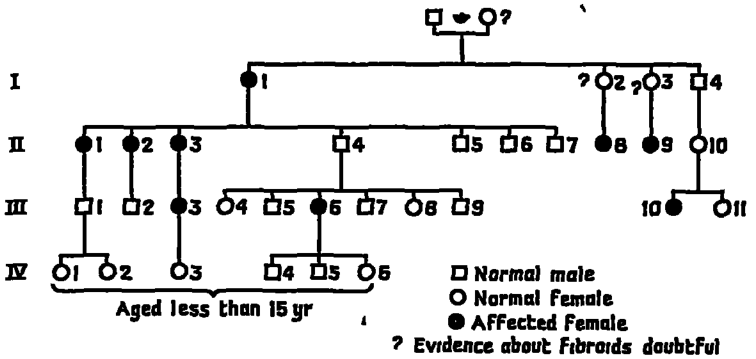
Uterine fibromatosis is not usually considered to be hereditary, but the occurrence of uterine fibroids in more than one member of a family has occasionally been noticed



Pedigree

Lockyer (1918) stated "It is certainly striking how fibroids run in families A patient of my own is one of five sisters, four of whom have had uterine myoma, and the fifth refuses investigation but is thought to be similarly afflicted"

Lagrona Weill-Hallé (1950) described two sisters, aged 19 and 22, with identical clinical features due to multiple small intramural uterine fibroids No family history was given

All the affected members of the family described here that I have managed to talk to had large uterine fibroids which produced a palpable abdominal tumour but no abnormality of the menstrual cycle They remained undiscovered until either they complicated a pregnancy or the abdomen was examined for some other reason

The Family

Generation IV (see figure) are all aged less than 15 and are excluded from the present survey At least 9 of the 15 females in generations I–III have had uterine fibroids I have talked to 5 adult members of the family independently, and all of these named the same relations as having had uterine fibroids, I have personally attended 3 of these patients, and 2 other cases were confirmed by the patient's own doctor

A typical case is that of III 3

> During a routine examination while she was in bed with influenza in March, 1956, a firm abdominal swelling extending up to the umbilicus was palpated That this was caused by several uterine fibroids was confirmed on bimanual examination The menses were regular and normal in amount At operation in August 1956, one large intramural fibroid and two medium sized subserous fibroids were found, and subtotal hysterectomy was done

Discussion

I 1 in the first generation had 7 children before undergoing a hysterectomy at the age of 44 This is an unusual number for a diseased uterus to bear Usually there are no, or only 1 or 2, children of a mother with uterine fibroids as in generation II This fact makes the disease self limiting by reducing the number of progeny

Uterine fibroids are rarely discovered before the fourth or fifth decade of life and even then may go unnoticed and symptomless It is therefore difficult to piece together a full hereditary picture, some with fibroids may be missed, particularly if they are unmarried or childless

From the family tree it looks as if the condition may be transmitted through males as well as females II 4, a man, has a daughter (III 6) with fibroids This might explain the occurrence of uterine fibroids in daughters of fibroid-free mothers and in women with no apparent family history of uterine fibroids at all

The presence of uterine myomas in three generations strongly suggests a dominant mendelian inheritance of a sex-limited type, the condition being confined to females There may be an instance here of the skipping of a generation, because II 10, herself apparently normal, has transmitted the gene from her father, I 4, to her daughter, III 10

A sine qua non of dominant genetic inheritance is the presence of the genetic trait in one or other parent, but, in a condition necessarily limited to females such as this, it appears to be possible to have normal parents with an affected daughter when the gene is transmitted through the male

There was no consanguinity

Summary

A family is described in which there is a high incidence of uterine myomas

The condition appears to be due to a dominant gene transmitted both by men and women, but of necessity expressed only in the latter

My thanks are due to Dr J A Fraser Roberts for his valuable comments on this pedigree

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Preliminary Communication

THE ELECTROCARDIOGRAM AFTER EXERCISE IN THE DETECTION OF LATENT CORONARY-ARTERY DISEASE IN R A F PERSONNEL

THE early and accurate diagnosis of coronary-artery disease, with all that it implies, is particularly important in pilots and aircrew However, it is well known that in many patients suffering from angina pectoris the diagnosis has to be made on the history alone without support from physical examination or the resting electrocardiogram (E C G) Thus, approximately a third to a half of patients with angina pectoris due to coronary-artery disease have normal resting E C G s, if those who have hypertension, or have had prolonged attacks of chest pain are excluded, the figure is higher [1 2] The E C G after exercise has been used as an aid in the diagnosis of suspicious chest pain for more than twenty years with varying efficacy and safety [3] In this study the technique and criteria of Wood and his collaborators [1] have been followed, since their results seem to correlate best with clinical findings

This work was undertaken (*a*) to delineate further the normal electrocardiographic response to exercise, and (*b*) to investigate the possibilities of the effort test in the diagnosis of ischæmic heart disease before the development of symptoms Although Wood's experience with his control series [1] suggested that the effort test might be put to this purpose, no report of such a study is known to have been published

MATERIAL

This consisted of 540 healthy male R A F personnel between the ages of 19 and 54 The sample over the age of 40 was obtained in a slightly different way to that under the age of 40 It contained for example, fewer officers than the younger group It is hoped to eliminate any possible errors due to this difference in sampling in a further study A preliminary interrogation, physical examination, chest radiograph, and resting E C G (I, II, III, IIIR, aVR, aVL, aVF, V_{1-6}) were done in each case on the day of the effort test, and any subject with symptoms or signs of disease or an abnormal resting E C G was excluded The interrogation was directed particularly at excluding those with any suspicion of cardiac pain

METHOD

The effort test consisted in twice running down and up a staircase of 66 steps, each 10 in high, the subject choosing his own pace * All men over the age of 50, and 47 men between 40 and 50, performed a single trip of 66 steps The time taken to complete the test was recorded by stop-watch in each case, so that the effect of rate of exertion could be studied Leads I, II, III V_4 V_5, and V_6, were recorded 1½ min, 3 min, and 6 min after the completion of exercise A Philips direct writing electrocardiograph ('Cardioluxe') was used throughout

RESULTS

None of the subjects experienced chest pain during or after exertion 473 of the post exercise E C G s were normal (group A) The remainder (67 cases) showed (1) flat or sagging depression of the RS–T segment 0 5 mm or more below the level of PQ with deformity or inversion of the T wave (subsequently referred to as "organic type" RS–T depression), or (2) biphasic, isoelectric, or inverted T waves without RS–T depression (subsequently referred to as isolated T-wave changes) Cases in which these changes occurred in lead III only were classified with group A So were cases in which a depressed RS–T junction sloped up to a normal T wave [1] 55 of these 67 cases were studied on a second occasion after the lapse of weeks or months in 44 the changes noted on the first occasion were confirmed, in 11 cases the second post exercise E C G was normal, and in a further 3 cases the changes on both occasions were doubtful (these were classified separately in group C) (table I) The anomalies in the 53 cases finally classified in group B are set out according to age in table II To exclude anæmia as a possible cause of the changes in groups B and C, a hæmoglobin estimation was done in every case, no evidence of anæmia was found

TABLE I—ABNORMAL E C G S

Age (years)	No of cases	Group B	Group C % (doubtful or inconsistent anomalies)
19–39	300	16 (*5 3%*)	4 (*1 3%*)
40–54	240	37 (*15 4%*)	10 (*4 2%*)

GROUP B AND AGE

The E C G s classified in columns 3, 4, and 5 (table II) are "abnormal" according to Wood's criteria Those in columns 2 and 6 are "borderline" Columns 3 and 4 represent cases with changes identical with those previously described as due to myocardial ischæmia The significance of isolated T wave changes without RS–T depression is less certain [4], many of the tracings in this group were similar to those illustrated in Wasserburger's study on the effect of hyperventilation in patients with anxiety [5] It is interesting that organic type RS–T depression is commoner at the older than the younger ages (as I have

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[1] Wood P McGregor M Magidson G Whittaker W *Brit Heart J* 1950 12 363
[2] Wood F G Morgan Jones A *Ibid* 1951 13 319
[3] Scherf O Schaffer A *Amer Heart J* 1952 43 927

* This study dealt with symptomless men Patients with chest pain should be exercised with discretion It is generally agreed that it is unsafe to exercise patients with abnormal resting E C G s

[4] Mattingly T W Fancher, P S Bauer I L Robb G P Report from U S Army Medical Service Graduate School 1954
[5] Wasserburger R H Lorenz T H *Amer Heart J* 1956 51 666

TABLE II—GROUP B SUBDIVIDED ACCORDING TO TYPE OF ANOMALY OF RS–T COMPLEX

Age (years)	(1) No of cases	(2) 0 5 mm RS–T depression with deformity of T not amounting to inversion	(3) 0 5 mm of RS–T depression with inversion of T	(4) 1 0 mm or more RS–T depression with deformity or inversion of T	(5) Diphasic, isoelectric, or inverted T waves without RS–T depression	(6) RS–T depression with deformity of T restricted to leads II and III
19–39	300	1 (*0 3%*)	2 (*0 7%*)	5 (*1 7%*)	7 (*2 3%*)	1 (*0 3%*)
40–54	240	11 (*4 6%*)	3 (*1 2%*)	15 (*6 2%*)	4 (*1 7%*)	4 (*1 7%*)

said, further work is being carried out to determine whether this difference is due to age or to the fact that the two samples of men were derived in different ways) On the other hand, there is no such increase in isolated T-wave anomalies over the age of 40

GROUP B AND OTHER FACTORS

There was no significant difference between group A on the one hand, and groups B and C on the other, in respect of (1) the resting heart-rate, (2) the heart-rate 1½ min after exercise, (3) the rate of completion of the exercise test, and (4) degree of athletic training in the three months before the exercise test

FAMILY HISTORY

In 529 cases the family history was recorded before the effort test was performed In 12 cases, all in group A, the family history is unknown, in 6 the man had been adopted by foster parents and did not know the fate of his family The remainder were the first 6 consecutive cases in the series in which, owing to an oversight, no details were recorded In table III column 2 shows the number of families in groups A, B, and C in which at least 1 relative (father, mother, brother, or sister) had suffered from coronary thrombosis or angina pectoris or had "dropped dead" In columns 3 and 6 these two groups are listed separately It will be seen that the incidence of positive family histories is consistently higher in group B than in group A The total number of sibs per family in the two groups is comparable Within group B 7 of the positive family histories occurred in the 37 cases with RS–T depression other than in leads II and III alone (mean age 42 3) and 1 positive family history in the 11 cases with isolated T-wave changes (mean age 35 3)

TABLE III—FAMILY HISTORY

Group	Age (years)	(1) Total no of family histories traced	(2) Positive family histories	(3) Coronary thrombosis or A P (alive or dead)	(4) Coronary thrombosis or A P (alive)	(5) Coronary thrombosis or A P (dead)	(6) Sudden death
A	19–39 40–54	276 185	13 (*4 7%*) 17 (*9 2%*)	9 (*3 3%*) 11 (*6 0%*)	1 1	8 10	4 (*1 4%*) 6 (*3 2%*)
		461	30	20	2	18	10
B	19–39 40–54	16 37	2 (*12 5%*) 7 (*18 9%*)	1 (*6 3%*) 3 (*8 1%*)	0 0	1 3	1 (*6 3%*) 4 (*10 9%*)
		53	9	4	0	4	5
C	19–39 40–54	4 10	1 1	0 1	0 0	0 1	1 0
		14	2	1	0	1	1

PROVISIONAL CONCLUSIONS

In a highly selected series of 540 clinically healthy males so far studied, 53 show a deviation from the usual electrocardiographic response to exercise In 11 of these the anomaly consists of isolated T-wave changes without RS–T depression If 5 cases in which the RS–T depression is restricted to leads II and III are excluded, there remain 37 cases with "organic type" RS–T depression identical in pattern with that found in myocardial ischæmia, in 20 of these the RS–T depression is 1 mm or more Preliminary analysis suggests (1) that "organic-type" RS–T depression is commoner over the age of 40 (this does not extend to cases with isolated T-wave anomalies), (2) that coronary occlusion, angina pectoris, and sudden death may be commoner in the blood relatives of subjects with an abnormal E C G after exercise than in the relatives of those with normal tracings The relationship of the anomalies in the post exercise tracings of group B to latent coronary-artery disease remains to be proved but it is felt that the evidence is sufficiently suggestive to make further study and an extended follow-up worth while

CHOLESTEROL AND LIPOPROTEIN ESTIMATIONS

By courtesy of Prof Sir Charles Dodds blood studies have been carried out by Dr G L Mills at the Courtauld Institute of Biochemistry in 45 subjects in group A and 33 in group B The results have not yet been analysed

I wish to thank Air Marshal Sir James Kilpatrick director general of medical services, R.A.F, for permission to publish this report, Air Commodore C A Rumball consultant in medicine, R.A F, and Dr D Evan Bedford, civilian consultant in cardiology, R A F, for help and guidance, Prof A Bradford Hill, F.R S, for statistical advice, and the officers and airmen of the R A F for their cheerful coöperation

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Medical Societies

HEBERDEN SOCIETY

THE annual meeting of this society was held in London on Dec 14 and 15, under the presidency of Dr ERNEST FLETCHER There follows a short report of the scientific proceedings

SUBLUXATION OF THE NECK IN ANKYLOSING SPONDYLITIS

Dr J SHARP and Mr D W PURSER (Manchester) called attention to the risk of spontaneous subluxation of the atlas on the axis in patients with ankylosing spondylitis Their first patient died with a spastic tetraplegia, and a photograph at necropsy showed vividly the protrusion of the odontoid process into the spinal canal when the head was flexed on the neck, with consequent pinching of the cervical spinal cord Since then they had recognised 9 further cases of this subluxation during life and certain features emerged The patients were all males, ages ranging from 31 to 64, in all of them the spondylitis was severe and of long duration and there was little or no residual normal spinal movement Most of them had severe lumbodorsal flexion deformities In 1 patient a prominent presenting symptom was the increasing difficulty of shaving under the chin because of the falling forward of his neck Later he developed twitching and weakness of his limb muscles, with three episodes of complete paralysis which followed attempts at bending down He needed treatment in an iron lung at one stage, but eventually made a complete recovery when the cause was recognised and the neck fixed in extension It was important to note that this patient and 4 others had minor cervical subluxations below the atlanto occipital joint Radiologically the latter were less easy to miss on ordinary cervical films, and might be blamed for the symptoms The atlanto axial subluxations, on the other hand, were best demonstrated by taking lateral films in flexion and extension, and were clearly the cause of the neurological symptoms Other patients presented with "painful instability" of the neck One, for example, with largely "burnt out" spondylitis of twenty years' duration, began to have pain in his neck which forced him to support his chin in his hands while riding in a car Some presented with severe pain in the neck or occipital region

Dr Sharp and Mr Purser now regarded the presence of neurological changes as an absolute indication for operative cervical fusion 6 patients who have so far been treated in this way have lost their symptoms Signs of cord damage, if any, have proved almost wholly reversible They suspected that this complication of ankylosing spondylitis was more common than was generally thought, and urged its early recognition, in order to relieve pain, to protect the cervical cord before irreversible changes occur, to ensure that such necks are not subjected to manipulation, and to spare the patient from X-ray treatment that might be given if the neck pain was assumed to be due to a recurrence of activity of the spondylitis

UNEXPECTEDLY RAISED SEDIMENTATION RATES

Dr B M Ansell and Dr E G L Bywaters (Postgraduate Medical School, London) reported that out of several hundred routine sedimentation-rates done on outpatients when first seen at a rheumatism clinic, there were 51, in a three year period, where the result was unexpectedly high and did not seem to correlate with the clinical findings In 31 of these this rate was elevated on two or more occasions, and these 31 patients had been recalled for extensive further investigation Most of the patients in whom a diagnosis could eventually be made proved to have rheumatoid arthritis, although in some the progression of the disease was unusual One, for example, had presented with no more than persistent œdema of the feet and high E S R Later she had attacks corresponding to palindromic rheumatism After two years, arthritis became constant, erosions appeared in the joint radiographs, and the differential agglutination test (D A T) became positive Another patient with mild articular symptoms and asthma developed myelomatosis In another the raised E S R was due to circulating cold agglutinins In only 1 was the raised E S R explained as the result of unrecognised malignant deposits Finally, in a few patients no cause was found, and in some of these the sedimentation rate was still raised

SACRO ILIAC JOINTS IN ANKYLOSING SPONDYLITIS

Dr J Forestier (Aix les Bains) reviewed his cases of ankylosing spondylitis in the light of Gilbert Scott's hypothesis that the disease was one of inevitable progression ceasing only when the sacro iliac joints were fused He could not support this, and found that the disease might arrest at any stage, or alternatively active spinal disease could be present when the sacro iliac joints were fused

DIURNAL VARIATION IN HAND GRIP

Dr V Wright (Leeds) had studied the daily variation in the strength of hand grip There was a diurnal rhythm in normal subjects the grip being weakest about 6 A M, rising sharply to a maximum at about 9 A M, after which it stayed more or less constant until a slow decline set in about 2 P M This was not related to blood sugar levels but there was parallel variation in the body temperature and inverse variation in the count of circulating eosinophils, and all three probably reflected the normal rhythm of intrinsic adrenocortical activity It took 18 days, however, before the administration of corticotrophin to a normal subject abolished this daily variation and the normal pattern was soon restored when the dose was reduced Patients with rheumatoid arthritis (unless their hands were severely deformed) also showed this variation of grip, but (in contrast with the findings in normal subjects) the variation was quickly and strikingly abolished when effective doses of corticotrophin were given Wax baths to the hands and injections of pitressin had no influence on the diurnal variation

SODIUM-RETAINING PROPERTIES OF CORTISONE AND PREDNISONE

Dr Ansell had used the technique of giving by mouth isotope sodium (^{22}Na) chloride to measure total body water and the turnover rate of body sodium Readings were made with the subject in a total body counter, and the radioactivity of a single specimen of urine was measured Several experiments confirmed the validity of the method, after which it was shown that cortisone caused a delay in the turnover of body sodium in patients with rheumatoid arthritis Prednisone (deltacortisone) had no such effect in equivalent doses, indeed the sodium-retaining action of cortisone was abolished when prednisone was given concurrently

PHYSIOTHERAPY IN THE RHEUMATIC DISEASES

Dr J S Lawrence (Manchester) gave details of the results of physical therapy in miners attending a diagnostic and rehabilitation clinic Seventeen different treatments were allotted according to a rota and were continued until the patients recovered or ceased to improve He measured his results in terms of the palliation of symptoms, the disappearance of abnormal physical signs, and the time it took for the patient to return to work, and he had analysed them according to the underlying disease process Only in osteoarthritis and degenerative disc disease did treatment materially improve the disability, and of the treatments given only infra red irradiation and saline or citrate ionisation gave seemingly significant advantage over placebo treatments Rheumatoid-arthritis patients were, if anything, made worse by prescribing active or passive movements

LABORATORY STUDIES

Dr H J Gibson and Mr N R Ling (Bath) had investigated the streptococcal hæmagglutination test The antigen in this test was a combination of a non specific polysaccharide (which could be extracted from filtrates of cultures of many gram-positive organisms, including streptococci) and human red cells The antibody was of widespread distribution, was present at birth, disappearing at six months, then reappearing with increasing age It was present in all body fluids, it fixed complement, and it caused the agglutination of the treated red cells The apparent serum titre of this antibody was often outstandingly high in rheumatoid arthritis, but did not always correlate with the differential agglutination test (D A T) They showed that the titre in the streptococcal agglutination test depended on two factors, one of which could be absorbed from the serum and which they thought was the antibody The other factor was an augmentor which was probably responsible for the high titres in rheumatoid arthritis, and it seemed likely that this augmentor was allied to if not identical with the substance responsible for positive agglutination in the D A T

Dr Baruch Blumberg and Dr A G Ogston (Oxford) had studied the effect of crystalline papain on the hyaluronic acid protein complex which could be isolated from ox synovial fluid by ultrafiltration The protein was essential to the physical properties of the complex, and could be almost entirely removed by this enzyme The solution of this complex exhibits an anomalous viscosity which is lost after digestion Trypsin and chymotrypsin were ineffective, and various control experiments showed that the action was not due to the contamination of the enzyme with lysozyme It was possible from the viscosity measurements to calculate the molecular weight and size of the digested hyaluronic acid

The Heberden Oration

In the 1956 Heberden Oration, Prof R E TUNBRIDGE (Leeds) discussed the connective-tissue system The three essential elements of the system were cells, fibres, and ground substance Recent work from the King's College group had shown that there were probably three types of fibroblast or fibrocyte Characteristic of these were intracytoplasmic granules which stained metachromatically, contained about 30% of protein, and were rich in hexosamine The granules were either the immediate precursors of collagen fibril formation or were in some other way intimately related to it The function of the mast cells was still not known with certainty Probably they stored heparin, and in addition they might be concerned with the synthesis of hyaluronic acid and also with local histamine release There was at present no acceptable evidence for an elastoblast Under the light microscope three types of fibre had been differentiated—collagen, elastin, and reticulin But there were fallacies in the histochemical techniques, since altered collagen might stain like elastin, and reticulin, which was differentiated mainly on its silver staining, could be shown under the electron microscope to contain collagen fibrils

A characteristic feature of collagen was its periodic banded structure with 640 Å spacing At least 10 sub bands had been demonstrated Collagens from different animal sources might show different periodicity Fœtal collagen might occur in sheets rather than fibres (its periodicity was still apparent), and Keech had shown that the fibril width increased with age Indeed there was a characteristic fibril width for different tissues Other differences in collagen fibrils could be demonstrated by silver staining, which could either be a uniform surface coating of the fibril, as in scleral collagen, or internal staining of certain of the bands—a feature of ageing collagen Wyckoff had shown that the fibrils were tubular Collagen contained more lysine, hydroxylysine, and arginine than elastin, which was richer in valine and leucine There was evidence that the small amount of carbohydrate in collagen was not just a contaminant Gross had illustrated the interesting variations in the structures formed when collagen was precipitated from solution in vitro

The concept of "collagen disease" as originally put forward by Klemperer had acquired a meaning that he never intended Primary disorders of the fibrous structure of the body were rare They included pseudoxanthoma elasticum, a disease which was uncommon before the second decade and which showed itself as redundant thickened skin and a tendency to calcification of the small blood vessels It was the result of an excess of altered collagen which stained like elastin under the light microscope In the Ehlers Danlos syndrome, on the other hand, occurring in infancy and childhood, the electron microscope confirmed that there was a true excess of elastin There was a naturally occurring inhibitor to the enzyme, elastase, which was present in increased amounts in this syndrome It was clear that rheumatoid arthritis was not a collagen disease in the literal sense and it was unlikely that lupus erythematosus could be so classified

Reviews of Books

Industrial Medicine and Hygiene

E R A MEREWETHER, CB, OBE, MD, FRCP, barrister at Law, H M senior medical inspector of factories, Ministry of Labour and National Service London Butterworth 1954–56 3 vols £10 10s. the set

THE need for an authoritative and comprehensive book on this rapidly developing subject has been felt for several years The subject being a composite one, Dr Merewether's task has been difficult and he has called on a wide variety of experts Such a team produces its own problems The editor must on the one hand allow contributors to conserve their individuality, while on the other he must persuade them to conform to an over-all pattern Perhaps in this instance the editor has not been ruthless enough, for the work, though good in parts, does not conform to a clear plan

The first volume which appeared in 1954, is the least attractive of the three It contains a few good sections, but much of it is uninspiring The section on the law provides an easy source of reference but it is a pity that no consideration is given to the history of our factory legislation—an enthralling story without which it is difficult for the reader to understand the present position There is a good section on the use of statistical methods in the occupational field and another on reablement and resettlement of disabled workers

The second volume, which also appeared in 1954 brings together much valuable material The subjects cover a wide range—from industrial dermatology to electric shock and from occupational psychology to the effects of ionising radiations There is a good account of compressed-air illness, though its importance could hardly justify the 46 pages allotted to it The section on industrial skin disease is concise and practical while the chapters on heating and ventilation and on lighting are readable expositions of highly technical subjects

The third volume, which has only recently appeared, is probably the best It deals with the dust diseases and with industrial carcinogens and toxicology Both these sections are of high quality and offer comprehensive summaries of present day thought and practice This volume is particularly well documented A vast amount of practical information about the fibrotic pneumoconioses is crammed into the first 120 pages while the following section provides an excellent and well balanced account of the diseases due to vegetable dusts The final section of this volume deals with industrial toxicology The writer has confined himself to an examination of the "mechanism of action of some industrial poisons" The result is stimulating, even though some may experience difficulty in following the biochemistry This method leads to certain practical difficulties—for instance some 25 pages are devoted to the anticholinesterases but benzene is not mentioned This might be excused in such an imaginative contribution if the foreword did not claim that "the approach to each subject is dogmatic and practical so as to meet the needs of all

In each section the references cover a wide range There are notable omissions in the text—for instance, one looks in vain for a section on accidents where some of the present day ideas on this important subject are brought together and in the chapter on electric shock the medical side is virtually ignored Some overlapping is inevitable and even beneficial in a book of this sort but occasionally it becomes annoying

These faults can no doubt be corrected in the next edition Dr Merewether has provided much that is of great value in these volumes, which are to be welcomed as an important pioneering effort Copies of this work should certainly be held in all medical and technical libraries and all health departments in industry

Family Medical Costs and Voluntary Health Insurance

A Nationwide Survey ODIN W ANDERSON, PH D, Health Information Foundation, JACOB J FELDMAN, National Opinion Research Centre New York and London McGraw Hill 1956 Pp 251 40s

TWENTY-FIVE years ago voluntary health insurance had hardly begun in the U S A, and the principle of health insurance was still being hotly debated In 1933 I S Falk, Margaret C Klem, and Nathan Sinai published the first nation-wide survey of the incidence of illness and the costs of medical care Since that time health insurance has greatly increased, and today about a hundred million people are covered in one way or another, but the most comprehensive health-insurance schemes now available hardly cover half of the cost of all services in a year Since 1950 private insurance has been gaining over Blue Cross, which in turn is ahead of Blue Shield Group-practice prepayment plans cover less than 5% of the population, but are gaining slowly

These and many other facts are well brought out in this book, which describes the first national survey of family medical costs undertaken since 1933 The authors conclude "the form that health insurance has taken and will take is a tenuous balance between the many elements that make up the complexities of personal health services - people, hospitals, physicians, insurance, and finance, interlaced with philosophies of government and private enterprise and with the level of public information and knowledge"

This readable book contains much information valuable to those concerned with administering and organising medical services

Principles and Methods of Sterilization

JOHN J PERKINS, M S, director of research, American Sterilizer Co, Erie, Pennsylvania Springfield, Ill Charles C Thomas Oxford Blackwell Scientific Publications 1956 Pp 340 60s

It is clear from this book that the author's main interest is sterilisation by heat

The importance of gravity displacement of air and automatic air and condensate discharge is made clear, but the statement that these have been almost universal since 1933 is unfortunately not true in this country There are detailed instructions for operating autoclaves and ovens, but the value of some of these is limited because they refer to equipment made by a particular manufacturer The importance of regulating autoclaves on temperature rather than pressure readings is stressed throughout the book The advice on preparing and packing loads for sterilisation is excellent, going well beyond the usual vague instruction to "pack loosely" Methods for sterilising most articles in common hospital use are given, these are generally sound, though blankets are only briefly mentioned and boiling them, as recommended, is unnecessarily destructive The wisdom of exposing rubber gloves to 121°C (15 lb per square inch) for 20 minutes may be questioned, for this could increase the risk of punctures during use For the operating theatre the author prefers autoclaving to boiling surgical instruments, and he rightly criticises water sterilisers

In this country the book could be profitably read not only by those who use but also by those who choose the sterilising equipment for our hospitals and laboratories

Annual Review of Microbiology

Vol 10 Editor, CHARLES E CLIFTON, Stanford University Palo Alto, California Annual Reviews Inc 1956 Pp 426 $7 50

FOR 1956 the number of articles of medical interest is less than usual Indeed, the time has come when the publishers might consider regrouping the whole series Microbiology—the study of very small living things—may seem a logical division of knowledge, but smallness itself and similarity in experimental method are not by themselves a satisfying link The great majority of those who term themselves "microbiologists" are primarily interested either in some small department of the subject or in its application to medicine, agriculture, or industry Accordingly there can be very few who will read more than 10% of this volume with interest or even with reasonable understanding Medical bacteriology by itself (or with medical virology) would provide enough material for an annual review, or it might be combined advantageously with pathology (in the Old World sense of the word) Some articles in this volume are fit for the review of biochemistry and others for some botanical publication

The standard of the contributions is at least as high as in any previous year J B Enright's review of the part played by bats in the transmission of rabies is as complete as anyone could wish and makes a story worth reading The increased interest in the lower plants is reflected in five articles on fungi and algæ A W Downie and K R Dumbell contribute an article on the pox viruses which might be a model for some other contributors

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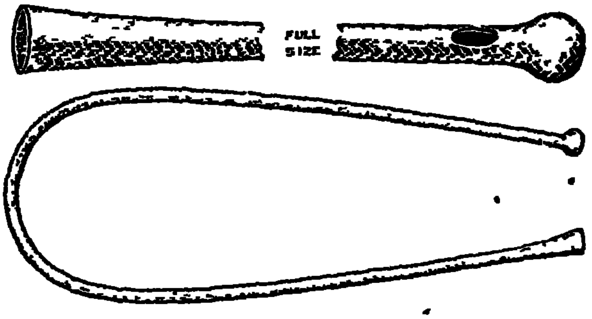
Surgery of the Hand (3rd ed Philadelphia Lippincott London Pitman 1956 Pp 1079 147s)—When this work by Dr Sterling Bunnell first appeared, in 1944, it was soon established as a classic Surgeons throughout the world will be grateful that Dr Bunnell has not been content to rest on his oars, the new edition is abreast with the times in matters of antibiotics, plastic repairs, and reconstructions—indeed in all aspects of hand surgery reflecting recent developments—and in most of these the author himself has been a pioneer

New Inventions

A GASTRIC CATHETER

THIS simple appliance has been found to have a range of usefulness out of all proportion to its modest cost The catheter is of gum-elastic It is 68 5 cm (27 in) long and has a diameter of 0 5 cm At the leading end there is a ball or olive tip 1 cm wide, just proximal to which is the aperture for aspiration

Owing to its large blunt end and semi-flexible material, the catheter may be passed with safety down the gullet of an anæsthetised patient It is then invaluable for aspirating the stomach, either when the patient has failed to swallow a tube before operation, or when the tube he swallowed has coiled up and has not entered the stomach



During a gastric operation the catheter may be passed by the anæsthetist so that its olive tip appears at the anastomosis It can then be used to draw into position an ordinary gastric tube, after this has been tied to the end of the catheter by the surgeon

The catheter is also readily passed on a *conscious* patient, particularly if he first sucks an amethocaine ('Decicain') tablet to anæsthetise the pharynx, and it has proved very useful when a patient urgently requires gastric aspiration but cannot swallow an ordinary soft tube

The catheter is useful for aspirating the gullet of a patient with an obstructing œsophageal lesion before operation The non-collapsible nature of the tube is an asset when aspirating, as is the fact that the ball end holds the aperture away from the mucosa

Again, I pass the gastric catheter before a gastroscopy, to empty the stomach This serves as a sort of trial run for the patient, and safely tests the patency of the route to be followed by the gastroscope It also does away with the need for the unpleasant preliminary swallowing of a soft tube for aspiration—a procedure which often leaves the patient keyed up and apprehensive and in no state to undergo gastroscopy I pass the catheter again after the examination to release the air from the stomach

The gastric catheters have been made for me by the Genito Urinary Manufacturing Co, Ltd, 28A, Devonshire Street, London, W 1 at a cost of 15s 9d each They can be made radio opaque for an extra 3s 6d

H DAINTREE JOHNSON
M B Camb, F R C S

London, W 1

THE LANCET

LONDON SATURDAY, JAN 5, 1957

Return to Planning

1957, we are told, should be a year of reappraisal, in which the nations consider whether their policies need modification to fit the facts revealed by recent crises For the medical profession in this country a similar review of ends and means may be desirable, since the year opens with a conflict that could go deep From the beginning of the National Health Service there have been many who doubted whether the State should be allowed to assume—however indirectly—responsibility for so much medical work and thereby for the livelihood and ' terms of service of so many doctors whose professional independence must be preserved These doubts could be countered only by supposing that in their share of this new social task a British Government could be expected, in the long run, to act reasonably By handling too cleverly the profession s case for higher remuneration, the Health Ministers have again made this supposition seem rash Admittedly the case has been presented to them mainly in legal terms, but in nine months they have found no opportunity to explain their negative attitude in a way that might be understood and respected by doctors, and if they continue to look like arbitrary employers rather than like friendly partners in a great enterprise they will certainly revive the ashes of controversy which have been smouldering since 1948 On the other hand, in the absence of heavy insurance, a conflagration is seldom beneficial unless carefully localised and anyone who thinks of urging doctors to leave the service, or to demand a new model, should be sure just how far he wants to go Believing that discussion of objectives could be useful at this juncture, we shall be glad in the next few months to publish constructive contributions on the service and one such appears in this issue under the heading of ' Reconstruction '

Certain weaknesses of the N H S are inherent, and must be accepted as the defects of its virtues Essentially the service is a device for enabling everybody to get medical care without paying for it directly, and it was welcome for three main reasons (1) because much disability can be prevented if people can get sound attention whenever they need it (2) because many families found the cost of illness more damaging than the illness itself, and (3) because discontinuance of charges by doctor to patient should allow everyday medicine to resume an older tradition of service—derived from the temple priest rather than the man of business But every fresh advantage carries its own disadvantage as soon as access to free medical care is recognised as a right somebody must see that any citizen can get it and even in a temple somebody must see that the priests are fed Though the primary aim of the N H S is to enable people to get, without paying the same kind of care as they would get if they paid, and though this care is given by the same doctors and the same institutions (who remain highly responsible for its quality), a certain amount of organisation is inevitable because private arrangements must give place to public arrangements Moreover if patients are not to pay at least a large proportion of what their illness costs, most of the money for the service must be found from some kind of taxation, and this means that what is spent on the service, and on those who work in it, must ultimately be controlled by the Chancellor of the Exchequer and by Parliament—i e, by statesmen or politicians Which is not to say that the service need be so rudely exposed to political vicissitudes as it has been to date, or that, even in England, consistency should forever be at the mercy of expediency In peace, as in war, the first seven years are always the worst

Also inherent in the service is the patient s right to medical care without payment—the absence of a financial fence between him and his doctor This, too, has its disadvantages When the patient had no rights beyond what he paid for, his expectations were limited, and the doctor very often had the great professional and human satisfaction of exceeding them—even to the extent of waiving his fees—for which the patient was grateful But there is less satisfaction in helping people who take everything for granted, and the pleasures of practice are definitely reduced by the occasional patient who believes that his insurance contributions have bought anything his doctor can do for him Perhaps chiefly for this reason, there is now a move towards replacing the annual capitation fee by the New Zealand system in which the doctor charges for each item of service and the patient recovers part or all of this charge by taking a certificate to the post-office But the number of services rendered is by no means necessarily a good index of the value of a doctor s work, and before any big change is made in the N H S arrangements the profession ought to make up its mind more clearly on how far it wants practitioners to remain in competition with one another The capitation system allows and encourages competition for patients the New Zealand system would restore competition, in addition, for fees while a salaried service would abolish financial competition altogether Each has its undesired consequences, and instead of abandoning the capitation fee, of which we now have considerable experience, it might be better to continue the process of making it more flexible, adjusting it not only according to the number of people on the doctor s list but also according to the number who are old, young disabled, or otherwise at special risk Another possibility would be to give the family doctor more chances of earning supplementary fees—for instance by undertaking the daily care, at home, of patients who could not otherwise be discharged from hospital And perhaps there is room in general practice for some variant of merit awards, now confined to consultants[1] By itself, without modification or supplementation capitation is too crude a means of deciding how much a doctor has earned and if medicine is to become a temple, we must certainly get away from the rule by which a priest can get most to eat if he does as little as possible for as many as possible

This brings us to weaknesses which are not inherent in a free service but come of failure to plan it as a whole. This failure is almost praiseworthy in so far as it reflects a wish to delegate responsibility for the various parts of the service, and, even though it causes overlapping and untidiness, there is much to be said for leaving the hospital authorities, the executive councils, and the local authorities to do their own work in their own way. But a minimum condition for the success of a tripartite service is that the decision as to what work each part should regard as its own shall be taken by some integrating authority which can adjust the financial incentives accordingly. In the N.H.S. too many incentives have worked too long in favour of sending people to hospital when they could be treated more economically at home[1], and though the Ministry of Health has become keen to promote home care it has not yet created financial conditions in which practitioners and local authorities will be eager to relieve the burden on hospitals. Strongly though we believe in preserving the responsibility of individual doctors and the institutions in which they work, we think the service has suffered and is still suffering from lack of a coherent policy—from lack, indeed, of a central brain such as its advisory machinery was originally intended to provide. The crisis over remuneration is only the latest instance of failure to plan ahead; and if, after so many years of inflation, the Government really have not begun to consider its implications for professional people working in a national service, the least they can do, surely, is to ask a properly constituted committee to advise them on how the intentions of the Spens Committees should henceforward be fulfilled. Meanwhile we trust they will not be unwilling to consider, as a matter of urgency, the situation of those groups in the service—medical and other—whose incomes in 1950 were barely sufficient and are now reduced by about a quarter. Thinking particularly of senior registrars and senior hospital medical officers, whose professional situation has so long been debated without conclusion, we have to recognise the planning responsibilities of the profession as well as of the Ministry.

After the war this country had its fill of planning, and the word began to evoke a touch of nausea. But this reaction has gone too far; and the time has come, surely, when we should consider how the lessons of the first decade of the N.H.S. can be applied in the second. Looking at the biggest issues, we may hope that, before many years are past, the service will be largely removed from current politics by being accorded as of right a defined proportion of each year's national income; but on the purely professional level also there are important changes to be made—in reducing the rigidity of specialties, for example, and in achieving wiser relations between teaching and other hospitals by such methods as the one Professor PICKERING proposes in his final paragraph on p. 2. In urging examination of the service's faults, we are none the less proud of its successes—of the steady if unspectacular improvement of the hospitals, of the reforming ardour seen today in general practice, in the treatment of the mentally ill, and in the care of the old; and especially of this country's place in medical research and teaching. Just as people say that universities are nothing like as good as they were before the first world war, so they say that medicine has suffered gravely from the social revolution. But in some ways the universities, in their abundant new life, are better than ever; and so is medicine. Certainly it is incalculably more useful, which is what matters most to the patient.

The Decline of Acute Rheumatism

IN both Great Britain and the United States rheumatic fever is by no means as common as it was. In this country the number of patients admitted, for example, to the convalescent hospital for rheumatic fever in Birmingham, has fallen from 116 in 1938 to 44 in 1955.[1] In Baltimore the outpatient clinics are no longer crowded, there are empty beds in the convalescent homes, and all patients with rheumatic fever who require hospital treatment can be accommodated.[2] In San Francisco, the number of patients suffering their initial attack has fallen from 116 in 1945 to 20 in 1955.[3] Valvular heart-disease was about twice as common in young men examined for the United States Forces in the first world war as it was in the second[4], and a study of rheumatic fever in American school-children has shown a steady fall from about 4·5 first attacks per 1000 children in 1927 to 1·8 per 1000 in 1953.[5] HEWITT and STEWART[6] estimated that in England and Wales, in 1948–50, about 3900 children fell ill with a first attack of acute rheumatism each year—an attack rate of 0·69 per 1000. HITCHINS[7] has made a valuable study, covering the twenty years 1931–1950, of the records of the local rheumatism service of the city of Cardiff, basing his observations on those patients with acute rheumatism and associated carditis and those with actual rheumatic heart disease. During the twenty years there was a substantial fall in the "first attack" rate, which was most striking soon after 1930, and by 1950 the rate had fallen to a third of the level of the early '30s. A similar decline was noted in acute rheumatism without evidence of cardiac involvement.

There is also evidence that the mortality of rheumatic heart disease has decreased. Though KNOWELDEN[8] was unable to demonstrate any significant change in either men or women, he did detect a decline in mortality in children. In America there are a number of observations illustrating this fall in mortality over the past twenty years—an improvement varying from 70 to 80%.[4,9] The association of rheumatic fever with infection by hæmolytic streptococci has naturally suggested that changes in the character of the hæmolytic streptococcus and the progressive betterment of living conditions are the two factors most likely to be responsible for what has happened. But little is known about the epidemiology of streptococcal infections and even less about possible unrelated causes of rheumatic fever; and it is therefore hard to give any concise explanation. There is nothing to suggest that the hæmolytic streptococcus is, in fact, any less powerful a producer of rheumatic fever than it was, indeed, **Rammelkamp**[10] suggests that the proportion of streptococcal infections that lead to rheumatism remains relatively constant between 2% and 4%. As for the frequency of streptococcal infections, the only figures readily available are those for the incidence and mortality of scarlet fever. **Hitchens** drew attention to the close, although perhaps fortuitous, connection between the decline of rheumatic fever and that of scarlet fever, which has become steadily less common and less menacing from 1935 onwards. From their study of Sheffield, Bristol, Grimsby, and Lincoln, and the administrative county of Lincolnshire, **Hewitt** and **Stewart**[6] decided that poor housing and economic conditions per se played little part. **Hitchens**[7] came to the same conclusion, pointing out that the change took place in Cardiff before economic conditions improved. The incidence of rheumatic fever increases when the hæmolytic streptococcus has more opportunities to start infections, as it has among people living in overcrowded conditions—a point well brought out by a number of investigations in the American Armed Forces.[10] **Hewitt** and **Stewart** found that children of unskilled workers suffered from rheumatism far more commonly than did the children of professional and skilled workers, and they believed that different risks of infection were the most likely cause for the social gradient. **Rammelkamp** concluded that latitude, altitude, crowding, dampness, economic circumstances, and age all had their bearing on rheumatic fever simply because of their influence on streptococcal infections in general. **Hitchens**, however, made an important point in discussing the search for the cause of rheumatic fever's decline: the change should not be considered on its own, but in relation to the comparable decrease in the incidence and mortality in all infectious diseases quite apart from any recent advances in treatment. It seems unlikely that this general improvement can be attributed simply to alterations in the host-parasite relationship of a number of different organisms, and consequently there must be some associated economic factor still to be considered. **Hitchens** suggested that the decline was likely to be related more closely to such things as "an improving quality of maternal care rather than to a straightforward economic or physical factor", and that the increased use of antibiotics did not play a big part in the decrease in rheumatic fever, which had already began before antibiotics were introduced. Though this is undoubtedly true, **Robinson**[3] reports that the recurrence-rate in San Francisco remained relatively high despite fewer initial attacks, but after a preventive campaign and the provision of prophylactic drugs (either a small daily dose of sulphadiazine or penicillin or the monthly injection of a long-acting penicillin) the number of recurrences fell from a yearly average of 22 for 1949–53 to 5 for 1954–55.

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[1] See *Lancet*, 1956, i, 237.

1. City of Birmingham School Medical Reports 1938–55.
2. Schwentker, F. F. *In* Rheumatic Fever. Minnesota, 1952.
3. Robinson, S. J. *J. Pediat.* 1956, 49, 272.
4. Wheatley, G. M. *Pediatrics*, 1949, 3, 685.
5. Kuskin, L., Siegel, M. *J. Pediat.* 1956, 49, 574.
6. Hewitt, D., Stewart, A. *Brit. J. soc. Med.* 1952, 6, 161.
7. Hitchins, R. A. N. *Ann. rheum. Dis.* 1956, 15, 160.
8. Knowelden, J. *Brit. J. soc. Med.* 1949, 3, 29.
9. Wolff, G. *J. Amer. med. Ass.* 1951, 145, 719.

Though the fundamental reason for the decline in rheumatic fever remains obscure, there seems no doubt of the importance of reducing the number and spread of hæmolytic streptococcal infections by improving social conditions and providing prophylaxis in suitable circumstances.[11]

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[10] Rammelkamp, C. H., Denny, F. W., Wannamaker, L. W. *In* Rheumatic Fever Minnesota 1952.

[11] See annotation *Lancet* 1955, i, 805.

Annotations

NEW YEAR HONOURS

The long list of honours announced last Tuesday contains relatively few medical names. Dr Janet Vaughan was eminent in hæmatology before she became principal of Somerville in 1945, and she has done fine work for the Nuffield Trust as well as for Oxford hospitals: *her new title must often have been used prematurely by her acquaintance because it is so clearly fitting.* Sir Arthur Porritt is created K.C.V.O. for his services to the Sovereign, and General Drummond, director-general of Army Medical Services, becomes K.B.E. The knighthood conferred on Prof. G. L. Brown, of University College, London, coincides with his election as a vice-president of the Royal Society: he has been a member of the Medical Research Council since 1951 and is chairman of its Royal Naval Personnel Research Committee. Finally, we note with pleasure the knighthood for Mr Charles Read, director of the Institute of Obstetrics and Gynæcology, whose helpful work as *president of the Royal College of Obstetricians and* Gynæcologists has been appreciated by colleagues both inside and outside his specialty. These names and others which are similarly respected will be found on p. 40.

POLIOMYELITIS VIRUSES BY MOUTH

Research on immunisation with live attenuated poliomyelitis viruses continues, and a *new report*[1] describes how infants of under 6 months were fed with live virus. It was known from earlier work[2] that immune serum-globulin given to children intramuscularly at the same time as live poliomyelitis virus was given by mouth did not prevent intestinal carriage of the virus or the development of an immune response. Obviously, therefore, infection with attenuated poliomyelitis viruses should be carried out in the presence of a serum-antibody "umbrella" which would probably reduce the chances of producing paralytic poliomyelitis without decreasing the immunising effect of the virus. Koprowski et al.[1] have infected a number of infants, most of whom had maternal antibody in their serum—that is, a natural umbrella. With the consent of their parents the infants were fed between 1000 and 100,000 infective doses of attenuated poliomyelitis viruses of types 1 and 2 in their bottles, the virus-formula mixture being given just before a regular feed. After they had had the viruses the infants were isolated in hospital and everything which was removed from the contaminated areas was disinfected.

Alimentary infection followed the virus feed, and virus was excreted in the stools for from 53 to 108 days. Antibody responses were satisfactory in ten infants aged 1–4 months, but of six infants less than a month old only three showed a satisfactory rise in antibody. The remaining three, who had high titres of antibody at birth, showed either a drop in antibody or stationary titres, and *further investigation of these infants will be needed to see* whether the present antibody titres persist. So far, antibody titres have remained high in five infants tested up to 7 months after feeding.

While it is useful to have this knowledge, its practical application will have to wait until the problem of virus excretion is solved. It might be possible to train children to such rigid habits of hygiene that they would not spread poliomyelitis viruses with which they were infected subclinically But the difficulties of controlling, outside hospital infants who are excreting virus for 3 or 4 months seem insuperable at the moment, and it may be wisest to concentrate on older children

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[1] Koprowski, H., Norton, T. W., Hummeler, K., Stokes, J., Hunt, A. D., Flack, A., Jervis, G. A. *J. Amer. med. Ass.* 1956, 162, 1281.

[2] Koprowski, H., Norton, T. W., Jervis, G. A., Nelson, T. L., Chadwick, D. L., Nelsen, D. J., Meyer, K. F. *Ibid* 1956, 160, 954.

FRIEDLANDER'S PNEUMONIA

PNEUMONIA caused by Friedländer's bacillus usually presents as an acute illness, but it often passes into a chronic phase characterised by suppuration and cavity formation Sometimes the disease is chronic from the start, and, as the upper lobe is often involved and penicillin is ineffective, tuberculosis or neoplasm may be suspected It is important to give appropriate treatment before the lung has been extensively destroyed, and it is widely believed that a characteristic, gelatinous, reddish-brown sputum is an early pointer to the diagnosis It is disconcerting to learn, therefore, that this type of sputum was seen in only 2 out of 17 cases of Friedländer's pneumonia recently reported by Erasmus[1], and these were the only 2 in which the diagnosis was made on clinical grounds In 14 of these cases Erasmus regarded the Friedländer bacillus as the primary invader of the lung, since it was isolated from the sputum in pure culture or as the predominant organism on at least two successive days, and it was thought to be a secondary invader in the other 3 cases in which it was recovered from the sputum in association with other organisms on at least two successive days Erasmus emphasises that a Friedländer infection is especially likely to be overlooked when it is superimposed on existing pulmonary disease

Amberson[2] suggested that Friedländer's pneumonia is caused by the aspiration of infected secretions from the upper respiratory passages into the lung, and Erasmus found evidence that both the primary and the secondary invaders reached the lungs in this way Compared with non-suppurative pneumonia, the disease showed a predilection for the posterior part of the upper lobe and for the apex of the lower lobe—sites favoured by non-specific suppurative aspiration pneumonia[3] In most cases there was either gross dental sepsis, with which the Friedländer bacillus is commonly associated,[4] or other upper respiratory tract infection Moreover, the Friedländer bacillus is present in the mouth or upper respiratory tract in 1–5% of normal individuals[5] In some older persons there was multifocal disease in the lower lobes, and this was attributed to the failure of a feeble cough to get rid of infected secretions

There is evidence that streptomycin,[6–13] chloramphenicol[14–16] and sulphadiazine[13 17–19] are effective in this condition In vitro sensitivity tests in Erasmus's series showed that the organisms were sensitive in all 15 cases tested to streptomycin, in all but 1 to chloramphenicol, and in two thirds to sulphadiazine All the organisms were resistant to penicillin and erythromycin, and more than half were resistant to chlortetracycline (aureomycin) and oxytetracycline (terramycin) Most of the patients were successfully treated with a combination of streptomycin and sulphadiazine, but Erasmus recommends that chloramphenicol should be substituted for these drugs after a few days since resistance to streptomycin may rapidly develop[11] In his experience with these patients, the disease, though serious, did not sustain its formidable reputation none of the patients died and in only 2 was the lung damage severe enough to require surgical resection The fact that effective treatment is now available makes early diagnosis all the more important, and Erasmus's experience suggests that this is more likely to be achieved by the bacteriologist than by the clinician

CONGENITAL ANGIOMA OF THE PAROTID GLAND

THE technique of operations on the parotid gland has improved in recent years Wide exposure through an incision that is cosmetically acceptable, and preliminary identification of the facial nerve, have enabled adequate excisions to be confidently though not lightly undertaken The conditions for which these methods can be applied include the parotid angiomas, which, though uncommon are by no means so rare as to be merely a medical curiosity, and Campbell[20] has lately reported 3 such cases treated by subtotal parotidectomy He states that angioma is the most likely cause of chronic unilateral parotid swelling in the first year of life (in a series of 21 parotid tumours in children Howard et al[21] found angiomas)

The angioma is usually noticed in the first weeks or months of life as a pre auricular swelling of the consistence of rubber A clue to the diagnosis may be given by a bluish colour of the skin or by an overlying cutaneous angioma, but no case has yet been recorded in which a parotid angioma was associated with the more serious congenital vascular abnormalities, such as intracranial cirsoid aneurysm The lesion has no capsule and may spread beyond the confines of the gland It grows rapidly during the first months of life but there is no evidence of true malignant change The gross appearance, Campbell remarks, "resembled nothing quite so much as an enlarged, coarsely lobated and cyanosed parotid gland"—a point of some importance in exploration of the lesion

Excision is usually advised In the 46 recorded cases treated by surgery there were 2 deaths Radiotherapy has also been used with some success, but it may be a dangerous weapon in the treatment of a benign condition in this situation in a growing infant Glaser et al[22] describe a uniformly disastrous course if the condition is not treated, leading to death in weeks or months due to invasion and compression of the vital organs of the neck But Campbell makes the pertinent comment that only two references to such death, with post mortem evidence, appeared in the literature he reviewed[23] There seems to be some doubt about the true natural history of the untreated lesion Wawro et al[24] noted greater mitotic activity in the younger children and a tendency to quiescence in the older patients A parallel might be drawn with the behaviour of cutaneous angiomas, and it may be that parotid angiomas would later regress as most of the cutaneous ones do[25 26] There certainly seems to be a case for deferring operation for lesions which are not enlarging rapidly when first seen, but it would be helpful to have more facts Surgery has been successful and there have been very few recorded recurrences, but

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1 Erasmus L D *Quart J Med* 1956 25 507
2 Amberson J B *Bull Johns Hopk Hosp* 1954 94 227
3 Brock R C Hodgkiss F Jones H O *Guy's Hosp Rep* 1942 91 131
4 Goadby K Diseases of the Gums and Oral Mucous Membrane London 1923 pp 112 339
5 Bloomfield A L *Amer Rev Tuberc* 1921 4 847
6 Nichols D R Herrell W E *J Amer med Ass* 1946 132 200
7 Bishop L K Rasmussen R F *Ibid* 1946 131 821
8 National Research Council *Ibid* 1946 132 470
9 Finland M Murray R Harris H W Kilham L Meads M *Ibid* p 16
10 Learner N Minnich W R *Ann intern Med* 1946 25 516
11 Harris H W Murray R Paine T F Finland M *New Engl J Med* 1947 236 611
12 Rosenthal I D *Lancet* 1949 ii 743
13 Gill F F *Amer J med Sci* 1951 221 5
14 Wasserman E Pomerantz H *J Med Ann Distr Columbia* 1951 20 135
15 Steinberg H Towbin M A *Dis Chest* 1952 21 455
16 Weiss W Eisenberg G M Alexander J D Flippin H F *Amer J med Sci* 1954 228 148
17 Feinstone W H Williams R D Wolff R T Huntington E Crossley, M L *Bull Johns Hopk Hosp* 1940 67 427
18 Hyde L Hyde B *Amer J med Sci* 1943 205 660
19 Welford N T *Illinois med J* 1946 90 187
20 Campbell J S *New Engl J Med* 1956 254 56
21 Howard J M Rawson A G Koop C E Horn R C Royster H P *Surg Gynec Obstet* 1950 90 307
22 Glaser K Mehn W H Schultz L W *J Pediat* 1946 28 721
23 McFarland J H *Arch Path* 1930 9 820
24 Wawro N W Fredrickson, R W Tennant R *Cancer* 19 8 595
25 Lister W A *Lancet*, 1938 i 1429
26 Rhoncke C I *Amer J Surg* 1953 86 376

the 46 cases that have been described included 11 in which facial palsy resulted. Campbell emphasises that though they are growing, these tumours are pathologically benign and that there is no justification for deliberate sacrifice of the facial nerve. The nerve runs an extremely superficial course in young children, but a careful technique should ensure that accidental damage is rare. Further knowledge of the natural history of the lesion, however, would make it easier to decide whether the operation is always justified or whether there may be a group in which it is wisest to delay. The impression is that this is one of those subjects in which much more experience and knowledge must exist than has been recorded.

HEREDITARY HÆMORRHAGIC TELANGIECTASIA

The odd condition called hereditary hæmorrhagic telangiectasia, which can cause serious bleeding from mucous membranes especially from the nose, has been known for a long time. Gawen Sutton[1] in 1864 described some curious cases of recurrent epistaxis and Babington,[2] in 1865 contributed a letter to our columns briefly listing members of 5 generations in a single family who had suffered from epistaxis; but neither of these physicians had any clue to the cause of the epistaxis in their patients. Just 80 years ago Legg[3] gave a paper to the Royal Medico-Chirurgical Society of London on "a case of hæmophilia complicated by multiple nævi": we should not now use the name hæmophilia, but there is no doubt about the nævi. This seems to be the first case of hæmorrhagic telangiectasia to be properly described, though the credit is usually given to Rendu[4] in 1896 and Osler[5] in 1901, who really gave an adequate description of the disease, noted its hereditary character and correctly ascribed the hæmorrhage to disease of the blood-vessels and not to any abnormality in blood-clotting.

Eponyms are now out of favour, and hereditary hæmorrhagic telangiectasia is the name used in all the textbooks. There are, as Stefanini and Dameshek[6] point out, two basic vascular abnormalities: in the first there are localised areas where the walls of the capillaries are extremely thin, being reduced to the endothelial layer only; in the second, there are visible dilatations of arterioles and capillaries which can lead to the formation of arteriovenous aneurysms especially in the lung. The telangiectases are normally much brighter in colour, with bigger visible vessels, than the spider nævi associated with liver disease. Their commonest site is in the nose, but careful inspection of affected patients nearly always reveals them on the lips and tongue, under the nails, and elsewhere in the skin, especially of the face and ears. The commonest form of bleeding is epistaxis, but hæmoptysis, melæna, and hæmaturia are quite frequent. Landau et al.[7] described a family in which conjunctival and retinal lesions were prominent. The hereditary nature of the abnormality is well established as a simple dominant affecting both sexes. The most striking example is that given in Wintrobe's textbook[8]: a Mormon with hæmorrhagic telangiectasia had 22 children by his 4 wives and 10 of these children were affected; in their turn these affected members of the family passed on the disease for another three or four generations and no less than 82 affected descendants of the original progenitor were known in this family when the list was put together. It is clear from this and other examples that unaffected individuals do not pass on the disease. There is also some evidence suggesting that the type of lesion is also inherited; thus, arteriovenous aneurysms are common in some affected families and never occur in others. The diagnosis of the disease is not difficult if its existence is borne in mind and if the characteristic lesions on the lips, tongue, or face or under the nails are sought in every case of recurrent epistaxis, melæna, or other bleeding for which there is no obvious cause.

The disease can be quite mild or it can be a serious burden to the patient because of the gradually increasing anæmia caused by repeated bleeding over many years. The anæmia is of the iron-deficiency type, and if the condition has been neglected it often fails to respond to oral iron and needs parenteral iron for its effective treatment. Sometimes blood-transfusion is needed to restore the hæmoglobin content of the blood as soon as possible to a safe level. The seriously affected patient may lead a miserable existence, always at the mercy of a recurrent hæmorrhage that his family doctor may be unable to control; and, if the bleeding is from an inaccessible site like the alimentary tract, admission to hospital and blood-transfusion are inevitable. The nasal, labial, and buccal telangiectases can be directly attacked. Several methods of applying pressure have been devised, and direct application of a thrombin spray will often stop the bleeding. Various escharotics, including X rays, radium, and electrocoagulation, have been tried, but they nearly always fail because new lesions tend to appear near the site of their application. Cochrane and Leslie,[9] however, were able to check bleeding in a patient with angiomas of the scalp and face by a small dose of contact X rays.

A quite different approach has been by way of treatment with œstrogens. This method arose from the observation that in affected women bleeding seemed to be worse at the end of the menstrual cycle and sometimes subsided spontaneously shortly after the onset of menstruation; so the bleeding was worst at a time when secretion of œstrogens is low and urinary excretion of gonadotrophins is relatively increased. Acting on this idea, Koch et al.[10] treated 5 patients with ethinyl œstradiol, using doses of 0·25 mg. daily—about ten times the dose given to control menopausal symptoms. In males, 5 mg. daily of methyl testosterone was given to counteract feminising side effects. Koch et al. claimed considerable success, but Stefanini and Dameshek,[6] for example, found the treatment of no value. Harrison,[11] at Guy's Hospital, has lately re-examined this form of treatment applied to 4 patients (2 men and 2 women) with typical lesions. He began by giving 0·25 mg. ethinyl œstradiol daily but gradually increased the dose to 1 mg. daily in both women and 1 of the men; the men were also given 5 mg. methyl testosterone daily. In spite of these large doses the only side effect was that 1 of the women had a uterine hæmorrhage after three months, but this did not recur in spite of continued treatment. All the patients were much improved and the hæmorrhages from the telangiectases were much less common or even stopped altogether. At the time of his report Harrison had not stopped the treatment; Koch et al. found that bleeding returned three weeks after œstrogens were stopped, and Harrison therefore proposed to reduce the dose gradually to try to find a minimum level for each patient, but he had no results to report at the time.

Sections of tissue from the inferior turbinates were taken before and after treatment in 2 cases, and they showed that the normal columnar epithelium had changed to a squamous one. It may in fact be this change which protects the telangiectases from trauma

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1. Sutton, H. G. *Medical Mirror*, 1864, 1, 769.
2. Babington, B. G. *Lancet*, 1865, ii, 362.
3. Legg, W. *Ibid*, 1876, ii, 856.
4. Rendu, M. *Bull. mém. Soc. méd. Hôp. Paris*, 1896, 13, 731.
5. Osler, W. *Johns Hopk. Hosp. Bull.* 1901, 12, 333.
6. Stefanini, M., Dameshek, W. The Hemorrhagic Disorders. New York, 1955; p. 49.
7. Landau, J., Nelken, F., Davis, E. *Lancet*, 1956, ii, 230.
8. Wintrobe, M. M. Clinical Hematology. London, 1951; p. 794.
9. Cochrane, T., Leslie, G. *Lancet*, 1950, i, 253.
10. Koch, H. J., Escher, G. C., Lewis, J. S. *J. Amer. med. Ass.* 1952, 149, 1376.
11. Harrison, D. F. N. *Guy's Hosp. Rep.* 1956, 105, 246.

and therefore makes them less likely to bleed The oestrogen treatment of telangiectasia thus seems worth a trial in severely handicapped patients, but, as Harrison emphasises, it is unwise to give 1 mg of oestrogen a day for long periods to young persons, and he suggests that the treatment should be restricted to women who have passed the menopause and to men of comparable age

TOADSTOOLS

To garner and consume the wild fruits of the earth is a pursuit so innocent and with such happy associations that the rare death caused by poisonous fungi is the more bitter to contemplate Our European neighbours are more venturesome than we are and are said to pay the penalty more often[1] [2] It surprised us to learn that the same peril threatens the ignorant in the Union of South Africa and that our own *Amanita phalloides* may be the species responsible (Is it a native of those parts or a chance introduction given in exchange for the nerine and the gladiolus ?) Steyn et al[3] describe two disasters which ended in the death of 5 out of 9 of those who had been tempted by the prevalence of "mushrooms" in a place where the arid climate makes them a rarity The history and symptoms showed no unusual features, but the account includes a valuable resumé of the present knowledge of the toxic effects of fungi other than *A phalloides* There is a satisfying agreement between the pharmacology of the specifically poisonous species and the symptoms which they produce *A phalloides* contains amanitine with a delayed hepatotoxic action, like phosphorus *A muscaria* and *A pantherina* contain muscarine (parasympathomimetic) and myceto-atropine (parasympatholytic) symptoms and treatment will depend upon which of these antagonists is the more abundant Both species, by the way, taste horrid The genus Inocybe contains muscarine alone Besides these, there are many species described as "sometimes poisonous" and that should be warning enough, even though one of these is named *Helvella esculenta*

The traveller in France who finds strange and flabby shapes on his plate will be comforted if he sees others eating the same dish, in some instances his palate will be rewarded If on his return he wishes to persuade his wife to add variety to his diet, he will be foolish if he does not arm himself with the Ministry of Agriculture's guide to epicurean adventure[4]

THYROXINE-LIKE ACTION OF ASPIRIN

As long ago as 1919, Barbour and Devenis[5] showed that single doses of aspirin caused an increase in both oxygen consumption and carbon dioxide output in normal persons These observations were confirmed a few years ago by Cochran,[6] and now Alexander and Johnson[7] have shown that the low basal oxygen consumption (B M R) of patients with myxoedema can be restored to normal by giving aspirin in doses of about 8 g (gr 120) daily They also showed that their patients' serum cholesterol levels fell during treatment with aspirin The two measurements of B M R and serum cholesterol are normally taken as the best objective index of response to thyroid hormone treatment, and in both these respects Alexander and Johnson's patients responded as well to aspirin as they did to triiodothyronine But they did not feel any better although warmer, they were still sluggish and sleepy, skin and voice remained characteristic of the myxoedematous state, and they did not lose weight These observations recall Dodds and Robertson's demonstration[8] that dinitro *o* cresol can restore the B M R to normal without changing the clinical signs of myxoedema—although in this instance the analogy with thyroxine is less close, because dinitrophenols do not affect the serum cholesterol[9] Alexander and Johnson's work shows clearly that neither a rise in B M R nor a fall in serum cholesterol, even occurring simultaneously, can be regarded as specific effects of the thyroid hormones

Alexander and Johnson have drawn certain practical conclusions from their findings Two of their patients had angina, which was apparently unaffected by the rise in B M R brought about by aspirin, although it became worse when an approximately equal rise was induced with triiodothyronine They go on to suggest that a mixture of aspirin with very small doses of triiodothyronine or thyroxine might be rational treatment for those difficult cases of myxoedema in which angina is induced (or aggravated) by thyroid preparations But it is hard to see that such patients would be any better off after the consumption of large doses of aspirin, for Alexander and Johnson showed that it does not make them feel any better The only hypothetical benefit from this combined treatment would come from the lowering of the serum cholesterol level There is certainly some as yet undefined association between serum cholesterol levels and the occurrence of coronary atherosclerosis, but it is not known whether lowering the serum cholesterol level actually retards the development of coronary disease At the moment, this hypothesis, interesting though it is, hardly seems to justify imposing on patients the side effects of large doses of aspirin

In a further suggestion of more immediate practical importance, Alexander and Johnson point out that patients with rheumatic heart-disease are often treated with large doses of aspirin, and that in some cases the increase in metabolic rate induced by aspirin may add considerably to the burden on the heart This is clearly something that needs investigation, but in the meantime it seems desirable not to prolong aspirin medication in acute rheumatism after the rheumatic process has subsided

THE REFUGEES

Of the two score medical refugees who have so far reached these shores from Hungary, some plan to remain here and others to continue their journey All are anxious for news of when they can travel or how they may obtain employment here

Employment —The Ministry of Health has not announced any special arrangements for the employment of refugee doctors in British hospitals, but there is reason to hope that regional boards will establish temporary supernumerary posts Inquiries regarding professional opportunities here and overseas may be addressed to the British Medical Association's International Medical Visitors Bureau B M A House, Tavistock Square, London, W C 1 (tel Euston 1490)

Finance —Refugees who have left official transit camps and hostels may apply to the local office of the National Assistance Board for regular grants Those needing money for special expenses, such as clothes and necessary journeys, should write to the *Lancet* office where a small fund has been started for this purpose[10]

Accommodation — We are in touch with medical households who have offered accommodation to Hungarian colleagues and will try to find a temporary home for anyone needing it

Inquiries or requests for help should be addressed either to this office or to Brigadier H A Sandiford M C, medical director of the B M A 's International Medical Visitors Bureau

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[9] Cutting W C Rytand D A Tainter M L *J clin Invest* 1934 13 547
[10] Further contributions would be welcome and are likely to be quickly used the aim is to distribute immediately small sums for emergency needs Cheques should be made out to The Editor and crossed Hungarian Doctors Account

Special Articles

MEDICOSOCIAL WORK IN A GENERAL PRACTICE

E MAURICE BACKETT
M B, B Sc Lond, M R C P, D P H
LATELY LECTURER IN SOCIAL AND PREVENTIVE MEDICINE IN THE QUEEN'S UNIVERSITY OF BELFAST

R P MAYBIN
M D Belf
GENERAL PRACTITIONER

YVONNE DUDGEON
SOCIAL WORKER, DEPARTMENT OF SOCIAL AND PREVENTIVE MEDICINE, THE QUEEN'S UNIVERSITY OF BELFAST

MUCH of the discussion on the changing rôle of the health visitor is about the extent to which she can act as a social worker as well as a public health nurse (*Medical Officer* 1954, Hughes 1954, MacQueen 1955, An Inquiry into Health Visiting 1956) As part of this argument it is often implied that there is an unmet need for social work in our community (e g, Roberts 1953) and that meeting this need is part of good medical care (Minister of Health 1953, Roberts 1953) If the job of the health visitor is to have more to do with the social care of the families which she and the family doctor serve, as the working party suggest, it is imperative to know the nature and extent of the need, particularly the unmet need, which exists

There have been few attempts to survey unmet medical or social need, and those that have been made (e g, Horder and Horder 1954, E M Backett and J C Evans unpublished) have faced great difficulties The discovery of an untreated case of diabetes, for example, clearly represents an unmet need for medical care and can be classified and described as such, but the discovery of a family breaking under the weight of problems such as overcrowding, unemployment, and the care of the elderly quick falls into no such clear cut category It is even doubtful whether a need for social care exists in such cases unless help is sought by the particular family, and there is great individual variation in the attitudes of practitioners to these problems Some view the social disorganisation of the home as a problem needing solution whether obviously related to the medical needs of patients or not and regardless of whether help is sought Others, mindful of the importance of the initiative coming from the patient, confine their activities to more strictly medical matters and feel that the most that is needed is to put the family in touch with any social agencies who can help

Purpose

We describe here an investigation of the need for social work in a general practice in 1954–55 The inquiry was part of a series of small scale studies of a general practice which ranged from an examination of the most convenient form of clinical record (Backett and Maybin 1956) to a study of family patterns of illness Its purpose was fourfold (1) to see how much someone trained in social work could help the family doctor, (2) to describe the extent of her work, and the types of problems encountered, (3) to measure the extent of unmet need for social care in the practice, and (4) to record the other agencies involved in dealing with problems among the families in the practice Finally, an important aim was to bring about closer cooperation between workers from the local health authority and the general practitioner by regular meetings for discussion

Because of the relative prosperity of the area, the almost complete absence of slum property, and the low level (for Northern Ireland) of unemployment, it was expected that few serious social problems would be met For this reason the study might serve the general purpose of giving a " base line " or an idea of the minimum of social work to be expected in general practice

Method

One of us who is a qualified social worker employed by the department (Y D) spent three-quarters of her full time working with the practitioner in his practice Her full time could have been made available if necessary Supervision of her work and of the study was arranged through weekly case conferences in the department or at the practice, when current medical and social work was reviewed and immediate aims were decided on

Records

The following records were kept for the full year 1954–55

(1) The age, sex, family, and occupational structure of the practice

(2) All episodes of illness observed and the consultations involved

(3) Diagnoses

(4) The day to day work of the social worker, the problems she met, and the families and individuals with whom she worked

During the early part of the study the address of every registered individual was visited and details of the practice population were recorded This visit was made the occasion for an explanation of the job of the social worker in the practice, and an opportunity was thus given for the raising of problems at once or for an invitation for a return visit Social work of some kind was undertaken where a need was found at this initial visit, where a request for help was expressed then or later, or where the practitioner asked the social worker to visit the family All new entrants were visited in the same way

Social Problems

To avoid the obvious difficulties of definition, a social problem was regarded as any problem tackled by the social worker with the agreement, or at the request, of the general practitioner A working classification is shown in table I

Results

THE PRACTICE

The practice in which this study was made had an average of 1371 persons registered with the principal during the year of the study It is a rural practice situated some six miles from a large city The standard of living and of housing is high, and the average earnings are good Work is mainly agricultural, but some of the population travel daily to and from the city An average of 185 individuals aged 65 or more (13 5% of the practice) were registered, and there was an average of 302 children

TABLE I—PROBLEMS CLASSIFIED BY TYPE AND METHOD OF ASCERTAINMENT

Type of problem	No of times encountered during the year	Ascertained through	
		Medical care	Social worker
Associated with chronic illness	28*(*24%*)	15 (*13%*)	13 (*11%*)
Marital family or neighbour friction	19 (*16%*)	11 (*9%*)	8 (*7%*)
Old age	13 (*11%*)	8 (*7%*)	5 (*4%*)
Administrative (e g, insurance)	11 (*9%*)	6 (*5%*)	5 (*4%*)
Housing	9 (*8%*)	2 (*2%*)	7 (*6%*)
Inability to maintain personal or family standards	9 (*7%*)	5 (*4%*)	4 (*3%*)
Financial	7 (*6%*)	4 (*3%*)	3 (*3%*)
Loneliness	6 (*5%*)	2 (*2%*)	4 (*3%*)
Other (see text)	16 (*14%*)	1 (*1%*)	15 (*13%*)
Total	118 (*100%*)	54 (*46%*)	64 (*54%*)

* Including 8 where a psychiatric diagnosis had been made

TABLE II—FAMILIES CLASSIFIED BY METHOD OF ASCERTAINMENT AND NUMBER OF TIMES VISITED

Method of ascertainment	No of visits				No of families *
	1	2–4	5–8	8 +	
Medical care	1(*5%*)	9(*45%*)	2(*10%*)	8(*40%*)	20(*100%*)
Social worker	14(*37%*)	18(*47%*)	4(*11%*)	2(*5%*)	38(*100%*)
Total	15(*26%*)	27(*47%*)	6(*10%*)	10(*17%*)	58(*100%*)

χ^2 = 10 71 DF = 2 0 01 > P > 0 001
(Combining cols 5–8 and 8 +)
* Includes 2 single persons living alone

aged less than 15 (21% of the practice) on the practice records

Families in the Practice

If a family is all the related persons living at an address, as well as single persons living alone, there were 467 families represented in the practice by the end of the year This figure included 27 elderly persons (i e aged 65 or more) and 23 young or middle-aged persons living alone

Of the families of two or more persons represented on the practice records, 78% were "complete"—i e, all members of the family were registered with the practice at some time during the study For these families, therefore, the doctor could be said to be a "family doctor"

THE NEED

In the course of the initial visits of the social worker to everyone in the practice or during medical care 118 social problems were met Social work directed toward meeting the needs of families with these problems was undertaken in 58 cases

Ascertainment of Need

Of these 58 families with social problems 20 were met in the course of medical treatment and the remaining 38 by the social worker during her routine visits (table I) None of the 64 problems of the latter had been brought to the notice of the practitioner before they were found by the social worker and they represent a crude measure of the unmet need for social care in the practice which existed at the time

Table I suggests that the social worker did not discover different types of problems from the practitioner except in the housing and "other" (unclassifiable) group Of the latter, 6 were based upon a fear of disease and others were problems associated with vocational guidance, illegitimacy, infertility, &c *In each there were obvious* reasons why the practitioner had not been consulted Some interest attaches to the problems where the social worker succeeded in encouraging consultation with the doctor There were 16 families where this was the case, and medical action taken after the consultation included an amputation of cervix, references to hospital fertility and birth control clinics the exclusion of carcinoma in several cases, and a variety of X ray and other diagnostic tests

Social problems ascertained by the social worker required significantly less visiting than those found during medical treatment (table II)

Frequency and Seriousness of Problems

23 families had only 1 obvious problem. 20 had 2 problems, and 15 had 3 or more For 2 of the latter there were 6 or more problems at the same time

No attempt has been made to estimate the seriousness of the problems encountered, because there are no objective criteria, but the extent of the care which was actually undertaken may be related to their seriousness. Two groups of families can be defined for this purpose (1) 28 families visited once or twice, and (2) 30 families visited three or more times

The needs of the less frequently visited group were largely concerned with appeals, applications, certification, &c, or with short or sudden problems of illness The needs of the more frequently visited families were for help with such long-term problems as relationships (e g, family or neighbour friction) or with problems of adaptation to chronic illness or old age

Requests for Help

35 families asked for assistance with their social problems The remaining 23 families permitted visits without encouraging them in this way and cooperated when necessary with the social worker Therefore, in these 58 families there seemed to be some recognition of their needs In none of her routine visits was the social worker refused admission, but there is, of course, no way of estimating the extent of problems not brought to her notice or to that of the practitioner Indirect evidence from practice records suggests that some serious problems were untapped by these methods of ascertainment

Of the less frequently visited families just under half, and of the more frequently visited families over two thirds, requested help at the beginning

THE WORK

In attempting to meet the needs set by the social problems of the 58 families 227 visits were made, involving 118 hours of social work The frequency of visiting is set out in table III, which shows that, for about a quarter of the families in the group, five or more visits were necessary, and that about 60% of all the social worker's time was taken up in their care Social work involved in assisting one family which was breaking up during the study took up as much time as did the 15 families for whom only one visit was necessary

Other Agencies

Sixty meetings with agencies on behalf of the 58 families were made during the year 33 of the families were already in contact with other agencies, usually of the local health authority Already concerned in the social problems of these families were the National Assistance Board and its visitors, the *Ministry of Labour* and National Insurance, the welfare authority, and the police Most common among agencies approached by the social worker were those of the local health authority

TABLE III—WORK OF SOCIAL WORKER

	No of visits																Total
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	
No of families *	15	13	7	7	2	3	1	3	1	3	1	1	0	0	0	1	58
Time (hr)	9 0	11 0	11 0	15 0	5 5	9 0	3 5	11 0	4 5	17 0	6 0	6 0	0 0	0 0	0 0	9 5	118 0
Per cent of all families	26		17				15					12					100
Per cent of time	8		31				25					36					100

* Includes 2 persons living alone

TABLE IV—COMPARISON OF FAMILIES WHO RECEIVED SOCIAL CARE WITH OTHERS IN THE PRACTICE

—	Age distribution of individuals (yr.)				Social class distribution of families (including 2 persons living alone)				Distribution of families of 2 or more by type of registration			Distribution of individuals according to living conditions			Distribution of 'complete' families of 2 or more by family size				Distribution of "complete" families of 2 or more by family type			
	0–14	15–64	65–	Total	I and II	III	IV and V	Total	Complete	Incomplete	Total	Alone	Not alone	Total	No. of persons 2–4	5–6	7–	Total	Category* 1	2	3	Total
The practice	302 (88%)	903	166 (12%)	1371	87 (19%)	246 (53%)	134 (28%)	467	324 (78%)	93 (22%)	417	50 (4%)	1321 (96%)	1371	237 (73%)	65	22 (27%)	324	120 (37%)	55 (17%)	149 (46%)	324
The social care group	43 (91%)	158	19 (9%)	220	11 (19%)	31 (53%)	16 (28%)	58	48 (86%)	8 (14%)	56	2 (1%)	218 (99%)	220	32 (67%)	13	3 (33%)	48	11 (23%)	9 (19%)	28 (58%)	48
χ^2	4·81				0·04				1·89			4·70			0·85				5·00			
DF	1				2				1			1			1				2			
P	0·05>P>0·02				0·99>P>0·98				0·20>P>0·10			0·05>P>0·02			0·50>P>0·30				0·10>P>0·05			

* 1, *young families or young couples*: young families are at least one adult living with at least one child aged less than 15; young couples are aged less than 45.
2, *young or middle-aged families with elderly persons*: these are at least two generation families in which there is at least one person aged 65 or more.
3, all other types of family.

In addition there were numerous other meetings with hospital almoners, psychiatric social workers, the Northern Ireland Housing Trust, the Care and After-Care Committee, the National Council for Social Welfare, Churches, the N.S.P.C.C., the Marriage Guidance Council, &c. Of the 42 first approaches made by the social worker to agencies, 36 were in the course of the social care of the frequently visited families—i.e., among those with whom most social work was done.

Meetings with other agencies were at the rate of 0·4 per family per annum in the less frequently visited group and at the rate of 1·6 per family per annum among the more frequently visited.

THE FAMILIES

Social Characteristics

Some distinguishing characteristics of the families needing social care were tested by comparing them with the practice as a whole. The results are given in table IV, which shows that the group of families and individuals cared for by the social worker differed significantly from the practice as a whole only in that it contained fewer old people and fewer people living alone. This finding was contrary to expectation. There was an excess (insignificant by conventional standards) of middle-aged families in the social-care group and more were completely registered. Differences in health experience between the social care group and the rest of the practice will be discussed elsewhere.

Differences within the social-care group itself distinguish the more frequently visited families as of lower social class than the less frequently visited families (P = 0·02). Again, among the more frequently visited families, consultations with the doctor (but not illnesses) were in excess of those among the less frequently visited families. There was no excess of serious illness among those visited more often by the social worker. Families which were "incompletely" registered took up a disproportionate amount of the social worker's time.

Discussion

Four questions were asked in this study:

(1) How much could someone with social work training help the family doctor?

(2) What was the extent of her work and the type of problem which she met?

(3) How much unmet need for social care was there in the practice?

(4) What were the other agencies involved?

(1) The question of how far the social problems of his patients should be the concern of the family doctor cannot be answered by this or any other study. Many of the social problems met during this inquiry were part of the repercussions of illness or were thought to be so by the patient. These were obviously the concern of the practitioner. Others were not even remotely connected with medical care, but in spite of this the family doctor was consulted. In this particular practice the doctor would have wished to deal with the social problems which he met, regarding such work as an essential part of his job. The presence of a social worker with time to care for the families was therefore of assistance to him only in the sense that it left him more time for what has been called "real medicine." The fact of her special skill in social work may also mean that the social worker did the job better than the doctor would have done it, though from his standing with his patients he would have gained initially.

Though a social worker was a help to the practitioner, there is no similar evidence from the point of view of the patient. The successes of curative medicine obviously have no parallel in social care. Though it is true that many agencies were mobilised to help those thought to need assistance, and that support was given to others in obvious need, a truly successful outcome of social care is hardly to be expected in view of the intractable nature of some of the problems. For example, of the 7 problem-ridden families visited nine or more times, with whom over a third of the work was done, all had long term problems which continue today, unchanged by the attentions of doctor or social worker. For 2 of the 7 (a young family in which the mother has rheumatic heart disease with severe decompensation, and a family in which a very difficult and ill grandparent is living) the social worker may have assisted in establishing some equilibrium. For the others the problems continue to disturb the household, and family crisis follows family crisis, some apparently serious (as when a young wife abandoned her husband and children), and others, from the doctor's point of view at least, trivial.

Probably the social worker was of most value to the doctor and his practice in uncovering problems which were medical as well as social and where she was able successfully to urge consultation.

(2) The extent of the work and the type of problem considered to be within the scope of the social worker have been described above. It is impossible to estimate how well the needs arising as a result of these problems could have been met by the general practitioner acting alone, or by other members of the domiciliary team—e.g., the health visitor. Undoubtedly some help would have been given, but it would have been relatively unskilled. However, it is worth noting in this context that, of the 118 problems tackled by the social worker, 4 of every 10 (45) were concerned with established illness

or with possible illness or were of the type where medical knowledge would be an advantage In dealing with this aspect of her work it was the social worker who lacked skill It is our opinion that the special relationship of the family doctor to his patients enables others working close to him to have ready access to them For various reasons an introduction from the doctor may be the best way to ascertain the patients' social problems The health visitor, unless she can be identified by the patient more closely with the general practitioner than is our experience elsewhere, will not benefit, and however skilled she may be she will not have such easy access This contention is supported by the experience of the health visitor who is now working in close cooperation with the doctor in this practice and is at the same time studying social case work in a nearby university department

(3) A measure of unmet need for social care is provided by the number of problems ascertained only by the social worker (64 of 118) The number of times that the families with these problems were visited suggests that the problems ascertained by the social worker were either among the less serious or more easily resolved Of the 38 families whose problems were ascertained by the social worker, 8 were already in contact with other agencies The hard core of unmet need therefore, which is left, amounts to 51 problems in 30 families (6 4% of all those registered)

(4) *Other agencies were already concerned in the care* of 33 of the 58 families, but their activities were uncoordinated and their individual duties limited In only a few cases was the work of the agency known to the practitioner and then through informal rather than formal channels The large number of contacts made with agencies by the social worker suggests that one of her main contributions to the work of the practice was in mobilising and coordinating this kind of help

Summary

Discussion of the changing rôle of the health visitor turns on the amount of social work which she should undertake To investigate the need for this type of work a social worker was attached for a year to a small practice in a moderately prosperous rural area Social work resulted from ascertainment of problems by the practitioner in the course of his medical work and by the social worker at routine visits to every family in the practice

Social work was undertaken among 12% of the families, the doctor ascertaining just under, and the social worker just over, half of their 118 problems Social work with these families involved 227 visits, 118 hours of interviews, and 60 meetings with other agencies

The families with whom social work was undertaken differed significantly from the rest of the practice only in that there were fewer old people among them and fewer persons living alone Unmet need for social work is represented by the 51 social problems of 30 families which would not otherwise have been ascertained Important contributions of the social worker were in encouraging consultation with the practitioner and coordinating the work of social agencies

The suggestion that social work in general practice be undertaken by a specially trained health visitor is discussed

It is estimated that one full-time and suitably trained worker might do the social work of a general practice of this type with a registered population of 4000

This study would not have been possible without a generous grant from the Northern Ireland Hospitals Authority

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NEW YEAR HONOURS

The list of honours published on Jan 1 contains the names of the following members of the medical profession

K C V O

Sir Arthur Espie Porritt, K C M G , C B E , M CH Oxfd, F R C S
Sergeant Surgeon to H M the Queen , surgeon to St Mary's Hospital, London

K B E (Military)

Lieut General William Alexander Duncan Drummond, C B , C B E , F R C S
Director general, Army Medical Services

D B E

Janet Maria Vaughan, O B E , D M Oxfd, F R C P
Principal, Somerville College, Oxford

Knights Bachelor

George Lindor Brown, C B E , M B Manc , F R S
Jodrell professor of physiology, University College, London

Charles David Read, M B N Z F R C S , F R C O G
President, Royal College of Obstetricians and Gynæcologists

C B (Military)

Major General Alfred Edward Campbell M D Belf , Q H P
Air Vice Marshal John Conrad Neely, C B E D M Oxfd Q H S

C B (Civil)

Sir Weldon Dalrymple Champneys, Bt D M Oxfd, F R C P
Lately deputy chief medical officer, Ministry of Health

C M G

John George Hunter M B Sydney
General secretary of the Federal Council of the British Medical Association in the Commonwealth of Australia

C B E (Military)

Surgeon Captain David Herbert Kernohan, M B Belf R N
Surgeon Rear Admiral Lionel Lockwood M V O D S C M B Melb

C B E (Civil)

Harold Maurice Cohen, M D L'pool
Principal school medical officer, Birmingham

Humphrey Francis Humphreys O B E M C T D M B M D S Birm F D S R C S D L
Vice chancellor and professor of dental surgery University of Birmingham

John McQueen Johnston, M D Glasg F R C S E M R C P E
A principal medical officer Department of Health for Scotland

RONALD EDEY LANE, M D Lond , F R C P
Member, Industrial Health Advisory Committee Nuffield professor of occupational health University of Manchester

JOSEPH ANTOINE RENÉ LAVOIPIERRE, M D Paris, L R C P E
Director of medical services, Mauritius

JOHN FREEMAN LOUTIT, D M Oxfd F R C P
Director, radiobiological research unit, Harwell

GEORGE WILLIAM JOHN MACKAY M B Edin
Medical superintendent, Rampton Hospital

WILLIAM NORMAN PICKLES, M D Lond , M R C P
Lately president, College of General Practitioners

RALPH WHISHAW, M B Sydney F R C P F R A C P
Honorary physician, Royal Hobart Hospital, Tasmania

CHARLES FRANCIS WHITE O B E M D Manc
Lately medical officer of health City of London , recently president Society of Medical Officers of Health

O B E (Military)

Lieut Colonel JOHN GEOFFREY WAUGH, L R C S E R A M C

O B E (Civil)

LESLIE WILSON BANKS, M B Edin
Senior medical officer (clinical), Western Region, Nigeria

WILLIAM JOSEPH BRANDAY M R C S
Superintending medical officer (specialist), Trinidad

ARTHUR BARRETT CARDEW, M C M B Lond F R C S E
Commissioner, St John Ambulance Brigade, Gloucestershire

WILLIAM MICHAEL COURT BROWN, M B St And F F R
Director group for research on general effects of radiation, Medical Research Council

WILLIAM RICHARD SHABOE DOLL M D Lond. M R C P
Senior member, statistical research unit, Medical Research Council

HENRY JOHN CHADWICK HANRAHAN M B Melb
Medical practitioner, Albany Western Australia

RICHARD WILLIAM DAVID MAXWELL, M B
Lately deputy director of medical services Fiji

SYDENHAM FREDERICK MOORE M B Oxfd
British subject lately resident in Egypt

HAYDN JONES MORRIS, M R C S
For public services in the Federation of Rhodesia and Nyasaland

ERIC PARRY, M B E , M B Lpool F R C S
Chief medical officer, Kuwait government

WALTER LAING MACDONALD PERRY, M D St And
Director, Department of Biological Standards National Institute for Medical Research

JOHN CHARLES ROBB, M D M CH Belf
Consulting surgeon, Downe Hospital Downpatrick, co Down

GEORGE SIMPSON, M B Melb , M R C P , F R C O G
For services to the Flying Doctor Service of Australia

WILLIAM ARTHUR LEIGH TUCKER F R F P S , F R C S E
Surgeon specialist, Aden

M B E (Military)

Major JOHN VAUGHAN BRADLEY, T D , M B , F R C S E

M B E (Civil)

OLIVE GUMPRICH M B
For social welfare services in Southern Rhodesia

SYDNEY DOUGLAS GUN MUNRO M B
Resident surgeon, Colonial Hospital, St Vincent Windward Islands

ALEXANDER DAVID BAIN MACKIE M B Birm
Chairman Birmingham ' Stirling ' Sea Cadet Corps unit

GEORGE DAVIS McLEAN, M R C S
Medical officer, St Kitts Leeward Islands

ROBERT CUTHBERT OGG, M B Edin
Formerly a medical officer in Basutoland

FRANK BLACKLOCK THOMSON M B Edin
Deputy chairman, Dundee National Service medical board

Reconstruction

IMPROVEMENT OF THE N H S

IN his Malcolm Morris lecture on Clinical and Community Medicine, given in London on Dec 6 under the auspices of the Chadwick Trust, Dr J N MORRIS said that maintenance of the quality of medical services is a responsibility of the profession to itself and to the community It is true that much medical care of the highest quality is going on all the time (and should not be taken for granted) , but it is also true that there are more and more procedures, easily performed, whose accuracy needs to be regularly checked By way of illustration he cited the following figures

Prevalence of Otitis Media per 1000

1951	School health inspections	7 6
1954–55	National Service examinations (rejections only)	32 0

Should not more cases have been found at the school examinations than at 18 years of age ? Such follow-up provides a means of assessing the work of the school health service—of laying on a routine check of the routine examinations—and it is applicable on local or national scale, sample or total basis

Every system in Dr Morris's view, needs itself to be regularly scrutinised, and routine systems need built-in controls of quality This is widely accepted in industry, in biochemistry laboratories, and in bacteriology and there is great scope for its application in clinical medicine and the health services At present remarkably little attempt is being made to ascertain how our £500 million health service is working what are the needs to be met and how well they are being met Take the prescription of drugs, for instance In 1954 the average prescription rate in the county boroughs was about 6 The following are the towns with over 7 and under 5

	Over 7 per head		*Under 5 per head*
Wigan	8 9	Tynemouth	4 2
Warrington	7 9	Southampton	4 5
Wakefield	7 6	Coventry	4 7
Liverpool	7 4	Middlesbrough	4 8
Manchester	7 3	Great Yarmouth	4 8
Oldham	7 2	Grimsby	4 8
Burnley	7 1	Ipswich	4 9
Salford	7 1	Gateshead	4 9
		Worcester	4 9

What do these figures mean ? Would not a cooperative inquiry by the local medical committees of these towns and, in particular a comparison of North-East with North-West be of far more than local value—not only in finding answers but in showing how to tackle such questions

Dr Morris mentioned a small investigation by the Central Middlesex Hospital where certain X-ray facilities are now freely available to practitioners The 160 doctors who used the service a little produced half the " positives," while the 40 who used it a lot produced the other half If the 160 had used the service as freely as the 40 the number of " positives " might well have been more than doubled All the big users had qualified since 1925 Dr Morris gave this as an example of analysis that can be made very easily and which yields results immediately applicable in an educational campaign among doctors Because the object of such investigations, of course, is to *improve* the quality of care

It may well be he added, that one of the main results of the Guillebaud Committee's work will be a considerable increase in " operational research " of different kinds on health services But it is to be hoped that their proposal that the research unit should be centred in the Ministry of Health will be examined very carefully What is needed is opportunities for a lively group of independent-minded research-workers to devote themselves to this kind of inquiry , and a Ministry might not be the ideal milieu There are several other possibilities

Turning to the structure and functions of health services, Dr Morris pointed out that this is a revolutionary era in medicine as in so much else, and the movement towards merging of clinical and community medicine—of curative and preventive medicine—will render the tripartite structure of the National Health Service out of date. As the chronic, metabolic, and "degenerative" diseases occupy more and more of the work of medicine, growing attention will have to be paid to what is called in America "secondary" prevention—the discovery of cases early so that their progress can be limited. In this context the distinction between "preventive" and "curative" (e.g., public health and general practitioner) serves no very useful purpose, especially if, as is conceivable, most of the preventive work in the future is done by the clinical services. In America the emphasis is on ad hoc screening to detect disease early: in our own country the realistic hope is that such programmes can be incorporated into the daily work of the health service. As for "primary" prevention, we are moving into a new era in preventive medicine where the individual will have to take an increasing responsibility for his own health in the light of the discoveries which are being made about smoking, diet, exercise, and so on. The kind of health education that is already needed involves the family doctor as much as, or more than, the medical officer of health. Whatever form of organisation is appropriate, it could scarcely be less geared to such tasks than the present division of local health authority, executive council, and medical committee. Meanwhile, as the rising figures of cigarette consumption in both sexes show, *Homo insapiens* is not being helped much by any of the services.

The successful treatment of the aged, with its emphasis on the maintenance of independence and the prevention of disability, involves the freest possible traffic between all the varied services now provided by the three parts of the health service and by the welfare authorities. The same principle now arises in the treatment of the mentally ill: hospitals, general practitioners, and social services; care, aftercare, and preventive care—all have to be used in combinations varying with the needs of the individual patient. The present structure of the N.H.S. is at best irrelevant to these problems. More generally this applies to the movement towards home and family care which is one of the healthiest in modern medicine.

"Today's answer to many of these problems is the intelligent use of the committee system and good human relations all round; but it may be questioned whether this is enough. And there are other problems, such as those of the provision of a comprehensive industrial health service, which raise issues that go further than any I have mentioned. For, in effect, we have a quadripartite and not merely a tripartite health service today."

In 1945–46, Dr. Morris thought, nothing very different from the National Health Service Act was possible. But after ten years of the Act, and now that the Guillebaud Committee has cleared away the confusions about finance, the question of a fundamental reconsideration of our health services arises. It may well be practicable to rearrange the structure so that it can be a positive stimulus and the active agent of further progress.

Public Health

THE HEALTH OF THE SCHOOL-CHILD

NOWADAYS children have a much better chance of surviving their schooldays than they had even a few years ago. In 1955, 2753 children aged 5–14 died, compared with 9017 in 1938. These figures are given in the report for the years 1954 and 1955 of the chief medical officer of the *Ministry of Education*.[1]

The vast majority of absences from school are due to infections, but the infectious diseases cause many fewer deaths than formerly; since 1938 the annual number of deaths due to tuberculosis has fallen from 973 to 51, and those due to diphtheria from 1733 to 5. But diphtheria occasionally breaks out, particularly where the proportion of children immunised is low; only by continuing to immunise most children can we hope to prevent a resurgence of the disease. Because of the havoc among children which can follow pulmonary tuberculosis in their teacher, initial and regular radiography of all teachers is desirable. A Medical Research Council trial showed that, after vaccination with B.C.G., the risk of tuberculosis developing in adolescence was roughly halved.

In 1955 the number of deaths among school children from infections of all kinds was almost equalled by the number of deaths from leukæmia and cancer, but was far exceeded by the number killed in accidents—401 on the roads and 185 elsewhere. As almost every accident is preventable these deaths are the most regrettable of all. Some maladies which cause suffering, loss of school time, and a few deaths are almost equally preventable. These include dysentery and food-poisoning. Much can be done at school, by repeated instruction in hygiene, to prevent outbreaks.

In the early days of the National Health Service there was a shortage of applicants for the posts of school medical officers, but recently there have been more good candidates. The number of dentists in the service is higher than ever before, but as many again are still needed.

The number of registered blind children, which had previously been falling, has been rising since 1918. Most of the increase is attributed to retrolental fibroplasia, and the numbers are expected to fall in future now that the cause is known and few infants are affected. The large numbers with defective vision (correctable by spectacles) and hearing emphasise the necessity for examining the children as soon as possible after they enter school. Headaches and suffused conjunctivæ due to watching television are becoming commoner, but are unlikely to be troublesome if the child sits on a level with the screen and over six feet away, and goes to bed at a reasonable hour.

Many new schools have been built since the late war, and some, notably those in Hertfordshire, have attracted much favourable attention from students of architecture. Inquiry in selected areas revealed no definite improvement in the health of children attending the new school, though some doctors, teachers, and administrators were convinced that there had been an improvement in the health, vitality, and bearing of the children.

The general condition of our school children seems to be improving. Their height and weight are increasing; the number reported as being in poor condition fell from 2·6 in 1952 to 1·5% in 1955, and most are well clad, well shod, and free from body vermin; the number with infestations of the scalp is still very large, but decreasing.

Few education authorities have taken advantage of a regulation of 1953 which allows them to experiment with fewer than three periodic medical inspections. "The need now is for more individual attention to be given to children who are not thriving or who are not making satisfactory progress at school, whether on account of physical, mental or emotional reasons." Mass examination of school entrants, mass radiography of teachers, mass inoculation—all have contributed much to the welfare of our children, but it is heartening to find in the report this emphasis on the special needs of the individual.

* * *

Expectation of Life

On the basis of the mortality experience of 1955 in England and Wales[1] the expectation of life of a boy at birth is 67.52 years and of a girl 72.99 years. The comparable figures based on the mortality experience of the years 1953–55 are 67.46 and 72.86.

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[1] The Health of the School Child: report of the chief medical officer of the Ministry of Education for the years 1954 and 1955. H.M. Stationery Office. 1956. Pp. 187. 6s.

[1] Registrar General's Quarterly Return. Quarter ended Sept. 30, 1956. H.M. Stationery Office. 1956. Pp. 21. 1s. 6d.

Towards Clean Air

Under an order[1] by the Minister of Housing and Local Government certain provisions of the Clean Air Act, 1956,[2] came into operation on Dec. 31. These include the provisions enabling local authorities to create smoke-control areas in which the emission of smoke from buildings will be an offence. Other provisions of the Act which came into force on Dec. 31 deal with the following:

New furnaces.—All new furnaces, other than small domestic boilers, must be, so far as practicable, smokeless. Notice of intention to install such a furnace must be given to the local authority.

Smoke measurement.—The Minister is empowered to make regulations requiring furnaces to be fitted with smoke density meters.

Height of chimneys.—The height of new chimneys, other than those of houses, shops, and offices has to be approved by the local authority.

Spoilbanks.—Owners of colliery spoilbanks must employ all practicable means for preventing combustion of refuse, and for preventing or minimising the emission of smoke and fumes from the refuse.

By-laws.—Local authorities may make building by-laws requiring the provision in new buildings of such arrangements for heating and cooking as are calculated to prevent, so far as practicable, the emission of smoke.

A similar Order has been made by the Secretary of State for Scotland. The remaining provisions of the Clean Air Act, which deal with the prohibition of dark smoke and the reduction of grit and dust from industry, will be brought into operation later.

Common Lodging-houses

Just before his death in 1955 Dr. Stuart Laidlaw was awarded the PH.D. for a thesis now published[3] in which he tells how he became interested in the human stories and the hitherto unexplored social histories of the misfits peopling the Glasgow common lodging-houses. At one time these places were hotbeds of infection, but Laidlaw believed that nowadays the inmates are no more likely than any other section of the community to spread infectious disease, except perhaps pulmonary tuberculosis. There were over 100 known cases of positive sputa.

Glasgow offers some 7000 hired beds of various rougher types—4893 in common lodging-houses, 1716 in working-mens hotels, and about 400 in seamen's boarding-houses and lorry-drivers' hostels. Laidlaw visited most of them to compare accommodation standards and the clients, with particular emphasis on the personal histories of some 800 users of common lodging-houses. He found that most of these men and women were unskilled or retired people depending on help from the National Assistance Board with or without additional pensions. Some 10% were ill.

Most common lodging-houses were founded for the shifting short-stay clients of the past century, but now use has changed to long stay: 44% of the men and 29% of the women had lived there for more than ten years; only 5% were casuals and vagrants. About a quarter of them liked the free-and-easy life of a common lodging-house, another quarter put up with it for economic reasons, and the rest stayed on because of social difficulties. The outside world had found no answer for their problems. The last words Laidlaw left for us are these:

No nation which aspires to greatness must despise even the lowliest of its citizens. Its aim must be to raise them on stepping stones of their dead bodies to higher things.

For the Young

Four cheery youngsters skip across the bright cover of the *Junior Health and Hygiene Manual* issued by the British Red Cross Society;[1] its shape and layout suggest that Health and Hygiene are among the exciting topics in a growing world. Not only are the society to be congratulated on breaking away from the tradition of stuffiness in manuals and bursting into contemporary idiom, but the product itself is good beneath the wrappings. It is directed towards Youth with a capital Y with ambition and vanity and drive: show the young what worlds there are to conquer and they will do the rest. Covering all the practical points of personal hygiene and running a home, its emphasis is on competition and the pride of achievement. Community hygiene and dietetics are treated with the pictorial and slogan techniques now so familiar on our daily travels, and these subtle methods of painless instruction are cleverly reinforced towards the end of the booklet with illustrated sections on hobbies and camping gadgets.

Methods of Chemical Analysis as applied to Sewage and Sewage Effluents, which was first published in 1929, has been issued in a new edition (H.M. Stationery Office. 1956. Pp. 96. 10s.)

A summary of the powers and duties of the Corporation of London as port health authority has been published by the corporation and is obtainable from the information officer, Guildhall, E.C.2 (Pp. 16. 1s. 6d.)

Medicine and the Law

Death after Insulin Treatment

THE Manchester city coroner recorded a verdict of death by misadventure at the inquest, on Dec. 14, on a woman who died in hospital following an injection of insulin given by her own doctor at home for the treatment of mental disorder. The coroner said he was satisfied that the injection was not of the right kind of insulin and that it ought not to have been administered by a general practitioner. He believed, however, that the doctor had acted honestly and with the best possible intentions in the special circumstances with which he was faced.

The woman, aged 45, died on Dec. 8 in Crumpsall Hospital from bronchopneumonia secondary to hypoglycæmic coma following the injection.

Her husband said that on Nov. 26 the doctor gave his wife an injection. She had been racing out of the house and it was becoming very difficult to keep her under control. His wife went to sleep. She was still asleep the next day. The doctor was called and, after examining her, recommended that she be allowed to come round of her own accord. In the late afternoon her husband noticed a trickle of blood from her mouth and she was making a noise in her sleep. He called in the doctor again, and his wife was removed to hospital where she died twelve days afterwards without regaining consciousness.

In evidence the doctor said that he had tried to get the patient admitted to a mental home, but an official had informed him that he was unable to help because there were much worse cases awaiting admission. Her husband was being driven nearly out of his mind by her behaviour, and their two daughters had begged for something to be done. "I knew what should be done and I knew where it ought to be done, but these places seemed to be beyond our reach. . . . I was there in the house and I had to do something. I knew it was a risk, but I also knew that if nothing were done it might end in tragedy for other members of the family."

The coroner said that the doctor had found the patient's husband "on his beam ends" and unable to stand the strain any longer. That was why he felt he simply had to do something about it. He had tried in vain to get the patient into a mental hospital and was acting in the way he thought to be right in those conditions.

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[1] Clean Air Act 1956 (Appointed Day) Order 1956.

[2] See *Lancet* 1956, i, [illegible] 517.

[3] Glasgow Common Lodging-houses and the People Living in Them. By STUART L. C. LAIDLAW. Glasgow: Corporation of Glasgow (obtainable from the health and welfare department, 23 Montrose Street, C.1). Pp. 261. 30s.

[1] From 14 Grosvenor Crescent, London, S.W.1. Pp. 64. 2s. 6d.

In England Now

A Running Commentary by Peripatetic Correspondents

I MYSELF stopped believing in Father Xmas some years ago, and have made no effort to perpetuate this delusion in my young But they actually saw him once, and the suggestion that it wasn't him but Uncle Donald fell on deaf ears after all Uncle Donald hasn't got a long white beard Then there are those presents inscribed (as Bill, at 5, can now just decipher) "Love from Father Xmas," and the unflinching belief of his colleagues at school, not to mention active indoctrination by the teaching staff, doubtless because they think we like it that way "Do you believe in Father Xmas?" I asked on Xmas Eve while pinning pillow-cases to their beds "Yes," they both affirmed promptly "Do you?" added Bill "No," I replied emphatically, but they were quite unconcerned "He's a nice man," said Bill Jo (3) was less sure "Don't let him come here, make him give all our presents to *Mummy at the end of the garden*" This was promised, and apart from a couple of screaming attacks the night passed peacefully We're all right now for another year

Long ago I remember an occasion (I was less psychodynamically orientated then) when I pretended to be Father Xmas before an audience below age 8, most of them well known to me So successful was my dissimulation that, as I changed upstairs, they ran to the window and *swore* that they all saw me climb into a sleigh and ride away On my return, the improbable excuse of having done the washing-up was accepted fully, and I was commiserated with at length for having missed this remarkable visitation Though the delusion is common enough, this is the only Father Xmas hallucination I have definitely met, its unanimity is noteworthy and the high I Q s of two of the 8-year-olds Yes, quite remarkable In fact I don't know silly damme, I wonder I wonder if they actually did see a sleigh out there

* * *

The ward Christmas party for patients and their visitors was held on Saturday afternoon

A quick round in the morning showed that all the beds were full with the usual selection of bronchitics, ulcers, and heart-failures But that did not deter Sister from putting on her decorations When I returned in the afternoon the ward had been transformed A large clearing had been made in the middle, and tables laden with sandwiches, cakes, and sweets had been placed along the walls The beds, together with their patients, had been moved to one end of the ward and arranged to give each patient a good view of the proceedings

These began with an entertainment Somebody played the piano A troupe of girls from the local dancing school, appropriately clad in tartans, performed a number of Highland dances with great agility A young woman sang Scotch folk-songs, sad and sweet The clergyman son of one of the patients did some conjuring, which went down well with the children A nurses' teddy-girl band played hot tunes with a tin flute, a tambourine, and a washing-board

Sister had laid on a marvellous tea, after which cigarettes were passed around and prim uniformed nurses were able to smoke with gay abandon for once in the year

As soon as the tables were cleared, dancing started Charlestons and Rock and Roll were favourites It was interesting to note convalescent progress The young woman with the subacute bacterial endocarditis was fox-trotting with the houseman The hemiplegic with jargon aphasia, beaming with smiles, was dancing with her son The obese grannie with hiatus hernia, who had defied a face-value diagnosis of myxœdema, for once did not complain of pain and was full of giggles After trifle with real cream—donated by Sister's uncle—the evening ended with Auld Lang Syne, during which my left hand was warmly clasped by the convalescent lobar pneumonia whose illness had probably followed her partiality for spirits

As I was leaving the wards the beds had already been straightened out with mathematical precision and the bedpan round was beginning

The junketings of a small-town Scottish hospital ma not last long, but while they last they could give t Chelsea Arts Ball points for verve

* * *

I sent my wife to get the petrol coupons A sm sandy-haired man fingered through the tattered pa of the log-book (the car has changed ownership as ma times as the Ministry of Transport spaces permit) an asked what horse-power it was My wife said she did know "Well," he said, "how many litres is it?" My wife tentatively offered 2, or it might be 6 They we through it together this time and found clearly mark "Cubic capacity 25,22 c c" They shook their hea sadly over this and wondered how many litres there we in a c c "Anyway," said my wife eventually after a other man had been consulted with equally blank effe "I know he was expecting to get the maximum amount She got it without further question In parting he sa that as a doctor I would get supplementary without an trouble at all, and, unasked, pressed a large form in her hand I meditated about this, and decided that I did old Stan's surgeries for him sometimes, and th odd visit, I could legitimately go for an extra gallo or two

I took the form and my log-book (yes, I *always* read th instructions, however small the print) and put them in a envelope with a stamp The trouble was where to sen it I asked the first policeman where the region petroleum officer lived He said it had just slipped h mind but the station was round the corner and woul certainly know The station officer was shocked that th information wasn't readily to hand and the apparatus o the Metropolitan Police was galvanised to instant actio —constables were dispatched to the ends of the statio and searched through files Ultimately, after 10 minute and two urgent phone calls to headquarters, they regaine their breath and said he lived at 97, High Street Neve have I placed a letter in Her Majesty's letter box wit greater confidence, proud of the zeal of the constabular in gathering accurate information for the most ban request of the most common of subjects Day followe day, and week followed week, and my colleagues proudl flaunted their supplementaries, granted in full to the las drachm My application, a difficult decision for them I thought, must be going up to Ministerial Level I came back yesterday scarred with the stamps of almo all the many local-government offices that live in th High Street (including about six in the Town Hall) A little note tells me that "the address of the Reg Petr Off can be obtained at any Post Office" But he certainl doesn't live in High Street

* * *

By all means let the pharmacists tell us of their products, provide us with blotting-paper, and offer us elegant little samples But would they please change their habi of delivering their samples by the Saturday morning post On that day there is no daily woman, the children do not have school, the breakfast might be a little late Bang goes the knocker, the postman has a sample he can't push through the letter-box, or even a registered packet Please post early in the week

* * *

LIONEL WHITBY

It is the remembering face of a warrior
Grooved by the chisel of pain
With the radiance of victory
Easing the grain

The voice is a teacher's bass
And the laugh, a student's fun
The halting step becomes a grace
In such a one

With power uncorrupt he strove
And gave humanity his love
Let grief submit and comfort find
In handing on the treasures of his mind

Letters to the Editor

THE FUTURE OF NURSING

SIR,—I hope that Dr Ritchie Russell's letter will not suffer the same fate as one which I wrote to you on April 23, 1953, when I voiced a similar alarm at the trend which I thought was already apparent The fact that what I then said elicited no response was a great disappointment to me, for it suggested that the medical profession no longer felt a sense of concern regarding the training of the nurse Yet the steps which are now being taken, or are contemplated, may result in a few years in the lowering of nursing standards in all hospitals with specialist interests A comparatively small body of women will have passed through a form of "officer class" training and will have little concept of the true needs of hospitals The specialist hospitals will then have to depend in the main upon nursing aides and orderlies whose training may often be indifferent

In my last letter I advanced the view, which I still hold, that nursing as a vocation should be allowed to develop only in line with the needs of the doctor and of the public whom we both serve Yet every doctor who works in hospital is aware that much of the training which the student-nurse must now receive is more in keeping with a training for some kind of junior house-officer A perusal of the examination papers which they are required to pass, and a knowledge of some of the things they are asked at oral examinations, make such an assertion quite proper.

It has been my own recent experience to be informed by a sister tutor that the nurses would require to have lectures (*a*) on the social aspects of infectious diseases by an almoner or social worker, and (*b*) on occupational therapy in tuberculosis by an occupational therapist Since the hospital at present boasts of neither of these officers I asked if I could not give (*a*) and the chest physician (*b*) The answer was "no", and when I asked if a perhaps second-rate lecture by some unknown persons would be preferred to lectures by doctors who were regarded as highly knowledged in these subjects, I was told that the regulations ought to be followed Now, of course, it may be alleged that this sister tutor was merely being stupid, but it must be pointed out that she was a properly qualified tutor

Does it not need to be stated very bluntly that the seniors in the nursing profession who contemplate these new changes are motivated by what would be properly called snobbishness? As the numbers of nurses required increase, they see more and more applicants who do not come from the social grades which were the usual source in the past Rather than give encouragement to such entrants, they say, let us constitute some higher grade which alone can carry the unqualified title of "nurse" These repositories of much half digested learning will be better able perhaps to follow the discussions of the consultant physicians regarding differential diagnosis, interpretation of laboratory reports, or definition of treatment But the poor patient will depend for his nursing on individuals whose claim to the title "nurse" must be qualified by the words "aide" or "auxiliary" or "assistant" One might wonder whether it would not be more proper to retain the word "nurse" for the person who really nurses and find some new title for this officer grade?

Meantime, thousands of girls pass nursing by—girls who in a more sensible world would find the nursing care of sick folks a rewarding career The loose statement is often made that hospital medicine today needs more highly trained nurses The fact is that this statement requires careful interpretation—for what is wanted are many many more ordinary nurses and a few who by post-graduate training have the capacity to take charge of wards, operating-theatres, &c The latter group is a very small proportion of the former

May one suggest that the time is ripe for a new *Lancet* Commission on Nursing which would allow the medical profession to redefine in terms of the 1950's the kind of nurse this country requires?

Glasgow THOMAS ANDERSON

HEALTH FROM THE HEALTH SERVICE

SIR,—Dr Joules's statement of Dec 8 represents enlightened opinion

The real achievement in preventive medicine should not screen our failures Dr Joules argues that the public health of young people is of such an order that we should reorientate our attention to the later decades where physical illness is our most urgent problem Nevertheless, what we know of the ætiology of lung cancer, hypertension, ischæmic heart disease, and peptic ulcer suggests the causative factors are established in the habitual activities of people while they are young The suggestion that the greatest enemy of the middle aged man is his wife, who, in compensation for some other inadequacy, is over indulgent in dietary attention, reminds us that people usually marry when young, and excess body-weight may be the ultimate reward of protracted matrimonial disharmony Information on school-leavers declares that physique has never been better, but their subsequent occupational and matrimonial adjustments are uncertain and confused Can it be that the foundation of physical disorder in the 50s and 60s stems from the emotional faux-pas in the 20s? With neurotic disorder omnipresent in urban populations, we can assert that we have a youth physically equipped but emotionally unprepared for the world in which they must adjust Is this not evidence that we have not even begun to approach a general state of mental well-being? Can we be sure that physical and mental well being are separate problems?

Prof O L Zangwill[1] can say of psychology that it has so far "failed to produce anything resembling a coherent and generally accepted body of scientific theory every psychologist has perforce to create his own psychology" Prof H J Eysenck,[2] speaking of data available, states they "do not prove psychotherapy to be valueless, but rather that they fail conspicuously to show any positive consequence following its use"

But what does Dr Joules say of this terrifying situation? "Mental health, in an acquisitive and densely crowded society, can come only from a wise education by which endeavour is canalised along routes likely to bring harmony rather than internecine competition" Would it be more honest to admit that we are unable to usefully predict our future, to acknowledge our ignorance, and to recognise mental health as our great problem wherein lies the opportunity for a tremendous advance? Should we be disappointed to discover no connection between mental health and the physical illness of the 50s and 60s, at least we can ensure that our potential longevity is worth having, and is not increasingly terminated in suicide, or in the chronic mental hospital

St Paul's Cray, Kent J D PAULETT

DANGEROUS CONTAMINANTS IN STORED BLOOD

SIR,—Deaths are best prevented by eliminating common causes—not rare ones In transfusion one estimates that hepatitis kills 1 recipient in 10,000–15,000, serologic incompatibility 1 in 4000–10,000, bacterial contamination something like 1 in 350,000 Dr Aidin (Nov 17 and Dec 22) wants us to do a special test to eliminate the 1 death in 350,000, forgetting that the hurry and worry of the extra test may increase the 35–90 deaths due to serologic error, or delay the transfusion so that an occasional patient may die.

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[1] Zangwill, O L New Outline of Modern Knowledge London, 1956, p 168

[2] Eysenck H J Use and Abuse of Psychology London, 1953, p 199

Dr Drummond's (Dec. 15) experience that 3·1% of entered bottles are contaminated is a sufficient refutation of Dr Aidin's belief that bottles can be entered without danger. His bacteriological test seems likely to kill more patients than it saves—at least if he continues to assume that he can enter the bottle without contaminating it. I maintain that the safest procedure is to use pilot bottles and to refrain from entering the main bottle until it is actually to be used.

Central Middlesex Hospital,
London, N.W.10.

GEORGE DISCOMBE.

SEVERE TOXIC REACTION TO HYDRALLAZINE

SIR,—Dr McNicol and Dr Hutchison described (Dec. 22) an unusual instance of the toxicity of hydrallazine[1] ('Apresoline'; 1-hydrazinophthalazine)—apparently *the first example of this disturbance to be reported* in the British literature. They thereby drew attention to a problem of some practical importance to the cardiologist, but of profound theoretical interest to those investigating the rheumatic diseases.

A small but significant number of patients treated with large amounts of hydrallazine for long periods have been found to develop a condition clinically resembling rheumatoid arthritis.[2,3] If the administration of this drug is continued after the appearance of these changes, a proportion of patients, again small, manifests signs which more or less closely mimic those of disseminated lupus erythematosus (D.L.E.). These changes, which include fever, anæmia, loss of weight, and splenomegaly,[4] may be accompanied by a skin rash of "butterfly" distribution. Histological examination of the involved skin may reveal changes resembling those of D.L.E.[5] In a few patients it has proved possible to demonstrate in the plasma a factor capable of inducing the formation of cells morphologically indistinguishable from the "L.E." cell of Hargraves.[6] The description of these undesirable pharmacological effects raised the hope that a means had been found by which the changes of D.L.E. might be reproduced in the laboratory animal. This suggestion has been investigated by Schroeder and his colleagues, and culminated in a description by Comens[7] of changes in the dog caused by the long-continued feeding of hydrallazine.

I have lately been able to substantiate the claim by Comens that dogs fed large doses of hydrallazine soon develop severe illness. In a paper submitted for publication elsewhere, the production by this means of severe and rapid weight loss, progressive non-deficiency anæmia, altered plasma proteins, and other changes has been described. The loss of weight was unrelated to the taste of the drug: *during the greater part of the experiment* the animals ate voraciously. Examination of suitable preparations of dog serum and human leucocytes revealed the appearance of cells resembling those described by Comens which he considered to be indistinguishable from the classic "L.E." cell; however, the histological examination of freshly fixed tissue from the majority of the organs from these dogs did not reveal changes similar to those found in D.L.E.

The question now arises: to what extent does this disorder of dogs provide an experimental replica of D.L.E.? The evidence given by Comens for considering these illnesses identical includes *the description of two specific* changes: (1) the demonstration in dog sera of a factor inducing the formation of cells similar to those produced in D.L.E., and (2) the discovery at necropsy of histological changes resembling those of D.L.E. in the human. The "L.E." cell of Hargraves,[6] to be accepted as diagnostic, must contain homogeneous basophilic material of nuclear origin.[8] The cells produced with dog sera in our experiments *do not conform to this description*. Among the histological changes regarded as being most characteristic of D.L.E. is the "wire loop" change in renal glomerular capillaries.[8] Changes of this general pattern may indeed be found in kidneys of the treated dog, they may also be found in the glomeruli of untreated animals of the same species, age, and sex.

The conclusion seems inevitable that the response of the dog to hydrallazine, while yielding an interesting parallel to the human "hydrallazine syndrome," does not provide a reliable experimental model of D.L.E. To what extent it may prove possible to reproduce D.L.E. in an animal species remains uncertain: the hypertensive rat responds to high doses of hydrallazine by the production *of glomerular lesions of a most unusual type* (personal observations, unpublished), but as with the dog it cannot be held that these resemble the lesions of D.L.E. in more than the most superficial manner.

Pathology Department,
University of Edinburgh.

DUGALD L. GARDNER.

CORTISONE AND ULCERATIVE COLITIS

SIR,—Mr Brooke[9] is right in saying that it is rare to find the large intestine adherent in uncomplicated ulcerative colitis, but we wonder if it is correct to attribute the other effects he speaks of entirely to steroid therapy. By their anti-inflammatory action steroids may sometimes predispose to friability and disintegration, but the state of the bowel may be the result simply of using ineffective therapy of any kind too long and/or allowing the disease to advance beyond the possibility of surgical help. That the condition Brooke describes may be due to the disease itself is illustrated by the following case-history.

A woman aged 34 was admitted to hospital ill, toxic, and incontinent of fæces, with a five weeks' history of severe ulcerative colitis. The only treatment received had been a short course of (?) chloramphenicol at the onset.

At sigmoidoscopy numerous deep excavating ulcers were seen, baring the muscle coat. Four days after admission, after two days' treatment with oral neomycin, colectomy was carried out by one of us (J. S.). At operation the colon was very friable and several perforations had occurred in the descending and sigmoid colon where the bowel lay against the anterior abdominal wall. There was no frank peritonitis. Extensive peritoneal fæcal soiling occurred from disintegration of the friable bowel during its removal. Most of the mucosa below the hepatic flexure had disappeared. The patient made a rapid and uninterrupted recovery, leaving hospital 43 days later. The neomycin may have been responsible for the absence of peritonitis although colonic fæces cultured at the operation were not completely sterile.

We agree that steroids should always be used with caution in ulcerative colitis, and we have never given them to patients with ulcers extending down to the muscular coat. This type of ulceration must be looked for, and can be seen easily on sigmoidoscopy and (perhaps less easily) on radiography. Brooke's comments and illustrations of the X-ray changes in severe cases are of great interest and importance. In patients with this type of deep ulceration we find that colectomy carried out promptly is better than any form of medical treatment. A short preliminary course of broad-spectrum antibiotic by mouth is justifiable to reduce infection in case of perforation.

In the Medical Research Council trials of steroid treatment in ulcerative colitis it has been clearly understood that the length of the course of treatment was governed by the patient's condition. Whether the trial treatment is continued for the full six weeks has always been decided by the physician in charge of the patient. Brooke says that steroid therapy should cease if there has been no response after one or two weeks. We have not found this necessary, and indeed it is common experience that patients may take much longer to improve with any medical treatment. What is needed is close observation, including repeated sigmoidoscopy and radiography, of the patient who shows signs of clinical deterioration. In this way deep ulceration may be discovered and surgery resorted to in time.

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[2] Morrow, J. D., Schroeder, H. A., Perry, H. M., jun. *Circulation*, 1953, 8, 829.
[3] Dustan, H. P., Taylor, R. D., Corcoran, A. C., Page, I. H. *J. Lab. clin. Med.* 1953, 42, 801.
[4] Lansbury, J., Rogers, F. B. *Bull. rheum. Dis.* 1955, 5, 85.
[5] Weiss, R. S., Swift, S. *Arch. Dermat.* 1955, 72, 103.
[6] Hargraves, M. M., Richmond, H., Morton, R. *Proc. Mayo Clin.* 1948, 23, 25.
[7] Comens, P. *J. Lab. clin. Med.* 1956, 47, 444.
[8] Harvey, A. M., Shulman, L. E., Tumulty, P. A., Conley, C. L., Schoenrich, E. H. *Medicine*, 1954, 33, 291.
[9] Brooke, B. N. *Lancet*, 1956, ii, 1175.

All who look after patients with ulcerative colitis will agree with Brooke's last point. Cases of ulcerative colitis of any severity are best treated by physicians and surgeons jointly.

West Middlesex Hospital,
Isleworth.

J. SCHOLEFIELD
W. J. FERGUSON
N. F. COGHILL

CARDIAC ARREST

SIR,—I was surprised to read in your annotation under this heading[1] the statement that the use of cardiac massage is restricted because a physician and even a general surgeon may hesitate to do an immediate thoracotomy. This sentence seems to indicate some confusion of thought. The restriction surely applies only to the ability or knowledge of the physician or surgeon and not to the use of cardiac massage. One would not expect to see an annotation headed "Laryngeal Obstruction" in your columns which contained the statement that the use of tracheotomy in the treatment of this condition was restricted because doctors might hesitate to perform it. The two situations are precisely analogous.

I fear that your annotation might encourage doctors in their hesitation to perform thoracotomy and might lead them to attempt the alternative methods which you outline. This could only have the effect of increasing the mortality from cardiac arrest which is still about 70%. In fact, several hundred people die from this condition every year.

The immediate essential in the treatment of cardiac arrest is not to re-start the heart but to maintain the cerebral circulation. As you state, an external electric shock *may* restore normal ventricular action. Cardiac massage always *will* maintain effective cerebral circulation, but it must be started immediately without recourse to other methods as a preliminary.

The time has now come when all, including physicians and general surgeons, who carry out any procedure on a patient which may cause cardiac arrest should be capable of dealing with the situation by thoracotomy and cardiac massage. Such procedures include local and general anæsthesia, injections, and investigations as well as operations. I have personal knowledge of cases in which physicians have performed cardiac massage and in which anæsthetists have had to persuade surgeons to open the chest and even, when the surgeon refused, have had to perform a thoracotomy themselves.

I do not think the position was put too strongly by Beck[2] when he stated:

> "I don't think we are doing the right thing for our patient unless we have knowledge of resuscitation procedures. I think it is a crime for a surgeon to walk away from the operating table, the patient dying, without doing anything. If I were on a jury in a court and had to make a decision about the responsibility for the death of a patient with a previously normal heart who died on the operating table, I would have to vote against the surgeon. There is no excuse, it seems to me, for a surgeon not knowing how to resuscitate a heart."

Brompton Hospital,
London, S.W.3.

B. B. MILSTEIN

THE USE OF PLASMA

SIR,—Some of the contentions with regard to plasma and its substitutes in Admiral Ramsford's letters of Oct. 27 and Dec. 15 should not be allowed to pass unchallenged. While his initial suggestion that homologous-serum jaundice should become a notifiable disease is one with which few would disagree, several of his subsequent statements are, to say the least, extremely controversial.

With regard to the risk of homologous-serum jaundice following plasma-infusion, Dr. Wallace (Nov. 3) has provided the correct figures and drawn attention to the view that modern plasma preparations can be used with relative impunity in this respect. Coagulation defects due to the citrate content are likely to be encountered only with massive transfusion in the presence of liver failure. The risks of dextran infusion are less clear, though there is increasing evidence that it may on occasion precipitate coagulation failure.[1]

The statement, however, that stored plasma is of no value in correcting coagulation defects is seriously misleading. It has been shown that dried plasma stored at room-temperature for three years has a high fibrinogen content.[2] This is the most widely available plasma preparation, and when infused in concentrated solution it has proved life-saving in cases of coagulation failure due to fibrinogen depletion. Deaths have occurred in such cases while attempts were being made to obtain fibrinogen from a distant source, while the immediately available crude plasma was ignored. It would be most unfortunate if Admiral Ramsford's remarks should lead to further tragedies of this nature.

Department of Obstetrics and
Gynæcology, University of Liverpool.

JAMES S. SCOTT

THE SCIENTIST AS CITIZEN

SIR,—Although it is highly relevant to medicine, Dr. Douglas McClean's paper[3] is concerned with a wider than medical issue.

Where scientists are concerned, I must confess that I belong to the ivory-tower school and believe that professionally they should, in Dr. McClean's words, only speak when spoken to. By this I mean that, while they have every right and capacity to advise about means to ends, *as scientists* they know nothing of ends themselves. In certain contexts they are most anxious to tell us so. They are rigidly anti-teleological in their attitude to discoveries in every field, and they remind us from time to time that they can discern no apparent purpose in the universe. They cannot therefore tell us what policies to adopt and what to reject in order to pursue universal ends, because no such things are known to them, nor have they any scientific criterion of what is "good." Our æsthetic sense (no doubt epiphenomenal) is offended by certain aspects of Nature, in plant, animal, and human existence, and we desire to avoid them because they are unpleasant to us and may deprive us of life, which we have an irrational urge to preserve; but as scientists can we say more than that according to our terms of reference?

The point which I think some scientists are apt to overlook is that science is a valid guide for only a small part of human experience, and those who want to increase its proportion do so by narrowing the field, as by ruling out many questions as unmeaningful, and not by extending its range. Dr. McClean, for instance, has in mind a number of objectives which he thinks scientists should act in concert to secure, such as the abolition of war, the avoidance of over-population, and the development of agriculture. But it is as citizen, not as scientist, that he has learned to regard these as worthy aims, contributing to a happier and more secure world that is a desirable goal not only to the humanist tradition The ideology to which a scientist subscribes—humanist, Christian, Communist, or what not—ought not to colour his observations of natural phenomena, but it seems to me that it is bound to determine how he applies his knowledge of them He serves some master or other in the employment of his talents, however much he might wish it otherwise

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[1] Lancet, 1956, ii, 1261.
[2] Beck, C. S. In Henry Ford Hospital International Symposium on Cardiovascular Surgery. Philadelphia, 1955; p. 464.

[1] Stefanini, M., Dameshek, W. The Hemorrhagic Disorders. New York, 1955.
[2] Scott, J. S. Brit. med. J. 1955, ii, 290.
[3] Lancet, 1956, ii, 1293.

Darlington JOSEPH V WALKER

PREGNANCY TOXÆMIA

SIR,—Mr Norman Morris and his colleagues at University College Hospital have shown (Sept 8, p 481) that the blood supply of the pregnant uterus is diminished by exercise, and that in toxæmic women the blood-supply is below normal even when the patient is at rest I warmly welcome this new evidence, but its great obstetrical importance cannot be fully appreciated unless it is related to other clinical and experimental data May I therefore give my explanation of the findings ?

In the toxæmic woman at rest, diminution of uterine blood flow is due in the first place to a mechanical factor—namely, tautness of the uterine muscle (Reynolds[1] has emphasised the tautness of the uterine wall in first pregnancies and has also shown that this diminishes the myometrial circulation[2]) But resistance to stretch, as seen in the virgin uterus or in one which has to enlarge abnormally to accommodate a big infant, twins, hydramnios, or concealed accidental hæmorrhage, also sets off the uterorenal reflex,[3] and this induces a variable vasoconstriction in the kidney, dependent on the strength of *the stimulus and the responsiveness of the kidney to it* Renal ischæmia in its turn induces a corresponding degree of splanchnic vasoconstriction,[3a] which (since the uterus lies in the splanchnic bed) further impairs the uterine *circulation*

Exercise, whether in the normal person or in the toxæmic patient, also induces vasoconstriction in the kidney In a normal person, exercised to the point of *discomfort, the flow of plasma through the kidney may* be reduced by a third[4] This effect is likewise evident in renal disease, for we know that in a patient with acute nephritis in whom the glomerular filtration-rate and the effective renal plasma *flow are already diminished*,[5,6] these will be further reduced even by the small effort involved in becoming ambulant after being in bed[7] Similarly in women with pregnancy toxæmia the renal plasma flow has been diminished by the uterorenal reflex, and, where renal ischæmia resulting from this reflex has been acute or long-continued, it will have caused glomerular swelling and exudate in Bowman's capsule,[8] further *diminishing* the renal *circulation* (Experimentally, similar anatomical changes have been provoked by ischæmia in the studies of Hoff,[9] Fajers,[10] and others) Exercise or effort, by increasing renal ischæmia, will increase *this damage* As *Morris* and his associates say, in pre eclampsia

> " the blood flow to the uterus is still sufficient for fœtal needs in spite of further reduction caused by maternal activity In the *extreme case however, the additive effect of reduction* of uterine blood flow by exercise and that dependent on the pre eclamptic vasoconstriction might endanger the growth or viability of the fœtus "

The physiological value of the renal-ischæmia mechanism is that it diverts oxygenated blood from the kidney to other parts of the body where such supplies may be particularly needed In exercise it increases the flow of blood to the muscles and in shock it maintains the flow to the brain Though the pregnant uterus stands to *gain by this diversion of blood associated* with renal ischæmia, it loses by the vasoconstriction which renal ischæmia induces throughout the splanchnic bed, and on balance it loses Considered teleologically, the deficiency of *circulation caused* when *the uterus resists stretch* could be the ultimate stimulus provoking the uterorenal reflex, and continuing deficiency in the blood supply to the uterus would keep the uterorenal reflex in action, *and increase renal ischæmia—the vicious circle suspected* by Morris Thus the defensive physiological mechanism may be so intense as to destroy the fœtus (by anoxæmia) and even the mother (by interfering with renal function *and by inducing hypertension and fits)*

In the uterorenal reflex we have the primary explanation of pregnancy "toxæmia" and its consequence Hitherto the chief evidence that there is such a reflex has been (1) that in animals blanching of the kidney has been seen to follow distension of the uterus, and (2) that in pre eclamptic women tocometric *tracings* in labour have—on one occasion so far—shown that heightened uterine tone precedes *hypertension* (presumably renal)[11] Also the satisfactory therapeutic effect of draining the liquor has frequently been reported But now there is also biochemical evidence, for McGaughey et al[12] have demonstrated, *in dogs, a mean reduction of* 23% in the urinary clearance of *p* aminohippuric acid following acute distension of the uterus—indicating a reduced renal plasma flow (I must add that these workers *do* not themselves *attribute* this change *to* renal cortical ischæmia, nor do they yet accept my interpretation of its part in the ætiology of toxæmia)

The University College Hospital investigators have not only provided a rational explanation of the benefit of rest to the toxæmic patient they have advanced our insight into the ætiology All their findings are compatible with the view that pregnancy " toxæmia " results from renal ischæmia induced, *through the* uterorenal *reflex*, by stretching of the resisting uterine muscle

London W 1 JOHN SOPHIAN

SHORTAGE OF RADIOGRAPHERS

SIR,—You are doing a service by calling attention to the shortage of radiographers, but I do not think you or Mr Baxter (Dec 22) are correct in assuming that this is primarily due to inadequate remuneration This dissatisfaction is largely confined to the few male radiographers

The shortage of entrants to diagnostic radiography is due to a variety of causes *The radiation hazard* you mention does deter some but not very *many* The other factor you mention—namely, the age of entry—is important for the reason you state This difficulty can be overcome *in some measure by offering* suitable candidates posts as dark-room technicians until they reach the required age of entry

The educational requirements before *a* girl is accepted as a trainee are *altogether* too high and the course itself should be completely revised The knowledge of physics and apparatus construction required by the syllabus is ridiculous In the old days, maybe, a radiographer was required to tinker with a faulty set, but nowadays no radiographer would be permitted to touch

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1 Reynolds S R M, Baker J T *Contr Embryol Carnegie Instn* 1951 34 Publ 592
2 Reynolds S R M Physiology of the Uterus New York 1950
3 Sophian J Toxæmias of Pregnancy London 1953
3a Shorr, E, Zweifach, B W L *Proc Amer Heart Ass* 1949, p 7
4 Smith, Homer W Principles of Renal Physiology Oxford 1956 p 168
5 Milne M D *Postgrad Med* 1951 30 640
6 Earle D P jun, Taggart J V, Shannon J A *J clin Invest* 1944 23, 119
7 Bradley S E, Bradley G P, Tyson C J, Curry J J, Blake W D *Amer J Med* 1950 9 766
8 Pollak V E, Pirani C L, Kark R M, Muehrcke R C, Freda V C, Nettles J B *Lancet* 1956 ii [illegible]
9 Hoff E C, Kell J F jun, Hastings N, Sholes D M, Gray E H *J Neurophysiol* 1951 14 317
10 Fajers C M *Acta path microbiol scand* 1955 suppl 108
11 Nixon W C W Personal communication, 1955
12 McGaughey H S jun, Walker H, Parker Anslow, W jun *Amer J Obstet* 1956 72 559

the "works" under any circumstances An abstruse knowledge of circuits, transformers, timers, stabilisers, &c, is therefore not required

Another hindrance to training is the fact that students must be attached to an approved school, though it may be granted that with the present syllabus it would be very difficult for a girl to pass the examinations without lectures from physicists

Since the N H S began, radiographers in hospitals must have the M S R qualification It is at once evident that the Society of Radiographers is in a powerful position and by making the examination far too difficult limits entry into the profession

The taking of a good radiograph consists of two essentials (i) positioning of the patient, and (ii) correct exposure of the film For neither of these is a knowledge of physics, mathematics, or English language essential Any intelligent girl of 17 or 18 with an aptitude for the work could be taught to do all that is necessary in twelve to eighteen months of practical training in a large and busy department

I must disagree with your suggestion that more superintendents should be appointed It is only in very large hospitals that a superintendent is required The radiologist in charge is automatically the superintendent

My own view is that radiography is essentially a job for a girl There is insufficient scope to give permanent satisfaction to most men I would be the last to decry the value of a first-class male superintendent and I think that male students should be very carefully selected with this ultimate objective in view

X Ray Diagnostic Department
General Infirmary Leeds
G H ILLINGWORTH

SIR,—In your annotation on this subject[1] you cite the top salary for a chief laboratory technician as £1025 This figure applies to chief technicians with a staff of twenty technicians, of whom there must be very few The top figure that the great majority of chief technicians can expect to obtain is £900 per annum

St David's Hospital,
Cardiff
T J A LIVSEY

X RAYS AND LEUKÆMIA

SIR,—Unlike Dr Rabinowitch (Dec 15) I would congratulate Dr Stewart and her colleagues on the evidence they have brought forward, which has already induced a caution in the requests for multiple X ray investigations

In 1932 I showed that in osteochondritis it was possible to see from radiographs the state of the bone and this permitted radiographic control of the treatment, though little change might be registered on radiographs taken at intervals of less than six months[2] Since then radiographic control has been extensively employed, particularly in chest and fracture work—in both of which I have seen as many as 100 films of a case I have seen patients who for one reason or another have been transferred for treatment to as many as six different institutions At each an X-ray investigation has been done, though the radiographs and reports of the former examinations have been available and the initial report later proved accurate Surely such repeat examinations involve unnecessary exposures and reveal a very unfortunate failure to respect the opinion of colleagues? This is apparent to the patients The multiplicity of repeat examinations for "radiographic control" actually does more harm than good to the patients since the intervals between them are so short that little or no change is registered, and the report "no change" must have a depressing influence on the patient No case with such multiplicity of radiographs has developed leukæmia to my knowledge

As an experienced radiologist who desires to give the best help he can to his patients and colleagues, I welcome any evidence, such as that produced by Dr Stewart and her associates, which will cause people to think before they demand of very hard-pressed departments multiple expensive examinations, or administer chemical or physical agents which may do more harm than good —fully acknowledging our ignorance of the possibilities

Birmingham
JAMES F BRAILSFORD

PSYCHOTHERAPY IN GENERAL PRACTICE

SIR,—That psychotherapy in general practice should be the subject of a leading article in your journal (Dec 29) suggests that it has at long last arrived, but your remarks were limited to the use of psychotherapy in general practice for patients with psychoneuroses Unfortunately this is only part of the story since psychoneuroses, according to various authors,[1-8] account for only 6–16% of all patients seen When we take into consideration those patients suffering from psychosomatic conditions (or stress disorders) the incidence rises considerably In a survey[4] in my practice the incidence was 42 8%, and Pougher[9] found that 47 6% of all consultations were sought by patients with some form of neurosis (including psychosomatic conditions)

For those who fear that physical disease is being misdiagnosed as neurosis, I would mention that in an analysis of all patients referred to hospital over a period of three years, 31 3% were found to be suffering from psychoneurotic illness or stress disorder[10]

In my experience, the use of psychotherapy in general practice is by no means limited to patients with frank psychoneurosis there are many conditions whose labels disguise underlying neurosis, so that they do not appear in any survey showing the incidence of neurosis Patients with these conditions are, nevertheless, amenable to psychotherapy, either with or without other forms of treatment It is hardly necessary to name them for those experienced in general practice but, since few psychiatrists would have had such patients referred to them, I might mention some that I have recently treated with psychotherapy with satisfactory results duodenal ulcer, asthma, dysmenorrhœa, psychogenic menorrhagia, pruritus vulvæ, hypertension, migraine, neurodermatitis, and spastic colon

In discussing the use of psychotherapy in general practice with many colleagues, several have queried, for purely material reasons, the wisdom of my doing so It has been pointed out to me that the general practitioner obstetrician receives a special fee for his services, which may take up twelve hours of his time over seven or eight months Psychotherapy may take two or three times this amount of time over the same period without any fee over and above the capitation fee This makes it necessary to keep one's list down to a manageable level, otherwise there would be insufficient time to give to those patients requiring it The result is a self imposed limit to one's income

In addition, therefore, to your excellent suggestion that means must be found to improve teaching, means must also be found to provide proper fees for special treatment carried out by general practitioners

It is all very satisfying to look after one's own patients and to treat them oneself, but it is not possible to bring up a growing family on satisfaction alone This could well produce an unfortunate conflict, as the way in which the general practitioner is paid encourages him to cultivate a large list which must make it impossible for psychotherapy to be used for many patients This is more than regrettable since I firmly believe that it is by

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1 *Lancet* 1956 ii 1296
2 *Trans med Soc Lond* 1932 55 234 Radiology of Bones and Joints 5th ed, London, 1953

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1 Chapman, H O *Med J Aust* 1953 ii, 407
2 Crawford J C C *Brit J prev soc Med* 1954 8, 81
3 Fry J *Med World* 1954 80, 657
4 Hopkins P *In* Modern Trends in Psychosomatic Medicine Edited by D O'Neill London 1955, p 1
5 Jansen M G *Med J Aust* 1954 ii 422
6 McGregor R M *Edinb med J* 1950, 57, 433
7 Pemberton J *Brit med J* 1949 i 306
8 Watts C A H, Watts B M Psychiatry in General Practice London, 1952
9 Pougher, J C *Brit med J* 1955, ii 409
10 Hopkins P *Ibid* 1956, ii, 873

psychotherapy more than any other method of treatment that more patients will be helped—not only for their existing illnesses but also as a form of preventing future ones in themselves and in their children

One last point you stated that almost every specialty began in a small way as part of the work of the general practitioner May I say that I sincerely hope that psychotherapy does not become a specialty but remains essentially a method of treatment to be used by the general practitioner in general practice

London N W 3 **PHILIP HOPKINS**

TREATMENT OF BURNS WITH PLASMA

SIR,—In the burns unit of this hospital we have been treating acute scalds, and some burns suitable for exposure, by painting them with concentrated reconstituted human plasma (1 gramme dried plasma to 5 ml Tyrode fluid) and then drying the area with a hair-dryer modified to filter the air This treatment is repeated once 6 hours later A crust is formed after 16–18 hours and becomes strong after 36–48 hours Whenever possible, depending on the extent of the damage, the area is immobilised with plaster-of-paris, to assist in the healing process

We are now going ahead with full clinical trials

Booth Hall Children's Hospital,
Manchester, 9

F DURAN-JORDA
A McDOWALL

DELIRIOUS PSYCHOSIS DUE TO MEGIMIDE

SIR,—May I make three comments on Dr Kjaer-Larsen's report[1]?

(1) The contradiction presented by the absence of "'Megimide' psychosis" among the patients reviewed by Gershon et al[2] and the frequency of this psychosis described by Kjaer Larsen I have treated only two comparable cases (neither of whom showed post treatment psychosis) and therefore I cannot comment directly, but in 1947[3] I recorded an outbreak of atropine poisoning associated with barbiturate narcosis and said "the conclusion can hardly be escaped that the narcotic not only masked the action of the atropine effectively, but also in some way reduced its excretion, so that at the end of treatment an effect was rapidly produced as if something like the total atropine given was acting as a single dose" (About 30 mg had been given over 10 days) The "atropine psychoses were practically identical with the "megimide psychoses" described by Kjaer Larsen both in character and in the time of onset relative to the barbiturate intoxication, and I wonder whether his patients could have taken hallucinogenic drugs such as mescaline, Indian hemp, or even amphetamine[4] shortly before the overdose of barbiturate

(2) Kjaer-Larsen describes, but does not classify, three kinds of hallucinations (*a*) lights, flashes, figures, colours, &c (to which might be added certain noises, smells, &c), (*b*) whole scenes (to which might be added intelligible scraps of conversation, associated smells, &c), (*c*) experiences inseparable from ideas (e g, of persecution) which are difficult to separate from delusions and are often supported by illusions and false interpretations It is a temptation to interpret these, in the case of visual experiences, for instance, as successively occipital, *temporal* and frontal brain phenomena, but at any rate some such classification should be kept in mind Further, each of these three kinds of phenomena may be straightforward sense experiences or abnormal distortions This is clearest in the case of (*b*) a scene may be an identifiable memory or a bizarre impossibility With (*a*) and (*b*) especially, unusual intensity is conceivably a 'release phenomenon

(3) Once again a case is reported of a schizophrenic who had no difficulty in recognising his vivid experiences as something apart from his long standing illness a common although not uniform finding in schizophrenics who are given hallucinogenic drugs and one comparable to the insight retained by the patients with temporal lobe lesions described by Penfield and Jasper[5] I have treated two schizophrenics who were sensibly perplexed by such phenomena for about a year before the ultimate diagnosis could be made—i e, before there was any failure to assess the abnormality as such and before any kind of delusion was manifest

St Ann's Hospital
Canford Cliffs Dorset

D N PARFITT

VACCINIA AS A POSSIBLE CARCINOGEN

SIR,—I have seen five cases of malignant disease arising a few weeks after smallpox vaccination

CASE 1 (previously reported[1])—A girl, at puberty, was vaccinated on the left thigh 3 weeks later a sarcomatous mass appeared in the right ischiorectal region It soon metastasised to the superficial lymph nodes and liver The child was dead 3 months after the illness began

CASE 2—A 44 year old soldier was revaccinated in the left deltoid region in 1942 A few weeks later he had enlargement of the left axillary lymph nodes, which became matted together The surrounding tissues were infiltrated Biopsy showed that the condition was a lymphosarcoma

CASE 3—A European woman of 65 said that she had been vaccinated in infancy, but there were no obvious scars She was revaccinated in the left deltoid region 2 weeks later the left axillary lymph nodes became enlarged, followed by the right axillary nodes and the inguinal nodes on both sides; an abdominal mass could be felt Biopsy of a lymph node showed lymphosarcoma

CASE 4—A European, aged 51, had been vaccinated in infancy He was revaccinated in the left deltoid region 3–4 weeks later he developed a lymphosarcoma, diagnosed by biopsy, in the left inguinal glands

CASE 5—A European, aged 58, developed abdominal pain 2 months after vaccination 2 months later he had a partial intestinal obstruction At operation a lymphosarcoma of the transverse colon was found, with involvement of the mesenteric nodes

I have seen all the last three cases this year Two others bear on this question

CASE A—Rea[2] reports a case of squamous carcinoma in an African woman aged about 40 It arose on a vaccination scar very soon after inoculation The vaccination in this case was apparently a primary one Dr Duran Reynals, of Yale University, has told me that he knows of cases in which epithelioma appeared after revaccination

CASE B—A child, aged 5 years, had a tumour of the left thigh which was diagnosed as a metastatic neuroblastoma At first it responded very well to radiotherapy, but later it became resistant The boy was then treated with 'C B 1348, an oral preparation of nitrogen mustard, and seemed to respond to this for a while, but after 2 months there was severe leucopenia and the drug had to be stopped 2 weeks later he had a generalised vacciniform eruption, with umbilicated vesicles which came out in crops and eventually covered the whole body There was a swinging pyrexia At this time the tumour appeared to spread more rapidly Vaccinia virus wa isolated from the fluid of the vesicles He had been vaccinated in infancy

The lesion produced by vaccination is usually only local, but the virus is disseminated throughout the body It has a special predilection for tissues of the reticulo endothelial system In 1952 Duran-Reynals[3] published a study of the dual rôle of certain viruses, which can act as cell stimulants or cell destroyers, depending on certain environmental influences of which age is of primary importance He also described experiments which showed that when a carcinogen, methylcholanthrene, was applied to the skin of fowls, a latent pox virus was activated, and that this virus could be recovered from the various neoplastic diseases which appeared when treatment with the carcinogen was continued

In most of the cases reported here the patient was over 40 This is interesting because in his experiments on birds Duran-Reynals found that the age of the host was of primary importance in deciding whether a virus

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[1] Kjaer Larsen J *Lancet* 1956 ii 967
[2] Gershon S Trautner E M Shaw F H *Ibid* p 1214
[3] Parfitt D N *J Neurol Psychiat* 1947 10 85
[4] Ivy A C Goetzl F R *War Med* 1943 3 60
[5] Penfield W Jasper H Epilepsy and the Functional Anatomy of the Human Brain London 1951

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[1] Helman, J *S Afr med J* 1939 13, 331
[2] Rea F *Ibid* 1956, 30 449
[3] Duran Reynals F *Ann N Y Acad Sci* 1952 54, 977

stimulated or destroyed cells In case 1 excess œstrogen may have been a factor In case B the nitrogen mustard (known to be carcinogenic for animals[4]) may have activated a latent vaccinia virus

Vasco, C P, South Africa J HELMAN

THE FAMILY DOCTOR

SIR,—Many extraordinary statements have been made in 1956, but there were two in particular which I find amazing beyond belief The first was the astounding announcement that the average practitioner receives £2222 per annum after he has paid his expenses, to an average Scottish practitioner this would be frankly laughable were it not for the damaging impression that it has given to the lay public The second, and perhaps more astonishing news appeared in your annotation last week, where we learned that a practitioner with 4200 patients "at risk" (a delightful phrase, I always think!) spends an average of 30 hours a week "in contact with patients, travelling between them, and administration," as established by stop-watch I cannot help wondering if the good doctor's stop-watch was slow, because I find myself spending not less than 48 hours in any week looking after about half the number (without too much risk, I trust) Nor can I accept that my organisation is at fault I do not need a stop-watch to confirm these facts, because for sheer, solid blocks of time in the day I simply never cease from "contact with patients, travelling between them, and administration"

The combination of these two extraordinary statements would suggest that the G P is grossly overpaid for a very leisurely job I would like to see much wider publicity given to an equally unbelievable fact which, however, is all too true, that for looking after each member of the demanding public for a year the practitioner receives about 5*d* a week regardless, from which he must meet *all* his expenses This is the root of the tragedy, it can be proved inescapably that from this simple fact all the evils of the National Health Service arise, from the destruction of the family doctor to the overwrought outpatient clinics, from the overwork among some of us to the sad fate of our colleagues who cannot find established employment

To revert to the personal I would say that without my few pleasant, appreciative private patients I would have neither the means nor the desire to survive in general practice

DYSPHAGIA

MEDICINE AND THE DRUG INDUSTRY IN GERMANY

SIR,—During a recent visit to Germany I learned of one significant aspect of the relationship between doctors and drug manufacturers that has not been commented on by your contributor in his most interesting article[5] Apparently there is an excess of doctors in that country, and vast numbers are unemployed As a result, the drug houses have no difficulty in persuading qualified practitioners to act as their representatives, and something of the order of two and a half thousand doctors are so employed, one company alone employs 250 for itself, a further 200 for its smaller subsidiaries, and the same number again for one of its American associates

These doctors do not actually sell drugs, they visit practitioners frequently, discuss various clinical matters with them, and notify them of new drugs that their company is marketing If the doctors show interest, the sales division then sends samples I was amiably escorted by one such representative on a recent fact-finding visit, as might be expected some practitioners were extremely friendly and helpful and were obviously pleased to see him, others treated him like a black sheep I made inquiries later both from his sales colleagues and from practising doctors and found that both groupings tend emotionally to regard these doctors as inferior, although objectively both realise that the unemployment-rate is so high that such a stigma must be, for the most part unjustified However, the situation is now so deeply ingrained that this enormous diversion of clinical training from bedside practice to commercial sales promotion has come to be regarded as normal amongst all but the eldest members of the profession

London, W 1 G B STANFORD

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[4] Griffin A C et al *J Amer med Ass* 1950, 144 571
[5] *Lancet* 1956 ii 1304

SAEGESSER'S SIGN

SIR,—I was interested in Mr Heslop's description (Dec 8) of Saegesser's sign—particularly in the statement that pressure over the phrenic nerve in the neck causes pain in the abdomen, even in its lower quadrants The fundamental fact for understanding the mechanism of any localised subjective experience, such as pain, is that it depends upon the activity of cerebral cells rather than on the activity of peripheral ones[1-3] Therefore it is unlikely that Saegesser's suggestion, that the secret lay in "the fact that the phrenic nerve carries sensory fibres from the capsule of the spleen," is the correct one, because, the afferent impulses, having circled round through the cœliac plexus to enter the phrenic nerve, would presumably share the common neurone pool of the other phrenic fibres in third and fourth cervical segments of the spinal cord The site of the subjective experience depends on the central connections of this cervical neurone pool, irrespective of their topographical origin, and would therefore, be referred to the "shoulder tip" even though they originated *in* the spleen

A further objection to Saegesser's explanation is that the necessary neuronal meandering, though possible, is hypothetical, no connection between the splenic plexus and either the left or right phrenic plexuses being mentioned by Mitchell,[4] Moreover it should be recalled that one of the features of referred shoulder-tip pain of phrenic origin which puzzled Lewis[5] was that the reference was always to the superficial structures and never in the reverse direction, and in my own experiments stimulation of the phrenic nerve in the neck of conscious patients never produced abdominal pain

Hoffman's account of the mechanism seems to be more hopeful, because it is very easy to activate the motor fibres of the phrenic in the neck, and the sudden contraction of the appropriate half of the diaphragm makes the conscious patient jump Such a contraction of the diaphragm could easily rub some of the blood clot across the costal margins of the diaphragm, and, as the diaphragm here has an intercostal nerve-supply, this could easily cause pain referred anywhere in the territory of D7–D12 inclusive Mr Heslop is, I think, correct in suggesting that the mechanism of this sign depends on the double sensory innervation of the diaphragm, but pain in the peripheral distribution of the intercostal nerves could not be produced by any flood of sensory impulses up the phrenic nerve, however strong it could be produced only by a contraction of the diaphragm, due to the motor fibres in the phrenic, exciting traction on the costal margin of the diaphragm, where the muscle and covering peritoneum are innervated by the intercostal nerves A year ago when I had a pneumonia in the left lower lobe, I noticed that any deep breath regularly produced pain in the tip of my left shoulder and in the left upper-abdominal quadrant, and

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[1] Woollard H H, Roberts J E H, Carmichael, E A *Lancet*, 1932 i 337
[2] Penfield W Rasmussen T The Cerebral Cortex of Man New York 1950
[3] Doran F S A, Ratcliffe A H *Brain*, 1954, 77, 427
[4] Mitchell G A G Anatomy of Autonomic Nervous System Edinburgh 1953
[5] Lewis T Pain London 1942

that it occurred with inspiration, but I confess that I did not compress my phrenic in the neck as a separate test

If Mr Heslop will agree that the link between the pain in the shoulder and the pain in the abdomen is the stimulation of the motor fibres in the phrenic by the digital pressure in the neck, causing a contraction of the diaphragm, I think his explanation can be accepted

Tutnall,
near Bromsgrove, Worcs
F S A DORAN

INJURY BY ENEMA SYRINGES

SIR,—I read with interest the report by Mr Large and Dr Mukheiber[1] and I should like to describe a further case

Five years ago a very fat man, aged 60, was brought to the university clinic of therapeutics with slight abdominal distension and severe lower abdominal tenderness and rigidity He said that twelve hours before, because he was constipated and was feeling ill, he had decided to have an enema He was in his garden, and he thought that the irrigation pump would be suitable He inserted the hard nozzle of it, and water was forcefully injected without the aid of any other person There was no evacuation of the bowel, but immediately he began to have lower abdominal colic, mild at first but gradually becoming more severe, and which was succeeded a few hours later by continuous abdominal pain At laparotomy a wide perforation just at the pelvirectal junction was found *The patient died a few hours later*

Athens
G E PAPAYANNOPOULOS

A SIMPLE SELECTIVE TEST FOR NURSES

SIR,—Mr Roberts (Dec 29) appears to have misunderstood my letter, the test was offered as a supplement to the more essential selection tests of intelligence and personality, not as a complete procedure in itself One would be temerous indeed in offering a single test in this rôle

What exactly does he mean by requesting a correlation for *each* student? Intrapersonal correlation coefficients, obtained with cattellian P technique, are unsuitable for relatively stable factors such as intelligence and reading ability Correlations for specific groups of nurses have been worked out 16 years ago by Professor Hunt,[2] who has shown *that reading comprehension correlates more highly with* examination results than any other test of this type—that is that presupposes no previous knowledge of the subject or previous scholastic attainment other than in language The rationale for such a test has been well formulated, the justification for its use rests solely on experience, the bar at which every selection procedure must stand trial

Mr Roberts's criticisms are on the whole irrelevant to the stated purpose of the test It makes no attempt to measure memory efficiency—this is better accomplished with a well standardised test such as the Wechsler memory scale Neither does it measure "writing fluency"—indeed, it has been specially constructed to eliminate this factor Most authorities differ from Mr Roberts in believing that writing fluency is a poor predictor in this field As Professor Ballard[3] says "it is egregiously bad as a basis of measurement It fails through its very wealth and complexity It confuses the examiner by telling him too much, and diverting his attention to irrelevant merits and defects" The test measures, inter alia concentration, but not as a separate quantitative factor Does your correspondent really expect such refinement in a preliminary test?

The mean difference of 1 quoted by him is quite meaningless (with or without the S D) unless one knows the group means for without these one cannot determine the statistical significance of such a difference

These are early days for nursing selection techniques—a period of trial and error, refinement, and modification, which will extend into the future for many years to come It is healthy—for test devisers in particular and the profession as a whole—that procedures should be challenged and criticised, for these are the spurs to progress, which comes to those humble in the face of their own inadequacies The greatest obstacle is surely the complacency expressed in the opinion that "the most efficient method" is one's own

Winterton Hospital
Sedgefield,
Stockton on Tees
L R C HAWARD

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[1] Large P G Mukheiber W J *Lancet* 1956 ii 596
[2] Hunt T Tests for Prospective Nurses Washington D C 1940
[3] Ballard P B The New Examiner London 1949 p 27

Parliament

A New Pattern for Dental Practice

ON Dec 21, shortly before the House of Commons rose for the Christmas recess, Mrs EVELINE HILL drew attention to our woeful shortage of dentists She wondered what would happen if all the expectant and nursing mothers and young children sought the dental treatment to which the health service said they were entitled for there were not enough dentists to go round A further difficulty was that about half of our 16,000 dentists were over middle age and would retire before 1966 Yet recruitment at present was not more than 650 a year The trouble was that there were too few places in the dental schools She believed that we needed 1000 places for new students each year

Miss PATRICIA HORNSBY-SMITH, replying for the Ministry of Health, readily agreed that we were short of dentists Though we had about 15,000 dentists on the Dentists' Register, only 14,000 lived in the United Kingdom That meant that there was only 1 dentist to every 3278 of the population, which was lower than in Canada, Sweden, Norway, or the United States Unfortunately we were now about to experience the results of the small entrance to the dental schools in earlier years and we should be losing all the dentists who took advantage of the 1921 Act and were now reaching retiring age But there had been a steady *improvement in the intake into the dental schools* in the past three years, and the schools were now practically up to capacity The possibility of attaining within the next ten years the 20,000 dentists needed to provide a really adequate service would clearly depend on the public demand, the effectiveness of dental health education, the proportion of dental skill which was applied *to the priority classes, the contribution* which ancillary workers could make, the development of fluoridation, diet, the extension of dental research, and the better organisation of the profession

The McNair Committee had recommended an annual intake of 1000 students But the dental schools had only 645 places, to provide another 350 places would raise *problems of capital expenditure and staffing* Another problem would be to get enough students of the right calibre In the past few years some applicants had lacked the necessary educational qualifications for the course The McNair Committee had come to the conclusion that the main reason for the shortage of dental students was the public's lack of recognition of the true *importance of dental health* As a result the profession did not enjoy the status which it merited Parliament had this year taken a big step towards improving the status of the profession by giving it self-government by the establishment of a General Dental Council But many of our present difficulties were due to the organisation of the profession

The preponderance of single-handed practices resulted in high overhead costs, a lack of opportunity for the dentist to concentrate on the work at which he was most apt, and a position in which the skill and experience of the older dentist was often not adequately used and which *failed to compensate for his growing inability* to work as long or as speedily as his younger colleagues This structure of the profession largely caused the peculiar pattern of earnings, which dropped considerably from middle age onwards The skill and experience *which came from a lifetime of practice should be recognised in the remuneration of a dentist if in fact he was* applying that skill and experience and not spending his time on the more routine type of case which could be dealt with as ably and more speedily by his junior Outside the hospitals and clinics the answer seemed to lie in group practice She suggested that the dental team of the future might consist of one member whose special interest lay in preventive dentistry and the care of children, another whose forte was conservative technique, another who had specialised in oral surgery, and another who had made the provision of dentures his specialty, all of them working under the leadership of the senior member of the firm, a man ripe in experience and diagnostic ability Such a team, backed by the skilled services of a dental hygienist and a dental technician, would, she believed, go far to satisfy the professional aspirations of the young dental man and woman of the future The time had perhaps come for the profession to give serious thought to the advantages which would lie in the introduction of group practices of that kind

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Diary of the Week

JAN 6 TO 12

Monday, 7th

MARLBOROUGH DAY HOSPITAL St John's Wood N W 8
8 15 P M Dr H C Becole Rôle of the Medical Superintendent in Modern Psychiatry

Tuesday, 8th

ROYAL SOCIETY OF MEDICINE 1 Wimpole Street W 1
8 P M *Psychiatry* Mr W Grey Walter D SC Brain as a Machine
BRITISH POSTGRADUATE MEDICAL FEDERATION
5 30 P M (London School of Hygiene and Tropical Medicine, Keppel Street W C 1) Sir Solly Zuckerman, F R S Biological Systems
INSTITUTE OF DERMATOLOGY Lisle Street, London, W C 2
5 30 P M Miss Phyllis Wade Radiation Treatment of Skin Cancer (First of two lectures)
CHELSEA CLINICAL SOCIETY
8 30 P M (Rembrandt Hotel Thurloe Place, S W 7) Sir Mortimer Wheeler Food
MANCHESTER MEDICAL SOCIETY
8 P M (Clinical Science Building York Place) *Surgery* Mr H A Maslowski Congenital Hydrocephalus and Diastematomyelia

Wednesday, 9th

ROYAL SOCIETY OF MEDICINE
4 30 P M *Physical Medicine* Dr F H Lumb Dr G A Rose, Prof C E Dent Generalised Aches and Pains from Metabolic Bone Disease
INSTITUTE OF DISEASES OF THE CHEST, Brompton S W 3
5 P M Mr Donald Barlow Œsophageal Obstruction.
INSTITUTE OF DERMATOLOGY
5 30 P M Dr R W Riddell Significance of Yeasts in Skin Diseases
MEDICO CHIRURGICAL SOCIETY OF EDINBURGH
8 30 P M (Royal College of Surgeons 18 Nicolson Street) Mr J J Mason Brown Recurrent Abdominal Pain in Childhood

Thursday, 10th

ROYAL COLLEGE OF PHYSICIANS Pall Mall East S W 1
5 P M Dr R M B MacKenna Acne Vulgaris (Watson Smith lecture)
ROYAL COLLEGE OF SURGEONS OF ENGLAND Lincoln's Inn Fields W C 2
5 P M Mr J I P James Paralytic Scoliosis (Hunterian lecture)
UNIVERSITY OF LONDON
5 P M (St Mary's Hospital Medical School W 2) Prof C A Janeway (Harvard University) Physiology of the Plasma Proteins (First of two lectures)
BRITISH POSTGRADUATE MEDICAL FEDERATION
5 30 P M Prof Geoffrey Hadfield Rôle of the Endocrine System in Breast Cancer
INSTITUTE OF DERMATOLOGY
5 30 P M Miss Phyllis Wade Radiation Treatment of Skin Cancer (second of two lectures)
ALFRED ADLER MEDICAL SOCIETY
8 P M (11 Chandos Street W 1) Dr Emerich Weissmann Unconscious in Adlerian Psychology and Psychotherapy
LIVERPOOL MEDICAL INSTITUTION 114 Mount Pleasant
8 P M Dr T Cecil Gray Dr J W Dundee Mr Leslie Temple Control of the Circulation During Surgery
ST ANDREWS UNIVERSITY
5 P M (Queen's College Small's Wynd Dundee) Prof Robert McWhirter Growth of Tumours

Friday, 11th

ROYAL COLLEGE OF SURGEONS OF ENGLAND
5 P M Prof Arnold Sorsby Neomycin in Ophthalmology
UNIVERSITY OF LONDON
5 P M (St Mary's Hospital Medical School) Professor Janeway Physiology of the Plasma Proteins (Second of two lectures)
INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330 Gray's Inn Road W C 1
3 30 P M Mr A R Dingley Cancer of the Mouth and Pharynx

Obituary

WILLIAM GEORGE BARNARD
C B E, F R C P

SINCE the war, in times which were at first difficult and which never became easy, Professor Barnard had been dean of St Thomas's Hospital Medical School and treasurer of the Royal College of Physicians In both offices he became responsible for war-damaged buildings, and, when material repairs were successfully completed, the start of the National Health Service gave rise to problems of administrative reconstruction To these tasks he brought judgment, ability, and an enthusiasm which was always turning his mind to plans for the future

He was born in 1892 in Tangier, where his father was a missionary, but on his father's death the family returned to Bath His medical studies at the London Hospital were interrupted by the 1914–18 war, during which he served in France with the Royal Field Artillery He came back to The London to captain the rugby XV and to qualify in 1920 Soon after qualifying he went to work in the pathological institute under H M Turnbull and became junior assistant director There he acquired the thoroughness and insistence on accuracy in observation and description which characterised his work as a pathologist

[Elliott & Fry

From The London in 1923 he went to A E Boycott's department at University College Hospital In 1927 he spent some time at Freiburg as a voluntary assistant in Aschoff's laboratory In 1931, however, the London County Council formed a pathological service for their newly acquired hospitals, and Barnard was one of the first pathologists appointed His task was to start the Central Histological Laboratory at Archway Hospital, the only one in the service entirely devoted to morbid anatomy and histology He set himself, with enthusiasm and tact, to bring home to all the doctors who could use the laboratory the value of reliable and comprehensive investigations in these branches He won their confidence and that of the administrative staff at County Hall, and in eight years he had created from nothing an active smooth-running laboratory with a staff of four pathologists and a fine museum It was organised so as to make the wealth of material from an almost virgin field easily available for research and he never ceased to emphasise the importance of this and to encourage it

Of his years at Archway Hospital A B B writes

"Barnard expected a high standard from his staff, but trusted them to give of their best, backed them loyally, and worked hard for their advancement it was a happy and enthusiastic lab To have taken part under his leadership in the development of the Central Histological Laboratory was a great experience"

In 1939 he was appointed to the chair at St Thomas's His first years there were spent against a war-time background of disorganisation and improvisation, and when he became dean in 1945 he realised that he would be steering the school through a period of administrative activity He immediately collected it together under one roof in London—a courageous but vital decision at a time when there were fewer than 200 beds available in St Thomas's He successfully guided it through the intricacies of the National Health Service Act and put its future administration on a sound basis With more money for education and increased departmental staffs, he was conscious of St Thomas's lack of accommodation, and he never lost sight of his cherished project to rebuild the school Despite these many activities he found time for his own department, which ultimately covered all the pathology of school and hospital

Of late years his shrewd judgment and administrative ability had greatly increased his work outside the hospital His main outside interest was perhaps his duties as treasurer of the Royal College of Physicians, to whose fellowship he had been elected in 1938 The finances of the college benefited from his discriminating supervision and its fellows' dinners from his interest in food and wine, his attention to culinary details, and his friendly presence He also sat on Government committees He had only a few months ago become dean of the faculty of medicine of London University As a chairman he was outstanding—firm, kindly, speedy His constant mastery of an agenda showed the thoroughness of his methods In 1953 he was appointed O B E

But St Thomas's was the centre of his work and there " he ruled as a benevolent autocrat "

Barnard (A L C continues) was essentially shy and reserved and he was undoubtedly held by many in considerable awe, but no student in difficulty or staff member with a worthwhile project ever left his office without help and encouragement In consequence more and more people turned to him with every sort of problem His inherent integrity, fair-mindedness, and high professional standing won him universal respect and affection Always a trifle remote from the students, he knew more of them than they suspected He appreciated the young and was proud of his flock Selection of students he regarded as a vital duty, and he was never absent from the chair of the interview board Realising that those with top academic brains can form only a small minority, he was happy to collect his share and then concentrate on character, personality, and versatility of achievement for the main body Artists and musicians were as valuable to him as rugger players and athletes His lean years as a student at The London gave him a real and understanding sympathy for the present impoverished generation No project for their well being ever lacked his support and he rejoiced in their successes—academic, sporting, or artistic His own wide interests aligned him with them far more than was realised, a good athlete in his youth, in later life his hobbies ranged from a considerable knowledge of old clocks and books to a keen appreciation of pictures

Never irritable or intolerant, he possessed a wonderfully equable temperament His working days, so full of abounding interests, had a solid foundation in a happy home life The tragedy of his death lies not only in the fact that he was achieving so much, but that delays beyond his control robbed him from seeing the new St Thomas's to whose future he gave such unstinted labour

In 1930 Professor Barnard married Margaret Roscoe Osler They had one son who is a house-physician at St Thomas's

A memorial service will be held in the chapel of St Thomas's Hospital at noon on Thursday, Jan. 17 A memorial service arranged by the Royal College of Physicians will be held at St Martin in the Fields on Thursday, Jan 31, at 3 P M

DOROTHY WOODMAN

M D, M Sc Lond

Dr Dorothy Woodman, lecturer in clinical pathology in the University of Bristol and consultant pathologist to Frenchay Hospital, died at her home in Bristol on Dec 21

She graduated B Sc in the University of London in 1917 and took honours in physiology two years later In 1921 she took the M Sc She joined the staff of the department of physiology at the London School of Medicine for Women and worked there for some years until she herself qualified in medicine from the school in 1931 After qualification she held resident appointments at the Royal Free Hospital, and in 1933 was awarded an A M Bird postgraduate scholarship in pathology In 1934 she took her M D She held a post as assistant pathologist at the Royal Cancer Hospital (now the Royal Marsden Hospital) in Fulham before she went to Bristol, where she was at first lecturer in pathology in the university Later she joined the department of preventive medicine as senior clinical pathologist, and when, under the National Health Service Act, she was transferred to the regional hospital board she retained, at considerable financial loss her association with the department She also helped to set up the clinical-pathology departments at Southmead Hospital and later at Frenchay Hospital and when that hospital was transferred to the regional hospital board she elected to remain there

R H P, who worked with her for many years, writ

Dorothy Woodman held a high standing in clinical patholog —not only in Bristol but in the whole country She will b remembered not only for her integrity but also for h stimulating help to many a young clinical doctor some o whom are today well known consultants She loved teachin and her students adored their teacher, but she detached hers from this academic field when she joined the preventi medicine department, and she often quoted this break as h one regret This feeling was often stirred anew when student continued to try and obtain her help with their work

The unexpected news of her death, arriving with h Christmas card and a friendly note, shocked us all with sense of irreplaceable loss This modest, shy, and friendl lady will be missed by all her friends—who were many

ROBERT CARMICHAEL

M B Edin

Dr Robert Carmichael, senior lecturer in pathology i the University of Leeds, died on Dec 19 He was skilled and mature exponent of the science of morbi anatomy, and the Leeds Medical School has lost a membe who will be recalled by many generations of medica students and by his colleagues with warm affection

After he graduated M B with honours in the Universit of Edinburgh in 1923, he held appointments in patholog in the university and Royal Infirmary and at the Roya Edinburgh Hospital for Mental and Nervous Disorders where he developed his special interest in neuropathology In 1931 he published his classical paper on the cerebra lesions in the chronic stage of epidemic encephalitis which was beautifully illustrated by the brush of his wife Soon after this he was appointed to the university department of pathology in Leeds, where, as lecturer and then senior lecturer, he spent the rest of his life At Leeds his research interests widened, especially in tumou pathology, and he was co-author of papers on adenolymphoma of the salivary glands and on metaplastic changes in the cervix uteri But he retained his first love for neuropathology, as was shown by his scholarly papers on the arterial lesions underlying cerebral aneurysms

F S F, who was already in the department of pathology when Carmichael came to Leeds in 1931, writes

We quickly became friends and the friendship deepened with the passing of the years Carmichael's outstanding characteristics were his innate modesty, his friendliness, and his sense of humour which had a delightful flavour all its own He never really hankered after a chair, this was partly on account of modesty, but perhaps mainly because he disliked the idea of having what he considered his real work interrupted by the claims of administration Yet three times he took charge of a department until a permanent incumbent should be appointed, and each time he gave unstinted time and effort to administrative duties, so that he was able to hand over his charge in a healthy, flourishing condition His last period as acting head of a department lasted for a little over a year and taxed his strength greatly, for it was during this period that his illness first manifested itself

R A W writes

Robert Carmichael's output of published work, excellent in quality though it was, is no adequate index of his contribution to the Leeds Medical School and to British pathology Whether in the post mortem room, in the museum, in the lecture theatre, or at his own laboratory bench, his work was done with systematic thoroughness and a palpable love for accuracy and truth He abhorred slipshod, hurried and untidy work of hand or mind, and he set an example of care and precision to colleagues, students, and technicians alike This was his greatest contribution to his subject—high standards of technical and scientific work, the artistry of pathology—and the more his former students and colleagues reflect on what he did and said with them, the more they will realise their indebtedness to him His colleagues both in and outside Leeds, often sought his help on their histological problems for no one was better able to give them a sound sane and helpful opinion They will long remember him, too for the humorous twinkle in his eyes, or the pithy comment or epigram with which he often resolved what had seemed a weighty question or with which he demolished pomposity or insincerity He had few interests outside his happy home life and his beloved pathology, which was his hobby For the greater part of his last illness, six months or more, he carried on his work as though nothing was wrong, indeed he worked until only a fortnight before his death, from an inoperable retroperitoneal tumour, which there is no doubt he himself correctly diagnosed some weeks earlier He was poised and smiling to the last

Dr Carmichael leaves a widow and a daughter

LORNA MURIEL ADELHEID GOULDEN BACH

M B C.S , D.P.H

Dr Goulden Bach assistant principal medical officer to the London County Council, died on Dec 26 She qualified from Westminster Medical School in 1930, and after serving at Westminster Hospital as house-physician and casualty-officer she took appointments at Queen Charlotte's Hospital and Battersea Maternity Hospital before joining the maternity and child-welfare and school health services in Barking, Essex In 1938 she was appointed an assistant medical officer of health for Wembley and during the late war she was responsible for the borough's refugees As assistant casualty officer for the area she was continuously on duty at night at the town hall

In 1946 she was seconded to the Ministry of Health as special assistant to the director of health services of UNRRA She was sent to do relief work in Athens, later she joined the antimalarial team in Macedonia The team also helped to establish public-health services under difficult and sometimes hazardous conditions, and Dr Goulden Bach was forced at one time to escape from bandits

In 1948 she was appointed as medical officer to the public-health department of the London County Council Her wide experience in public health and outstanding administrative ability were early recognised, and she was transferred in 1950 to the central staff at County Hall In 1952 she was promoted to assistant principal medical officer A colleague writes "Her capacity for establishing good personal relationships as well as her deep knowledge of child health made her advice valuable Her high courage in her illness was an inspiration and, at the same time, humbling to her friends"

Dr HUBERT WYERS

G F K writes.

Hubert Wyers's attitude to his specialty was never sectarian and he held strongly that "Medicine should not rest on any theoretical system of ideas, for once one part is discredited the whole is liable to suffer loss" Since he acted as adviser to several firms he was in a happily independent position which accorded with his temperament and enabled him to speak with authority on such diverse hazards as asbestosis and vanadium poisoning No doubt his earlier experience in industry also made it possible for him to see things in the factory from the point of view of people other than the doctor, he had no time for empire builders in occupational health and he had the firm opinion that doctors in industry only undermined their position as specialists in their own field when they encroached on the problems of the engineers or other specialists

Hubert Wyers was *simpático* to a degree and by many he will be remembered best as their friend however little they could aspire to his erudition and achievements He had had more than his share of anxiety and troubles one way or another but he never gave more than a hint of his difficulties, and there is no doubt that he was greatly sustained by his deep religious feeling which led him through Anglo Catholicism to be received quite recently into the Roman Catholic Church

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Births, Marriages, and Deaths

BIRTHS

DIXON —On Dec 23 at King's College Hospital to Gabrielle wife of Dr W M Dixon M.R.C.P —a son Peter (a brother for Christopher)

Notes and News

SICKNESS BENEFIT FOR CERTAIN WIDOWS

CERTAIN widows who are not at present entitled to National Insurance sickness benefit will become eligible for it from Jan. 7, 1957 The widows who may be affected are those who in the past have drawn a widow's benefit but are no longer getting it and those who are now drawing a widow's benefit of less than 40*s* a week, including the widows on 10*s* contributory pension

Some widows may not be aware of this change Any practitioner attending a widow whom he considers to be incapable of work and who is not receiving sickness benefit or a retirement pension may like to suggest to her that she should inquire from her local National Insurance office to find out whether she is now entitled to sickness benefit

FOOD AND AGRICULTURE

THERE was no major change in the world food and agricultural situation in 1955–56 Agricultural production continued to increase and in all regions of the world was some 2 5–3% above the average of the previous quinquennium Estimates of the increase of populations varied from 0 7% in Western Europe to 2 4% in Latin America With the general food situation throughout the world for once stable, F.A O has devoted most of its annual report[1] to special factors influencing national and international trade

The main interest in the report is in economics In general, farm incomes have fallen and possible deterioration of the farming population in many countries must give rise to anxiety There appears to have been no corresponding fall in retail food prices The "marketing margins" have probably increased, in the U S A. the increase was 3% The basic dilemma of most governments is how to reconcile the dual responsibilities of maintaining the economic position of the farmers, at the same time providing consumers with adequate food-supplies at low prices

PHYSIOLOGY OF VOLUNTARY MUSCLE

A NEW number of the *British Medical Bulletin*[2] is devoted to the physiology of voluntary muscle The medical reader who is unfamiliar with such matters should not be discouraged, for, though he may not understand the details of what he reads he cannot fail to grasp the main points in each of these interesting articles Moreover, some of the remarks deserve attention because their meaning has application far beyond the *immediate context, for instance, A. V. Hill comments* that it is never safe, because one sees a particular need, to assume that a muscle 'is ideally designed to meet that one alone under other conditions other demands also must be met" In the chapter on comparative physiology of muscle, C F A Pantin points out that the physico-chemical basis of movement is very often substantially the same "This restricted pattern of variation is not simply of evolutionary origin it depends also upon the peculiarly limited chemical materials available for living systems, and the limitations set by the properties of matter"

A F Huxley and H E Huxley write elegantly on the ultrastructure of muscle and on the function and composition of the familiar striations K. Bailey and S V Perry give lucid accounts of present ideas on contraction and relaxation and on the part played by the various muscle proteins and phosphates B Katz is, as usual, clarity itself in discussing the rôle of the cell *membrane in muscular activity*, and the account of the nervous gradation of muscular contraction by P H Hammond, P A Merton and G G Sutton is very well done A V Hill's article on the thermodynamics of muscle makes it easy to understand the kind of information which can be obtained by physical measurements of this type Of great interest too are the accounts of energy production in muscle, its comparative physiology, activity during locomotion, problems of fatigue, and changes after death The article on muscular effort is written by R G Bannister, whose knowledge is both subjective and objective To anyone whose interest in physiology is largely based on a desire to understand human physiology the chapter on familial periodic paralysis by B McArdle will be of particular interest, since it provides an admirable summary of possible causes underlying one variety of this disease, whose nature can only be rightly understood, and therefore rightly treated, if the normal physiology and biochemistry of muscle is appreciated

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[1] The State of Food and Agriculture, 1956 Rome Food and Agriculture Organisation Obtainable from H M Stationery Office Pp 143 7*s* 6*d*

[2] *Brit med Bull* 1956 12 no 3 Price 15*s*

Into a brief preface Sir Rudolph Peters packs some history and much wisdom He knows how the clinician may be exasperated because the scientist works in apparent remoteness from the obvious practical situation, but he points out the importance of studying basic problems as a means of getting practical results as well as illumination of knowledge.

University of Cambridge

On Dec 15 the following degrees were conferred

M D—J H Gough J W T Redfearn
M B , B Chir—A O Peters

Dr L B Cole has been appointed deputy for the regius professor of physic, and Dr F G J Hayhoe deputy head of the department of medicine

University of London

Dr Eric Neil, reader in physiology at Middlesex Hospital Medical School, has been appointed to the John Astor chair of physiology at the school

Dr Neil graduated B SC with first class honours in physiology in the University of Leeds in 1939 and M B in 1942 For the next three years he served as demonstrator in physiology at the Leeds Medical School In 1945 he was appointed temporary lecturer and a year later lecturer in physiology at the school From 1949 to 1951 he spent some time each year in Stockholm working at the royal veterinary college under Professor Zotterman In 1950 Dr Neil was appointed senior lecturer in physiology at Middlesex Hospital Medical School, and in 1952 he was appointed to the readership in physiology His published work includes a study of methods of artificial respiration and papers on chemoceptors and the circulation

The title of reader in pharmacology has been conferred on Dr J A Nissim in respect of his post at Guy's Hospital Medical School

University of Manchester

At recent examinations the following were successful

M B , Ch B—K S Ansell, P J Barber Kenneth Bass Arthur Booth, A T Cartmell B W Chant, J D Corcoran Joan M Curtis I W Dade, Moira P Dillon, Cynthia M Dixon, A M Easty, W O Goldthorp, Brian Graham, E A G Hamilton, G A Harris D D Hilton, Irene Holbrook Keith Horsfield, H C Jennings T A Lambros Elizabeth J Larrad J R Ledwich Brenda J Lovejoy, K A Mackenzie, Peter McKelvie, Elizabeth M B McKenzie, Edith M Meyer Peter Morris, Harold Nickson J P O'Loughlin Amos Pacovsky, H W Proctor A R Robertson D T Robinson J H Scotson, Barbara S Seymour, D B Shaw N M Shaw S A Silver, J J Slater Eleanor M Stocks A G Tetlow M H Vause, Desmond Walker, W B Waring, R D Wood, A B Wootliff

D P H—Cecilia F G Wild

University of Liverpool

At recent examinations the following were successful

M D—J Ainsworth N Coulshed, J A Donnellan, J F Foulkes D Holbert E S Watkins

M Ch Orth—R M Bhansali J C N Joshipura A H McKenzie R B J Peiris, A E Pritchard, S K Roy W A L Thompson

M B Ch B—Stella R Alsop J L Bowmer, P G Bullough, G G Copeland, H W C Davies, H J P Diggory, H Gordon, H G P Jones Zoe Kenyon, W W Littler Eileen M Millward, Mary W Pritchard F Richards, N G Roberts, P F Toebay, A J Williams Margaret V Wilson

D P H (Part II)—W A Jones B J Kelly N T W Power

D T M & H—J A Attard E P, Brown J J Y Ch'Ual B Das G S Dhaliwal Nishat Fahmy, K N Ghose Mehar Q Hasan H Hollis T J G Howie A Lanzo Yvonne G R Mahabir, M Masuduzzaman P N Mehrotra, G A Parsons, I Rahim A Z Rizavi, S Sen A K Shakir O P Sharma, P N Sharma, Premila Singh, S Sukondhamana, C R W Turner

Royal Society

Prof G L Brown has been appointed a vice president of this society for the coming year

Fulbright Travel Grants

The United States Educational Commission in the United Kingdom have announced that these grants are available to citizens of the United Kingdom and Colonies to go to America for an academic or educational purpose, such as study, research, or lecturing Further particulars may be had from the commission, 71 South Audley Street London, W 1

United Hospitals Catholic Society

This society has arranged a course of lectures on medical ethics The lectures will be held at the Chaplaincy, 13 Devonshire Place London W 1, on alternate Mondays at 6 15 P M The Rev John McDonald will give the first lecture on Jan 7, and other speakers will be Dr F Harwood Stevenson Mr Ambrose King Mr John Ryan Mr Leslie Williams Mr J A O Sullivan, and Dr Charles Burns

Release of Prednisone and Prednisolone

From Feb 1 prednisone and prednisolone will be supplied on prescription

World Health Organisation

Dr P M Kaul, formerly director of W H O 's division of external relations and technical assistance, has been appointed assistant director general in charge of the department of advisory services

Awards for Medical Films

The *Presse médicale* is again offering a prize (fr 100,000) and other awards for unpublished amateur films (16 mm) Films must reach the secretariat of the journal, 120, boulevard *Saint Germain, Paris VI*, by Feb 28

Research Board for the Correlation of Medical Science and Physical Education

The William Hyde award (£300) for 1956 has been made to Squadron-leader C B Wynn Parry for his work on physical medicine in the Royal Air Force This is the last award, for the board, having completed its research investigations is closing, and is transferring its remaining funds to the Physical Education Association of Great Britain and Northern Ireland

Reciprocal Agreements on Social Security with the Federal German Republic

Reciprocal agreements on social security have been signed by Ministers of the United Kingdom and the Federal German Republic One agreement covers unemployment insurance and assistance, and the other covers all other national insurance and *industrial injuries* benefits A *protocol* on health services entitles people who go from the United Kingdom to Germany for employment, and certain groups of national insurance beneficiaries, to take advantage of the German health services in return for the facilities available to Germans in this country The agreements will not come into effect until they have been ratified

Prof W W Mushin is to address the New York State Medical Society at its sesquicentennial celebrations in February, and in March he will be a visiting professor of surgery (anesthetics) at the University of California medical centre in Los Angeles

Appointments

BROOKE, BARBARA M., M B Leeds assistant M O for maternity and child welfare, Leeds
DREW, D W A M R C S , D A assistant anæsthetist (S H M O) Oxford and Banbury area
GOWING, N F C M D Lond pathologist, department of morbid anatomy Royal Marsden Hospital, London
GREVILLE ELINOR M , M R C S , D P H M O school health service Manchester
HARRIS, D W T , M R C S D I H D P M consultant psychiatrist Westwood Hospital and Ashfield House Bradford and other hospitals
KIERS, R Y , M D Edin F R C P E consultant chest physician Cheshire Joint Sanatorium
MACKIE MOIRA R , M B Glasg D I H assistant M O for maternity and child welfare Glasgow
MOLLISON A W M B Glasg clinical pathologist Woodend General Hospital Aberdeen
NEWALL JOSEPH M B Edin M R C P E D M R T consultant radiotherapist Royal Infirmary and Western General Hospital Edinburgh
NOCK PAULINE A L R C P I school M O and assistant M O H Leicester
PHIR G W M B Lond , D I H principal assistant M O H Westminster and Holborn
RANKINE ROBERT M B Glasg S H M O in geriatrics West Fife group of hospitals
SHELDON MARGARET M B Lond assistant chest physician Dudley and Stourbridge group of hospitals
SHIELDS MARGARET A M B Birm deputy M O H and deputy principal school M O West Bromwich
WIXMAN, PHILIP L R C P I , D P H M O H Ilkeston

East Anglian Regional Hospital Board

BASHFORD A L , M B Lond registrar in psychiatry Hellesdon Hospital
BECK G A M B Lond M R C P part time consultant dermatologist King's Lynn Wisbech and Peterborough area
GHIN A K , M B D P M assistant psychiatrist, Little Plumstead group of hospitals
OULTON L A H M B Dubl anæsthetic registrar United Norwich Hospitals

Colonial Appointments

GIDROSI M W T , M B M O Sierra Leone
HASHURST B J M B Edin M O Northern Nigeria
HENLEY A St J M B N U I L R C S surgeon Public Health British Guiana
KEY I A M B Lond M O Tanganyika
McANDREW F J M B N U I M O Northern Nigeria
PARATIAN P M B Glasg M O Mauritius
SNOW, W S L R C S I M O Barbados

PORTACAVAL ANASTOMOSIS

R Milnes Walker
M S Lond , F R C S
PROFESSOR OF SURGERY IN THE UNIVERSITY OF BRISTOL

With illustrations on plate

In a previous communication (Walker 1952) the opinion was expressed that venous shunts had a definite place in the treatment of portal hypertension, and that an end-to-side portacaval anastomosis was the most satisfactory if it could be done As a result of further experience, definite indications for the operation were laid down (Walker 1954), and since that time there has been no reason to modify these indications or the type of operation then advocated Now that more than 50 patients in this department have survived the operation and some of them have been followed for five years or more, the time seems appropriate to review the results

Indications for Operation

The indications adopted may be set down precisely Hæmorrhage from œsophageal or gastric varices due to intrahepatic venous obstruction, and the risk of such hæmorrhage when large varices are present, are the only indications Certain contra-indications may exist in patients who have had such hæmorrhage For example, the liver function may be too severely impaired, the portal vein may be thrombosed or "cavernomatous" and therefore unsuitable for such an anastomosis, or in elderly patients the risk of subsequent thrombosis may be considered too great

These indications and contra-indications can now be reviewed in greater detail That the hæmorrhage comes from varices may be suspected by finding that the patient has an enlarged spleen or ascites, but their presence is usually confirmed radiologically or, on occasions, by œsophagoscopy If varices are present, it may be presumed that they are the source of the bleeding, but in some cases a peptic ulcer is present also, and then it may be very difficult to decide which is the cause

That the venous obstruction is intrahepatic is not so easy to demonstrate, but previous jaundice, ascites, and impaired liver function suggest intrahepatic disease Extrahepatic obstruction, however, may be present at the same time, from thrombosis in the portal venous system It is here that transsplenic portal venography plays an important part in the investigation and selection of these patients because it will indicate the site of the obstruction and show whether the portal vein is sufficiently healthy for the operation (fig 1) This investigation was made on all the patients operated on since 1952 except one who had had his spleen removed The state of the portal vein was indicated so clearly that, in every patient but one in whom the operation was planned, it was possible to complete the anastomosis

The exception was a woman, aged 66, who in 1948 had a cholecystectomy and three years later further exploration of her common bile duct In June, 1953, she had her first hæmatemesis, and between December, 1953, and March, 1954, she bled at short intervals A period of a few days without bleeding was thought to be possibly the last chance for operation, which was attempted in spite of the fact that she bled again just before the anæsthesia was induced Very dense vascular adhesions, the result of her previous operations, led to the abandonment of the operation, and she died after further hæmatemesis next day At her age, and because the bleeding recurred just before operation, a change of plan and a direct operation on the œsophagus would have been a wiser course

Before the use of routine transsplenic venography to localise the venous obstruction 4 patients were explored with a view to a portacaval anastomosis but the operation was impossible because they were found to have complete thrombosis of the portal vein—in 3 secondary to cirrhosis of the liver, and in the 4th due to a primary extrahepatic obstruction In 1 patient, owing to mural thrombi in its lumen, the portal vein was so adherent that it could not be approximated to the inferior vena cava , so a side-to-side anastomosis was made with an autogenous vein-graft to bridge the gap

Without a venogram it is sometimes impossible to distinguish whether the obstruction is intrahepatic or extrahepatic A few patients seemed eminently suitable for a portacaval anastomosis until this radiological investigation showed that they had extrahepatic obstruction and the portal vein was unsuitable for anastomosis (fig 2) On these patients an alternative operation had to be done

A portacaval anastomosis was not advised if there was evidence of severe liver disease, indicated by jaundice, gross ascites, or abnormal liver-function tests Moderate ascites, however, is not a contra-indication The liver-function test to which most weight was attached is the serum-albumin level, and no end-to side portacaval anastomosis in this series was done on a patient whose serum-albumin level was below 3 g per 100 ml at the time of operation Most patients had normal serum-alkaline phosphatase levels, but in 10 the level was above 20 King-Armstrong units, and in 3 it was exceptionally high, though there was no evidence of obstructive jaundice 1 patient, with a level of 43 units, had schistosomiasis of the liver , another, with 51 units, developed postoperative jaundice, which persisted for three months, but still no cause of obstruction was evident , and the 3rd, whose phosphatase level was 62 units, had a stone in the common bile duct, though she had never had jaundice A high serum-alkaline-phosphatase level is therefore no contra-indication to the operation

Flocculation tests were abnormal in about half the cases , this finding is no contra-indication to the operation, but the liver deficiency which they indicate may predispose to neurological complications afterwards Bromsulphalein excretion tests were done on only a few of the patients in the group

Patients

The present series comprises 56 patients who had end to side portacaval anastomoses, and 53 of them survived the operation and left hospital The cause of the fibrosis in the liver is only definitely known in a minority 2 patients had hæmochromatosis , 1 had Wilson's disease , and 1 had schistosomiasis A few gave a history of attacks of acute or subacute hepatitis, but only 2 gave a definite story of alcoholism (1 drank 5 pints of cider and 4 pints of beer daily for twenty years, and the other 7 or 8 bottles of stout daily from the age of 16 to 45) Many were seen within a few months of their first hæmatemesis, but others had had repeated hæmorrhages for periods up to eleven years 3 gave no history of bleeding but complained of either lassitude (2 cases) or diarrhœa (1 case) and were found to have splenomegaly and large varices

2 patients had already had their spleens removed, but the bleeding had recurred with renewed virulence Another had had a splenorenal anastomosis, which had become occluded The ages at the time of the first bleeding ranged from 5 to 53 years and at operation from 7 to 57 years

Operation

In every case the exposure was by a right thoraco abdominal approach through the bed of a rib, usually the ninth, the incision extending across the costal margin The diaphragm was split to allow upward displacement of the liver, the portal vein was divided as high as possible, and its lower end was anastomosed by continuous everting mattress sutures to the side of the inferior vena cava At 48 operations, before the anastomosis was made, the portal pressure was measured either in the portal vein itself or in one of its tributaries, and ranged from 160 mm H_2O to 570 mm H_2O (average 330 mm H_2O) In 8 cases some thrombosis was found in the portal vein, usually an old adherent mural clot, but in 4 cases portions of clot were removed to enlarge the lumen The presence of thrombosis in the portal circulation adds to the severity of the disease, because 2 of these 8 patients died Splenectomy seems to add to the risk of thrombosis, because both patients who had had their spleens removed previously had mural thrombi, and these 2 are the only survivors who have had any serious bleeding since the operation

In many cases, when the anastomosis is completed the turbulence set up by the inflow of portal blood can be seen through the thin wall of the inferior vena cava Anticoagulants were not used as a routine postoperatively Postoperative venography was done on 6 patients only, but all these showed a free flow into the inferior vena cava (fig 3)

Results

All the patients were followed up either by attendance or by correspondence for periods ranging up to five and three quarter years after their operation 3 patients died while still in hospital

(1) A woman, aged 38, had a severe hæmatemesis five months before her operation, previously she had had a subarachnoid hæmorrhage and petechiæ on her legs Her albumin/globulin ratio was 1 1 3 and bromsulphalein retention 22% after one hour On the day after operation she became drowsy and comatose, a tracheotomy was done to ease her breathing, and her state of consciousness varied, but she died on the thirtieth postoperative day At necropsy the anastomosis was patent

(2) A boy had bronchiectasis following an empyema at the age of 14 Hæmatemesis first occurred in 1944 at the age of 23, and during the next eight years he received more than 50 pints of blood, transfusions being necessary on six occasions during the year before his operation His portal vein contained adherent clot, which was removed with difficulty Two days after the operation he became unconscious but recovered fully, only to lapse into unconsciousness again on the twelfth postoperative day, after resuture of his wound, which had partly given way during a bout of coughing He died two days later, and a necropsy was not permitted

(3) A man, aged 45, had had numerous hæmatemeses during the previous two and a half years Two laparotomies had been done, at the first some veins had been ligatured, and at the second an attempt had been made to ligature the hepatic artery Though a lumen was present, his portal vein contained much organised thrombus, and, when the clamp was released, there was only a slow stream of blood When the liver was incised for biopsy, arterial blood spurted out, showing that the hepatic artery was patent This patient became drowsy on the fifth postoperative day and died two days later Necropsy showed extensive thrombosis in the portal system, the anastomosis being almost occluded and the splenic vein entirely blocked Fresh bleeding had taken place from a ruptured œsophageal varix It is clear that this patient was unsuitable for the operation, because the occluded splenic vein would prevent decompression of this part of the portal circulation, in the venograms a large collateral had been mistaken for the splenic vein

5 patients who left hospital have died since 1 of these died of general peritonitis due to a ruptured pyosalpinx four months after her operation, at necropsy the anastomosis was patent The other 4 died as a result of their liver disease

(1) A man had a side to side splenorenal anastomosis without removal of the spleen in 1949, after further bleeding a direct operation on his varices was done in 1951, in spite of this he bled again and his portacaval anastomosis was done in 1951 He died after further hæmorrhage eight months later At necropsy the splenorenal anastomosis was closed, but the portacaval opening was patent without any thrombus The explanation of his death may be that, the splenic vein being thrombosed, the anastomosis did not relieve the hypertension in the spleen

(2) A woman had three severe hæmorrhages in March 1954, for which she was transfused with 12 pints of blood Her other complaints were pain in the right upper quadrant of her abdomen, breathlessness, and a little swelling of her leg Her liver was hard, and radiography showed much calcification in its capsule She also had severe leucopenia (600 white cell per c mm) and thrombocytopenia A portacaval anastomosis was made in May, 1954 She was well for some months but increasing hæmolytic anæmia called for further blood transfusions and, because this was thought to be due to hypersplenism, her spleen was removed in August, 1955 Shortly before this operation she had an episode of hepatic coma lasting three days After the splenectomy the anæmia improved, but she had further episodes of drowsiness, and died in coma in February, 1956 Histological evidence showed that she had hæmochromatosis

(3) and (4) 2 patients died of liver failure thirty three and twenty eight months after operation without any recurrence of hæmorrhage

Apart from the cases referred to already, only 2 patients had any recurrence of hæmorrhage

(1) A man was diagnosed as having anæmia while in the Royal Air Force in 1943 Two years later, after numerous attacks of melæna, his spleen was removed Eight months after this he had the first of a series of hæmatemeses, and a portacaval anastomosis was made in 1951, at that time his portal venous pressure was 300 mm H_2O Slight melæna occurred in 1952, and a year later he had a severe hæmorrhage A direct operation on his varices was undertaken, and in the three years since then he has had two slight hæmorrhages, otherwise he remains well

(2) A man had his first hæmorrhage in 1942 at the age of 19 In 1944 his spleen was removed, but repeated hæmorrhages continued, and he required many blood transfusions In January, 1953, the portacaval anastomosis was made, and at that time a thrombus was adherent to the anterior wall of the portal vein His portal venous pressure was only 160 mm H_2O Only eight weeks after this operation bleeding recurred and, after a severe attack in the following September, a direct operation on his varices was done Since then bleeding has not recurred, œsophagoscopy shows hardly any varices, and he works as a radio engineer

The reason for the recurrence of bleeding in these 2 patients is not clear, but the only 3 patients in this series who have had any significant bleeding after leaving hospital had all had either a splenectomy or a failed splenorenal anastomosis No other patient in the series had had the spleen removed, and no patient who had a portal venous system which had not previously been interfered with has had any serious bleeding since the operation

Complications of Operation

Complications of the operation were, with one exception, rare slight wound infection in a few cases, a pneumothorax once, and transient jaundice The serious complication is the neuropathy associated with portal systemic shunts, whether natural or produced by the surgeon (Sherlock et al 1954) It has already been noted that coma was the cause of death in the 3 patients who died in hospital 9 other patients had episodes of encephalopathy In 1 the only manifestation was excessive salivation, which persisted for two years after his operation but has now subsided 4 had episodes of coma, 1 has already been described (see above), in another the attacks persisted for four months after her operation, and 1 patient had a single attack, five weeks after operation, from which she made a rapid recovery In the 4th of these patients the coma followed partial gastrectomy for peptic ulcer nearly two years after his venous shunt 1 patient was so queer on returning home that her doctor sent her into a mental hospital, but when the nature of her condition was recognised and appropriately treated, she made a complete recovery

3 more had transient mental disorientation, usually soon after returning home, and the patient who died of a ruptured pyosalpinx was definitely slow mentally for the first six postoperative weeks One patient has had periods of depression and mental distress during the three years since her operation, but biochemical tests suggest that she does not fall into this group of hepatic neuropathies

It seems that the danger of these complications is greatest soon after patients return home, and the episode may be precipitated by eating a large protein meal Usually there is a quick response when the patient is put on a protein-free diet, and in most cases a steady return to normal diet can be permitted Patients with defective liver function are much more liable to these complications, but 5 of the 13 who developed neurological symptoms had normal liver-function tests

Two symptoms were noted during the follow-up (1) occasional epistaxis and œdema of the legs occurred in 2 patients and may be the result of the operation or may be caused by the disease of the liver, and (2) 1 patient has ulcerative colitis four years after her operation—an example of the well-recognised association between these two diseases

In the great majority of patients there has been no evidence of deterioration of the function of the liver during the years that they have been followed up, the cirrhosis appears to be static Liver-function tests were made on practically all of them and usually showed little change from the preoperative values Some of the patients had leucopenia and thrombocytopenia before the operation, and this tended to improve slowly, in only 1 case (see above) was it considered necessary to remove the spleen because of continued hæmolysis, thought to be due to hypersplenism The reduction in size of the spleen is most striking within the first day the apex recedes, but after this further reduction is slow and may continue for years, until often it eventually ceases to be palpable Only a few patients had recognisable ascites before operation, and in no case was it necessary to do paracentesis afterwards

Most of the patients are leading normal lives, in the few who are incapacitated, so that they cannot work, the cause is to be found in the associated disease of the liver

Conclusions

As a means of preventing hæmorrhage from œsophageal varices in patients in whom the operation is feasible an end-to side portacaval anastomosis is most effective By careful selection of patients the operative risk is small (3 deaths in 56 cases), and the results are most satisfactory unless some disease is causing progressive deterioration of the function of the liver The most serious drawback of the operation is the neuropathy which may result from a large portal systemic shunt Symptoms, usually transient, develop in about 20% of cases but are rare in those whose liver function is normal

In a follow up extending to five and three-quarter years 2 patients who had previously undergone splenectomy both had a recurrence of hæmorrhage but after an operation on their varices they returned to their occupations There was no recurrence of hæmorrhage from varices in the 50 survivors who had not had a previous operation involving the portal venous system but 4 died subsequently 1 of hæmochromatosis 2 of their cirrhosis, and 1 of unrelated disease Of the 46 remaining 35 have no symptoms and are leading perfectly normal lives and 7 have been operated on too recently to be back at their occupations

This series of cases shows that an efficient end-to side portacaval anastomosis will greatly reduce the risk of further hæmorrhage in cases of portal hypertension due to intrahepatic disease

My thanks are due to so many people who have coöperated in the management of these patients that I cannot mention them all, so I refer only to the sisters, nurses, and house-surgeons who have given them such great care and the doctors—specialists and general practitioners—who have entrusted me with the care of their patients and assisted in following them up Part of the cost of the recording manometer used was defrayed by a grant from the Medical Research Council

REFERENCES

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Walker R M (1952) *Ibid* i 729
— (1954) *Ann R Coll Surg Engl* 14 145

"PNEUMOCYSTIS CARINII" PNEUMONIA

T Bird
M.D Durh
LECTURER IN PATHOLOGY IN THE UNIVERSITY OF ST ANDREWS

J Thomson
M.B Edin, F.R C.P.E
CONSULTANT PÆDIATRICIAN, ROYAL INFIRMARY, DUNDEE

With illustrations on plate

From the atypical pneumonias of infancy, European observers have separated a specific clinical and pathological entity which they called interstitial plasma-cell pneumonia This disease, as seen on the Continent, affects chiefly premature and immature weakly infants, aged 2–5 months, many of whom have been in institutions for some time Although it is sometimes preceded by diarrhœa or an acute infection of the upper respiratory tract, its onset is generally insidious, mild ill health being followed by respiratory upset with tachypnœa, dyspnœa, and cyanosis, these increase gradually or rapidly, and death, if it happens, occurs with extreme asphyxia Cough is trivial The objective findings are curiously slight, thus there is little or no fever, and clinical examination of the chest may reveal nothing abnormal In striking contrast with this is the radiological picture which shows obvious mottled opacity, sometimes even before respiratory symptoms have appeared The illness lasts 1–6 weeks, occasionally longer The variation of the reports on mortality, from 15 to 100%, no doubt reflects the difficulty of clinical diagnosis Histopathological diagnosis has in recent years become more certain, the two main features being an intra alveolar "exudate" of unusual foamy or granular appearance and thickening of alveolar septa by an infiltrate of mononuclear cells often rich in plasma-cells The ætiology is still very much a matter of debate, and the term "pneumocystis" pneumonia has come into use on the basis of one of the ætiological hypotheses (see below)

Most of the published cases have been in Switzerland, Czechoslovakia, Germany, and Finland, where pneumocystis pneumonia is considered a relatively common disease, in these countries small epidemics have also occurred, of five to twenty cases, usually in hospital wards The disease next appeared, or was recognised, in Italy, Hungary, Sweden, Denmark France, and Holland, but thus far usually as sporadic cases Its first mention in America was in 1955 (Lunseth et al 1955), and a detailed study of a case followed in 1956 (Dauzier et al 1956) Five cases have now been described in Canada (Donohue 1956, Gagne and Hould 1956) The first case to be published in England was seen by Baar (1955), who later in that year recognised from the photomicrographs (Hutchison 1955b) that a case of congenital agammaglobulinæmia in Glasgow reported by Hutchison (1955a) had the characteristic pulmonary changes

During the past year two children have died in Dundee with a clinical and pathological picture which we believe conforms with this curious disease, although both children were older than is usual in the Continental cases

The Illness

FIRST CASE

A male infant, aged 9 months was admitted to Dundee Royal Infirmary on July 23, 1955, because of recurrent vomiting, failure to gain weight, a cough for 3 months, and a discharge from the right ear for 1 month

He had been born by spontaneous breech delivery at term, weighing $6^3/_4$ lb Fed on National dried milk, he had always had a poor appetite and gained weight slowly, and latterly he had seemed to be wasting Vomiting started at the age of 7 weeks and came on thereafter for periods of about 2 weeks, with free intervals of the same duration, it was sometimes forceful and happened during or after feeding When 3 months old he had a frank convulsion, and in the succeeding 3 months he had attacks in which his limbs stiffened and his eyes rolled up At 6 months he developed a cough, which persisted without remission until he was admitted to hospital Both parents, who are not related, and four older children are all in normally good health, with normal chest radiographs

On admission he was poorly nourished, looked toxic, and weighed 14 lb 3 oz He was apyrexial but moderately dyspnœic, with respirations 40–50 per min Muscle tone was poor The gums were red and inflamed, and he had a few shallow white ulcers on his palate The alæ nasi moved with respiration, and there was slight intercostal indrawing Percussion note and air entry were normal throughout the chest, but occasional crepitations were heard at both bases Chest radiography showed diffuse fluffy mottling throughout both lung fields (fig 1)

Course in Hospital

A diagnosis of bronchopneumonia was made and treatment with penicillin and sulphamezathine was begun

There was little improvement during the next week, cough being persistent, vomiting still fairly frequent, and the X-ray picture unchanged Streptomycin was substituted, and there was some improvement for the next 12 days, but radiography showed increased mottling (fig 2) On Aug 12 the baby's condition changed rapidly, with dyspnœa, tachypnœa, and cyanosis His pulse and respiration rates rose, and he died on Aug 18

Laboratory Investigations

The white cell count on admission was 31,000 per c mm, with a preponderance of neutrophils, hæmoglobin 12 g per 100 ml, and erythrocyte sedimentation rate (E S R) 10 mm in 1 hour (Wintrobe) Nothing abnormal was found in the urine, and lumbar puncture revealed normal cerebrospinal fluid The Mantoux reaction was negative (1 2000), and no tubercle bacilli were found in gastric washings Stool examinations for tryptic activity were positive, and repeated culture of the stools did not produce any pathogens

The white cell count settled around 12,000 per c mm (differential count normal), and the E S R remained at 10 mm in 1 hour *Staphylococcus aureus* was grown on one occasion from throat swabs, but fungi were not isolated

The most striking findings in this infant were the negative physical signs in the chest, in contrast to the increasing dyspnœa and cyanosis, and the gross radiological changes throughout the illness

SECOND CASE

A male infant, aged 11 months, was admitted to Arbroath Infirmary on Jan 18, 1956, because of cough which had persisted for 3 months

He was born at term and weighed 9 lb 7 oz Everything seemed normal then, and he was breast fed for 9 months His only illness was infantile eczema, because of this he was not vaccinated or otherwise immunised Both parents are healthy and have normal chest X rays There had been two other children, both male The first died in 1952, aged 4 months, with *Shigella sonnei* dysentery, and the second died in 1954, aged 5 months, with gastro enteritis associated with *Escherichia coli neopolitanum 055* and pneumonia No necropsies were performed

When 8 months old he developed a running nose, and the discharge soon became yellow and purulent Cough appeared and persisted 6 weeks before admission he had an attack of wheezing, shortness of breath, and pyrexia This was treated with penicillin and chloramphenicol orally with considerable improvement but the cough persisted 3 days before admission he developed thrush in his mouth and became restless and feverish with rapid breathing

On admission he was an ill child, irritable and poorly nourished There was slight dehydration and hypotonia He had fever (103°F) with respirations 50 per min, but there was no dyspnœa or cyanosis The percussion note was impaired over the right chest anteriorly, and pneumonia of the right middle lobe was demonstrated radiologically (Dr T Sprunt)

Course in Hospital

Penicillin and sulphadimidine were given His temperature fell to normal within 48 hours, and there was rapid resolution of physical and radiological signs in the chest His general condition improved, but his cough persisted and after 7 days radiography showed diffuse fluffy mottling throughout both lung fields, most marked towards the hilum with relatively clear peripheral fields During the next 2 weeks these changes increased despite the absence of physical signs (fig 3), and pneumocystis pneumonia was tentatively diagnosed

He was transferred on Feb 11 to Dundee Royal Infirmary, where treatment was continued with courses of penicillin sulphamezathine, streptomycin, erythromycin, and tetracycline, with no obvious benefit His clinical condition remained unchanged without causing undue anxiety, but radiography showed progressive pulmonary changes (fig 4) Hypogammaglobulinæmia was first sought and found on Feb 21 2 days later his condition changed rapidly, and he became dyspnœic, with respirations up to 90 per min and a pale greyish cyanosis, relieved only by oxygen

Gamma globulin was given intramuscularly in doses of 1 g to a total of 6 g during the next 12 days with no apparent effect

Because of the pattern of the illness, with tachypnœa dyspnœa, cyanosis, and negative physical signs, but gross radiological changes and failure of response to antibiotics we felt more confident of the diagnosis of pneumocystis pneumonia He was given pamaquin 2 mg five times daily for 6 days, followed by mepacrine 25 mg twice daily for 6 days and for 2 days by 'Infant Acetylarsen' 1 ml daily (Dvorak and Jirovec 1953) Chloramphenicol was substituted for other antibiotics (Eberle et al 1955)

From the time of this dramatic change in his condition he steadily deteriorated and was cyanosed whenever out of oxygen On Feb 26 he developed transient clubbing of the fingers and toes for 4–5 days

The temperature, white cell count, and E S R remained normal The picture was now one of steadily increasing asphyxia (fig 5) The infant became gradually thinner, more fretful, and apprehensive, and on March 18 he developed subcutaneous emphysema over his neck and upper chest, with bilateral pneumothorax He died next day

Laboratory Investigations

On admission to Dundee Royal Infirmary his white cell count was 10,000 per c mm (differential count normal) hæmoglobin 14 8 g per 100 ml, and E S R 4 mm in 1 hour (Wintrobe) His urine was normal on several occasions, and proteinuria was never found

Extensive investigation of his blood chemistry showed no abnormality In view of the association reported between interstitial plasma cell pneumonia and hypercalcæmia (Hallman et al 1954) it may be noted that the plasma calcium level

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LEGENDS TO ILLUSTRATIONS ON PLATE

DR BIRD, DR THOMSON

Fig 1—Case 1 (July 23, 1955) bilateral opacities radiating from hila and diffuse finer nodular opacities

Fig 2—Case 1 (Aug 8, 1955, ten days before death) increase of opacities and interstitial change, especially in left upper zone

Fig 3—Case 2 (Feb 10, 1956) bilateral poorly defined shadows radiating from hila

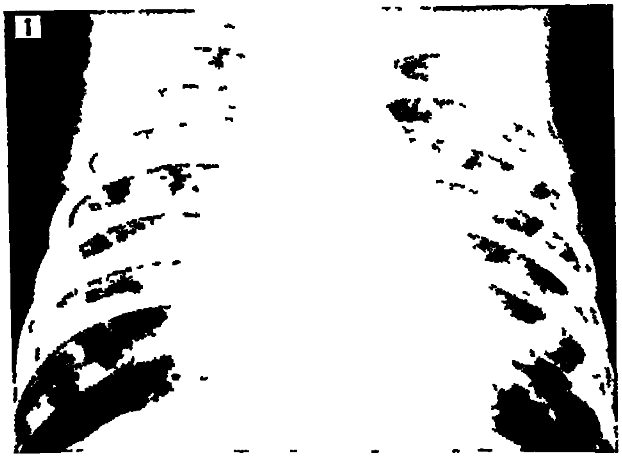
Fig 4—Case 2 (Feb 28, 1956) increase of opacities especially in upper zones, tending to become confluent.

Fig 5—Case 2 (March 6, 1956 twelve days before death) opacities now more confluent and there is diffuse consolidation

Fig 10—Case 2 silver impregnation (Le Tan Vinh 1954) showing intra alveolar mass containing cysts Note septal reticulin well stained but erythrocytes and cell nuclei not stained by this method (× 636)

Fig 11—Case 2 imprint from lung showing cysts containing spherical bodies (Giemsa × 1858)

DR BIRD AND DR THOMSON "PNEUMOCYSTIS CARINII" PNEUMONIA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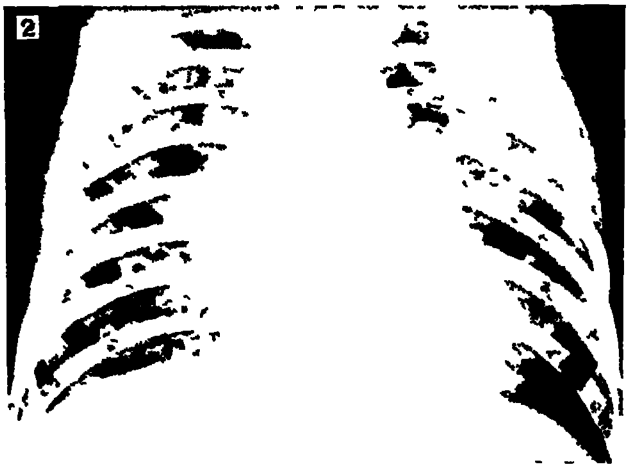
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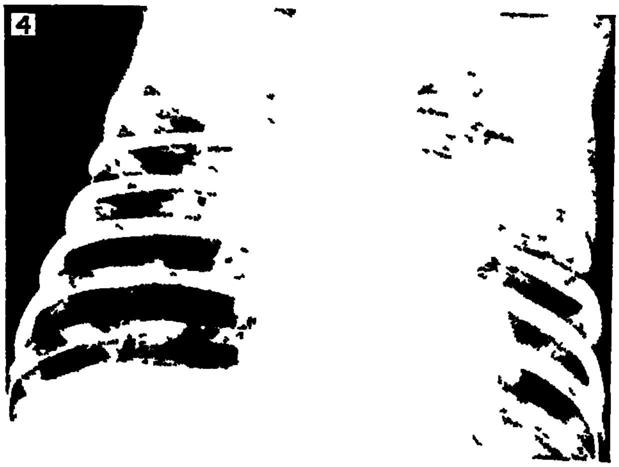
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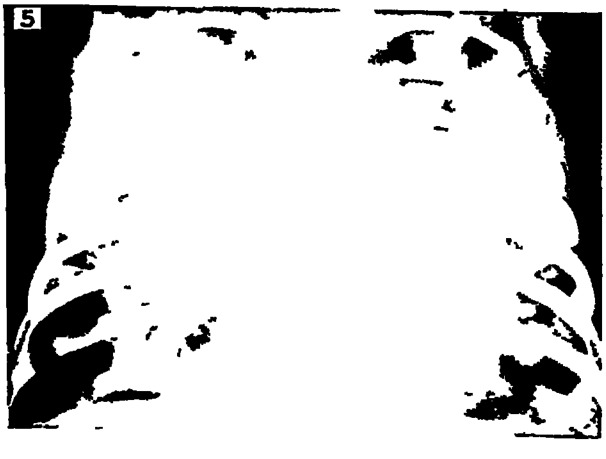
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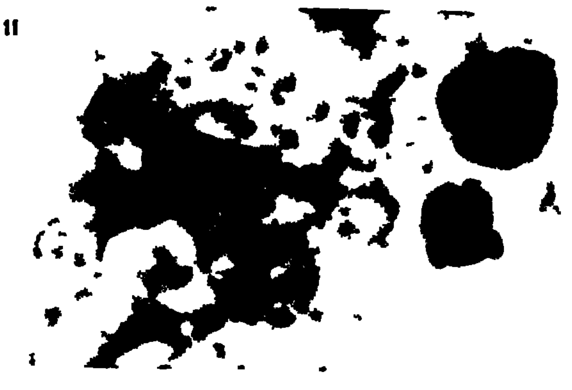
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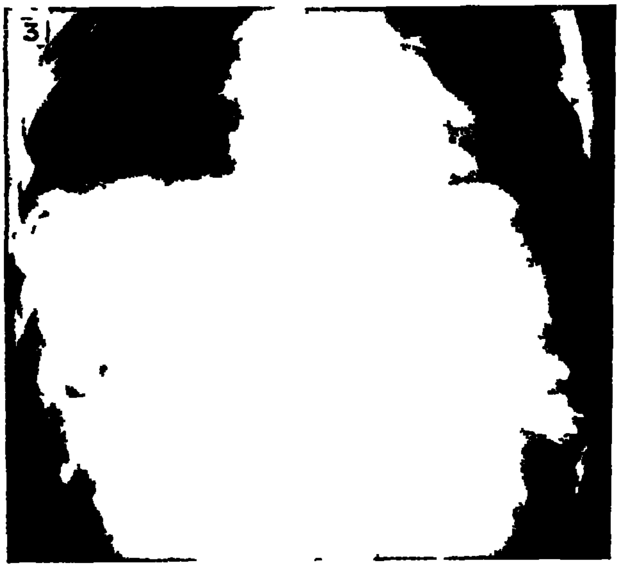
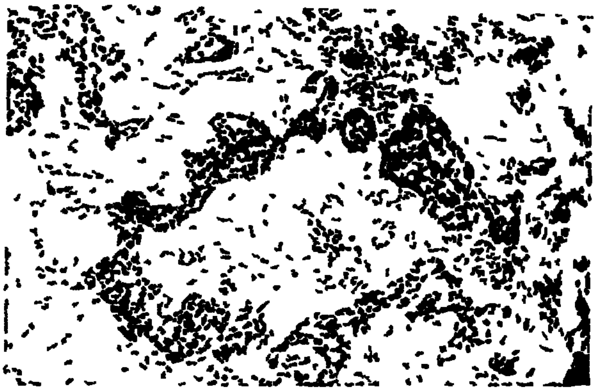
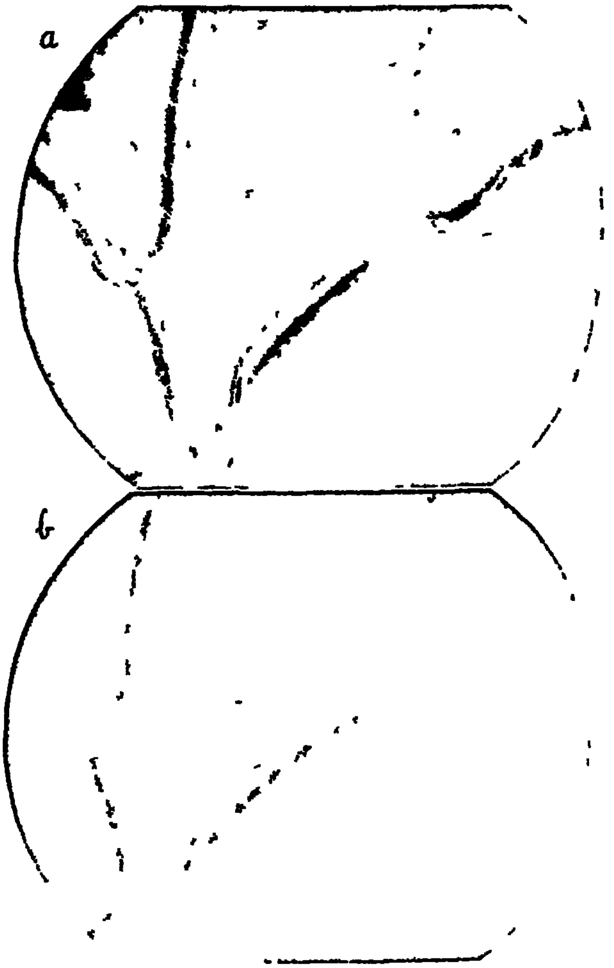
PROF MILNES WALKER PORTACAVAL ANASTOMOSIS



PROF GILLMAN AND OTHERS ALLOXAN



DR SNOW SLUDGING OF BLOOD



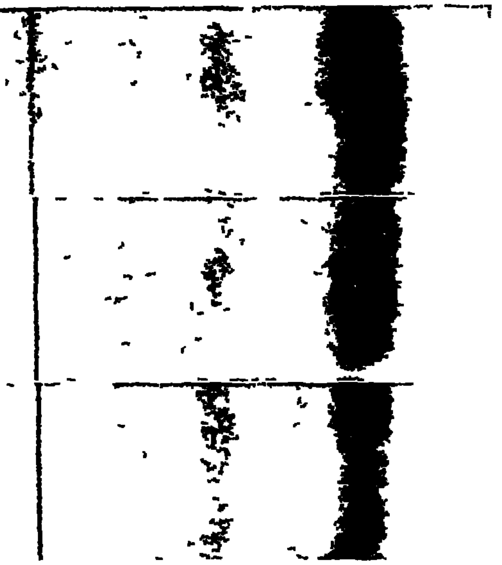


Fig 6—Top register "normal" infant aged 12 months, middle register case 2 showing absence of gamma globulin (Feb 21, 1956), bottom register case 2, after intramuscular gamma globulin 6 g showing no obvious change (March 6, 1956)

was only 9 8 mg per 100 ml and the plasma phosphorus level 4 2 mg per 100 ml on two occasions

Pancreatic trypsin was demonstrated in the fæces on several occasions The white cell count varied from 7000 to 10,000 per c mm, and differential counts showed a slight increase of polymorphonuclear cells The hæmoglobin was always more than 14 g per 100 ml

Staph aureus, resistant to all antibiotics tried, was twice isolated from the nose During the last week *Esch coli neapolitanum 0119* was isolated from the stools, but there was no diarrhœa

Serum proteins were low from the time of admission The total was never more than 4 9 g per 100 ml, the albumin varying from 3 2 to 3 4 g and the globulin from 1 5 to 1 7 g Paper electrophoresis (fig 6) on Feb 21 showed an absence of gamma globulin, confirmed on following days, and chemical fractionation (Wolfson et al 1948) revealed levels of about 75 mg per 100 ml (Miss R Haslock) There was a slight increase of alpha 1 and alpha 2 globulin The normal level of gamma globulin at the age of 12 months is 450–700 mg per 100 ml (Moore et al 1949, Corbiel et al 1954) and rises to the adult level of 1000–1200 mg in later childhood

No changes were noted during the remainder of the illness after the administration of gamma globulin in large doses, apart from an increase in alpha 1 globulin

Electrophoresis and chemical fractionation of both parents' serum gave normal findings

The blood group was O Rh-positive, and no iso agglutinins anti-A or anti-B could be demonstrated at 4°C, room temperature, and 37°C by the methods recommended by Dunsford (1953) (Dr F S Graham)

Comment on Radiographs (Dr C Pickard)

A widely disseminated granular lesion of the lung fields but detailed examination shows the opacities to have a fluffy irregular outline, unlike the discrete characteristics of miliary lesions There is no evidence of hilar glandular enlargement The pattern progresses to more widespread and confluent fluffy opacities The general impression is of a disseminated alveolar lesion becoming lobular and ultimately widespread

Post-mortem Findings

FIRST CASE (Dr H G Morgan)

Examination 16 hours after death A slightly dehydrated infant, the only significant gross findings being in the lungs There was no pleural reaction or fluid, and both lungs showed an identical appearance, being finely nodular throughout all lobes, with no predilection for any site The pattern suggested bronchopneumonia, but even the smallest of the visible bronchi appeared unaffected Most of the nodular areas were 1–3 mm in diameter, whitish, and firm, and the intervening lung was firmer and drier than normal, with small areas of emphysema The larger bronchi contained a little mucus but no pus or aspirated material The paratracheal and bronchopulmonary lymph-nodes were not enlarged

Culture of lung tissue produced a growth of pneumococci and *Candida albicans*

Other organs showed no abnormality, and there was no lymphadenopathy or splenomegaly The middle ears contained no pus

Microscopy

In the nodular areas described in the lungs there is a diffuse interstitial infiltration of mononuclear cells, including plasma-cells, with only occasional polymorphs The alveoli and alveolar ducts are filled with a weakly eosinophilic exudate of granular, foamy, or honeycomb appearance The sponge-work is brilliantly fuchsinophil with the periodic acid Schiff reaction, but is completely negative for fibrin, mucin, and glycogen (fig 7) With the Schiff method, Giemsa's stain, or toluidine blue, many of the clear spaces, particularly at the periphery of the honeycomb, are seen to contain one or more free lying tiny granular bodies In most places the intra alveolar exudate is quite acellular, but there is frequently a prominent alveolar lining with cuboidal cells Desquamated cells occasionally seen in the exudate sometimes contain finely granular fat or Schiff-positive granules In other places the exudate appears to have undergone necrosis, and the peripheral cells then are of foreign-body giant cell type In these small granulomatous foci the necrotic exudate has taken up calcium, but this is rare and not likely to be the explanation of the severe and widespread radiological change Between the nodular areas of consolidation the lung shows a *moderate* diffuse infiltration of the alveolar septa by a mononuclear cell infiltrate, associated often with areas of emphysema There is no evidence of cytomegalic or other inclusion bodies

Sections made from other viscera, including lymph nodes, spleen, and bone marrow, are all normal, and there is no evidence of inclusion disease in pancreas, kidney, or salivary glands The lymph nodes from numerous sites are small, containing only a few primary, and no secondary, follicles Smears and sections from the nodes, spleen, and bone marrow show only a very occasional plasma cell In the kidneys an occasional tiny focus of calcium deposition is seen in collecting tubules, sometimes associated with a slight granulomatous reaction

SECOND CASE

Examination 2 hours after death showed a thin wasted cyanotic infant, with subcutaneous emphysema over the chest

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LEGENDS TO ILLUSTRATIONS ON PLATE

PROF MILNES WALKER

Fig 1—Venogram showing intrahepatic obstruction in man, aged 24, who had had two severe hæmorrhages Note filling of œsophageal varices and a healthy portal vein

Fig 2—Venogram showing extrahepatic obstruction in woman aged 23, who had a severe hæmatemesis with no previous symptoms Extensive varices were present, but, before venography there was no indication that the obstruction was extrahepatic.

Fig 3—Venogram after portacaval anastomosis in same patient as in fig 1

PROF GILLMAN AND OTHERS

Fig 2—Case 2 sclerotic primary tumour representative of the liver at necropsy (×72)

Fig 3—Case 2 characteristically sclerotic metastasis in abdominal lymph-nodes (×72)

DR. SNOW

Retinal vessels *a*, uncompressed *b* during compression

To slow the stream sufficiently for photography, relatively firm pressure was applied to the eye by the patient himself hence the appearance of sludging in the arteries as well as the veins When the photograph was taken, the E S R was 50 mm in one hour, and the serum globulin level 5 g per 100 ml A diagnosis of Hodgkin's disease was established three months later

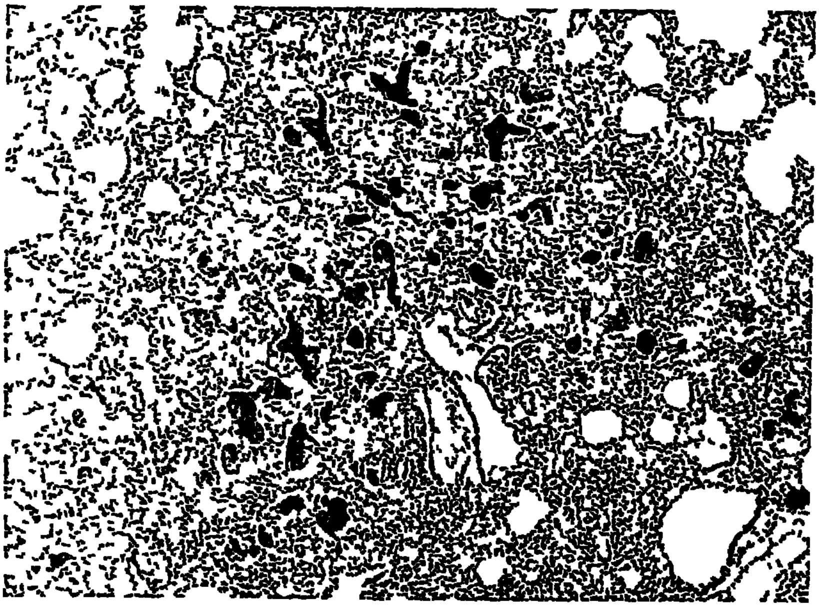

Fig 7—Case 1 lung showing "exudate" as dark masses in alveoli and as grey granular material in bronchiole Note thickening of alveolar septa by cellular infiltrate (Periodic acid Schiff × 60)

posteriorly and reaching up to the root of the neck Gross changes were confined to the thorax There was bilateral pneumothorax, but the lungs were bulky and retained their shape The pleural surfaces were normal apart from occasional small subpleural hæmorrhages and interstitial emphysema, and there were collections of air at the hila, extending behind the parietal pleura to reach the neck

The lungs were pinkish-white and diffusely firm, with a rubbery consistence, and all the lobes were equally affected Only the margins obviously contained air, and here occasional subpleural spaces up to 0 5 cm in diameter were seen Throughout both lungs the lobular pattern was accentuated, and, with the colour and consistence, resembled pancreas or thymus—suggesting the term "pancreatisation" The bronchi contained a little viscid mucus, their cut surface was rather dry, and only a little serous fluid was obtained on scraping

The paratracheal and bronchopulmonary lymph nodes were small There was a mild thrush œsophagitis, and the only other striking feature was the striking deficiency of lymphoid tissue throughout the body, though the spleen was of normal weight No abnormality was seen in other organs

Microscopy

The changes in the lungs are essentially the same as in case 1, but more widespread and uniform There are no areas of necrosis and granulomatous change, and no plasma cells are seen in the interstitial infiltrate (figs 8 and 9) The lungs therefore resemble more closely the Continental descriptions except for the absence of plasma cells

There is no evidence of inclusion disease of parasites in the other viscera The lymph nodes, spleen and bone marrow are similar to those in case 1, but no plasma cells can be seen

Sections and material were sent to Professor Hamperl (Bonn), Professor Vanek (Prague), Dr Le Tan Vinh (Paris), and Dr E K Ahvenainen (Helsinki) all agreed that this was the disease they had described and were willing to accept the absence of plasma cells as in some way associated with hypogammaglobulinæmia Using the modified del Rio Hortega method of Le Tan Vinh (1954) we have succeeded in showing in sections the cysts described by him and shown by Hamperl (1956b) by phase contrast microscopy in smears (fig 10) Dr Le Tan Vinh was kind enough to stain and study our material and said that he regarded the cysts as pathognomonic

We hope to describe the microscopy of this disease more fully elsewhere, but meanwhile it may be said that the interstitial changes are moderate, plasma cells are not the predominent type in either case, and the pathognomonic feature in both cases is the intra-alveolar spongework (see below) It is generally agreed that the responsible organisms are best seen in lung imprints In our hands Giemsa's stain gave the best results, and fig 11 shows the appearance in smears made at necropsy The honeycomb structure apparent in the sections is again seen, but in addition there are more obvious cyst like structures, 5–9 µ in diameter, containing small round bodies which are uniformly basophilic Routine cultures and injection of lung extracts into guinea pigs and rabbits did not produce pyogenic bacteria or fungi

Discussion

Clinical Definition

The clinical definition of this disease is likely to become sharper with the advent of the new histopathological criteria The question, however, will probably remain whether all the many cases described in the past as interstitial plasma cell pneumonia were the very specific anatomical entity which at present goes under the name of pneumocystis pneumonia

Clinically characteristic of the fatal cases is the fact that the radiological changes, from an early stage in the disease, are of a striking degree and quite out of proportion to the symptoms and signs There is a complete lack of response to antibiotics, and later an increasing oxygen starvation Laboratory methods do not yet give any real help in diagnosis, though Vivell (1954) and Navratil et al (1954) have claimed good results with complement fixation tests using extracts of lung from proven cases Braestrup (1956), however, thinks that there is little to be gained clinically by further diagnostic analysis during life We can liken the situation to that

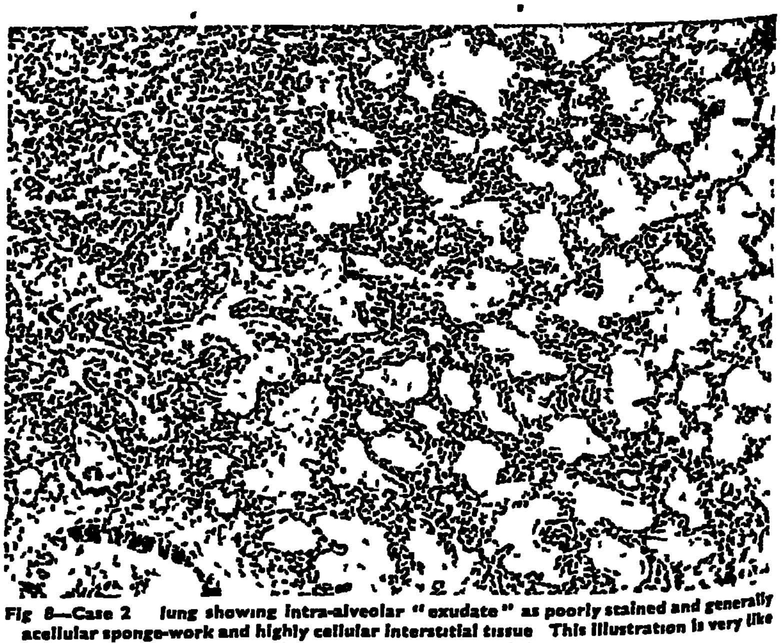

Fig 8—Case 2 lung showing intra-alveolar "exudate" as poorly stained and generally acellular sponge-work and highly cellular interstitial tissue This illustration is very like fig 3 of Hutchison (1955a) (Hæmalum and eosin × 70)

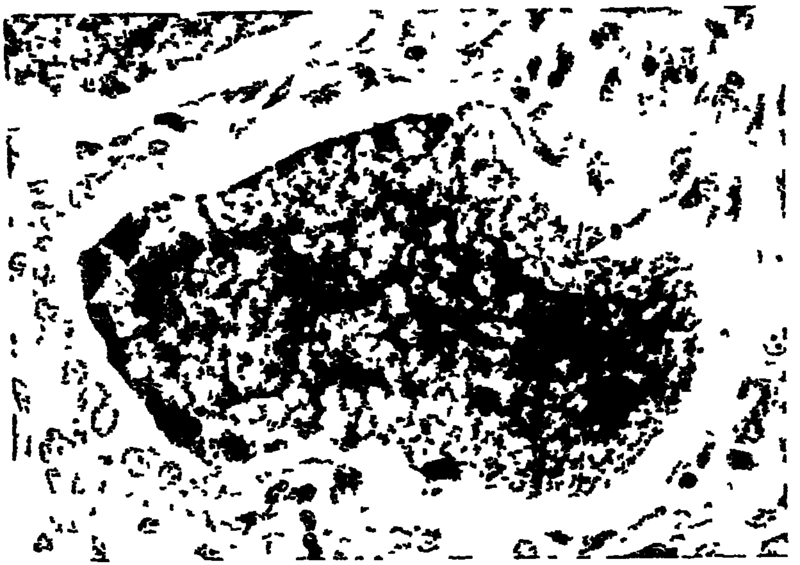

Fig 9—Case 2 details of intra-alveolar honeycomb and its constituent cysts. Note prominent alveolar lining (Periodic acid-Schiff × 479)

of leprosy thirty years ago, where the morbid anatomy was clear cut and accurately indicated the diagnosis, an organism was known but could not be satisfactorily incriminated, and treatment was both empirical and ineffective

Ætiology and Therapy

The only practical knowledge yet available is the reported occurrence of epidemics among infants in hospital, and the Continental workers believe that prophylactic segregation is of value (Reiseterbauer and Braun 1955, Hamperl 1956b) Tobler (1956) claims that the disease has been eliminated in his unit in Switzerland by the use of ultraviolet ray sterilising-lamps in the nursery cubicles for premature infants Many agents have been tried in treatment of the established disease, but the value of none has been confirmed The antiprotozoal drugs (pamaquin, mepacrine, emetine, and organic arsenicals) have been commended by Vanek et al (1953), fungicidal drugs by Petersen (1953), and chloramphenicol by Eberle et al (1955) Gamma-globulin has also been recommended (Sternberg and Rosenthal 1955), but this, like the other therapies, proved of no value in our hands

Morbid Anatomy of the Lungs

The original descriptions of interstitial plasma-cell pneumonia were not very sharply drawn and did not separate it from non-specific chronic inflammation The recognition of the peculiar character of the intra-alveolar exudate (Ammich 1938, Benecke 1938, Vanek and Jirovec 1952) now allows a definite diagnosis to be made post mortem Having observed two cases in Dundee within a short time, we naturally wondered how many cases had been missed After all, this is a widespread disease on the Continent and Switzerland, with its population of 7 million, had 700 cases in 1941–49 (Deamer and Zollinger 1953), while Jirovec (1954) estimates the number of cases in middle Europe at about 500 in 1951–53 A study of 218 infantile cases of pneumonia coming to necropsy in Dundee in 1935–55, and of the comparable cases in Newcastle upon Tyne in 1945–51, did not reveal a single example Baar's experience in Birmingham (Baar 1955) also suggests that the disease is new to Britain

Intensive study of the intra alveolar "exudate" as the probable site of the infective agent has produced a sharp division of opinion On the one hand, there is strong support (Hamperl 1952, 1956a and b, Herzberg et al 1952, Le Tan Vinh 1954, Baar 1955) for the view of Jirovec and Vanek (1954, 1956) that the "exudate" is a mass of protozoa (*Pneumocystis carinii*) On the other hand is the view that the infection is fungal Csillag and Brandstein (1954) favour blastomyces, whereas Simon (1953) believes it to be an unusual form of candida occurring in debilitated people The most likely is perhaps saccharomyces (Bruns and Bottger 1955), which Schmid (1955) believes to be able to form not only the intra alveolar masses but also the cyst like structures which supporters of pneumocystis claim to confirm their view Saccharomyces has been grown by Schmid (1955) from cases with this curious sponge-work in their alveoli, but the pneumocystis has not been cultured or transmitted or defined in any way other than by visual observation of smears, imprints, or sections

Pneumocystis carinii

This protozoon was described first by Chagas (1911) and later by Carini and Maciel (1915) in the lungs of guineapigs infected with *Trypanosoma cruzi and T lewisi* It was later seen by Delanoe and Delanoe (1912) in the lungs of rats without trypanosomes, these workers recognised that this was a separate organism and named it *Pneumocystis carinii* (Wenyon) The cycle of pneumocystis has been studied extensively by Vanek et al (1953), who describe it as a round or an oval mass of chromatin, 1–3 μ in diameter, enclosed in a mucous capsule 5–10 μ in diameter The organism reproduces by division into 2, 4, 6, and finally 8 spore-like structures within a thickened cyst-wall The hosts now known include rats, mice, dogs, cats, goats, and sheep, and the distribution is world-wide

Pneumocystis carinii has been found in the lungs of adult humans with pneumonia associated with Hodgkin's disease (Vanek 1952), myeloid leukæmia (Jirovec and Vanek 1954), and cytomegalic inclusion disease (Hamperl 1956a) In a fourth adult it was found without pneumonia (Van der Meer and Brug 1942) It has also been found in older children aged 5 years by Dr Pavlica (Prof J Vanek, personal communication) and 2 years (Le Tan Vinh 1954) dying with pneumonia in association with neoplastic disease of the reticulo endothelial system.

Most of the Continental workers (Le Tan Vinh 1954, Hamperl 1956a, Jirovec and Vanek 1956) favour the pneumocystis as the causal agent of this peculiar pneumonia of infants

The evidence incriminating *Pneumocystis carinii* is not, in our view, complete enough to absolve other organisms—e g, a fungus such as saccharomyces Our reason for using the name "pneumocystis" in the title of this paper is our inability to coin a more neutral adjective which would be familiar to those who have already studied the disease, would indicate this very specific anatomical change, and would be as easily pronounced

Associated and Predisposing Abnormalities

The disease is almost confined to infancy, and most of the infants affected have been premature, immature, or otherwise weakly There seems to be no special seasonal prevalence The rarity of cases after the first 6 months of life, and the odd fact that the reported adult cases all had a disease involving the reticulo-endothelial system, naturally suggest that an alteration of plasma-globulins has some predisposing influence

The plasma gamma-globulin level is known to be lowest in the normal infant at about the 3rd month, thereafter the waning of the supply received from the mother is countered by intrinsic formation It is not known whether the weakly infant has a longer period of diminution of circulating gamma globulin Infants with pneumocystis pneumonia do not show a serum-protein pattern different from that in unaffected controls (Vanek 1956), but Vanek (1956) does not mention the subdivisions of the gamma globulins, and perhaps antibody activity is particularly localised in the subfraction gamma 2 (Martin 1954) The suggestion of a relation between plasma proteins and pneumocystis pneumonia (Gormsen 1950) was reinforced by Baar's (1955) recognition that the lung illustrated in Hutchison's (1955a) report of a case of congenital agammaglobulinæmia was that of pneumocystis pneumonia This observation gains significance by the finding in case 2 of an almost complete absence of gamma-globulin from the plasma In our other case, and in Hutchison's (1955a) first case the plasma-proteins were unfortunately not estimated, but the fact remains that of the four cases of pneumocystis pneumonia observed in Scotland, two had so-called agammaglobulinæmia

Diminution of gamma globulin therefore seems likely to be a significant predisposing factor in the development of pneumocystis pneumonia Indeed it is possible that the four cases in Scotland occurred because the infants had exceptionally little gamma-globulin In two of the cases there was no estimation to support this view, but all four infants were males, and congenital agammaglobulinæmia (strictly speaking it is hypogammaglobulinæmia) is perhaps confined to males (Good and Zak 1956), and sections from Hutchison's (1955a) patients, aged 6 months and 20 months, which Dr A M MacDonald, pathologist to the Royal Hospital for Sick Children, Glasgow, was kind enough to send us, show the same virtual lack of plasma cells as do the Dundee cases In both these respects the Scottish cases are unusual, because on the Continent the sex-incidence is equal in pneumocystis pneumonia, and the cellular infiltrations are composed mainly of plasma cells, a deficiency of plasma cells is known to be characteristic of congenital hypogammaglobulinæmia The absence of hæmagglutinins in the two present cases adds further support to this view (Good and Zak 1956) The case reported by Dauzier et al (1956) was in a boy aged 21 months, and the history of recurrent pyogenic infections of the respiratory tract suggests that this was a comparable case, unfortunately there is no mention of the serum-proteins

We do not wish to emphasise unduly the suggestion that all four cases were examples of this congenital inability to form gamma-globulin, but the two proven cases raise another interesting point Usually hypogammaglobulinæmia in infants is characterised by recurrent bacterial infections, especially of the respiratory system and the skin (Bruton 1952, Good and Zak 1956), and these pyogenic infections have been controlled by intramuscular administration of gamma globulin On the other hand, in all four Scottish cases there was, at necropsy, a remarkable absence of any sign of pyogenic infection, and we suggest that the organisms in the alveolar spongeworks, be they protozoa or fungi, may have been producing some substance inhibiting pyogenic bacteria Admittedly antibiotic therapy had been given, but in Hutchison's (1955a) first case and in one of ours the disease was well established before such therapy was begun

Conclusion

The disease widespread in Central Europe and known originally as interstitial plasma cell pneumonia of infancy is now recognised as an intra-alveolar infection due either to a protozoon, *Pneumocystis carinii* or to a fungus, possibly saccharomyces

Five cases have now been reported in Britain of what we may in the meantime reasonably call pneumocystis pneumonia If this disease is becoming more prevalent, increasing awareness of the possible diagnosis in atypical pneumonias of infancy may lead to more definite information about the cause

Summary

Two fatal cases of pneumocystis pneumonia in infant are described Of the four now reported from Scotland, two showed extreme deficiency of gamma globulin ("agammaglobulinæmia"), and three of the infants were older than is usual in the Continental cases

Pneumocystis pneumonia is characterised clinically by progressive tachypnœa, dyspnœa, cyanosis, and minimal clinical signs with gross radiological changes On this basis we made a confident provisional diagnosis in one case *during life*

Histologically the changes agree closely with those seen in the interstitial plasma cell pneumonia of the European Continent

Intra alveolar networks and cysts are present, identical with those described by some as the causal protozoön, *Pneumocystis carinii* and by others as a pathogenic fungus

Attempts to isolate the causal agent were unsuccessful

We are grateful to Prof A C Lendrum for his help and criticism during the preparation of this paper Our thanks are also due to Mr J W Corkhill for the illustrations, to Sister M D Crichton for her special care of the infants, and to all those colleagues mentioned in the text, who have been most generous with their help

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THE SLUDGING OF BLOOD IN THE RETINAL VEINS

A LITTLE-KNOWN PHYSICAL SIGN

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With illustrations on plate

It is the purpose of this paper to call attention to an ophthalmoscopic sign consisting of visible sludging or clumping of the red cells in the retinal veins when the blood-flow has been slowed by pressing on the eye The sign is non-specific, but, since it is usually associated with organic disease, its presence may be helpful in prompting further investigation of patients who are thought to have no organic disease or who have an unconvincing history and physical signs

Elicitation of Sign

The vessels at the optic disc are viewed through an ophthalmoscope, and pressure is exerted with the thumb of the free hand on the lateral aspect of the upper eyelid Usually the pressure causes slight medial movement of the eye, but with a little practice distortion of its shape, which interferes with ophthalmoscopy, can be avoided The pressure required is only enough to induce partial diastolic collapse in the retinal arteries Attention is transferred to the retinal veins, where, if the sign is positive, the column of blood becomes at first granular and then forms into larger discrete particles which move slowly towards the disc (see figure) The time required for these to become obvious is usually about 5–8 seconds, and there is no point in prolonging the pressure if no response has been elicited The rate at which the clumps pass along the veins varies with the pressure on the eye, but, as soon as flow speeds up, they immediately disintegrate

After fairly lengthy pressure a slightly granular appearance in the retinal vessels may be induced even in some apparently healthy persons (particularly in women during menstruation), but only the formation of separate coarse granules is considered to have pathological significance

In practice there is usually little doubt as to what constitutes a positive result, indeed it is not until some familiarity with the sign has been established that lesser degrees of granularity are appreciated

Results

The present series comprises 90 patients in whom sludging was seen by me on one or more occasions That sludging occurs only in certain conditions is shown by the fact that it was not seen in 31 healthy people (15 males and 16 females) or in 150 outpatients with the following disorders

Disorder	*No of cases*	*Disorder*	*No of cases*
Functional disorders	33	Angina of effort	6
Peptic ulcer	17	Infection of renal tract	6
Neoplasm	9	Hiatus hernia	5
Chronic bronchitis	8	Miscellaneous	51
Spondylosis	8		
Hypertension	7	Total	150

Because of the obvious similarity of the phenomenon to the erythrocyte sedimentation rate (E S R), and since it was first seen by me in multiple myelomatosis, both the E S R and the serum globulin level were estimated to discover whether they had any relation to sludging, and also to provide objective indices of abnormality other than the clinical impression of disease

The E S R was estimated by Wintrobe's (1946) method, the upper limits of normal being taken as 12 and 20 mm in one hour for males and females respectively, and the serum globulin was estimated by Reinhold's (1953) method, the upper normal limit being 3 5 g per 100 ml

Of the 90 patients with sludging 79 had definite organic disease, as follows

Disease	*No of cases*	*Disease*	*No of cases*
Active tuberculosis	17	Systemic lupus	3
Carcinoma	10	Reticulosis	3
Cirrhosis	6	Leukæmia	2
Bronchiectasis	6	Myocardial infarction	2
Myelomatosis	5	Ulcerative colitis	2
Pyrexia of undetermined origin	5	Miscellaneous	10
Pneumonia	4		
Rheumatoid arthritis	4	Total	79

In 11 no disease was found 62 patients had raised E S R —above 30 mm in one hour in 49 of them In 5 no figures were obtainable 55 patients had raised serum-globulins —above 4 g per 100 ml in 35 of them Either or both the E S R and the serum-globulin were raised in 73 patients

Of the 11 patients who had no definite organic disease all had normal E S R, and all but 1 had a normal serum-globulin 2 of these 11 patients were pregnant, and another was first seen during the puerperium Sludging was not present in this latter patient when reviewed three months later Ploman's (1920) studies of this phenomenon were made mainly on pregnant women, and I have seen it in pregnancy on several occasions, so probably the effects of pregnancy were responsible for the sludging in the 2 pregnant women mentioned above

4 other patients, reviewed at intervals varying from three to twelve months, showed no alteration in the sludging or any satisfactory explanation of it, but 1 of them had serum-globulin levels of 3 9 and 3 6 g per 100 ml over an interval of twelve months

4 other patients did not attend for review, but 1 of them was known to be menstruating when seen, and this may explain the sludging, because I have observed it during menstruation in some (but not all) healthy women who do not show it during the intermenstrual period

Of the 90 patients in the series, therefore, there were only 7 in whom no explanation for the sludging has yet been found

Discussion

Agglutination of the formed elements of the blood in the retinal veins into macroscopically visible particles was observed by Reimar (1899), who did not correlate the phenomenon with the patient's disease Independently of this observation, Fahraeus, as a result of his studies on the suspension stability of the blood, suggested to Ploman the possibility of observing rouleaux formation in vivo in the retinal veins Ploman (1920) confirmed this and correlated the rate of formation of visible " clumps " with the E S R, but since then there seems to have been no further interest in the phenomenon in the retinal veins, although Wintrobe (1946) mentions its occurrence in myelomatosis An extensive literature, summarised by Knisely (1951), has, however, accumulated on the sludging of blood in conjunctival and similar capillaries This is almost certainly the same phenomenon as that observed in the retinal veins, but, because of the relatively elaborate apparatus required and ill-understood significance of sludging in vessels of this size, it has little clinical application at present

Sludging in the retinal veins, on the other hand, is easily elicited and, being apparently much less sensitive than its capillary counterpart, has some clinical value

The phenomenon is essentially qualitative, for, although Ploman tried to make it semiquantitative by timing the appearance of agglutinated particles, this is actually impracticable because they do not suddenly appear but build up gradually with no definite end-point Moreover their rate of formation is affected by the rate of blood-flow and hence by the variable pressure on the eye

I shall not here consider the factors responsible for sludging, and the E S R and the serum-globulin estimations were mainly in the hope of providing objective indices of abnormality other than the clinical impression of disease In fact the E S R and/or the serum-globulin levels were raised in about two-thirds of the patients, but both were also found raised in the absence of sludging, and the relation is evidently not close A better correlation existed between sludging and the clinical condition, and sludging sometimes seems to be a more sensitive index of disease than either of these laboratory tests

It must be admitted, however, that apparently false positive results may occur, for 11 of the patients had no obvious disease, although pregnancy in 2 and menstruation in 1 of these was almost certainly responsible

It should also be emphasised that not all diseases are associated with sludging, and that its absence does not imply the absence of organic disease

The value of the test is therefore limited, but, if pregnancy and menstruation are excluded as causes, the large majority of patients showing sludging will be found to have organic disease

A surprising feature was the high proportion of patients who turned out to have either active tuberculosis or cancer, and it is clear that sludging may occur in a wide variety of diseases other than myelomatosis, which, so far as I know, is the only specific disease in which sludging in the retinal veins has hitherto been described (Wintrobe 1946)

In most patients the presence of organic disease was all too obvious and did not need confirmation 14 patients, however, had complaints which were thought at first to be functional or of a simple non inflammatory nature, and the finding of sludging suggested further investigations, which in each case disclosed a more serious unsuspected lesion, usually tuberculous or neoplastic

The following 3 case reports illustrate this application of the sign

Case-reports

Case 1 —A man, aged 25, presented with a four week history of severe sciatic pain attributed to a prolapsed intervertebral disc The presence of sludging, however, was not in keeping with a purely mechanical cause for his pain, and further investigation revealed tuberculosis of the right sacro iliac joint

Case 2 —A woman, aged 28, was admitted with hæmatemesis Sludging was noted after she had recovered from this and did not seem to be adequately explained by a peptic ulcer Radiography revealed a gastric ulcer and active pulmonary tuberculosis

Case 3 —A man, aged 55, presented with left sided chest pain for which no cause was at first found Radiography was normal At a second attendance a month later sludging was observed, and the patient was admitted for further investigation, which disclosed erosion of the pedicle of the fourth thoracic vertebra, not previously present and eventually found to be due to a metastatic adenocarcinoma

Summary and Conclusions

Sludging or clumping of the red cells in the retinal veins when the blood stream is slowed was observed in 90 patients It was found almost exclusively in certain diseases, or in pregnancy and (to a lesser extent) during menstruation It was sometimes associated with a raised erythrocyte sedimentation rate and a raised serum-globulin level, but it may occur independently of either Its sphere of usefulness is similar to that of the E S R, for it appears to be a fairly reliable indication of organic disease It can, however, be elicited immediately and has been found to be particularly useful in bringing to light unsuspected organic disease in patients with few or unconvincing symptoms

I wish to thank Prof Robert Platt and Dr H T Howat for permission to study their patients

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"ESSENTIAL" FATTY ACIDS, DEGREE OF UNSATURATION, AND EFFECT OF CORN (MAIZE) OIL ON THE SERUM-CHOLESTEROL LEVEL IN MAN *

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The serum cholesterol level in man can be lowered by substitution of carbohydrate for the common meat and dairy fats in the diet, and this effect does not depend on the intake of cholesterol itself (Keys 1953, 1954, Keys et al 1950, 1955, 1956) Different food fats, however differ in their effect, and certain vegetable oils may depress the serum cholesterol level (Ahrens et al 1954 Bronte Stewart et al 1956, Friskey et al 1955, Kinsell et al 1952)

Ahrens et al (1955) found corn (maize) oil particularly effective, and they suggested that the effects of dietary fats on the serum cholesterol level in man depend on the relative degree of saturation of their constituent fatty acids But corn oil has a relatively high content of the "essential" fatty acid linoleic acid, so it is intriguing to speculate on whether hypercholesterolæmia is an expression of a deficiency of essential fatty acid in the diet—a deficiency that could be corrected by the consumption of a fat, such as corn oil, rich in linoleic acid (Bronte-Stewart et al 1956, Kinsell et al 1956, Sinclair 1956)

One result of such considerations is enthusiasm for food fats even richer in linoleic acid, and/or more unsaturated than corn oil, as agents for combating hypercholesterolæmia and so, it is hoped, for preventing atherosclerosis and coronary heart-disease We have urged caution about premature conclusions in this direction (Keys 1953), but already there is commercial interest in sunflower seed oil, as a very rich source of linoleic acid, and in fish oils as the most unsaturated of the food fats The fish industry is heartened by imaginative statements that coronary heart disease is absent in Eskimos and rare in Norwegians because of their consumption of marine oils (Sinclair 1956), though actually the incidence of coronary heart disease among Eskimos is entirely unknown and the disease is anything but rare in Norway

Fish oils contain little or no linoleic acid and only minute amounts of arachidonic acid, so, if they were in fact more effective than corn oil in reducing serum cholesterol this would support the view that unsaturation is responsible If, on the other hand, sunflower seed oil were more powerful in decreasing blood cholesterol, this would suggest that linoleic acid is the active agent Obviously a direct comparison between corn, sunflower, and fish oils is essential

Present Experiments

We have examined these and related questions in dietary experiments with physically healthy men in a completely controlled metabolic research unit of the Hastings State Hospital, and present here a summary of data on corn oil versus sunflower seed oil, corn oil versus fish oil, and a final comparison with butter fat, as regards

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TABLE I—CHARACTERISTICS OF OILS TESTED

Item	Corn oil	Sunflower-seed oil	Sardine oil	Butter fat
Iodine number	120	131	188	32
Linoleic acid content	45%	61%	0–2% (?)	3%

the serum-cholesterol level Characteristics of the oils used are given in table I The iodine numbers were determined in this laboratory, and the linoleic-acid content values are those published for samples of these fats of similar iodine number

The test oils were fed in quantities of 100 g daily as part of a diet constant in all other respects and designed to provide an average of 100 g of proteins, 300 mg. of cholesterol and 40 g of mixed food fats in addition to the test oil Calorie balance was maintained by individual adjustments in bread and jelly, and a fixed level of physical activity was maintained throughout The subjects were 26 schizophrenics selected for physical health, metabolic normality, and demonstrated cooperativeness

Before the experiments with these oils the men were all maintained at calorie balance on a fixed diet for several months, including a stabilising period of four weeks with 100 g of butter fat The men were divided into four groups matched as to age, relative obesity, and habitual level of voluntary activity. The design of the experiment with the test oils is shown in table II Groups W and X contained 7 men each, and groups Y and Z contained 6 men each

The mean values of the four groups for age, initial and final body-weights, and daily consumption of calories are given in table III For the entire 26 men the mean body-weight changed only by 0 19 kg from the start to the end of the tests, demonstrating the accuracy of the calorie equilibrium maintained by the diets

TABLE II—EXPERIMENTAL DESIGN FOR FEEDING CORN OIL, SUNFLOWER SEED OIL, SARDINE OIL, AND BUTTER FAT

Inclusive dates	Group			
	W	X	Y	Z
June 8–21	Corn	Sunflower	Corn	Sardine
June 22–July 5	Sunflower	Corn	Sardine	Corn
July 6–21	Butter	Butter	Butter	Butter

Samples of blood were drawn at the end of each week and analysed for serum total-cholesterol (in duplicate) and the cholesterol in the α and β lipoprotein fractions of the serum, separated by paper electrophoresis The methods have been described by Anderson and Keys (1956) Here, for the sake of brevity, it is enough to consider only the mean blood-cholesterol levels at the end of the second week on each diet, the levels at the end of the first week are similar and show, as we have found before (Keys et al 1950), that a large part of the cholesterol response to a change in diet is produced in the first week

TABLE III—MEAN VALUES FOR EXPERIMENTAL GROUPS JUNE 8–JULY 21

Item	W	X	Y	Z
Age (yr)	46 4	46 8	48 4	48 7
Initial body weight (kg)	69 7	67 3	65 7	66 2
Final body weight (kg)	70 0	67 1	66 2	66 6
Intake of calories daily	3375	3391	2922	3074

Results

The average serum cholesterol level on the butter-fat diet was 216 9 mg per 100 ml All the groups had significantly lower serum cholesterol levels on the corn-oil diet, the average difference being 45 1 mg per 100 ml for the W and X groups and 60 0 mg for the Y and Z groups The serum cholesterol levels were also lower on the sunflower seed-oil diet ($\Delta = 35$ 8 for W and X groups) and on the sardine oil diet ($\Delta = 39$ 8 for Y and Z groups) These differences were primarily due to changes in the β-lipoprotein-cholesterol level The most interesting results, however, are for the direct crossover comparisons summarised in table IV

In the change of 7 men from corn oil to sunflower-seed oil, and in the reverse change made simultaneously with the other 7 men, the serum total-cholesterol was higher on the sunflower-seed oil than on the corn oil, the difference being statistically significant at about the 1% level of probability In groups Y and Z the serum cholesterol level was higher on sardine oil than on corn oil, the difference being highly significant ($t = 5$ 38, and, at 11 degrees of freedom, $P < 0$ 001) As in the case of the comparisons with butter fat, the cholesterol in the β-lipoprotein fraction seems to be primarily involved in the total cholesterol differences, the percentage of the total cholesterol found in the β fraction tends to be lowest when the men are on the corn-oil diet

TABLE IV—DIFFERENCES IN SERUM TOTAL CHOLESTEROL LEVEL AND IN PERCENTAGE OF TOTAL CHOLESTEROL IN THE β-LIPOPROTEIN FRACTION OF SERUM

Diet comparison	No of men	Total cholesterol (mg per 100 ml)	% of total cholesterol in β lipoprotein
Corn-sunflower	14*	−9 29 ±2 81	−1 08 ±2 16
Corn-sardine	12	−20 17 ±3 75	−4 25 ±1 34

* For total cholesterol 12 men only for β-lipoprotein (one value missing in each of the groups W and X)

The net result is that both sardine oil and sunflower-seed oil are more, rather than less, cholesterol-increasing than is corn oil Or, to put it the other way round, corn oil has the greatest cholesterol-depressing effect of the fats tested The attempt to discover whether the high content of essential fatty acids or the high degree of unsaturation is responsible for the cholesterol depressant action of corn oil had the surprising result of showing that corn oil is remarkable in some way not measured by either of these two characteristics

Discussion

While the above findings were being belatedly summarised for publication, Jones et al (1956) reported, in cholesterol-fed chicks, an anti cholesterol effect of corn oil, and still more so of corn germ, and provided evidence that this effect cannot be explained on the basis of the fatty acid composition of the oil The results of other experiments on animals had cast serious doubt on the validity of both the unsaturation and the essential-fat hypotheses of the control of the serum cholesterol level (Lin et al 1955, Swell et al 1955) Unfortunately the differences between animal species in the metabolism of fat and cholesterol make it dangerous to extrapolate from such experiments to man It is not possible to state, for example, what may be the relevance to man of the interesting observation that rabbits fed a diet high in peanut oil but low in saturated fat and devoid of cholesterol slowly develop progressive hypercholesterolæmia and, within a year, atherosclerosis (Steiner and Dayton 1956) Perhaps this finding is most significant as a warning against judging the ultimate cholesterogenic and atherogenic effects of diets on the basis of short time experiments

It is interesting to ask what may be the relevance of the present experimental findings to the fact that low serum-cholesterol levels are characteristic of human populations who habitually subsist on low-fat diets (Keys 1953, 1954, Keys et al 1955) Are such low serum-cholesterol levels explained by the low-fat diets, or do relatively high intakes of essential or highly unsaturated fatty acids contribute to the picture? The intake of linoleic or combined polyethenoic fatty acids in the average American diet is about twice that in the typical low-fat diets of Japan and Italy, which are associated with average serum cholesterol levels of only about 150–200 mg per 100 ml No natural human diets approach the situation of the present experiments where 50–60 g of linoleic acid was ingested daily (in the experiments with corn oil and sunflower-seed oil) or where fish oils accounted for nearly 30% of the total calories Even among the fish eating Japanese no more than 2–3% of the total calories is supplied in the form of fish oils

As populations increase the fat content of their diets, they do so by consuming more saturated *and* unsaturated fats, though the increase in the latter is smaller It seems, then, that among most of the populations of the world the characteristic serum-cholesterol levels are directly related to the total consumption of fat rather than inversely related to the consumption of essential or highly unsaturated fatty acids And, if we are to advocate dietary alterations on a population scale to control the serum cholesterol level, it seems wiser to attempt to reverse the trend towards more and more luxurious high-fat diets than to advise consuming more vegetable and fish oils as a counter measure But in so far as there is simply a choice of the kind of fat to be used, corn oil may have special virtue

Summary

Serum total and β-lipoprotein cholesterol levels were measured in rigidly controlled experiments on 26 men in calorie balance on a diet constant in all respects except for the character of test fats—corn oil, sunflower seed oil, sardine oil, and butter fat—which were fed in quantities of 100 g daily Other mixed food fats in the diet amounted to 40 g daily, and total fats represented 39 8% of the total calories

The mean serum total cholesterol level on the butter-fat diet was 52 0 mg per 100 ml higher than on the corn-oil diet, 35 8 mg higher than on the sunflower seed oil diet, and 39 8 mg higher than on the sardine oil diet

The serum total cholesterol level rose after the change from corn oil to sunflower seed oil and fell after the reverse change, the average difference being 9 3 mg per 100 ml

The serum total cholesterol level rose after the change from corn oil to sardine oil and fell after the reverse change, the average difference being 20 2 per 100 ml

The level of cholesterol in the β-lipoprotein fraction of the serum was primarily involved in the above changes

These findings do not support the view that the serum-cholesterol level in man is a simple inverse function of the essential fatty acid content or of the degree of unsaturation of the fatty acids in the diet

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EFFECT OF HYPOTENSIVE DRUGS ON RENAL FUNCTION IN CHRONIC RENAL DISEASE

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High blood-pressure is one of the commonest and mo t serious complications of all forms of acute and chronic primary renal disease The possible mechanisms involved in the production of such hypertension have recently been reviewed (Wilson 1953) Therapeutic reduction of the blood-pressure is justified by the well established experimental evidence that hypertension may cause renal vascular damage and progressive deterioration in function Secondary hypertensive lesions in the kidney constitute the most serious prognostic factor in certain forms of chronic Bright's disease and probably play an important part in the development of the malignant type of hypertension which occurs in many cases

Within recent years the medical treatment of hypertension has become feasible, following the introduction of different drugs which effectively lower blood pressure Many reports describe the satisfactory use of these drugs, but analysis of these shows little correlation between treatment and the ætiology of the hypertension in the individual case Most are concerned solely with the hypotensive effect of the drugs, and apparently most of the cases of hypertension so treated were of the essential variety without impairment of renal function

Nevertheless a diagnosis of the underlying cause is essential for accurate prognosis and rational therapy The rôle of hypertension varies considerably in different forms of renal disease, and treatment that might be beneficial in some cases may well be harmful in others

The indications for lowering blood-pressure may be classified as symptomatic or prophylactic

Symptomatic indications include heart-failure (both the acute left ventricular and the chronic congestive varieties), encephalopathy, and retinopathy In this paper we have used the term retinopathy to indicate at least the presence of retinal hæmorrhages and exudates We believe that, in renal disease, the appearance of these retinal changes whether or not visual impairment is present, constitutes an absolute indication for lowering the blood-pressure The advent of papillœdema indicates the onset of the malignant phase of hypertension, and, in the absence of therapy, rapid deterioration due to renal vascular damage, heart-failure, or encephalopathy is inevitable Heart-failure may reduce *glomerular filtration* and lead to nitrogen retention in chronic renal disease, *hence* its relief by hypotensive therapy may well lead to improvement in renal function The *prophylactic indications* call for prolonged observation and treatment Here th

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aim of therapy is to prevent deterioration in renal function caused by the secondary effects of hypertensive vascular damage to the kidney and to delay the onset of the malignant phase

To assess the results of treatment it is imperative to take into account the natural history of untreated renal hypertension The exact nature of the renal lesion is important for the course and prognosis of different forms of nephritis vary greatly It is important also to estimate the relative contributions of nephritis and hypertension to the progress of the disorder in the individual case

Many patients with chronic renal disease live for years with normal renal function and slight or moderate hypertension Chronic type I nephritis in its slowly progressive course (Ellis 1942), may behave in this way, and so also may chronic pyelonephritis When eventually incapacitating symptoms appear these are usually of hypertensive rather than renal origin After many years of slight or moderate hypertension, a relatively steep rise in blood-pressure commonly occurs, accompanied or followed by a rapid deterioration in renal function If no active steps are taken to reduce the blood-pressure, malignant hypertension supervenes in about half the cases, in the remainder a more slowly progressive uræmia develops Fig 1 illustrates a typical case of this "hypertensive transformation" (Wilson 1955)

Some patients with kidney disease present a different picture In them there is obviously a continuing active glomerulonephritis, indicated by anæmia, microscopic hæmaturia, and frequent granular casts in the urine Here the primary renal condition has evidently a more significant effect on the natural history of the disease than have secondary hypertensive changes Although, in these patients, hypotensive therapy may be necessary to control encephalopathy or retinopathy, the same degree of benefit is not to be expected as in the previous group It is particularly in the more severe cases of type-II nephritis that this progressive inflammatory element is found, and in such cases deterioration of renal function may antedate the terminal rise in blood-pressure

With these considerations in mind we studied the effect on renal function of lowering the blood-pressure in patients with hypertension and renal impairment We wanted, first, to determine whether normotension could be achieved without provoking acute deterioration in renal function; this was readily established in a series of comparatively short-term observations Secondly, patients with renal hypertension were observed for longer periods in an attempt to discover whether the usual deterioration in renal function could be retarded or even halted, and whether the onset of hypertensive complications, particularly the malignant change, could be prevented Thirdly, we were interested to see whether the different types of renal disease described above differed in their response to hypotensive therapy

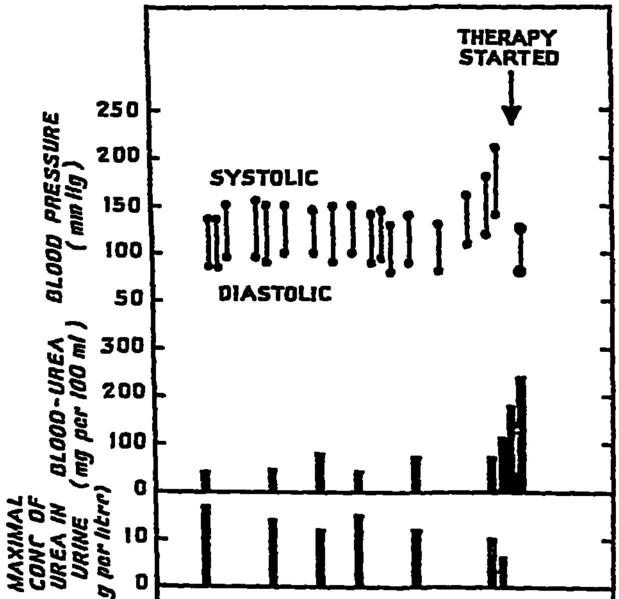

Fig 1—Case 17 chronic type-II nephritis showing rapid deterioration of renal function associated with rise in blood-pressure Although hypertension was controlled, renal failure was progressive

Clinical Material and Selection of Cases

All the patients reported in this series were treated in the nephritis clinic of the London Hospital and selection followed the indications outlined above Treatment was instituted either for the relief of acute hypertensive manifestations, such as heart-failure, encephalopathy, and retinopathy, or for prophylactic purposes In the former group the hypertension was usually severe when the patient was referred to us, and renal impairment and retinopathy were often present In most of these patients the diagnosis was chronic type-I nephritis Patients with type-II nephritis, on the other hand, had usually been under observation for months or years with normal renal function and little or no hypertension This afforded a good opportunity for correlating the development of hypertension with change in the renal function and for starting treatment when the blood-pressure began to rise Some of these patients were free from symptoms when hypotensive therapy was begun

Observations were made on 32 patients—16 with chronic type-I nephritis, 7 with type II nephritis, 4 with other forms of renal disease, and 5 with essential malignant hypertension The last-named are included for comparison with primary renal disease Renal function was impaired in all the cases at the time therapy was begun The clinical details and particular indications for treatment are listed in tables I–IV

Methods

Treatment followed standardised lines Initially ganglion-blocking agents alone were used—always by injection—and pentolinium ('Ansolysen') was the drug of choice More recently we have used reserpine ('Serpasil') in combination with ansolysen by mouth or 'Ecolid' (4 5 6 7-tetrachloro-2-(2 dimethylamino ethyl) iso-indoline dimethochloride) also by mouth All the patients were admitted to hospital for preliminary investigation and initial therapy Their blood-pressures were recorded hourly throughout the day in the standing and lying positions After about a week hypotensive drugs were administered and further blood-pressure curves were obtained, the dosage of the ganglion-blocking agent being gradually increased until an optimal effect was gained

The regime was varied to suit the patient's requirements and idiosyncrasies, sometimes the blocking agent was given twice and sometimes thrice daily, but always at least half an hour before food We found it unnecessary to give more than 1 mg of serpasil daily in divided doses and often 0 25 mg twice daily sufficed In a few cases serpasil alone proved effective, but there appears to be no means of foretelling such a response

Renal function was measured before therapy was started and again after two to four weeks, when optimal lowering of blood pressure had been achieved After discharge from hospital the patients were seen monthly in the outpatient department, and renal function tests were repeated at regular intervals Any cardiac deterioration, or improvement, was checked by serial electrocardiograms and chest radiographs We used the blood-urea level, urine urea concentration, and creatinine clearance as tests of renal function, being well aware of their inherent fallacies

Experience has shown that, in the individual case, this group of tests, performed at regular intervals, satisfactorily indicates the general trend of renal function Reliance should not be placed, however, on any individual reading, for discrepancies arise from variations in urine output, superimposed extrarenal retention of nitrogen, or incomplete emptying of the bladder

Results

Control of Blood pressure

High blood-pressure due to renal disease responds to hypotensive drugs in much the same way as essential hypertension, and there seems to be no greater resistance to therapy Indeed some patients are remarkably sensitive to these drugs, possibly owing to delayed excretion (Harington 1953)

Our results suggest that papillœdema responds more rapidly than in malignant essential hypertension, in all the cases of primary renal disease reported here papillœdema had subsided within a month of treatment being started

Most patients with malignant essential hypertension require larger doses of hypotensive drugs than are needed to control renal hypertension We have rarely had to give more than a total of 200 mg daily of ecolid by mouth together with 0 5–1 0 mg of serpasil, and normotension has often been attained with a lower dosage In our cases of essential malignant hypertension 400 mg of ecolid daily has sometimes proved insufficient, even when combined with serpasil, and papillœdema has been correspondingly refractory

We believe that the blood-pressure should be brought as near normal as possible in all cases, the dose being progressively increased to the limit of the patient's tolerance

Immediate Effect of Lowering Blood-pressure on Renal Function

In tables I–IV are listed the renal function and blood pressure immediately before treatment, and again after two to four weeks in hospital, when optimal control of blood-pressure had been achieved Such observations were available in 14 patients with chronic type I nephritis The blood-urea level did not change significantly in 10 cases, rose in 3, and fell slightly in 1 The other tests of renal function showed substantially the same results In

TABLE I—SHORT-TERM EFFECTS OF HYPOTENSIVE THERAPY IN CHRONIC TYPE-I NEPHRITIS

Case no	Sex	Age (yr)	Blood pressure (mm Hg)	Indications for therapy	Drugs used	Renal function †			
						Before and after treatment			Interval ‡ (weeks)
						Blood urea (mg per 100 ml)	Max conc urea in urine (g per 100 ml)	Creatinine clearance (ml per min)	
1	M	39	240/160	Retinopathy *	1 Ansolysen inj 2 Serpasil, Ansolysen } oral	59 57	1 45 2 5	87 58	4
2	M	60	240/140	Retinopathy	Serpasil, Ecolid }	57 60	1 08 1 5	49 58	2
3	M	52	220/120	Rising B P	Serpasil	197 159	0 55 0 6	5 6	2
5	M	54	210/145	Papillœdema	Serpasil, Ecolid }	95 125	1 0 1 4	25 45	4
7	M	54	250/170	Papillœdema Congestive heart failure	1 Ansolysen inj 2 Serpasil, Ansolysen } oral	72 70	1 3 1 8	35 96	4
8	M	39	190/115	Retinopathy	Serpasil, Ansolysen } oral	45 73	1 3 1 5		4
9	M	70	300/180	Retinopathy	Ansolysen inj	136 134	1 58 0 8	53 34	4
10	F	27	220/140	Retinopathy	Serpasil, Ecolid }	45 50	1 44 1 2	45 44	2
11	F	21	240/140	Papillœdema	Ansolysen inj	105 95	1 2 1 4	24 23	4
12	M	45	235/150	Papillœdema	Serpasil, Ecolid }	90 80	1 7 1 2	25 40	4
13	M	42	230/160	Retinopathy, lt heart failure	Ansolysen inj	57 60	1 7 1 8	42 50	4
14	M	53	240/140	Rising B P	1 Ansolysen inj 2 Ansolysen, oral	159 155	0 6 0 6	23 16	3
15§	M	48	270/170	Papillœdema	Ansolysen inj	88 99	1 1 2 2	53 31	4
	,	49	260/170	Papillœdema	Ansolysen inj	71 117	1 4 1 7	29 26	4
16	M	40	200/140	Rising B P	1 Serpasil, Ansolysen } oral 2 Serpasil only	40 45	1 25 1 4	75 90	4

* "Retinopathy" denotes presence of exudates or hæmorrhages or both

† Normal values (*a*) blood urea upper limit 40 mg per 100 ml , (*b*) maximal concentration of urea in urine lower limit 2 g per 100 ml (*c*) creatinine clearance lower limit 80 ml a minute

‡ "Interval" is the time separating the two sets of observations before and after treatment

§ Case 15 was treated in two episodes of malignant hypertension a year apart

TABLE II—SHORT-TERM EFFECTS OF HYPOTENSIVE THERAPY IN RENAL HYPERTENSION FROM CAUSES OTHER THAN GLOMERULONEPHRITIS

Case no	Sex	Age (yr)	Diagnosis	Blood-pressure (mm Hg)	Indications for therapy	Drugs used	Renal function			
							Before and after treatment			Interval (weeks)
							Blood-urea (mg per 100 ml)	Max conc urea in urine (g per 100 ml)	Creatinine clearance (ml per min)	
24	M	56	Polycystic disease	260/185	Congestive heart failure	Serpasil Ecolid	171 180	0 5 0 6	22 22	2
25	F	22	Amyloid kidney	200/125	Lt heart-failure	Serpasil Ecolid	126 120	0 6 0 4	11 18	2
26	M	26	Pyelonephritis	265/170	Papillœdema	Serpasil Ecolid	50 60	1 2 1 6	70 70	4
27	M	35	Amyloid kidney	195/120	Rising B.P	Ansolysen inj	51 51	1 4 1 6	36 44	3

the great majority of cases of type-I nephritis, therefore, hypotensive therapy had no immediate harmful effects

The same may be said of the results obtained in renal hypertension from causes other than nephritis (table II, cases 24–27) and in malignant essential hypertension (table III, cases 28–32) There was no evidence in these groups that lowering the blood-pressure was detrimental to renal function, and neither the age of the patient, the sex, the degree of hypertension, nor the extent of renal impairment at the start of therapy seemed to make any difference to the result

In type-II nephritis, however (table IV, cases 17–23), the results were somewhat different There were 7 patients in this category, and in 4 the renal function was definitely worse after this short period of treatment, whilst in 3 it was unchanged 1 patient (case 17) died in uræmia two months after therapy was begun Lowering of the blood-pressure probably played little part in this deterioration, for in all 4 cases where it was observed there had been a rapid worsening of renal function just before treatment was started This sequence is illustrated in fig 1 It seems likely that, in these cases, renal failure was the result of severe progressive glomerulonephritis

TABLE III—SHORT TERM RESULTS OF HYPOTENSIVE THERAPY IN MALIGNANT ESSENTIAL HYPERTENSION WITH RENAL IMPAIRMENT

Case no	Sex	Age (yr)	Blood pressure (mm Hg)	Drugs used	Renal function			
					Before and after treatment			Interval (weeks)
					Blood urea (mg per 100 ml)	Max conc urea in urine (g per 100 ml)	Creatinine clearance (ml per min)	
28	M	48	230/180	1 Ansolysen inj 2 Serpasil Ecolid	40 45	1 6 1 6	65 75	4
29	M	37	280/160	Serpasil Ecolid	39 45	1 6 1 2	53 45	3
30	M	32	250/160	Hexamethonium inj	42 51	1 02 1 0	88 138	4
31	M	53	260/160	Serpasil Ecolid	73 47	1 7 1 4	56 53	4
32	M	63	230/140	Serpasil Ecolid	57 51	3 3 2 4	100	3

Long term Results

The long-term results of therapy lend themselves less readily to analysis than the short-term Only those patients who were treated with hypotensive drugs for at least six months have been included, and for several reasons these are few

When treatment was started, many patients were seriously ill, with poor renal function, very high blood-pressure, and other serious complications, 3 died in uræmia in less than six months (cases 3, 17, and 24) Moreover several patients, especially those who were treated for prophylactic reasons, were unwilling to persevere with a treatment which produced unpleasant symptoms Thus 6 abandoned treatment and have been excluded (cases 9, 11, 15, 16, 23, and 27) In addition 7 patients have not yet been treated for six months (cases 2, 8, 10, 19, 21, 25, and 29)

A further complicating factor is the variable degree of control of the blood-pressure in the individual case, for, though normotension was readily obtained during the initial period of treatment, the blood-pressure often rose after discharge from hospital This may have been due either to acquired tolerance to the drug or to lack of

TABLE IV—SHORT-TERM RESULTS OF HYPOTENSIVE THERAPY IN TYPE-II NEPHRITIS

Case no	Sex	Age (yr)	Blood-pressure (mm. Hg)	Indications for therapy	Drugs used	Renal function			
						Before and after treatment			Interval (weeks)
						Blood urea (mg per 100 ml)	Max conc urea in urine (g per 100 ml)	Creatinine clearance (ml per min)	
17	F	22	210/140	Retinopathy	Serpasil Ecolid	111 156	0 6 0 7	12 7	4
18	M	44	225/125	Rising B P	Serpasil	45 40	1 7 1 8	50 48	4
19	M	37	225/125	Lt heart-failure	Serpasil Ecolid	158 210	0 8 0 9	9	2
20	F	29	230/125	Retinopathy	Ansolysen inj	64 65	0 8 0 75	27 25	2
21	F	25	220/130	Rising B.P	Serpasil Ecolid	48 54	1 2 0 6	36 33	2
22	F	25	180/110	Rising B.P	Serpasil Ecolid	63 84	0 9 0 7	18 18	2
23	M	31	270/120	Papillœdema	Ansolysen inj	132 121	0 6	33 24	4

cooperation We encouraged all the patients to return to a normal active life, and increased physical activity may have diminished their response to hypotensive drugs In some patients dosage was satisfactorily readjusted, in others this was impossible, and we had to be content with a suboptimal lowering of the blood-pressure

The control of blood-pressure during long-term treatment was classified as good if the blood-pressure fell to 150/100 mm Hg or below in the standing position, poor if the diastolic pressure was persistently above 120 mm Hg, and fair between these extremes

16 patients were treated for six months or longer (table V) The diagnosis in 8 of these was chronic type I nephritis, in 3 type II nephritis, in 1 chronic pyelonephritis, and in 4 malignant essential hypertension Of the patients with type-I nephritis, renal function improved in 2, remained unchanged in 2, and became worse in 4

The period of treatment varied between seven and twenty-four months, and, not unexpectedly, the degree of renal impairment at the start of therapy was important in prognosis

An example of a good therapeutic response is shown in fig 2 In the 4 patients whose renal function deteriorated the initial creatinine clearance was low (23–52 ml per minute), the average being just under 34 ml The initial blood-urea level was more variable but was above 70 mg per 100 ml in 3 cases The patient with pyelonephritis (case 26) showed persistent improvement in renal function after seven months' therapy, but there was only slight renal impairment when treatment was started

4 patients with malignant essential hypertension were treated for periods of six months to four years Renal function has not deteriorated in any Renal impairment was greatest in case 31 (blood urea 73 mg per 100 ml creatinine clearance 56 ml per minute), in the other 3 patients it was only slight

2 of the 3 patients with type II nephritis showed deterioration in renal function after treatment for twenty six and six months, both had grossly impaired renal function at the onset (creatinine clearances 27 and 18 ml per minute) In the 3rd patient the creatinine clearance was initially 50 ml per minute, and treatment has been maintained for nine months without apparent deterioration With 1 exception, patients in any group who showed no deterioration of renal function on prolonged hypotensive therapy had an initial creatinine clearance of 50 ml per minute, or more (range 25–100 ml average value 67 ml)

Mortality

There were 3 deaths in this long term series, all examples of chronic type I nephritis

One patient, in whom papillœdema was initially observed, died of cerebral hæmorrhage after eighteen months, during which time control of blood-pressure was considered poor (case 7) A cerebrovascular accident was the cause of death in a 2nd patient (case 13), after fifteen months' therapy, with only fair control of blood-pressure, at the beginning of treatment this patient had severe retinopathy and left heart-failure The 3rd patient died from uræmia, after fourteen months' therapy, with fair

TABLE V—LONG-TERM EFFECTS OF HYPOTENSIVE THERAPY ON RENAL FUNCTION

Case no	Sex	Age (yr)	Diagnosis	Renal function				Control of blood-pressure	Comment on renal function
				Before and after treatment					
				Blood-urea (mg per 100 ml)	Max conc urea in urine (g per 100 ml)	Creatinine clearance (ml per min)	Interval (months)		
1	M	39	Chronic type I nephritis	59 45	1.45 2.2	87 80	24	Good	Improved Alive
12	M	45	Chronic type I nephritis	90 60	1.7 1.4	25 38	10	Poor	Improved Alive
4	M	42	Chronic type I nephritis	73 60	1.89 1.86	73 62	7	Poor	Unchanged Alive
6	M	44	Chronic type I nephritis	60 57	1.2 1.2	60 57	18	Good	Unchanged Alive
5	M	54	Chronic type I nephritis	95 200	1.0 1.1	25 12	8	Fair	Worse Alive
7	M	54	Chronic type I nephritis	73 70	1.2 0.9	35 22	18	Poor	Worse Died of cerebrovascular accident
13	M	42	Chronic type I nephritis	57 75	1.7 2.0	52 34	15	Fair	Worse Died of cerebrovascular accident
14	M	53	Chronic type I nephritis	159 400	0.6	23	14	Fair	Worse Died of renal failure
26	M	26	Pyelonephritis	50 40	1.2 2.0	70 80	7	Fair	Improved Alive
18	M	44	Type II nephritis	47 42	1.7 1.8	50 18	9	Good	Unchanged Alive
20	F	29	Type II nephritis	64 108	0.8 0.6	27 12	26	Good	Worse Alive
22	F	25	Type II nephritis	63 108	0.9 0.9	18 8	6	Fair	Worse Alive
28	M	45	Malignant hypertension	40 40	1.6 2.1	[illegible] 80	24	Fair	Improved Alive
31	M	52	Malignant hypertension	73 47	1.7 2.04	56 80	12	Fair	Improved Alive
30	M	32	Malignant hypertension	42 40	1.02 0.95	85 100	48	Fair	Unchanged Alive
2	M	63	Malignant hypertension	57 42	3.3 3.12	100 51	6	Poor	Unchanged Alive

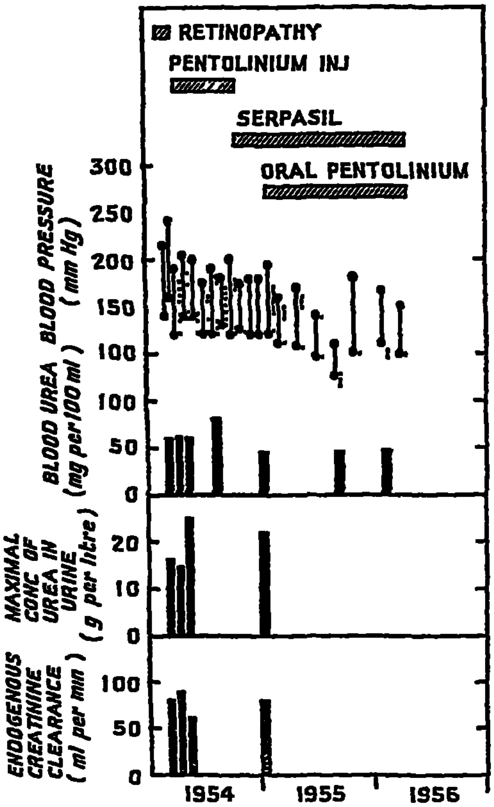

Fig 2—Case 1 chronic type-I nephritis showing sustained control of hypertension by serpasil and pentolinium without further deterioration in renal function over 2 years B-P in lying position is represented by continuous lines, and in standing position by interrupted lines

control of blood-pressure (case 14), here renal failure was advanced when the patient was first seen, and therapy was only undertaken with considerable misgivings for the relief of symptoms

Few conclusions should be drawn from these fatalities, but cerebral hæmorrhage still remains an important cause of death, and here the effectiveness of controlling the blood-pressure may well be important In none of these fatal cases was there a malignant termination—i e, appearance or reappearance of papillœdema was not observed

In the whole series of 32 patients other deaths occurred either before six months' therapy had been concluded or after therapy had been discontinued These fatal cases are considered below

Discussion

Several reports have been published of the pharmacological actions on the renal circulation in man of ganglion-blocking agents and other hypotensive drugs

Mackinnon (1952) found that, both in normotensive subjects and in patients with benign or malignant essential hypertension, pentamethonium iodide reduced the glomerular filtration rate and effective renal blood flow The reduction in renal blood flow was greater than could be explained by the fall in blood pressure—indicating a selective vasoconstrictor effect on the kidney

Similar results were obtained with hexamethonium by Moyer and Mills (1953), the ætiology of the hypertension was not specified

According to Moyer et al (1955) and Andreae and Smith (1955) the rauwolfia alkaloids have no direct effect on renal hæmodynamics

'Apresoline' (hydrallazine) on the other hand increases renal blood flow (Mackinnon 1952), and it therefore appears to be the drug of choice when ischæmic renal disease is present Unfortunately we have found it valueless in chronic renal hypertension

If the above results were applicable to patients with impaired renal function we might expect ganglion-blocking drugs to cause further deterioration, but clinical experience has not substantiated this

Morrison (1953) treated hypertensive patients with parenteral hexamethonium and reported that, of 5 with initially a raised blood urea level, 3 showed no further rise during treatment, and in 2 the observed rise was no more than would be expected in the natural course of the disease

In a series reported by Harington and Rosenheim (1954) 9 patients were treated when the blood urea level was above 40 mg per 100 ml, in 4 of these the level rose with treatment and in 5 it fell These workers concluded that renal disease was no contra indication to treatment with ganglion blocking agents

Our results support these earlier observations Evidently the changes in renal hæmodynamics observed in an acute experiment bear no definite relation to the therapeutic response which follows long-confirmed lowering of the blood-pressure

Ellis (1942), comparing the histological findings in type I nephritis and type-II nephritis, wrote

> "Of special significance is the difference in the chronic stage, for whereas in type 1 nephritis the early lesions give place to secondary hypertensive changes resulting in focal renal destruction, in chronic type 2 nephritis there is a progressive glomerular hyalinisation with diffuse renal destruction in which the hypertensive process appears to play relatively little part"

The results which we report here lend support to this observation, for it was in chronic type-I nephritis that the treatment of hypertension was most satisfactory A similar result might be expected in chronic pyelonephritis In type-II nephritis, on the other hand, where hypertensive vascular damage is not conspicuous and there is evidence of progressive renal destruction from the nephritic process, the results of hypotensive therapy are disappointing

There have been 11 deaths in this series, the 3 which took place after prolonged hypotensive therapy have already been discussed 4 patients died during the first six months of therapy; 2 of these had chronic type I nephritis with severe renal failure (cases 3 and 9) at the start of treatment, the 3rd was an elderly man with a blood-urea of 171 mg per 100 ml due to polycystic disease (case 24), and the 4th was a girl, with very active type-II nephritis, who died in uræmia after three months' treatment (case 17) Thus there were 7 deaths during therapy, in 5 the cause was uræmia and in 2 a cerebral vascular lesion There was no instance of a malignant termination

4 other patients died after they had abandoned treatment (cases 11, 15, 23, and 27) In 2 there was a malignant termination (cases 11 and 23), and 2 died in uræmia without the development of papillœdema (cases 15 and 27)

From these figures it is obvious that hypotensive drug therapy was of little use in the late stages of renal failure The important fact remains, however, that, when renal function was only slightly impaired, adequate control of the blood pressure in patients with chronic type I nephritis or malignant essential hypertension was not accompanied by any serious deterioration in renal function over the period of observation In addition to this possible prophylactic effect, symptomatic improvement was striking in most instances Most of our patients had severe headaches, some had distressing dyspnœa, and some had impaired vision Hypotensive therapy provided relief in such cases and for this reason alone appeared well justified—regardless of the ultimate prognosis

Summary and Conclusions

27 patients with primary renal disease, hypertension, and impairment of renal function, were treated with

hypotensive drugs 5 patients with malignant essential hypertension and renal impairment were included for comparison

The results of therapy depend largely on the initial degree of renal impairment and partly on the type of renal disease Usually cases of chronic type-I nephritis, pyelonephritis, and malignant hypertension showed no deterioration of renal function when the initial creatinine clearance was over 50% and the blood-urea level below 60 mg per 100 ml Renal failure progressed when the initial creatinine clearance was below 30% and the blood-urea above 70 mg In chronic type II nephritis the results are less favourable

Adequate control of the blood-pressure seems to prevent the malignant hypertensive termination in renal disease, but cerebral vascular accidents still happen

Hypotensive therapy had no value in staying the onset of renal failure in type-II nephritis There was no satisfactory evidence that lowering the blood-pressure was responsible for deterioration of renal function in these patients, but that possibility must be considered

The need for accurate diagnosis of the renal lesion, before hypotensive therapy is given, is emphasised

We thank Messrs Ciba for generously providing supplies of 'Ecolid'

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RENAL HÆMODYNAMIC EFFECTS OF HYPOTENSIVE DRUGS

I ACUTE EFFECTS OF HEXAMETHONIUM BROMIDE BEFORE AND AFTER TREATMENT WITH RESERPINE

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PARENTERAL administration of the ganglion-blocking agents hexamethonium and pentamethonium to hypertensive patients reduces the glomerular filtration-rate, the renal plasma flow, and the excretion of water and sodium The renal vascular resistance tends, as a rule, to increase, but it may decrease during the peak action of the drug as judged by the arterial blood-pressure (McQueen 1952, Mackinnon 1952, Mills and Moyer 1953, Freis et al 1953)

In the work reported here these findings were confirmed and the effect of preliminary treatment with another hypotensive agent, reserpine ('Serpasil'), on the changes induced by hexamethonium were investigated

Material and Methods

Thirteen patients with sustained hypertension were studied Nine were women and four were men, their ages ranging from 24 to 72 One patient had chronic bilateral pyelonephritis (case 6), one had chronic unilateral pyelonephritis (case 3), and in one hypertension was first observed during a pregnancy (case 13) The remainder were considered to be cases of essential hypertension of varying severity with case 7 presenting in the malignant phase of the disease

To attain as basal states as possible the patient had an initial rest period of 2 weeks in hospital, without treatment, before each test (In the patient with malignant hypertension the period of observation was only 6 days, because her condition was deteriorating) All the tests were made at the same time of day, about 3 hours after a light breakfast Water, 1000 ml, was given in the 45 minutes before the start of each test All the measurements were made with the patient recumbent The glomerular filtration-rate (G F R) and renal plasma flow (R P F) were measured by the clearance rates of inulin and *p* aminohippurate respectively, the plasma levels of these substances being kept constant by a continuous intravenous infusion After 45 minutes allowed for equilibration, urine was collected in three periods, each of about 15 minutes, the bladder being emptied by washing with distilled water and air and by suprapubic compression During this time the blood pressure in the arm was measured by auscultation every few minutes, and the pulse rate was recorded After these control observations hexamethonium bromide 5–45 mg was injected via the infusion tubing, and observations were continued during three further periods

TABLE I—EFFECTS OF INTRAVENOUS HEXAMETHONIUM BROMIDE ON RENAL FUNCTION

Case no	Sex	Age (yr)	Period	Blood pressure (mm Hg)	Pulse rate	Glomerular filtration rate (ml per min)	Renal plasma flow (ml per min)	Filtration fraction	Renal vascular resistance	Urinary excretion (m eq per min)		Urine flow (ml per min)
										Sodium	Potassium	
1	F	40	C	233/136	91	106	382	0 28	0 20	0 64	0 10	9 6
			D	177/107	94	45	165	0 27	0 36	0 28	0 04	[illegible]
			E	127/92	96	61	346	0 18	0 14	0 02	0 07	0 6
			F	134/95	97	70	366	0 19	0 13	0 01	0 13	0 6
2	M	41	C	165/116	71	95	375	0 25	0 17	0 38	0 06	3 9
			D	113/83	83	43	167	0 26	0 27	0 19	0 03	1 6
			E	109/85	87	104	541	0 19	0 08	0 05	0 05	0 6
			F	127/94	89	92	402	0 23	0 12	0 05	0 13	0 5
3	F	30	C	176/119	73	77	302	0 21	0 23	0 27	0 06	5 1
			D	168/118	90	67	206	0 21	0 27	0 21	0 05	1 6
			E	161/114	94	53	237	0 22	0 33	0 15	0 01	1 5
			F	165/116	93	68	341	0 20	0 23	0 21	[illegible]	1 5
4	F	37	C	158/111	80	100	366	0 27	0 19	0 18	0 04	3 1
			D	153/109	86	68	231	0 29	0 30	0 13	0 03	[illegible]
			E	141/105	93	77	270	0 28	0 24	0 12	0 03	0 5
			F	158/114	92	78	280	0 28	0 24	0 09	[illegible]	0 6
5	M	72	C	247/113	65	73	270	0 27	0 31	1 08	0 12	[illegible]
			D	205/100	67	52	158	0 33	0 44	0 43	0 08	3 5
			E	199/104	68	62	239	0 26	0 30	0 37	0 10	[illegible]
			F	231/111	69	78	206	0 29	0 30			1 9
6	M	38	C	145/102	64	36	168	0 21	0 40	0 20	[illegible]	3 1
			D	146/104	74	39	160	0 24	0 42	0 16	0 07	2 1
			E	150/105	79	30	149	0 26	0 46	0 13	0 05	1 5
			F	149/107	72	35	165	0 23	0 46	0 14	0 06	1 5
7	F	56	C	251/153	72	38	124	0 31	0 87	0 23	0 04	3 0
			D	189/128	76	19	69	0 27	1 32	0 10	0 02	0 9
			E	171/123	75	20	84	0 24	0 94	0 01	0 01	0 1
			F	191/133	75	28	121	0 23	0 73	0 01	0 03	0 3
8	F	31	C	177/127	73	90	265	0 34	0 22	0 27	0 05	6 0
			D	171/123	91	62	198	0 31	0 42	0 18	0 04	[illegible]
			E	167/121	94	89	302	0 29	0 27	0 20	0 04	1 4
			F	175/131	96	89	306	0 29	0 23	0 23	0 05	1 1
9	M	24	C	225/140	76	57	270	0 21	0 31	0 12	0 12	6 3
			D	215/132	82	44	215	0 21	0 28	0 20	0 00	[illegible]
			E	211/127	93	50	199	0 25	0 40	0 13	0 07	1 1
			F	211/131	95	52	214	0 24	0 38	0 12	0 07	1 0
10	F	59	C	221/112	71	90	400	0 25	0 20	0 32	0 12	[illegible]
			D	213/111	71	78	318	0 25	0 24	0 22	0 10	4 5
			E	208/111	63	60	269	0 22	0 28	0 14	0 07	1 9
			F	218/113	64	89	405	0 22	0 20	0 27	0 12	2 3
11	F	55	C	222/111	85	81	317	0 25	[illegible]	0 15	0 05	[illegible]
			D	130/73	81	39	158	0 25	0 31	0 04	0 02	[illegible]
			E	135/78	76	8	30	0 27	1 73	0 01	0 01	[illegible]
			F	147/80	76	20	125	0 16	0 14	0 01	0 01	0 1
12	F	58	C	218/119	60	74	293	0 25	0 28	0 69	0 08	[illegible]
			D	143/91	63	19	78	0 24	0 76	0 18	[illegible]	[illegible]
			E	126/85	58	22	132	0 17	0 41	0 06	[illegible]	0 6
			F	120/85	[illegible]	29	191	0 15	0 28	0 02	0 03	[illegible]
13	F	45	C	204/124	78	47	185	0 25	0 49	0 14	0 07	3 6
			D	179/118	90	40	101	0 24	0 50	0 10	0 05	2 0
			E	180/118	91	30	173	0 22	0 48	0 03	0 04	[illegible]
			F	187/123	88	52	233	0 22	0 37	0 06	0 07	[illegible]

C, control average of three periods of about 15 min each
D, E F three consecutive periods of about 15 min each after injection of hexamethonium

TABLE II—EFFECTS OF INTRAVENOUS HEXAMETHONIUM BROMIDE ON RENAL FUNCTION IN HYPERTENSIVES UNDER TREATMENT WITH RESERPINE

Case no	Sex	Age (yr)	Period	Blood pressure (mm Hg)	Pulse rate	Glomerular filtration rate (ml per min)	Renal plasma flow (ml per min)	Filtration fraction	Renal vascular resistance	Urinary excretion (m.eq per min.) Sodium	Urinary excretion (m.eq per min.) Potassium	Urine flow (ml per min)
9	M	24	C	195/127	71	61	265	0 23	0 30	0 18	0 12	4 6
			D	194/120	70	51	242	0 21	0 32	0 14	0 11	2 2
			E	178/119	72	56	203	0 28	0 37	0 10	0 12	2 7
			F	174/117	73	58	222	0 26	0 33	0 12	0 13	1 9
10	F	59	C	233/111	54	102	404	0 25	0 20	0 40	0 15	9 1
			D	201/202	56	80	364	0 22	0 19	0 23	0 12	3 2
			E	211/103	55	66	290	0 23	0 25	0 17	0 09	1 1
			F	214/109	53	79	456	0 17	0 16	0 31	0 15	1 8
11	F	56	C	210/96	63	80	322	0 25	0 24	0 18	0 09	5 5
			D	144/77	69	28	141	0 20	0 40	0 02	0 03	0 5
			E	136/75	65	30	181	0 17	0 30	0 02	0 02	0 2
			F	143/77	65	33	227	0 14	0 25	0 00	0 03	0 1
12	F	58	C	188/101	56	76	297	0 26	0 25	0 56	0 08	6 6
			D	156/90	62	35	132	0 26	0 48	0 22	0 04	2 1
			E	146/85	54	55	257	0 21	0 23	0 14	0 06	0 8
			F	149/88	54	61	262	0 23	0 22	0 19	0 08	1 3
13	F	45	C	184/110	66	53	199	0 27	0 41	0 14	0 09	8 4
			D	161/103	70	48	194	0 25	0 38	0 10	0 07	6 3
			E	162 105	71	48	180	0 27	0 41	0 10	0 06	7 1
			F	166/108	68	46	206	0 22	0 37	0 11	0 07	5 8

C, D E F, as in table I.

of about 15 minutes each An attempt was made to estimate by a previous test dose the amount of hexamethonium necessary to produce a moderate fall in blood-pressure in each patient

Inulin in the plasma and urine was measured by the method of Roe et al (1949), and *p* aminohippurate by the method of Smith et al (1945) Urinary sodium and potassium concentrations were determined by flame photometry The mean arterial blood-pressure (M B P) was estimated as one third of the pulse pressure plus the diastolic pressure, and the renal blood-flow (R.B F) was calculated as $\frac{\text{Renal plasma flow}}{1\ \text{Hæmatocrit}}$

The renal vascular resistance (R V R) was expressed as units of $\frac{\text{M B P}}{\text{R B F}}$ The G F.R, R P F, and R V.R were corrected for a body-surface area of 1 73 sq m

In five of the thirteen patients (cases 9–13) the above-mentioned procedure was repeated after 2 weeks during which oral reserpine 0 5 mg t i d was given The dose of hexamethonium administered to each patient on the second occasion was the same as that given during the first test

Results

The results in the thirteen patients after the injection of hexamethonium are shown in table I Table II shows the effects of hexamethonium in the five patients during treatment with reserpine Fig 1 illustrates the changes induced by hexamethonium in the thirteen patients, and fig 2 the changes induced by hexamethonium in one patient before and during treatment with reserpine

The average blood pressure was 203/122 mm Hg before the injection of hexamethonium After injection the pressure fell in most cases to an average of 160/105 There were, however considerable individual differences in the response to hexamethonium the blood pressure sometimes remaining unchanged and sometimes falling precipitately with symptoms of hypotension The average pulse-rate rose after injection of hexamethonium, but in some patients either no change or a decrease was observed

Both the G F R and R P F usually decreased after the injection of hexamethonium In patients in whom the blood pressure fell considerably a substantial decrease in the G.F.R and R.P F was usually seen However, even when the blood-pressure was only slightly decreased, considerable alterations in the G F.R and R P F were observed in some patients The greatest change seen was immediately after injection Towards the end of the observation periods both the G.F.R. and R P.F. tended to rise—the R P F. more rapidly than the G.F.R This was reflected in the filtration fraction which tended to decrease during the period of recovery of G.F.R and R.P F.

After the injection of hexamethonium the average R V R rose initially but it diminished towards the end of the period of observation In some patients the more rapid recovery of the R P.F following the initial decrease resulted in the R V R falling below control levels, while the blood-pressure remained low; in others recovery was less rapid and the R V.R remained high

After injection of hexamethonium the average rate of urine flow fell progressively from the control levels, a greater fall being observed when the blood-pressure fell considerably At the same time the excretion of urinary sodium decreased, tending to parallel the rate of the urine flow The urinary excretion of potassium decreased immediately after injection but increased towards control values at the end of observation

In the five patients treated with reserpine the average blood-pressure before treatment was 218/121 mm Hg and during treatment 202/109. The pulse-rates were slower during treatment with reserpine, being 74 before treatment and 62 after treatment No great differences were noted in the G F R R P.F, or filtration fractions before or during treatment The R V R averaged 0 305 before treatment and 0 278 during treatment with reserpine reflecting the slight fall in the arterial blood-pressure

After the injection of hexamethonium in these five patients the alterations in renal hæmodynamics and in the excretion of water and electrolytes resembled those observed before treatment with reserpine Quantitative differences were, however, noted in some patients

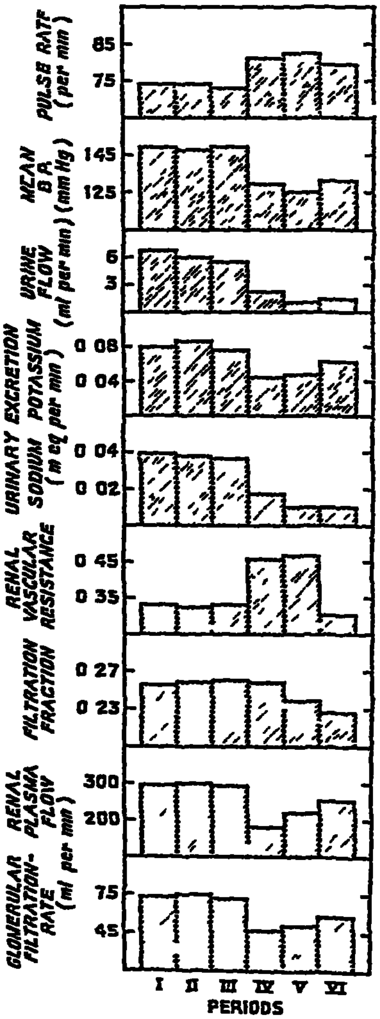

Fig 1—Changes induced by intravenous injection of hexamethonium bromide in 13 hypertensives Values are means of 13 patients Periods I–III are control observations and periods IV–VI those after injection

Discussion

These results confirm the observations that the injection of hexamethonium in hypertensive people tempor-

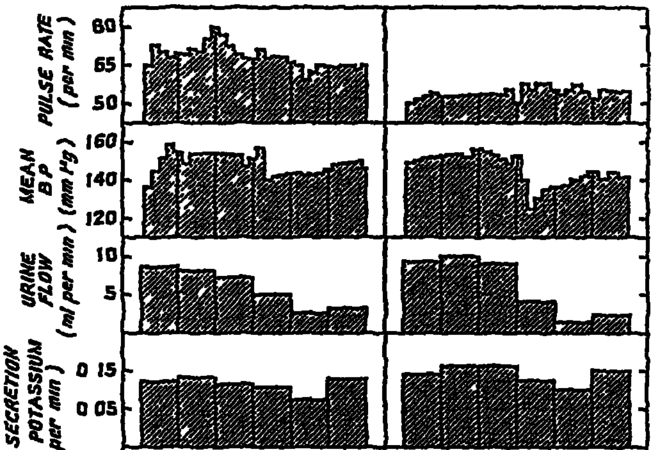

Fig 2—Case 10 effect of intravenous hexamethonium bromide before (A) and during (B) treatment with reserpine Hexamethonium injected at beginning of period IV.

arily alters the renal hæmodynamics and the excretion of water and electrolytes Freis et al (1953) did not observe alterations in the renal circulation when the injection of hexamethonium produced no fall in the blood pressure, but Mackinnon (1952), using pentamethonium, noted changes even when the blood-pressure did not fall In the present series minor alterations in blood pressure were sometimes accompanied by considerable alterations in the R P F and G F R Hexamethonium causes peripheral vasodilatation with increased blood flow to the extremities (Freis et al 1953), this may lead to the borrowing of blood from other parts of the body, including the kidneys, with a consequent reduction in blood-flow through these structures without any change in the systemic blood-pressure

Hexamethonium may either increase or decrease the R V R at the height of its action, judged by the blood-pressure (Mills and Moyer 1953) Both responses were observed in this series The result may depend on the ability and rapidity with which the renal circulation adjusts itself to sudden changes in blood-pressure In patients in whom the renal blood flow rapidly recovered while the blood pressure was low the R V R decreased below control values When the R B F recovered more slowly while the blood-pressure was rising, the R V R was increased *at the time of the peak action of the hexamethonium* In the two patients in whom the R V R was decreased renal function was good, judged by ordinary clinical tests In all the patients with impaired renal function R V R increased The severity of the disease, as it affects the *renal vasculature*, may determine the type of response

Mills and Moyer (1953) suggested that the increase in R V R may be explained on the basis of reflex vasoconstriction in response to the fall in blood pressure, *and that this is mediated via the* sympathetic nervous system through incompletely blocked ganglia On the other hand, the R V R is expressed as the ratio of the M B P to R B F, and the vasoconstriction inferred from this measurement may be the result of a shift of blood away from the renal circulation, together with a decrease in both the cardiac output (Werko et al 1951, Freis et al 1953) and *the* blood-pressure, and *consequent* arteriolar constriction

The effect of reserpine may take days or weeks to become apparent In this series 2 weeks' treatment was allowed before the second test, and a decrease in the *pulse rate* was *taken to indicate that* the reserpine was acting Moyer (1954) found no effect on the G F R and R P F in eight hypertensives during treatment with oral reserpine for 3 or more months In the five patients studied in this series the levels of G F R and R P F were similar before and after 2 weeks' treatment with reserpine The R V R was slightly less during treatment with hexamethonium in four of these patients owing to a slight fall in the blood pressure The pattern of response to hexamethonium before and during treatment did not differ Quantitative differences, however, were observed in some patients Case 11 developed hypotensive symptoms during the first examination, and the alteration in the renal circulation were more pronounced during this test than on the second occasion On the afternoon after the first examination the patient became pyrexial owing to an infection in a submaxillary salivary gland *from an impacted calculus* This could explain the differences observed It was found also that the effect of equal doses of hexamethonium in the same patient varied at different times Sometimes a test dose which had produced considerable changes in the blood pressure caused *only a slight* effect *during* the investigation Sometimes the opposite happened Familiarity with the procedure and small differences in technique may have affected the state of the patients and could explain the variations found These factors must be considered in interpreting the results

Parenteral hexamethonium decreases the rate of urine flow and the excretion of urinary sodium Though the fall in G F R may explain this in part, the fact that it persisted even when the G F R was again rising suggests increased *tubular reabsorption* of water and sodium as another factor The mechanism of this retention of sodium and water is unknown Preliminary treatment with reserpine did not alter the pattern of response as regards the rate of urine flow and the excretion of sodium and potassium except in one case in which no obvious reason for the difference was apparent

Summary

In thirteen patients with hypertension the effects of *intravenous hexamethonium on the renal circulation* and on the excretion of water and electrolytes were studied and in five of these patients examinations were repeated under treatment with reserpine

The effects of hexamethonium on renal hæmodynamics have *been confirmed—namely*, temporary decreases in glomerular filtration rate and renal plasma flow, usually an increase in renal vascular resistance, and a decrease in the rate of urine flow and in urinary excretion of sodium

Preliminary treatment with reserpine did *not* affect the changes produced by intravenous hexamethonium on the renal circulation

I am indebted to the medical committee of the Institute of Clinical Research, the Middlesex Hospital, for providing the facilities for this work In particular I thank Dr A Willcox, in whose unit it was done, for his constant encouragement and advice, and Prof A Kekwick, director of the institute

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RENAL HÆMODYNAMIC EFFECTS OF HYPOTENSIVE DRUGS

II EFFECTS OF ORAL MAINTENANCE THERAPY WITH PENTAPYRROLIDINIUM BITARTRATE AND RESERPINE

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IN most hypertensive patients the systemic blood-pressure is lowered by adequate therapy with hypotensive drugs, and in some of them there is clinical evidence of arrest or regression of vascular disease The fall in blood-pressure must be accompanied by either a decrease in the total peripheral resistance or a fall in cardiac output, or both Such a readjustment of the circulation may lead to inadequate blood-flow through the essential circulations of the kidney, heart, or brain

The present study was designed to measure any change in the renal hæmodynamic pattern of patients with severe hypertension in whom a satisfactory clinical response to hypotensive therapy had been obtained The renal and vascular effects of continuous oral hypotensive therapy with reserpine ('Serpasil') and the ganglion-blocking agent pentapyrrolidinium bitartrate ('Ansolysen') are reported Parenteral administration of another ganglion blocking agent (hexamethonium bromide) causes a striking temporary alteration in the renal hæmodynamic pattern, which is unaltered by previously administered reserpine (Goldberg 1957)

Material and Methods

Of a larger series of patients receiving hypotensive therapy for severe sustained systemic hypertension, six were studied (four women and two men, aged 52–62) Case 7 had malignant hypertension, the remainder had severe hypertension, which was considered to be essential and which was associated with impairment of cardiac renal, and retinal function in varying degrees in the different patients, none of whom was in cardiac failure at the time of study In all the patients the systolic blood pressure before treatment was at least 210 mm Hg, and the diastolic at least 110 mm

The patients were admitted to hospital for an initial period of rest, during which no specific hypotensive therapy was given, and were observed until their blood-pressures became stable Renal plasma flows and glomerular filtration-rates were respectively measured by the *p* aminohippurate and inulin methods, as previously described (Goldberg 1957) The results reported are the averages of three periods each of about 15 minutes Hæmatocrits were recorded, and the renal blood-flow, filtration fraction, and renal vascular resistance calculated Cardiac outputs were determined by a dye dilution method using 'T 1824' and a photo-electric ear densitometer (Milnor et al 1953) All measurements were made with the patients recumbent

Hypotensive therapy with reserpine and pentapyrrolidinium was then started When a satisfactory sustained therapeutic effect had been obtained, and an adequate maintenance dose of the drugs established, the above tests were repeated The dose of pentapyrrolidinium varied in different patients and the second examination was made after periods of treatment varying from 17 to 80 days, these were kept as short as possible, so that progressive deterioration of renal function, due to the disease itself, would be unlikely to affect the results

Results

The results are shown in the accompanying table

Blood-pressure and Pulse-rate—The blood-pressure was lowered before and during the second study in all but one patient (case 18), in whom the pressure was temporarily raised to former levels at the actual time of the second study, although before it there had been good control In all patients except one (case 7) the pulse-rate was slower after treatment than before

Glomerular Filtration-rate (G.F R)—The average G F.R in the six patients was 70 ml per minute before treatment and 64 ml during treatment There was no marked change in G F R in any patient, in the five patients in whom the blood-pressure was reduced at the time of the second study the G F.R was slightly lower than before, and in the remaining patient (case 18) it was slightly higher

Renal Plasma Flow (R P F)—There was no significant change in R P F in the six patients before and during treatment, the average was 254 ml per minute before treatment and 256 ml during treatment

Filtration Fraction (F.F)—The average F F in the six patients was 0 279 before treatment and 0 253 during treatment The slight decrease reflected the lower G F R which usually occurred with treatment

Renal Vascular Resistance (R V R)—In the six patients the R V R averaged 0 400 before treatment and 0 309

EFFECTS OF MAINTENANCE TREATMENT WITH PENTAPYRROLIDINIUM BITARTRATE AND RESERPINE ON RENAL FUNCTION IN HYPERTENSIVE PATIENTS

Case no	Sex	Age (yr)	Period	B.P	G F R.	R P F	F F	R.V R.
14	F	61	A	225/120	83	329	0 252	0 254
			B	206/99	75	335	0 224	0 224
15	M	62	A	257/129	64	290	0 211	0 307
			B	155/81	59	303	0 195	0 109
16	F	60	A	214/128	81	271	0 299	0 326
			B	163 111	73	275	0 266	0 276
17	F	52	A	210/137	94	234	0 401	0 364
			B	171/117	80	248	0 323	0 307
7	F	56	A	251/153	38	124	0 306	0 881
			B	205/117	35	143	0 241	0 633
18	M	56	A	210/110	57	276	0 206	0 267
			B	199/107	64	230	0 278	0 304

A before treatment
B after treatment
B P blood pressure in mm. Hg The figures are averages for numerous observations at the time of each study
G F R glomerular filtration rate (ml. per min.)
R P F renal plasma flow (ml per min.)
F F filtration fraction
R V R renal vascular resistance

during treatment The decrease was due to the fall of blood-pressure

Cardiac Output—No uniform response as regards cardiac output was found in this small number of patients Some showed an increase in cardiac output and others a decrease

Discussion

The effects on renal function of a combination of drugs, the ganglion blocking agent pentapyrrolidinium bitartrate and reserpine, commonly used in hypotensive therapy, have been studied No marked alteration in the renal hæmodynamic pattern was found with maintenance oral therapy except a decrease of the R V R Ford et al (1953) observed the effects of maintenance therapy with oral hexamethonium in 13 hypertensive patients In the recumbent position no marked alterations in the G F R and R P F were observed, although there was a significant fall of the blood-pressure and a decreased R V R In 7 of their patients the effects of ambulation were studied before and during treatment, the postural reduction in G F R and R P F was somewhat greater during treatment than before

Oral reserpine was similarly found to produce no significant change in R P F (Moyer 1954, Andreae and Smith 1955) In the present study the combination of reserpine with another ganglion-blocking agent, pentapyrrolidinium, likewise did not alter the R P F, at least in the recumbent position The findings during treatment were similar to those found during the recovery phase following the injection of hexamethonium, with or without the previous administration of reserpine (Goldberg 1957) The renal circulation apparently adapts to the decrease in blood-pressure following maintained oral therapy with pentapyrrolidinium and reserpine, and maintains the renal blood flow

In the five patients in whom the blood-pressure was lower during the second study the G F R was then slightly less than before, and the F F was reduced During severe hypotensive episodes which can occur during treatment a more profound alteration in the renal hæmodynamic pattern is possible, but probably temporary Although the decrease in G F R was consistent, it is unlikely to be materially significant in these patients, because no evidence of progressive reduction in renal function was found with continued treatment Reduction in renal function, as judged by simple clinical tests, was exceptional in other patients who were treated with this combination of drugs and observed over long periods by one of us (L McD 1954, unpublished) When renal function did progressively deteriorate, there was evidence of critically impaired function before the start of treatment A small absolute decrease in the G F R in these patients could represent a considerable proportional reduction and be sufficient to aggravate existing renal insufficiency In this regard it was found that further deterioration tended to occur early in treatment, and was made manifest by a rising level of blood-urea (McDonald 1954 unpublished, Stover et al 1956) If this form of therapy is still indicated in patients with critically impaired renal function, it is our practice repeatedly to determine the level of the blood urea, particularly during the early stages of treatment

Hexamethonium given intravenously to hypertensive patients has been found to decrease cardiac output (Werko et al 1951, Freis et al 1953), to increase it in the presence of heart failure (Freis et al 1953), and to cause no significant change in cardiac output (Gilmore et al 1952) The present findings are inconclusive as regards the effect of oral pentapyrrolidinium and reserpine on cardiac output The changes observed differed in individual patients and, in view of the error of the method were of doubtful significance

During hypotensive therapy the possibility of interference with essential circulations exists It is concluded that optimal lowering of blood pressure, which is a criterion of successful hypotensive therapy, appears rarely to interfere significantly with renal function, and that simple clinical tests of renal function should detect such interference No evidence was found, in this small series, of a diminution in renal blood flow or of relative renal ischæmia, which might mitigate the advantages of hypotensive therapy

Summary

Renal plasma flow, glomerular filtration-rate, filtration fraction, renal vascular resistance, and cardiac output were measured in six patients with severe hypertension, before and during treatment with oral pentapyrrolidinium bitartrate and reserpine

Little alteration in the renal hæmodynamic pattern was observed, apart from a lowering of the renal vascular resistance

In patients in whom the blood pressure fell, the glomerular filtration rate and the filtration fraction were slightly reduced This is usually not of clinical significance, except in patients with critical impairment *of renal function before treatment, further deterioration* may then occur during treatment

Of the simple clinical tests of renal function, the blood-urea level especially appears to be a good guide *to the progress and management of such cases*

It is a pleasure to thank Prof Alan Kekwick, director of the Institute of Clinical Research, Middlesex Hospital, for encouragement and facilities for this work, the clinical research committee of the Institute for a grant *to one of us* (L McD), Dr T M Chalmers for helpful comment, and Dr Evan Bedford, Dr Walter Somerville, and Dr Arthur Willcox for encouragement and allowing us to study patients under their care

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HYPERCALCÆMIA IN ACUTE LEUKÆMIA

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THE association of acute leukæmia and hypercalcæmia is rare and justifies record of the following case, in which many of the clinical features were attributable to the raised serum-calcium level

Case-report

In March, 1956, a soldier, aged 20, serving in Kenya, fell from a lorry and struck the left side of his chest For the next two weeks he had pain in the left lower chest, aggravated by movement and inspiration At the end of March he lost his appetite He was awakened on April 2 by epigastric pain and nausea, followed by repeated vomiting, which continued until admission to hospital in Nairobi two days later

On admission epigastric tenderness, a temperature of 101°F, and injection of his conjunctivæ were the only abnormal physical signs found Radiographs of his chest showed callus formed round the 7th left rib posteriorly Examination of his blood showed hæmoglobin 80% (11 8 g per 100 ml), white cells 8000 per c mm (neutrophils 31%, lymphocytes 59%, monocytes 1%, eosinophils 9%), and erythrocyte sedimentation rate 40 mm in the first hour (Wintrobe) A Mantoux test was positive 1/100 Widal agglutinations and culture of the blood were normal Routine testing and microscopy of the urine showed no abnormality

Progress

During the ensuing weeks the abdominal discomfort improved but the anorexia and vomiting continued The patient's temperature was often raised (99–102°F) in the evenings, and on April 16 he complained of aching pains in both hips and both knees

On May 22 evidence of renal damage was found the blood-urea level was 80 mg per 100 ml , and the highest specific gravity of the urine was 1 012 , and the urine often contained red and white cells and hyaline and granular casts Intravenous pyelography did not outline the kidneys Radiography showed rarefaction of the pelvic bones and femoral heads The hæmoglobin had decreased to 52% (7 7 g per 100 ml) The patient was given a blood-transfusion and flown home to hospital in England on May 26

Severe anorexia and vomiting, four or five times daily, continued , he complained of thirst and was passing an abnormally large volume of urine His obvious loss of weight, pallor, and injected conjunctivæ were the only abnormalities found on physical examination No enlargement of lymph nodes, liver, or spleen was detected Eye changes were a feature throughout the illness leashes of injected vessels ran from the cornea to the canthi , near the limbus, along the course of these vessels, were several small yellowish plaques which did not stain with fluorescein, but otherwise the picture was similar to phlyctenular conjunctivitis

Further investigations showed Hb 62% (9 3 g per 100 ml), white cells 2500 per c mm. (neutrophils 11%, lymphoctyes 63%, monocytes 5%, myelocytes 1%, primitive cells of uncertain type 20%), platelets 45,000 per c.mm An occasional normoblast was present A similar blood picture was found on repeated examinations over a period of weeks Bone marrow was difficult to obtain, aspiration being attempted from several sites, but satisfactory smears were made which showed sheets of primitive cells of lymphoid type Repeated examinations of the serum proteins, including paper electrophoresis, showed no abnormality, nor was Bence-Jones protein ever demonstrated in the urine The serum calcium level was consistently raised on many estimations, being 17–24 mg per 100 ml The levels of inorganic phosphate and alkaline phosphatase in the serum were always within normal limits The blood-urea level was raised, being 57–74 mg per 100 ml. The daily output of urine was about 3 litres of sp gr 1 010 Albumin, cells, and casts were constant findings The urinary excretion of calcium was 560 mg daily and of phosphate 1 2 g daily Radiographs showed widespread skeletal rarefaction, especially in the pelvis and femoral heads

Treatment

On June 15 the hæmoglobin had decreased to 36% (5 3 g per 100 ml), and the patient was started on a course of cortisone 300 mg daily and given repeated blood transfusions During the next few weeks he improved steadily His appetite recovered, vomiting ceased, and he gained weight and was able to get out of bed The biochemical picture also changed The serum calcium was within normal limits on several occasions The level of alkaline phosphatase in the serum rose to 21 K.-A units, and the excretion of calcium and phosphate, although still abundant, became much less The hæmoglobin increased to 13 g per 100 ml , but the white cells were still only 1500–2000 per c mm , and " blasts " were still present in the blood film. Platelets remained constant at about 40,000 per c mm There was no radiologically demonstrable change in the bones

Death

Towards the end of July the patient began to vomit again and to complain of anorexia and headache His hæmoglobin, despite transfusions decreased steadily, and the serum-calcium level was again high—15–16 mg per 100 ml On Aug 8 he developed widespread purpura vomited blood, and after three epileptic fits, became comatose and died

Necropsy Findings

Fourteen hours after death there were numerous petechial hæmorrhages in the skin and pericardium

Reticulo endothelial system —The bone marrow of the sternum femora, vertebræ, and ilium was replaced by red gelatinous material interspersed with many yellow areas Microscopically the marrow showed replacement of normal hæmopoietic tissue by sheets of large immature round cells of uniform size with little cytoplasm and vesicular nuclei containing a nucleolus , these cells corresponded to the lymphoblasts seen in the marrow smears Lymph nodes in the para-aortic, mesenteric, and axillary groups were moderately enlarged, up to 2 cm. in diameter, and their cut surfaces appeared uniformly pink , microscopically the normal architecture was lost, with an increase of large lymphoblasts Subcapsular and medullary sinuses were dilated and contained many large macrophages The spleen (440 g) had a normal cut surface and microscopical architecture but contained much iron pigment The liver (2060 g) had a normal cut surface, and microscopically showed infiltration of large lymphocytes in the portal tracts

Urogenital system —The kidneys (right 200 g , left 220 g) showed pale cut surfaces with a narrow cortex , wedge shaped nodules of infiltration involved both cortex and medulla Microscopically the nodules consisted of large uniform round cells similar to those seen in the marrow , there were numerous deposits of calcium in the cortex and medulla, but the glomeruli showed little change

Endocrine system —The parathyroid glands were of normal size and structure

The brain showed focal cortical hæmorrhages, especially in the frontal and temporal cerebral lobes

Discussion

This case of acute lymphoblastic leukæmia of the " aleukæmic " type presented unusual features Rarefaction of bones and severe hypercalcæmia, accompanied by anorexia, abdominal pain, and vomiting, with polydipsia and polyuria, may occur in hyperparathyroidism (Snapper 1952) Sarcoidosis too may present with similar clinical features and a high serum-calcium level (Dent et al 1953, McSwiney and Mills 1956) Myers (1956), reviewing 61 cases with hypercalcæmia, noted 1 case of acute leukæmia with a serum calcium level of 11 8 mg per 100 ml , and in a case of lymphosarcoma he found a serum calcium level of 20 4 mg per 100 ml. We have found no other record of hypercalcæmia in leukæmia nor any description of leukæmia presenting a clinical picture like that in the present case

Leukæmia has long been known to cause bony abnormalities Erb (1934) described rarefaction as one of the changes in the bones of children with acute leukæmia Kalayjian et al (1946) reviewed 144 cases of leukæmia with radiological evidence of bone involvement and found that 96% were of lymphoid type In a recent survey Griffiths (1955) has emphasised the association of bone changes with the " aleukæmic " forms of acute leukæmia in children

Hypercalcæmia, usually of moderate degree, may occur in any case of neoplastic invasion of bone—e g , by metastatic carcinoma and by myeloma Absence of new bone formation and the consequent normal level of alkaline phosphatase in the serum are features of myelomatous invasion (Snapper 1952)

In the absence of any detectable change in the serum-proteins we considered two possible explanations of the high blood calcium level and rarefaction of the bones in the present case hyperparathyroidism and invasion of bone by leukæmic tissue The remote possibility of a coincidental primary hyperparathyroidism was considered, but the alkaline phosphatase level was normal and at necropsy the parathyroid glands were normal There was considerable damage to the kidneys in the present case from leukæmic infiltration of the kidneys and, later, presumably from nephrocalcinosis Parathyroid overactivity secondary to renal failure may give rise to hypercalcæmia, but in the present case the normal alkaline phosphatase level and the lowered serum-calcium level after treatment with cortisone are points against this explanation

We suggest that the likely cause of the hypercalcæmia was continued and widespread leukæmic invasion of bones Temporary remissions of acute lymphoblastic leukæmia after cortisone therapy are known (Wilkinson 1953) Such a remission took place in the present case and was reflected by a fall in the serum-calcium level and a rise in the serum alkaline-phosphatase level, presumably owing to cessation of bone destruction with some attempt at new bone formation A similar sequence of events occurred in a case of lymphosarcoma treated with nitrogen mustard and cortisone (Myers 1956) and in cases of sarcoidosis treated with cortisone (Dent et al 1953) Some regression in the bony changes, shown radiologically, was noted by Dresner (1950) after the treatment of cases of acute leukæmia with aminopterin

The chronic symptomless conjunctivitis was an interesting feature for which we can offer no satisfactory explanation, post-mortem section of the eyes not being permitted Leukæmic deposits in the conjunctivæ have been described (Wintrobe and Mitchell 1940), but the descriptions do not seem to fit the changes in the present cases

Summary

In a case of acute lymphoblastic leukæmia, hypercalcæmia was probably due to invasion of bones by leukæmic tissue

We are grateful to Lieut Colonel J A G Carmichael, R A M C, physician in charge of the patient, and Lieut-Colonel P D Stewart, R A M C, for advice, and the technical staff of Eastern Command laboratory for help with the investigations

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Preliminary Communication

ALLOXAN AS A POSSIBLE THERAPEUTIC AGENT FOR PRIMARY CARCINOMA OF THE LIVER

With illustrations on plate

The relationship of endocrine action to the genesis and therapy of advanced cancer has received considerable attention in recent years, and especially during the past year[1 2] This approach may yet prove of value in elucidating host tumour relations and tumorigenesis

In the experimental field there is evidence that the production of alloxan diabetes in rats almost entirely prevents the induction of hepatomas by feeding azo-dyes,[3] and inhibits tumour growth or reduces the mortality rate in rats receiving implants of carcinoma (but not sarcoma)[4] More recently Ingle[5] has reported that diabetes induced in rats by partial pancreatectomy suppressed tumour growth

Hepatocellular carcinoma in man is invariably fatal, usually 4–6 weeks after clinical diagnosis[6] No form of therapy has hitherto been found to be of any value, even in prolonging life

Bearing all these experimental and clinical data in mind and despite the fact that alloxan had not, to our knowledge previously been given to man we considered it worth while to study the effects of alloxan on patients with primary hepatic carcinoma Diabetes, if induced, would be controllable with insulin

CLINICAL TRIAL

The preliminary results in three hopelessly advanced cases (for example see fig 1) and one with a slowly growing tumour, studied over the past year, are reported here The diagnosis of primary hepatic carcinoma was proved in all four cases by needle biopsy of the liver

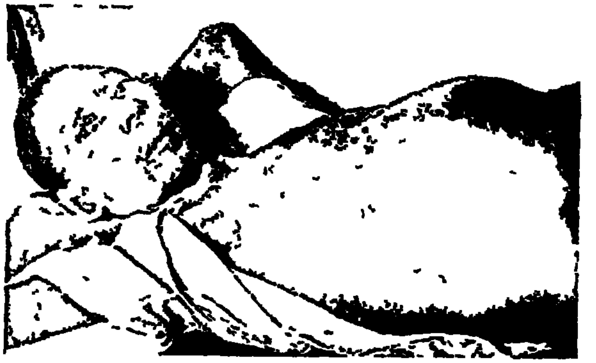
Fig 1—Case 2 immediately after paracentesis, showing bulging nodular liver

Alloxan 70–150 mg per kg body weight was administered intravenously, over a period not exceeding one minute, as a fresh 20% solution of alloxan monohydrate in distilled water These doses are known to be diabetogenic for most animals There was no significant untoward reaction to any of the seven injections given to our patients

Cases 1 and 2, African males aged 48 and 40, with typical, rapidly growing, and metastasising cancers, each received two injections of alloxan (case 1 at 16 day and case 2 at 58 day intervals), and lived for 18 and 103 days, respectively, after the first injection Case 3, an African male aged 56, was moribund before receiving a single alloxan injection He died within a few days, no post mortem being obtained, death could not be attributed to the treatment Case 4, an African female aged 28, with a slowly growing cholangiocellular carcinoma, has had two injections of alloxan and is still in hospital with no deterioration in her clinical condition

After the first alloxan injection case 1 experienced dramatic cessation of pain, which did not return In cases 1, 2, and 4 the liver became slightly but measurably smaller The fasting blood sugar levels in cases 1 and 2 initially rather low, showed slight transient rises after alloxan but always remained well within normal limits Glucose tolerance tests, before and after alloxanisation in these cases, showed no significant changes Case 4 had normal resting blood-sugar levels at all times, but her glucose tolerance tests, before and after alloxan, showed lag storage, which seemed slightly greater on the latter occasion *Assessment of therapy in this case* will be difficult because of the longer history and the quite different type of cancer

Histological study of necropsy material, obtained from cases 1 and 2 only, revealed extensive necrosis of primary and secondary tumours *Unusually marked sclerosis* was present both in the primary and in *all* secondary tumours in case 2 (figs 2 and 3) Since necrosis of hepatic carcinomas often develops spontaneously,[6] this may not be significant However, the extent of the necrosis, and especially of the tumour sclerosis in case 2, may merit special emphasis Also of interest was the absence of any histological evidence of damage to either pancreatic islets or kidneys in the one case studied

CONCLUSIONS

We consider the following findings *to be of some interest and perhaps attributable to the treatment* (1) the cessation of pain in case 1, (2) the reduction in size of the liver in cases 1, 2, and 4, (3) the extensive sclerosis in both primary and secondary tumours especially in case 2, particularly (4) the unusually long survival of case 2 (with a rapidly growing hepatocellular

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[1] *Brit med J* 1956 i 101
[2] *Lancet* 1956 i 676
[3] Salzberg D A Griffin A C *Cancer Res* 1952 12 294
[4] Goranson E S Botham F Willms M *Ibid* 1954 14 730
[5] Ingle D J *Endocrinology* 1956 59 259
[6] Berman C Primary Carcinoma of the Liver London 1951

carcinoma) for more than 5 months after the onset of symptoms (Berman[6] found that " the duration [of primary carcinoma of the liver] was never more than 4 months from the first appearance of symptoms "), and (5) the absence of hyperglycæmia and glycosuria after alloxanisation—noteworthy especially because decreased glycosuria has been reported in human diabetics developing certain tumours[7] and in diabetic rats bearing tumour transplants[5] Moreover, alloxanised rats bearing tumours have lower blood-sugar levels than alloxanised tumour-free controls[4]

In the light of these findings we consider that the alloxan therapy *may* have had some effects in two of the cases, and *may* perhaps have prolonged the life of case 2

The primary object of this note is to arouse interest in the possibility of treating with alloxan primary carcinoma of the liver, and possibly advanced carcinomas arising in other sites Our findings provide some basis for recommending further and more extensive investigation of the significance and interactions of alloxan injections on cancers, as well as of the abnormal carbohydrate metabolism occurring spontaneously in association with cancers[8] However, at the present time, we do not feel justified in making *any* special claims for this form of treatment

Since the above was written, three further cases of primary carcinoma of the liver have been given 1 injection each of alloxan (100 mg per kg body-weight) On the day following his injection, the third patient developed total anuria lasting 4 days, confirming the potentially nephrotoxic action of alloxan already described in animals

Our thanks are due to Dr. S Disler, hospital superintendent for permission to publish our findings, to Dr R Pooler and Dr F J Davidson for clinical material, to Prof I Gordon and Dr J Wainwright for necropsy findings to Dr M W Susser, Dr Z A Stein, and Dr L S Lange for clinical assistance, and to Prof J Maisin for encouraging us to make this preliminary report

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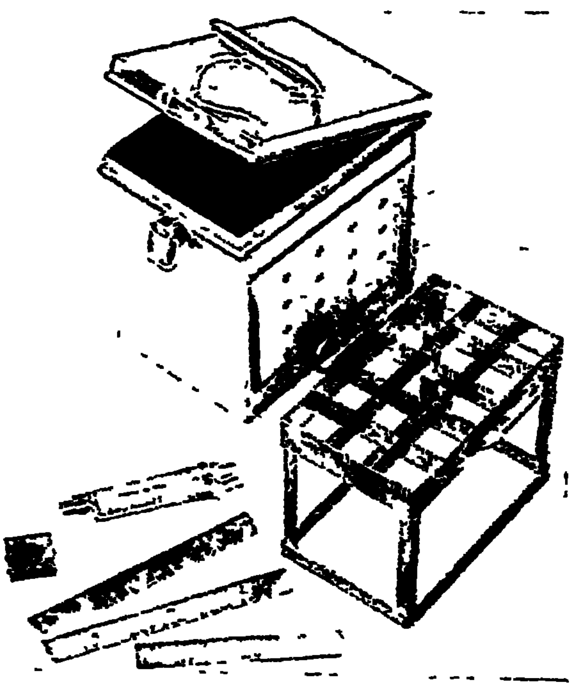
New Inventions

ST JOHN'S HOSPITAL SYRINGE CARRIER

A CENTRAL syringe-sterilising service is essential to all hospitals but it involves much time-consuming labour in the wrapping of individual syringe pistons, barrels, and needles The materials involved—polyethylene, glass metal, and specially tailored cotton containers—are all expensive

The container illustrated here has been designed to solve these problems so far as the anæsthetist is concerned It consists of a box measuring $7\frac{1}{2} \times 5 \times 7\frac{1}{2}$ in and containing a frame holder designed to take 14 assorted syringes and 15 needles By manipulation of the central bars the contents can be varied to suit an individual operating-list and combinations of syringes varying from 2 ml to 20 ml in capacity can be arranged for sterilising to suit individual requirements

All parts of this carrier are easily removable for cleaning It can be used in an autoclave or in a hot-air oven Its construction of heavy-gauge copper enables it to withstand heavy wear Cultures placed inside an assembled syringe in the centre of the box and surrounded by a full complement of syringes have been rendered sterile in experimental tests



This instrument is made by Messrs W H Bailey & Son Ltd, London, S W 1

L H Lerman
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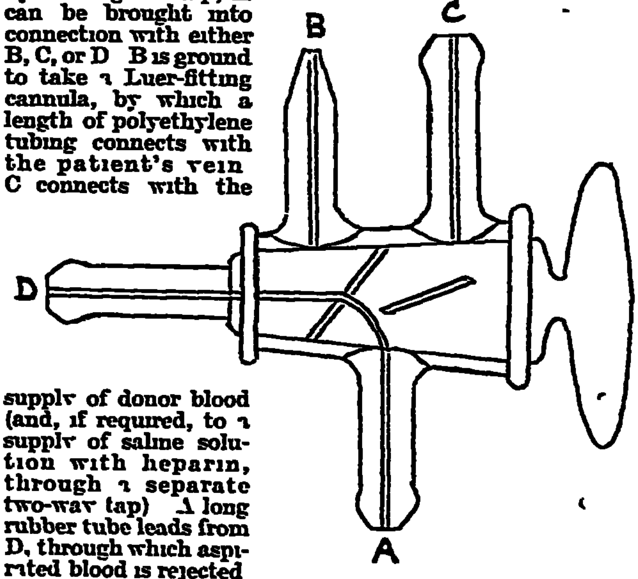
A THREE-WAY TAP FOR EXCHANGE TRANSFUSION

THE design of the tap, which is made of glass, is apparent from the accompanying figure A syringe is fitted to A by means of a short piece of rubber tubing by turning the tap, A can be brought into connection with either B, C, or D B is ground to take a Luer-fitting cannula, by which a length of polyethylene tubing connects with the patient's vein C connects with the supply of donor blood (and, if required, to a supply of saline solution with heparin, through a separate two-way tap) A long rubber tube leads from D, through which aspirated blood is rejected



The two parts of the tap are dry-sterilised separately and assembled after the surface of the tap has been lightly smeared with sterile lubricant—e g, soft paraffin

The advantages of this glass tap over metal taps with a similar purpose are lightness and ease of cleaning and of sterilisation It has been thoroughly tested in use over the past five years

The tap is made by Camlab Glass Ltd, 50a, Burleigh Street Cambridge

Douglas Gairdner
D M Oxfd, F.R C.P

Cambridge Maternity Hospital

Reviews of Books

Diseases of the Breast

C D HAAGENSEN, M D , professor of clinical surgery, College of Physicians and Surgeons, Colombia University
Philadelphia and London W B Saunders 1956
Pp 751 112*s*

THIS is the most important book on diseases of the breast which has appeared for many years Dr Haagensen is well known for his contributions to our knowledge of the breast, and he has now distilled the wisdom from twenty-five years' concentration on the subject His data are the records, large in volume and perhaps unique in the detail with which they have been investigated, of the Colombia Presbyterian Center in New York over the past forty years Dr Purdy Stout has been the pathologist chiefly associated with Dr Haagensen, and his influence is as clear in the text as in the beautiful photomicrographs

Dr Haagensen's chapters on the complex which used to be called chronic mastitis are interesting and thought provoking, though not perhaps entirely in line with British thinking so far as epithelial proliferation is concerned His chapter on mammary duct ectasia is masterly, as one might expect from the man chiefly responsible for distinguishing this entity from chronic mastitis More than half the book is devoted to carcinoma The chapter on the choice of treatment contains a description of a method of trephine biopsy of lumbar vertebræ and its results, and it also discusses very fully the well known criteria of operability of Haagensen and Stout The sections on radiotherapy and hormone treatment are, as one might expect from a surgeon, shorter than the chapter on surgical treatment, in which Haagensen describes in detail the careful radical mastectomy on which he relies for the early case

This work is a personal statement by a man who has read widely and thought deeply and objectively about breast disease, and who is humble enough to include a section on personal diagnostic errors The book is well illustrated It will command attention from all who are interested in its subject

Human Perspiration

American Lecture Series YAS KUNO, M D , member of Japan Academy Springfield, Ill Charles C Thomas
Oxford Blackwell Scientific Publications 1956
Pp 416 72*s*

IT *is some twenty years since the author first* summarised contemporary knowledge of the physiology of perspiration In the present volume he presents the results of his lifelong study of the subject, making available data from much hitherto unpublished research carried out in his own laboratory The book will be read by physiologists, and its lessons should be assimilated by the thoughtful dermatologist and tropical practitioner , but it contains a wealth of information to interest the pediatrician and the student of electrolyte metabolism, as well as the neurologist and the surgeon concerned with the autonomic nervous system Above all, it provides the pleasure of following with the author the evolution of knowledge in a field that he has made peculiarly his own This is an exhilarating book

Schizophrenia 1677

A Psychiatric Study of an Illustrated Autobiographical Record of Demoniacal Possession IDA MACALPINE, M D , and RICHARD A HUNTER, M D M R C P , D P M London
William Dawson 1956 Pp 197 £6 10*s*

THIS beautifully produced volume gives a full account of the mental illness of an Austrian artist, Christoph Haizmann, in the year 1677

Haizmann thought that he had made a pact with the Devil and his illness broke out at the time when his agreement to sell himself to the Devil was due to take effect His mental distress was relieved by exorcism and by what he and the priests who succoured him held to be the intervention of the Blessed Virgin He then joined a religious order, and although tempted by apparitions of fiends managed to live fairly peacefully for another twenty three years

Haizmann left pictures of the Devil in the guises, all progressively more diabolic, in which he appeared to him on nine occasions, also of the miraculous worsting of the fiend by the Virgin These are reproduced in colour, and the original manuscript of Haizmann is given in photolithography

The body of the book is taken up by a full account of the painter's illness, and a discussion of this in relation to the development of Freud's theories regarding paranoia The authors' previous examination of psycho analytic thought, as exemplified in Freud's writings on the Schreber case, is here expanded

Head Injuries and Their Management

FRANCIS ASBURY ECHLIN, M D , C M , M SC , MED SCD , F A C S , professor of clinical neurosurgery, New York University—Postgraduate Medical School Philadelphia
J B Lippincott London Pitman Medical Publishing Co 1956 Pp 127 24s

THIS is a sound and practical account for general surgeons of the handling of head injuries The danger of transporting unconscious patients in the supine *position are, however, not emphasised , and the section* on reablement and post-traumatic epilepsy are disappointing in comparison with the excellence of the chapters on the acute stage

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British Surgical Practice Surgical Progress 1956 (London Butterworth 1956 Pp 396 47*s* 6*d*) —The latest volume of this work, edited by Sir Ernest Rock Carling and Sir James Paterson Ross, follows the course of its predecessors Of the 11 original articles, all of them excellent, those by W J Sharrard on poliomyelitis, by D H Patey and A C Thackray on parotitis, and by F W Holdsworth on traumatic paraplegia seemed especially good There are five critical surveys, Hamilton Stewart's beautifully illustrated contribution on partial nephrectomy being outstanding The abstracts contain summaries of *150 important surgical papers* published mostly in 1955 and early 1956 The ' noter up ', (an ugly title for a valuable section) keys the new information to the parent volumes This is a useful book

Diagnostic Procedures for Virus and Rickettsial Diseases (2nd ed New York American Public Health Association 1956 Pp 578 $7 50) —Since the first edition of this book, edited by Prof Thomas Francis and Dr Joseph F Smadel, appeared in 1948 there have been important advances in the techniques of investigating viruses The second edition thus appears very different from the first and includes a great deal of new information on tissue culture techniques For anyone who is starting to do work with viruses and who would like authoritative information on how to handle them this is a most valuable book The treatment is very uneven, however, and there are some anomalies It is surprising that measles is dealt with in half a page, while inclusion blennorrhœa has eight pages The new adeno viruses are considered under primary atypical pneumonia, this is a doubly unfortunate chapter since it gives very little prominence to other diseases caused by adenoviruses, and it does not mention the recent work of Liu, Eaton, and Heyl on the virus which they recovered from cases of primary atypical pneumonia accompanied by an increase in cold hæmagglutinins *Finally, it is odd to see great stress laid on* the hæmagglutination test in the diagnosis of dengue while this valuable test is sadly neglected in the chapters dealing with other viruses of the same group—i e yellow fever and encephalitis viruses Nevertheless this book is likely to be in frequent use in many bacteriological laboratories

The Dental Treatment of Maxillo-Facial Injuries (2nd ed Oxford Blackwell Scientific Publications 1956 Pp 372 17*s* 6*d*) —When first published, this book brought together in a small space most of the current knowledge on its subject The second edition, edited by Sir William Kelsey Fry and Mr Terence Ward is basically the same book with the addition of a chapter on the use of antibiotics and a section on the use of alveolar wires Many of the elisions and errors of the first edition remain uncorrected and there is little reference to the vast increase in knowledge in the past *fourteen years* but the book is well laid out and the chapters on the general care of the patient, and particularly on feeding and on the use of antibiotics, are excellent

THE LANCET

LONDON SATURDAY, JAN 12, 1957

The Support of Medical Research

AN international symposium on the support of medical research met in London two years ago[1] under the chairmanship of Sir **HAROLD HIMSWORTH** and a report,[2] now published, represents the outcome of their deliberations Few will disagree with the opinions and advice set out therein, but agreed aims on the final common purpose of medical research are hard to translate into action when they involve nations so far apart on the economic scale as Yugoslavia and the United States In this respect the report is curiously detached the meeting seems to have recorded no dissenting voices It will be noted however, that many of the ideas expressed at the symposium were previously embodied in the white-paper on clinical research in the National Health Service[3], and the 81 articles to which the conference agreed suggest that the organisation of the Medical Research Council was accepted as a pattern Certainly, the aims and purposes these articles embody are closely related to our own situation

In Britain the State has become the great patron of research through, on the one hand, the University Grants Committee and the universities and, on the other, the Privy Council and the research councils For the tremendous work done by the M R C there can be little but admiration It finances projects beyond the purse of the university, it seeks out promising men for research careers, it supports and develops good research wherever it is perceived, and it undertakes large international responsibilities, such as keeping track of the influenza virus in the National Institute for Medical Research at Mill Hill Before we pass it on for export and emulation, however, we should consider a question that is often asked and is hard to answer with certainty does a large central institute, remote from medical schools and hospitals, drain away too much research and teaching talent from the universities? Perhaps the conference had qualms about this, for the report makes much of the traditional place of the universities in the expansion of knowledge, and it emphasises the importance to the investigator of teaching and other university contacts which often miraculously clarify his mind Thus it is considered vital that the investigators should continue to teach and inspire the young, and that research organised by a central body should be closely integrated with university work

The central body or research council has a heavy responsibility—for initiating research and for choosing and sometimes even discarding investigators (The minds of those who must make early choice of promising investigators can never be free from anxiety about the human difficulties that may arise when a research-worker of, say five years' standing has to seek ordinary professional work) Since the members of the M R C can hardly be expected to have supernatural powers of judgment, occasional errors are possible at all their levels of function, and it is therefore essential that the universities, with the help of patrons and private benefactors, should also be in a position to reach an independent evaluation of research, supporting it if necessary out of local endowment funds There are indeed risks in too much government aid for medical research—for example, it could degenerate into applied research for the Services, or it could be subject to political control and interference Though the M R C and the profession are very much on their guard against such abuses in this country, others may be less favourably placed Moreover, as Sir **ERIC ASHBY**[4] has explained, the patronage of private wealth is still important in maintaining academic freedom In these days the private patrons are often big business firms, and the help which some of these have given both at home and abroad, has been as enlightened as it is generous **ASHBY** pointed out, too, that the universities are not always staffed by research geniuses in every department first-rate administrators enthusiastic teachers, and good reviewers and organisers are all needed Because it is in a position to make far wider use of talent of all kinds, a university can maintain a flexibility denied to a body concerned only with research When the head of a department has research talent, the university should be able to provide on his staff the administrative and teaching assistance needed to keep the balance, and vice versa The report of the symposium recognises fully that the universities provide the intellectual climate, best suited for research development and that it is with their work that the activities of the central research body should be most closely integrated

If the universities accept this policy, some further hard spade-work, at both the preclinical and clinical levels, will lie ahead before all the fruits can be harvested The symposium noted with regret the falling recruitment of medically qualified men and women to the preclinical sciences, but it did not mention the gross differences in salary which are largely responsible—and which must be corrected before the situation can really improve If Northern Ireland can give its preclinical teachers distinction awards, it should not be impossible to ensure corresponding recognition of merit on this side of the Irish Sea At the clinical end of medicine there are also obstacles still to be overcome While the university clinical unit is strongly established in the Scottish schools and is expanding into almost all the provincial medical schools, the University of London has recently lost a professorial unit, and six of its twelve undergraduate schools have never had one Whatever the merits and demerits of such units as a means of teaching, they have certainly become the focusing points for the development of clinical research It is unfortunately obvious that the existing London units cannot absorb all the gifted and energetic young men seeking facilities for investigation Without more academic bridgeheads into the clinical field the best-laid plans for research can come to nothing The M R C lacks the powers to create these bridgeheads, and the task has to be faced by the university, where it is capable of taking the initiative If the universities wish to accept the proffered support for clinical research, they must make their own contribution in improving the organisation of university medicine The need is urgent, since already a generation of young and promising workers in medicine are beginning to feel that their training and talents are not appreciated Their enthusiasm can wither into cynicism, and we are in danger of either wasting their genius or allowing it to trickle away overseas

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[1] See *Lancet* 1954 ii, 864

[2] The Support of Medical Research A Symposium Organised by the Council for International Organisations of Medical Sciences Edited by Sir HAROLD HIMSWORTH F.R.C.P. F.R.S and J F DELAFRESNAYE M.R.C.S Oxford Blackwell Scientific Publications 1956 Pp 170 17s 6d

[3] See *Lancet* 1953 ii 123

[4] Ashby E *Listener*, 1955 53 421, 455, 513

Some non-teaching hospitals with whole-time staff are now winning a higher reputation for research and quality of service (which go hand in hand) than the older teaching centres Such competition is healthy, but some teaching hospitals lock as though they are failing to rise to the challenge Unless they can read the writing on the wall, they will face slow decay The teaching centres, in particular, while avoiding self-satisfaction, must accept the tasks of leadership with all the support which can be theirs for the asking If the recommendations of this report are accepted as a policy to be pursued by the M R C, our universities must make equal efforts to ensure that the plan will work

Hypotensive Drugs and Renal Function

IN the armoury of modern therapeutic weapons there are few with so wide a popularity as the drugs which reduce blood-pressure, and there can surely be no other treatment in which the target is so blurred, the aim so erratic, and the motive power so uncertain How many patients receive homœopathic doses which have negligible effect on the blood-pressure? How many whose blood-pressure is effectively reduced have on that account a longer expectation of life, a greater freedom from complications, or even a relative relief from incapacitating symptoms? In how many do sudden or serious accidents follow lowering of the blood-pressure? On what criteria are we to select patients for treatment and what are the contra-indications? Nearly ten years after the introduction of the hypotensive drugs, there are, for the large majority of patients treated, still no clear answers

In this issue we publish three articles from two groups of investigators who have been studying the effect of hypotensive drugs on renal function Many patients with high blood-pressure are suffering from primary renal disease or from essential hypertension with renal involvement—so called malignant hypertension Since the prognosis is serious, there is a natural inclination to try any treatment that might help, so it is important to know whether renal function can really be improved by lowering the blood-pressure, or whether there is, in fact, a danger of impairing it further High blood-pressure may worsen the prognosis in renal disease in a variety of ways it may produce heart-failure, which in turn depresses renal function, it may give rise to cerebral complications, such as hæmorrhage or thrombosis, or more rarely to reversible attacks of hypertensive encephalopathy, it may lead to impairment of vision due to retinal hæmorrhages, or, more seriously, the malignant form of hypertension with papillœdema may ensue All these complications are commoner in renal than in essential hypertension Apart from extrarenal complications, there is good evidence, as the experiments of WILSON and BYROM[1,2] and of FLOYER[3] have shown in animals, that hypertension of sufficient degree produces renal vascular damage which may seriously affect prognosis There are thus ample reasons for attempting to lower the blood-pressure in patients with hypertension of renal origin But it is important to know whether it is safe to do so in the presence of impaired renal function, whether renal failure may be precipitated, and, on the positive side, whether the natural course of the disease may be prolonged by protecting the kidney from hypertensive vascular damage

Occasionally idiosyncrasy to ganglion-blocking agents or excessive dosage may cause severe hypotension As in circulatory shock, anuria may result[4] and it is then an urgent matter to raise the blood pressure—for example, by methedrine or adrenaline injections Apart from this mishap, which is usually avoidable, the healthy kidney possesses an effective mechanism for maintaining its circulation in the face of wide variations in systemic blood-pressure A temporary reduction in glomerular filtration rate (G F R) and renal plasma flow (R P F) and an increase in renal vascular resistance (R V R) usually follow the administration of ganglion-blocking drugs, and may *be observed even when the blood-pressure does not* change[5] Dr GOLDBERG reports on p 74 that the effect of hexamethonium on R V R depends on the initial *state of renal function, impaired function being* associated with increased R V R MOYER[6] found that in hypertensive patients reserpine did not affect G F R and R P F GOLDBERG adds that preliminary treatment with reserpine does not alter the effects of hexamethonium on renal circulation Apresoline differs from the other hypotensive drugs in producing an increase in renal blood-flow[5] These observations on the "acute" effects of the hypotensive drugs do not seem to be of much immediate value in predicting the results of treatment, particularly if renal function is impaired Apresoline should be the drug of choice, since an increase in R P F might be expected to improve kidney function Unfortunately it has proved disappointing in the treatment of patients with renal hypertension On another page Dr MCDONALD and Dr GOLDBERG report that, in essential hypertension maintenance therapy with oral pentapyrolidinium bitartrate ('Ansolysen') and reserpine produces no diminution in renal blood-flow or other evidence of renal ischæmia, and they conclude that in patients with initial renal impairment simple clinical tests of renal function, especially the blood-urea level, are an adequate guide to progress

Dr ABRAHAMS and Professor WILSON describe the effects of ganglion-blocking agents, with or without reserpine, in patients with varying degrees of renal impairment due to primary renal disease or malignant hypertension Repeated measurements of blood urea urinary urea concentration, and creatinine clearance were made during short treatment for two to four weeks and during maintenance therapy continued for up to two years Satisfactory reduction of blood

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1 Wilson C Byrom F B *Lancet* 1939 i 136
2 Wilson C Byrom F B *Quart J Med* 1941 10 65
3 Floyer M A *Clin Sci* 1951 10 405
4 Carter A B Payne R W *Lancet* 1956, ii 577
5 Mackinnon J *Ibid* 1952 ii 12
6 Moyer J H *Ann N Y Acad Sci* 1954 59 82

pressure did not lead to further deterioration of renal function unless considerable impairment was initially present—i e , blood-urea over 70 mg per 100 ml and creatinine clearance less than 30% They emphasise, however, the need for accurate diagnosis of the underlying renal disease , for reduction in blood-pressure is more likely to precipitate uræmia than in patients with a progressive active nephritis (e g chronic type-II nephritis) in patients with a relatively inactive inflammatory lesion, such as chronic type-I nephritis or chronic pyelonephritis, in which hypertensive renal damage is now thought to be the dominant cause of renal failure ABRAHAMS and WILSON point out that in many patients with chronic renal disease the sudden deterioration of renal function in the late stages is preceded by a relatively abrupt rise in blood-pressure If therapy is introduced at this point and the hypertension is well controlled, there is evidence that the onset of renal failure may be delayed In those patients who persevered with treatment, the malignant form of hypertension so common in renal disease, was not observed These clinical results lend support to the conclusions derived from experimental studies in animals—namely, that, in certain forms of chronic renal disease, hypertension leads to renal vascular damage and accelerates renal failure Nevertheless, when renal disease has progressed to the stage of nitrogen retention, hypotensive therapy can lead to only a limited increase in the expectation of life—a few years at the most As in essential hypertension cerebral vascular accidents remain a major hazard

Vancomycin

THE present-day pharmaceutical equivalent of the Gold Rush is the intensive and systematic screening of soil samples for new antibiotics Thousands of soil samples are being collected by amateur and professional mycologists all over the world, and submitted to various industrial and university laboratories Aqueous extracts are prepared and analysed for their microbe content, and these organisms are then screened for possible antibiotic activity Many samples may seem promising at first, but only a few satisfy the rigid criteria demanded for clinical trial To the investigators' chagrin, some promising antibiotics turn out to be identical with those already in clinical use , and others become discredited by their toxicity. Finally, one out of the thousands of soil samples survives the stiffest of hurdles clinical evaluation, and is acclaimed on an Olympic pedestal alongside its predecessors Various species of the genus streptomyces have so far produced streptomycin, chloramphenicol, neomycin, chlortetracycline (aureomycin), oxytetracycline (terramycin), nystatin, erythromycin, carbomycin, novobiocin, and oleandomycin

A recent addition is vancomycin, isolated from soil obtained in Borneo and India Although vancomycin-producing strains were subsequently found in soil from other parts of the world, including North America, the species has been designated *Streptomyces orientalis*[1] Vancomycin hydrochloride is a white solid very soluble in water, and relatively stable[2] It is bactericidal, and like that of penicillin, its principal action is against gram-positive bacteria, particularly when they are multiplying Organisms sensitive to it include pneumococci, streptococci staphylococci, and clostridia FAIRBROTHER and WILLIAMS[3] recently reported that in vitro, the gram-negative gonococcus was also highly susceptible The main indication for the use of vancomycin, however, is an infection due to strains of *Staphylococcus aureus* resistant to other antibiotics This usually implies a strain found in hospitals, where the wide use of antibiotics has encouraged the emergence of drug-resistant organisms It is fortunate that such strains are at present rarely encountered in infections outside hospitals, but how long they will remain thus confined no-one can say In-vitro sensitivity tests must be performed before the most potent antibiotic can be chosen to deal with a serious staphylococcal infection Until the results are available, the clinician must in an emergency decide which agent is most likely to be successful If the infection has been contracted outside a hospital penicillin will probably and tetracycline will almost certainly be effective On the other hand, *serious* infections contracted in hospital should be treated at the outset with an antibiotic which is in least current use in that particular hospital This will do much to ensure early control of the organism and may prevent an outbreak of cross-infection in the ward As we have often declared, the wisest course is to hold in reserve an antibiotic which will subdue staphylococci that are resistant to other forms of attack , erythromycin has been the one most often held back in this way and there have been signs that chloramphenicol was returning to popularity, despite its occasional association with blood disorders The introduction of other antistaphylococcal drugs including vancomycin novobiocin, and oleandomycin now permits a wider choice for the strategic reserve If the laboratory report subsequently shows that the reserved drug is not the only one to which the infecting organism is responsive then the erythromicin (or whichever drug it is) can go back into reserve The actual reserve drug for each hospital should be changed from time to time in the light of laboratory reports

Whereas novobiocin and oleandomycin are well absorbed from the intestine, vancomycin must be given intravenously to produce any action other than in the intestine After either oral or intravenous vancomycin, the fæces become odourless and strains of clostridium and *Streptococcus fæcalis* disappear or become much fewer but the gram-negative flora persists The persistence of the gram-negative organisms in the intestine should prevent the emergence of yeasts, and mucocutaneous moniliasis has not so far been reported after the administration of vancomycin When vancomycin is taken by mouth most of it is excreted in the fæces and only negligible amounts can be detected in the blood or urine After intravenous injection, it is rapidly excreted in high concentration by the kidneys As only small quantities reach the bile, it seems that vancomycin unlike many other antibiotics, is not concentrated and excreted by the biliary system It is detectable in pleural, pericardial, synovial, and ascitic fluids after intravenous injection It does not diffuse into spinal fluid which is not unexpected in view of the relatively large size of the vancomycin molecule The only toxic reactions observed by GERACI and his co-workers [2] at the Mayo Clinic were occasional rigors, erythematous or morbilliform rashes, and phlebitis at the site of repeated intravenous injections The dose of oral or intravenous vancomycin is 0 5 g six-hourly, continued for about one week, depending upon the severity of the infection and the response to treatment Such doses have produced good results by mouth in staphylococcal enterocolitis and intravenously in staphylococcal septicæmias and osteomyelitis

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[1] Pittenger R C Brigham R B *Antibiot Chemother* 1956 6 642

[2] Geraci, J F, Heilman F R, Nichols D R Wellman W E, Ross, G T *Proc Mayo Clin* 1956 31 564

[3] Fairbrother R W Williams B L *Lancet* 1956 ii 1177

It remains to be seen whether vancomycin is best used alone or in combination with another antibiotic It is even more important for the community's sake to decide whether a combination of antistaphylococcal drugs is more likely to delay the emergence of resistant organisms, as it does in the chemotherapy of tuberculosis Strains of staphylococci made resistant to vancomycin in vitro retained their sensitivity to other antibiotics, suggesting that so far there seems to be no cross-resistance between it and other antibiotics This is a point of some importance, for new antibiotics are not really welcome unless they remain therapeutically distinctive Chemically similar analogues of antibiotics tend to have the same disadvantage of cross-resistance, and they are no more helpful when given in combination

Annotations

WELCOME TO A CENTENARIAN

AMONG the long established medical weeklies of the world, the *Nederlands Tijdschrift voor Geneeskunde* is individual alike in character and in the way it is managed Formerly the journal of the Netherlands medical association, it became after the war a purely scientific weekly, and its ownership passed to a separate society, of some sixty members, who produce it for the benefit of the medical profession Both the editor and the assistant editor hold university chairs (Dr J R Prakken in dermatology at Amsterdam and Dr J W Duyff in physiology at Leiden), and the only full-time medical member of the staff is the secretary (Dr M M Hilfman), but they have the help of a small board, consisting mostly of professors, who serve for three years and afterwards become members of the society Last week, when the journal started on its second hundred years, it changed its familiar small format for a larger one with double columns, which its friends will come to like even better Normally there are English summaries of all the articles, but the century opens with a special issue composed of some of the best contributions previously published The story of the last fifty years is told in a commemorative volume, by Dr C T van Valkenburg

At the decorous but cheerful celebrations in Amsterdam last Saturday, the other centenarian medical weeklies were represented by the editors of the *British Medical Journal*, the *Ugeskrift for Læger*, and *The Lancet*

HUMAN RELATIONS

THE Tavistock Institute of Human Relations has the responsible and exacting task of providing training and conducting research in the social sciences related to psychological medicine and acting as consultant to industrial organisations Government departments, and community services It is heartening to learn that, thanks to the support of American foundations, its annual budget for this work in the coming years will be of the order of £100,000 About half of this will go to the projects which the institute has undertaken jointly with the Tavistock Clinic and the other half to independent social-science programmes outside the medical field

From the start of the National Health Service, the North West Metropolitan Regional Hospital Board has supported the educational work of the institute, especially through the postgraduate courses offered at the Tavistock Clinic for psychiatrists, psychologists, child psychotherapists, and social workers External courses have also been run for general practitioners, public health workers, teachers, probation officers, family care workers, and industrial personnel officers, including students from overseas For this side of its work the institute received last year from the Old Dominion Foundation £89,000 (to be spent over seven years) and from the Grant Foundation £25,000 (to be spent over three years) which was given specially for the training of people working among children and parents

During 1956 the institute also received grants for its research The Ford Foundation gave £80,000 (to be spent over five years) and the Josiah Macy, jun, Foundation £13,000 (to be spent over three years) It is planned to extend the work of the institute's child development unit from problems arising from the deprivation of maternal care, to which it has been giving special attention, to the conditions which promote the development of a healthy personality Another research group has been making an exploratory study of a small number of London families who have different income but are otherwise alike This work grew out of experience in marriage counselling at the clinic and at the institute's Family Discussion Bureau, and towards it the Grant Foundation has given £5000 to be spent during 1956 and 1957

The Home Office, the London County Council, and British foundations which have aided the institute with this work in the past will share the institute's pleasure at this international recognition of its work and practical help towards its achievement

BODY FAT IN CHILDHOOD

"PUPPY fat" is a convenient term of abuse or of defensive hope for the future it covers, perhaps, a multitude of sins Just what it connotes anatomically, however, is harder to say Recently reliable growth curves for subcutaneous fatty tissue in childhood have been prepared, thanks to the efforts of those engaged in longitudinal studies here and in America There are four methods of obtaining information about body fat by taking soft-tissue radiographs, which enable the investigator to distinguish and measure individually the bone, muscle, and subcutaneous tissue, by pulling with the thumb and forefinger a fold of skin and subcutaneous tissue away from the underlying muscle and measuring its thickness with pinch callipers, by calculation from the specific gravity of the body, itself obtained through underwater weighing and application of the principle of Archimedes, and by calculation from the amount of body-water estimated by chemical or isotopic dilution techniques The last two of these have not yet yielded sufficient data during childhood to warrant much discussion, though potentially they are the most valid measures of the amount of total body fat, since the other methods measure only the thickness of the subcutaneous layer There is, however, good evidence [1] that the internal fat is, under most circumstances closely proportional in amount to the fat stored beneath the skin

The *soft-tissue* X ray technique was initiated by Stuart [2] and his associates at Boston, who studied the growth of bone, muscle, and fat in the calf of the leg. It has been elaborated by Reynolds[3] and his successor Garn,[4] at the Fels growth study in America, and in this country by Tanner[5] at the Harpenden growth study, where techniques have been developed for obtaining quantitative tissue growth data for arm, calf, and thigh. Measurement by skinfold callipers has a much longer history, but the results are less illuminating than they might have been because of the absence of an efficient calliper giving a constant pressure to the skinfold at all thicknesses picked up, and also of a generally agreed technique. Recently, however, a wide acceptance has been found for the Harpenden skinfold calliper,[6] and Hammond's extensive cross-sectional survey[7] of skinfolds from age 2 to 18 has been reported in these terms.

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[1] Brozek J, Keys A *Brit J Nutr* 1951 5 194

[2] Stuart H *Monogr Soc Res Child Develop* 1940 5 no 3, *Child Develop* 1942 13 195, *J Pediat* 1946 28, 637 *Child Develop* 1950 21 220

The main growth curves of subcutaneous fat are now fairly clear. From the age of 1 year onwards there is a steady loss of fat; the amount lost per year becomes smaller and smaller as the child gets older, until somewhere between five and eight there is neither loss nor gain. After this, fat gradually begins to accumulate, and this process continues to adult life, with the exception that for a year or more at adolescence boys lose fat and girls usually cease to gain it. The greatest rate of fat increase, at least in boys, is immediately before the beginning of the adolescent growth spurt, and this gain has been called the pre-adolescence fat spurt.[5] It is this period which is usually called the "puppy fat": the anxious parents can be assured that the boy will lose a good deal of this fat during the next two years; but they should also be warned that most or all of it will return during the two or three years after that, unless something is done to restrict the intake of food.

The course of events during the first year of life is intriguing and may have more profound physiological implications. The details have been clarified in a new paper by Garn[8] in which, in contrast to so many studies of growth, exemplary use is made of the longitudinal nature of the data. Between birth and three months the infant puts on a very great deal of fat; the calf subcutaneous tissue at the maximum diameter increases on average by 5·7 mm. between one and three months. Between three and six months the increase is 4·6 mm. and between six and nine months 0·7 mm. Thereafter calf fat decreases; the average infant is fattest at nine months of age. Some babies, however, start losing fat at six months, and about 15% are still gaining at one year. Though Garn's study was of the calf only, the skinfold calliper data of the Child Study Centre in London[9] show exactly the same time relations for fat over the arm and on the trunk. What is the physiological mechanism of this wave of fat deposition and withdrawal in infants we have no idea. We do not know whether fat at this period goes into the same fat cells as the fat accumulated later, or even whether its composition is the same. In trying to explain the genesis of different body builds, Tanner[10] has suggested that fat cells, like muscle cells, may be laid down in utero, and that the ability to become fat, so to speak, may be limited by the number of cells present, just as is the ability to grow large muscles. If so, one wonders whether relatively great fatness in the infant presages the necessity for diet in the adult. Or perhaps the physiology of the infant is really quite different? Clearly this period provides uncharted ground for the pædiatrician with a flair for investigation.

RESEARCH IN ROAD ACCIDENTS

IN the public eye, the bogy of road accidents has lately been obscured by some bigger ones. Though between four and five thousand people are killed on the roads every year in Britain, about as many commit suicide, many more are killed in home accidents, and four times as many die from lung cancer. But the misery (about ten people are seriously injured for every one killed) and the economic damage caused by road accidents are shocking enough, especially when we consider that nearly every casualty could be prevented by imposing a speed limit of ten miles an hour. If the public conscience condones this sacrifice to the need (or lust) for speed, the least we can do is explore every means of reducing the numbers of killed and seriously injured, both by preventing as many accidents as possible and by mitigating the severity of the rest. If St. George will not slay the dragon, he must try to blunt its teeth.

Two years ago[1] when we discussed various ways of doing this, more research into the nature and cause of accidents was clearly needed. Unless we know the most important causes of injury we cannot direct our efforts to the most profitable end. A new pamphlet,[2] prepared by the Department of Scientific and Industrial Research, gives some account of research done in the United States, where the death-rate on the roads is even higher than it is here (705 people were killed during the recent Christmas holiday). Much of this research was done at Cornell University Medical College.

The information is being gathered in three ways: (1) details of accidents and the injuries sustained in them are collected in sample areas; (2) accidents are studied experimentally, using dummy passengers, cine films, and other recording equipment; and (3) protective devices are designed and tested. Many results are to hand and have already been applied in the design of vehicles in the United States.

Many injuries fatal to the driver were caused by his chest striking the steering column. The risk can be lessened either by padding the hub of the wheel, which distributes the force of the blow over a wider area, or by using a wheel which projects several inches above the hub, so that most of the force is spent in bending the supports of the wheel. To minimise the serious injuries to the head, face, and knee caused by the dashboard or other parts of the car, these parts may be strategically padded with foam plastic. Crash-helmets would also be useful, though motorists would probably be even harder to persuade to wear them than are motor cyclists. Windscreens and doors accounted for nearly as many injuries as the steering-wheel and dashboard. The risk of striking the head against the body of the car can be reduced by safety harness, which must be attached to the frame of the car and not to the seat, for if the seat is dislodged in a collision and its weight added to that of the sitter, the force with which he strikes the body of the car will be greater. Perhaps most helpful, and less cumbersome to the motorists, are improved door-locks; for the chances of being killed or badly injured are doubled if the occupant is thrown out of his car.

Most of these devices can now be fitted to modern production models as extras if the purchaser wants them. It will be noted that they protect only those inside the vehicle, which is appropriate in a country such as the United States where three quarters of the deaths are in motor-vehicle drivers or passengers (most of the other deaths are among pedestrians and only about 1% each among cyclists and motor cyclists). But in Britain only a sixth of those who die are motorists, nearly half are pedestrians, a quarter motor cyclists, and the rest pedal-cyclists. The American findings can be used in this country and may save the lives of motorists (though different road conditions and styles of vehicles may lead to different injuries here), but it is important to find ways of protecting other road users. Some research has been done in the nature of their injuries (thus, in motor cyclists most deaths are due to head injury and the legs are damaged more often than the arms, while in pedal cyclists the arms suffer more than the legs), but there is much more to be learned. Three phases of research, similar to those undertaken in the United States, are planned, the first has begun on a small scale in Slough. Protective clothing, improved external design of vehicles to protect pedestrians, and alterations to motor cycles to protect the riders are foreseen.

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[3] Reynolds, E. L. *Child Develop.* 1944, 15, 181; *Anat. Rec.* 1948, 102, 45; *Monogr. Soc. Res. Child Develop.* 1950, 15, no. 2.

[4] Garn, S. M. *Hum. Biol.* 1953, 25, 144; *Ibid*, 1954, 26, 59.

[5] Tanner, J. M. Growth at Adolescence. Oxford, 1955; *Nature, Lond.* 1955, 176, 1180.

[6] Edwards, D. A. W., Hammond, W. H., Healy, M. J. R., Tanner, J. M., Whitehouse, R. H. *Brit. J. Nutr.* 1955, 9, 133.

[7] Hammond, W. H. *Brit. J. prev. soc. Med.* 1955, 9, 201.

[8] Garn, S. M. *Hum. Biol.* 1956, 28, 232.

[9] Tanner, J. M. International Children's Centre Conference of International Growth Studies, London, July, 1956.

[10] Tanner, J. M. *Advanc. Sci.* 1955, 12, 110.

[1] See *Lancet*, 1956, ii, 797.

[2] Research on Injuries Sustained in Road Accidents. By H. J. H. STARKS, B.SC., PH.D., D.I.C., F.INST.P. Road Research Technical Paper no. 37. H.M. Stationery Office (for the Department of Scientific and Industrial Research). Pp. 14. 2s.

Everything that can be done by improved design of vehicles must be done, but more might be gained by improving the roads and changing the laws governing those who use them. It is even more important to realise (and constantly remember) that no big reduction in the number of dead and injured can be expected until more care and skill are shown by those who use the roads.

FAST VITAL CAPACITY

THE measurement of lung volumes has long been used in the assessment of respiratory disease, and the determination of vital capacity not only is easy for the patient to understand and perform but also requires only a spirometer for its execution. The introduction of respiratory rate and capacity into lung-volume tests came with the measurement of maximum breathing capacity (M.B.C.), this measurement was designed to estimate the patient's over-all ability to move air into and out of the lungs, and the result therefore depends on the muscular effort achieved as well as on the physical properties of the lungs.

More recently the "timed vital capacity" has been advocated, in this test the patient makes a maximum volume shift of air into or out of the lungs as rapidly as possible, and the volume is recorded against time. These manœuvres give the inspiratory fast vital capacity (I.F.V.C.) and expiratory fast vital capacity (E.F.V.C.) respectively, and from the resulting curves information can be obtained about the state of the lungs, the curve itself is interpreted in one of two ways, either directly or as it relates to the M.B.C. These interpretations have been discussed by Bernstein and Kazantzis[1] and by Shephard.[2] *The direct interpretation of the curve* relies, for example, upon the measurement of the one second volume, while the interpretation of the M.B.C. is more closely connected with the maximum flow rate achieved—on the hypothesis that the M.B.C. test allows the respiratory effort to operate over the optimal parts of the E.F.V.C. and I.F.V.C. curves in such a way that the shift of air is a maximum.

Such tests, depending as they do on the measurement of rapidly changing quantities, require apparatus that can respond quickly and without "overshoot" if the results are not to give rise to misleading interpretations. Indeed, some of the earlier work on F.V.C. was carried out on the conventional heavy spirometer bell and gave false results. More recently a lightweight spirometer bell or the pneumotachograph has been used to measure volume shift in F.V.C. The pneumotachograph measures air-flow rate and requires integration over time to give volume, it has been used by Shephard[2] to investigate F.V.C. Both these types of apparatus offer little resistance to respiration, and both seem suitable for rapid F.V.C. measurements, *interference from such factors as inertia* of the bell and the temperature of the respired gas is of little significance. Shephard points out, however, *that the complex resonating system*, made up of the spirometer bell and the U-loop of the water seal, linked together by the elastic gas volume, introduces certain errors when the F.V.C. is recorded by the spirometer. These errors include the failure to indicate the true starting-*point of the manœuvre, and the obscuring of the end-point of the one second volume capacity* by bell oscillations. Shephard considers the volume delivery over the first second to be the most useful measurement derived from the F.V.C., provided that it is related to the total time of delivery, and he admits that for this measurement the errors introduced by the lightweight spirometer bell are unimportant clinically. Thus, for this purpose *the more complex apparatus* needed *for pneumotacho*gram recording and integration is unnecessary.

It is claimed, not without reason, that the F.V.C. test is much less exacting for the patient than the M.B.C. and that the F.V.C. can be made to give as much information as, or more than, the M.B.C. Though these claims are probably true, it must be remembered that it is only the volumes of gas shifted and the rate of shifting which are being measured, and not the pressures required to produce the movement. When volumes only are measured there can be no indication of the respiratory work involved, which is determined by both pressure and volume changes during respiration. In so far as respiratory work is important, as in emphysema, F.V.C. by itself provides an incomplete assessment of the respiratory state of the patient, and this view accords with the conclusions of Attinger et al. to which we lately referred.[3] Nevertheless, the F.V.C., when properly performed and interpreted, can give valuable information, and it is *a satisfactory compromise between* the extent of the measurements required and the increasingly complex and specialised apparatus necessary for the collection of important data.

THE REFUGEES

WHATEVER their plans, Hungarian doctors who have reached this country are eager to learn English without delay.

Many education authorities run courses in English for foreigners, and some propose to start special courses for Hungarians. In London application should be made to the education officer at County Hall, S.E.1, in writing or in person (room 76) or by telephone (Waterloo 5000, extension 441). The county council is waiving fees.

The B.B.C. has a series of quarter hour English lessons for those who already know some English, each day on its European service (232 metres) starting at 5 and 6.45 A.M. and 12.15, 5.15, 7.15, and 9.15 P.M. The 9.15 P.M. transmission is likely to be heard best, and at this time classes at elementary level are given on Mondays, Wednesdays, and Fridays.

Two special long playing records *to teach* English from the start have been made for the B.B.C. These are obtainable at 15*s* each, and two corresponding textbooks at 2*s* each (or 3*s* 6*d* for the two), from *the B.B.C., English by* Radio, Bush House, London, W.C.2. Cheques should be made payable to the B.B.C. Club. Alternatively, copies of the *records and books may be borrowed from The Lancet* office.

A series of five books for instruction by the direct method is published by Berlitz, and is obtainable from K. Sussapfel, Publisher, 36, Maiden Lane, Strand, London, W.C.2. The first of these costs 6*s* 6*d* (plus 9*d* postage).

Further offers of temporary homes for Hungarian doctors may be addressed *to* this office and are likely soon *to* be taken up—especially those from the London area. The fund established by *The Lancet* to meet special immediate expenses of medical refugees and their families is being distributed. Applications—and further contributions—are invited.

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[1] Bernstein L., Kazantzis G. *Thorax* 1954, 9, 326.

[2] Shephard R. J. *Ibid* 1956, 11, 223.

[3] See Annotation *Lancet* 1956, ii, 1031.

Special Articles

MEDICAL ADMINISTRATION IN MENTAL HOSPITALS *

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THE clinical side of work in mental hospitals has greatly expanded in recent years, and it is largely because of this that there is discontent among some consultant psychiatrists who are not medical superintendents I shall try to analyse the present situation from the point of view of the clinical consultant, though I am fully aware that other interpretations of this situation can be given

Perhaps the first impulse has been to stifle this discontent, or to ignore its existence , but in the long run suppression exaggerates the difficulties, whereas public discussion will lead to a constructive and healthy solution We must not forget, as Stanton and Schwartz (1954) have so admirably shown, that dissent in high places produces only one result—deterioration in the patient's behaviour and morale

Advances in treatment, a greater knowledge of the causes of mental illness, and far reaching changes in legislation have produced a greater readiness to accept treatment in the early stages of mental illness, and consequently the number of annual admissions has greatly increased In 1929, the year before the Mental Treatment Act came into force, the annual admissions to mental hospitals in England and Wales were 22,000, whereas in 1954 they had increased to 71,000 (Logan 1956) In addition there has been a considerable increase in the number of outpatient attendances at the clinics associated with the mental hospitals

All this has meant that much more time has been spent in investigating and treating individual cases Much of this work has fallen to the lot of the clinical consultant Since the emphasis has now shifted from custodial care to active psychiatry, we must ask ourselves whether the present administrative arrangements embodied in the Lunacy Act, 1890, and the Mental Treatment Act, 1930, are best suited to deal with this new burden

Results of Investigation

I have investigated the present situation by sending a questionary to clinical consultants in thirty of the larger mental hospitals in England and Wales To this I have had twenty five replies, and I am much indebted to the consultants concerned for the care they have taken in presenting the facts Briefly these are

Five consultants stated, without any reservations whatsoever, that the present methods of medical administration were completely satisfactory, and that no difficulties of any kind had been experienced

Against this, in four of the hospitals considerable dissatisfaction was expressed so much so that a near breakdown in interpersonal relationships seemed to have existed

The remaining sixteen consultants, though admitting that the present arrangements could and did work harmoniously, given a sensible and liberal interpretation of existing statutes and rules, nevertheless qualified this in some way or another

In the four hospitals where greatest friction existed, this arose largely because the medical superintendent had so interpreted the legal position as to regard himself as the final authority not only in administrative matters but also in clinical ones and had accordingly thought it his duty to authorise and select the type of treatment of any patient he wished

One consultant held that this attitude had in the past hampered the progress of mental science by certain treatments having, in some hospitals, been actually prohibited

Another said that a consultant in the mental hospital service had a much lower status than consultants in other branches of medicine

All agreed on the lack of complete responsibility felt by the clinical consultant

In the sixteen hospitals where relations were harmonious but some dissatisfaction with existing arrangements was expressed the following observations were made

Six of the consultants thought that the only realistic way to make the existing legal arrangements harmonious and satisfactory to all concerned was to have an effective, responsible, and properly constituted medical advisory committee to settle any differences in private without reference to lay committees

One consultant emphasised that the medical policy of the hospital as a whole should be constantly under review by such a committee, which should not be used solely to bolster up the authority of the medical superintendent when he found himself in difficulties with his lay-committee, as was sometimes the present tendency

Three others suggested that it was no longer possible to run a modern mental hospital on authoritarian and dictatorial lines, because this would inevitably lead to a great deal of friction and would make conditions impossible not only for the clinical consultant but also for the medical superintendent, and the people who would suffer most would be the patients

The least difficulties seemed to have arisen where the medical superintendent had direct clinical charge of some of the patients

Three of the replies showed that, in this connection, the most effective way of meeting the various difficulties connected with medical administration was the introduction of "clinical firms," one under the direction of the medical superintendent and others under that of clinical consultants, the latter having complete autonomy concerning the admission and discharge of patients under their care It is of interest here to note that the Expert Committee on Mental Health (1953) regards the treatment of each patient as "a team responsibility in which several doctors and several nurses actively participate" Even with such arrangements into teams, it was pointed out in one of the replies, it was still theoretically possible for a clash to occur, but it was equally possible for there to be no such clash and for all senior medical staff to have the status that they enjoyed in other specialties Despite these conclusions it was nevertheless felt that some authoritative clarification of existing rules should be made because of other interpretations

Three other consultants expressed the view that most of the difficulties arose because the consultant did not feel that he had complete charge of his patients, despite official assurances to the contrary

Another thought that, if a consultant in the mental hospital service did not experience a sense of full clinical responsibility, it was largely his own fault

Lay administration was recommended by two consultants, while a third thought that this would some day overwhelm us all, whether we liked it or not

One consultant was convinced that the mental hospital consultant had now come of age and no longer required a 'father figure", but another would not be a party, under any consideration whatsoever, to the formation of any Secret Society for the Abolition of Medical Superintendents

Another pointed out that, almost overnight, whether by accident or design, the position had been completely revolutionised by the introduction of the National Health Service Act in 1948, whereby clinical consultants were appointed in most of the mental hospitals, whereas they had previously been known as assistant medical officers Unfortunately a tendency persisted in some mental hospitals for the medical superintendent still to regard all the other doctors in the institution including the consultants, as his assistant medical officers, a state of affairs which caused considerable dissatisfaction

Several consultants felt a sense of frustration because the regional hospital board and even the hospital management committee appealed to medical superintendents only when seeking advice about general medical policy in matters of psychiatry

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* Based on a paper read at a quarterly meeting of the Royal Medico Psychological Association on Nov 16 1956

Discussion

I shall state the problem as it appears to me after analysing all the opinions submitted There are two factors which are to some extent mutually at variance yet *must somehow be made complementary*

(1) *Mental hospitals differ from general hospitals* in that sound clinical administration is essential to establish within the hospital a therapeutic community in which the human and social needs of the patients (some of whom have to stay for a long time) are properly understood and adequately met (only two consultants mentioned this) It is difficult to see how such reforms as the "open-door hospital" could have come about unless the clinical administration had been in the hands of a clinically experienced medical administrator who could see the problem as a whole

Maxwell Jones and Rapoport (1955) have drawn our attention to the importance of the concept of "administrative psychiatry" and have pointed out that "informal social processes are more important to therapy than has usually been assumed" The Expert Committee on Mental Health (1953) said "that the creation of the atmosphere of a therapeutic community is in itself one of the most important types of treatment which the psychiatric hospital can provide" It is furthermore pointed out that the nearer a mental hospital approaches the organisation of the general hospital the less successful will it be in applying effective psychiatry

But, because of the changing nature of the clinical problem already outlined, such a régime is insufficient to meet the needs of psychiatry today Important though it is, it must be coupled with ever-increasing clinical treatment of each separate case

(2) *A traditional and fundamental requisite of all such individual treatment is that there should be a sound doctor-patient relationship* By this I mean that the patient should be able to look to one doctor as personally responsible for diagnosing his illness and supervising his treatment On the doctor's part it will be implicit that he will feel privileged that the patient has sought his advice, and that, if he values his reputation, he will not be content until he has given of his best The Expert Committee on Mental Health (1953) said "it is desirable that the patient, throughout his stay in hospital, should feel that there is one doctor who is his—one doctor who knows him well and whom he knows"

If such a relationship is the basis of all successful treatment, whether in general practice or in the specialties, it is especially so in psychiatry, where it is one of singular intimacy and subtlety But it is in mental-hospital psychiatry that this traditional relationship is at its weakest, as many of the replies have shown, and it is here that the fundamental conflict arises, because, on the patient's admission to the mental hospital this personal sense of responsibility felt by the consultant towards his patient is undermined In the general hospital the physician or the surgeon admits the patient to one of his own beds and has absolute responsibility for him In the mental hospital the patient, if certified, is committed in law to the responsibility of the medical superintendent, who alone can authorise his discharge, because Act of Parliament amended by Statutory Instrument (1948) no 419 paragraph 4 designates him as the chief officer of the institution

In actual practice amicable arrangements usually exist whereby the clinical consultant will discuss with the superintendent the question of discharge, but the fact remains that the superintendent has the power of veto and cannot be blamed if he uses it since it can be interpreted that he alone is responsible if anything goes wrong

The same remarks apply, though perhaps with less force to voluntary patients Whether certified or voluntary, a patient may sometimes become aware of a dispute about the advisability of his discharge He may then realise that his case is not the sole responsibility of the consultant concerned and his trust in the doctor looking after him may be damaged

Not to have complete responsibility engenders a sense of frustration, and, if the mental-hospital service is to attract the right kind of doctors, it is vital that these arrangements should be modified The Central Health Services Council (1956) states that the absence of a sufficient number of psychiatric consultants is related to the insufficient number of entrants into the specialty, the over-all shortage being about 20% of establishments

By conferring full responsibility on the consultant as in other branches of medicine, his status will be correspondingly enhanced, and potential recruits might thereby be attracted in greater numbers than at present What is perhaps more important, his therapeutic effectiveness will be strengthened, and he will come to have an accepted and authoritative position in society equal to that of the physician or the surgeon

Suggestions

Because the requirements of effective administrative psychiatry and the need to give the clinical consultant full responsibility are to some extent conflicting, it is not easy to find or to apply a remedy, but it is essential that one should be devised without undue delay, for the scope of the mental hospital as regards the mental health of the community is likely to widen to a degree unknown at present, and the mental hospital may change out of all recognition

I therefore make some suggestions as a basis for discussion

Working Party

Now that the shortcomings of the present system of administration are so apparent that the public press has become interested, it is desirable that the Royal Medico Psychological Association should appoint a working party consisting of equal numbers of medical superintendents and clinical consultants to examine this problem

If clinical consultants are to have a more effective voice in shaping the future of psychiatry, they should be better represented in the various committees of the Association The parliamentary committee of the association is composed of 29 members, of whom 16 are medical superintendents and only 2 are clinical consultants in mental hospitals In defence of this it might be argued that superintendents have a greater interest in parliamentary affairs because of their statutory responsibilities, but the membership of the education committee of the association shows a similar distribution of 34 members 24 are medical superintendents and only 4 are clinical consultants in mental hospitals

Medical Superintendents

In the present stage of evolution of the mental hospital—because of the problems concerned with the establishment of a therapeutic community—medical superintendency should continue *It is furthermore essential that medical superintendents should continue to be pre eminent in the clinical field*, for only thus can they command the respect and allegiance of their medical colleagues It is, however, difficult to see how outstanding men will be attracted to a post which daily carries more and more responsibility and less recognition It might therefore be an advantage to introduce some features of the system of medical staff organisation elaborated during the past thirty years by the American College of Surgeons and now widely practised in American hospitals generally

Under this each specialty is organised into a team under the direction of a leading clinician whose chief endeavour is to maintain a high standard of clinical work in that specialty by continued supervision, by the organisation of regular clinical conferences, and by guidance of the work and training of junior staff Such supervision does not however, go to the length of placing one consultant in the position of directing or criticising another's work, thus avoiding one of the worst features of the present mental hospital system existing in this country Upon the leading clinician devolves much administrative responsibility, and it is he who, with the help of a medical-staff committee, directly advises the lay administration on matters of medical policy.

It seems to me that such a system could well be adapted to the administrative needs of mental hospitals here, with a considerable raising of the general standard of clinical work, because the medical administrator would first have had to show that he was a clinician of the first rank. It might be objected that good clinicians do not necessarily make good administrators; but the two disciplines have much in common, and the organisation of courses in administration (already planned in this country) would do much to remedy any imperfections. The clinical consultant and the medical administrator would have a common goal, and the present regrettable tendency in the mental hospitals for a gulf to develop between them would be avoided.

The American system allows of full integration with other specialist services and with teaching and professorial departments. If such a system were applied here, the mental hospital in isolation would be a thing of the past, and it would become instead an effective unit for providing all psychiatric services to the community, and, acting through the Universities, it would in some cases perhaps also cater for the needs of students and postgraduates, which are at present inadequately met.

In this country medicine has tended to be very much of a personal affair between doctor and patient, and I have been at pains to emphasise the importance of this relationship; but there is already a tendency to organise some specialties into teams under the direction of a full-time professor, and if ever a specialty needed team-work it is psychiatry. Perhaps in some of the mental hospitals of the future the medical superintendent will come to have professorial dignity.

If such a system were adopted, it would be necessary to differentiate between the varying responsibilities of consultants, and the present methods of remuneration might therefore have to be revised.

Informal Admission

Coupled with such possible methods of administration there might also be an extension of developments already apparent in some of the more enlightened mental hospitals. I refer to the increasing tendency to admit patients informally to premises excluded from designation, as at Park Prewett, Warlingham Park, Graylingwell, and Mapperley Hospitals. Controversial issues over the admission and discharge of patients arising from the Lunacy Act and the Mental Treatment Act are in this way avoided. Perhaps we might also see the development of small psychiatric units, of 200 beds or so, attached to general hospitals and fully integrated with rehabilitation and other social services. We do not know for certain, but it might be possible in this way to prevent chronic mental illness in a large measure, as foreseen by the General Board of Control for Scotland (1956).

Sharing of Duties

It is essential that legislation should be introduced whereby the admission and discharge of patients should rest not only with the medical superintendent but also with the clinical consultant. This, together with the provision of smaller psychiatric units within the general organisation of the mental hospital, would give the consultant freedom to develop such units in his own way and in keeping with his own personality.

By all these means it should be possible for medical superintendents and clinical consultants to work together and to obviate the present tendency to a cleavage. Better understanding of the burdensome problems with which the medical superintendent has to deal might be gained if the clinical consultant could interest himself in some aspect of administration. At my own hospital, for example, I am privileged to deal with such matters as kitchen hygiene, and also the educational requirements of the nurses.

For a proper balance to be maintained it is furthermore desirable that the medical superintendent should be able to understand the point of view of the clinical consultant by himself having direct clinical charge of some beds.

Since many of the issues I have raised are controversial, it is only fair to state that at my own hospital relationships between the medical superintendent and the clinical consultants are happy and harmonious, and that many of the features I have mentioned receive de-facto recognition.

I wish to thank Dr E. S. Stern for his generous help in preparing this paper, and also the numerous consultants, whose opinions have been freely quoted, but who must remain anonymous.

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THE REMUNERATION CLAIM

Statements after Meeting with Ministers

FOUR representatives of the Negotiating Committee, Sir Russell Brain, Dr A. B. Davies, Dr J. D. S. Cameron, and Dr S. Wand, met the Minister of Health and the Joint Parliamentary Under-Secretary, Scottish Office, on Friday, Jan. 4.

The Minister of Health explained that he had not given a reasoned reply to the committee's supplementary memorandum because he had been advised that there were constitutional objections to his doing so. All that he could say about the legal aspect of the remuneration claim was that, according to the advice he had received, the Government were not under any legal contractual obligation to the profession. As to the merits of the claim, he could not even begin to examine these in the present economic circumstances of the country, since this, in his view, would start a "chain-reaction" in other quarters which would endanger the country's financial stability.

The representatives of the committee vigorously opposed the Minister's attitude and emphasised, in particular, that it was not merely a dispute about money but a crisis of confidence which went to the roots of the relations between the medical profession and the Government. At the end of a fruitless discussion the Minister offered to meet the committee's representatives again after he had given further thought to the problem and discussed it again with his colleagues. This offer was accepted and it was agreed that the further meeting should take place before the end of January.

After the meeting with the Ministers the Negotiating Committee met and unanimously expressed approval of the action taken by its representatives. Later on the same day, these representatives held a press conference. By this time the Ministry had issued its own press statement, in which it had again given the figure of 137% as representing the increase which had already taken place in the average pre-war remuneration of general practitioners. The Negotiating Committee's representatives explained to the press that this was an unfair and misleading statement, since it concealed the fact that the Spens Committee had found the actual pre-war incomes to be too low. The increase over the figure agreed with the Ministry, in the light of the Spens report, as the correct average in terms of the value of money in 1939 was only 100%.

The Ministry's press statement said that the claim was for an increase of not less than 24% over present levels of remuneration (which in the case of general practitioners were on average already 137% above pre-war) The extra cost to the country would be about £20 million a year The Minister had explained that the claim had *not* been rejected but, as he had already tried to make clear, the Government were responsible to the country for doing everything they could to combat inflation, and present economic circumstances made it impossible for them to consider the claim at the moment In other words, nothing he had said expressed any opinion one way or another on the merits of the claim It simply was that it could not be afforded under present conditions Regarding the profession's contention that the Government were under a legal contractual obligation, the Minister had said that the Government were advised that this was not the case The detailed reasons for this legal advice could not be given, for obvious constitutional reasons, in case of action against the Crown in the courts He regretted that the claim could not be examined on its merits at the moment He was already actively considering how best to deal with the problems raised by these issues, and all that the Negotiating Committee had said at their meetings with him on Aug 1 and last week would be taken fully into account in this review

Public Health

Antioxidants in Food

THE Minister of Agriculture, Fisheries, and Food has announced his decision to accept, with some changes, the Food Standards Committee's recommendations on antioxidants.[1] The use of four antioxidants (propyl, octyl, and dodecyl gallate, and butylated hydroxyanisole) will be allowed, up to certain limits, in "oils and fats, essential oils and butter used for manufacture" The committee's recommendation that the use of antioxidants should be disclosed to the purchaser is to be considered

Occupations and Ages

Analysis of the complete figures on personal occupation derived from the 1951 Census[2] shows that of the occupied men 29% were aged under 30, and only 4% more than 65, of the occupied women 44% were under 30, while 5% were 60 or over 88% of men aged 60–64, 47% of men aged 65–69, and 27% of men aged 70–74 were gainfully occupied, compared with 89%, 79%, and 53% respectively in 1921

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[1] See *Lancet* 1954, ii 711

[2] Census 1951 England and Wales Occupation Tables H M Stationery Office 1957 £7 7s

Infectious Diseases in England and Wales

Disease	Week ended December				
	1	8	15	22	29*
Diphtheria	7	4	6	10	3
Dysentery	727	830	808	696	348
Encephalitis					
Infective	3	9	5	4	5
Post infectious	3	3	2	2	
Food poisoning	191	247	319	177	112
Measles excluding rubella	4514	5979	6497	6641	6878
Meningococcal infection	20	24	39	25	20
Ophthalmia neonatorum	31	34	23	18	19
Paratyphoid fever	1	2	2	2	2
Pneumonia primary or influenzal	421	539	550	408	400
Poliomyelitis					
Paralytic	47	55	49	42	39
Non paralytic	25	27	24	18	10
Puerperal pyrexia	193	207	188	198	142
Scarlet fever	806	846	766	730	524
Smallpox					
Tuberculosis					
Respiratory	605	644	578	506	387
Meninges and C N S	14	10	10	6	4
Other	63	75	79	64	56
Typhoid fever	3	5	1	1	2
Whooping-cough	2115	2131	1983	1742	1265

*Not including late returns

Conferences and Congresses

HOSPITAL COCCAL INFECTIONS

ON Jan 2 a symposium on hospital coccal infections was held in London, under the auspices of the Association of Clinical Pathologists, with Prof A A MILES in the chair

Dr A C CUNLIFFE pointed out that hospital infection could be defined in clinical or bacteriological term Both must be used to obtain a true picture, for *Staphylococcus aureus* could be recovered from 10% of all wounds showing no clinical sepsis, whereas wounds might break down without being infected The prevalence of sep had been falling before antibiotics were discovered, it was now rising

Dr R E O WILLIAMS spoke of the principles of investigation of an outbreak of hospital infection Sepsis should be routinely recorded, and the outbreak considered epidemiologically, bacteriologically (including assessment of the serotypes or phage types involved), and hygienically thus if one type only was involved there was likely to be a single source, but if there was more than one type there might be some general or specific lowering of aseptic standards Phage group I was common in maternity units and group III in surgical wards

Dr B R FRISBY (Oxford) described two outbreaks of staphylococcal diarrhœa, these involved 31 patients (of whom 14 died) including 14 who had undergone gastrectomy (of whom 7 died) All had had antibiotics, but only 5 had had broad-spectrum antibiotics The onset and course were rapid, with rice water stools and collapse Pathogenic staphylococci were found all over the ward, which was quickly infected by a single patient Dr Frisby recommended that antibiotics should be given to surgical patients only when there was a definite indication, and then the patient should be isolated, side wards were ineffective for this

Dr E J LOWBURY (Birmingham) agreed that staphylococci of phage group III predominated in burns, and wondered whether the decreased incidence of streptococcal infection was due to a reduced virulence of the organism Dr FRISBY said that 1 case of staphylococcal diarrhœa had followed neomycin therapy, and that in his cases smears of the stools were loaded with staphylococci, indicating that these probably caused the diarrhœa and were not an incidental finding 6 patients had responded to erythromycin Dr O M LIDWELL spoke of the advantages and drawbacks of various methods of ventilation, and Prof J W HOWIE (Glasgow) said that an inefficient steriliser was worse than useless, for it could concentrate polluted air

Theatre Infections

Dr R A SHOOTER gave an account of the sharp drop in wound sepsis (9% to 1%) when the ventilating system of an operating-theatre was changed so that air was no longer sucked in It was useful to have a brisk horizontal flow of air over the table

Dr R BLOWERS (Middlesbrough) said that a wound could be assumed to have been infected at operation if sepsis quickly followed, if there was deep but not superficial sepsis, or if infection was persistently associated with the presence of a certain person in the theatre Experiments with a slit sampler had shown that the contamination of air could be reduced greatly if movement in the theatre was restricted to the minimum necessary, if the patient was put in position on the table before he was brought into the theatre, if everyone in the theatre wore proper clothing, and if blankets were not used In half the septic wounds the same organism was present on the patient's skin, more attention might be paid to its sterilisation

Dr D B **MOORE** (Exeter) said that long operations and self-retaining catheters predisposed to wound infection There was a higher incidence of infection with virulent staphylococci if an "umbrella" of antibiotics was used

Dr W A **GILLESPIE** (Bristol) said that after 1081 operations there had been 85 staphylococcal infections, it was thought that 19 had originated in the theatre and 55 in the ward Staphylococcal wound infections arising in the ward were often due to phage-group III, and furunculosis to phage-group I which was found in the nurses' noses

Ward Infections

Dr **LOWBURY** spoke of burns He said that primary excision and grafting was the best prophylactic measure against infection When grafting must be delayed, infection could be reduced by dressing burns in an air-conditioned room using a no touch technique, and by using chemotherapeutic creams If *Streptococcus pyogenes* appeared, specific chemotherapy should be given The exposure method probably did not protect burns against contamination

Dr **JANET JELLARD** said that in nurseries the babies, which were often handled without gloves and with inadequate hand-washing, were the chief reservoir for infection The umbilical cord was especially dangerous and should be either covered or treated with an antiseptic

Dr E S **DUTHIE** (Southampton) described an outbreak of infection due to phage-type-80 staphylococcus in two general hospitals in the same group There were infections of the skin, eyes, wounds, bedsores, and urinary tract, and bronchopneumonia but no enteritis He agreed that babies were a reservoir of infection, and had found that prompt isolation of infected patients and staff was helpful, and that reducing the number of nasal carriers and the dust content had some effect

Dr J D A **GRAY** said that strict attention to cleanliness and asepsis in nurseries was essential Many staphylococcal infections, though resistant to other drugs, were sensitive to chloramphenicol and erythromycin, eye infection responded to sulphonamides and cord infection to gentian-violet Streptococci might survive penicillin treatment because of coexistent penicillinase-producing staphylococci Dr J G P. **HUTCHISON** (Newcastle upon Tyne) agreed with previous speakers that babies are the culture medium, infecting their mothers and other patients Dr M H **GLEESON-WHITE** (Cambridge) mentioned 15 cases of rapidly fatal hæmorrhagic staphylococcal bronchopneumonia All of them had probably had pulmonary œdema

Investigation and Control

Dr **WILLIAMS** listed the steps in the investigation of an outbreak These included keeping a theatre and a ward book recording all infections, and watching ward and theatre techniques as they were carried out in practice

Prof **RONALD HARE** described experiments showing that nasal carriers produced air contamination owing to infection of the skin and clothes, movement, dressing, washing, &c, spread the organisms more than did sneezing or talking A few carriers contaminated the air much more than the rest

Dr J C **GOULD** (Edinburgh) spoke of methods of reducing contamination by carriers Creams containing common antibiotics such as penicillin and tetracycline were the most effective in eliminating staphylococci from the nose, but these had drawbacks, and a mixture of neomycin or bacitracin and chlorhexidine ('Hibitane') was almost as effective In practice such creams reduced the incidence of auto infection and cross infection

Dr **BLOWERS** emphasised that laundering did not sterilise blankets, but heat sterilisation ruined them Woollen blankets could be sterilised about twenty times by a quaternary ammonium rinse after laundering He showed three experimental blankets that could be boiled, they were made of terylene, turkish-towelling and a cotton weave, and were respectively much more, a little more, and less expensive than woollen ones

Dr H B **MAY** spoke of the administrative aspects He said that one consultant in each hospital should concern himself with all hospital infections there All infections should be notified to him by the ward sisters He should investigate infections and advise on prevention and treatment The infected patient cost half as much again as the uninfected patient

Dr **MARY BARBER** said that staphylococci in pus were probably more virulent than those in the noses of carriers, it was therefore important to separate septic surgical patients in wards and operating-theatres Dr H G H **RICHARDS** (Winchester) said that hospital overcrowding predisposed to infection and that more and better hospitals were needed

GASTRO-ENTEROLOGY

A **CONFERENCE** on gastro-enterology, under the auspices of the Postgraduate Education Committee of the University of Glasgow and of the Royal Faculty of Physicians and Surgeons, was held on Nov 26–30

Treatment of Ulcerative Colitis

Dr S C **TRUELOVE** (Oxford) said that in the treatment of ulcerative colitis the correction of fluid and electrolyte depletion, particularly that of potassium, was important Blood-transfusion and administration of cyanocobalamin (vitamin B_{12}) or folic acid were valuable, oral iron should be avoided The diet should have a high protein and calorie content, in those with anorexia, a fortified intragastric milk drip was given at night Either cortisone, prednisolone, or corticotrophin could be given, and oral cortisone could be combined with the daily instillation by rectal drip of hydrocortisone Colonic dispersal by this route had been found satisfactory, and there were rapid remissions in many cases Antibiotics reduced the risk of pyogenic complications, and propantheline relieved abdominal pain

Dr W I **CARD** (Edinburgh) emphasised the considerable protein loss and the intensive replacement needed Surgery should be avoided during the acute phase if it were needed cortisone should be discontinued In surgical treatment Prof J C **GOLIGHER** (Leeds) opted for primary colectomy with permanent ileostomy Occasionally, irritation of the adjacent skin or stenosis of the stoma followed Mr A B **KERR** recommended primary ileostomy in some cases, with colectomy later The ileostomy bag need not be adhesive Dr **BERNARD LENNOX** said that biopsy of colonic mucosa was valuable in investigating the disease Often large areas of mucosa were shed this loss was irreparable and influenced the results purely medical measures

Peptic Ulcer

According to Mr R A. **JAMIESON**, the true prevalence of peptic ulcer in this country was about 10% for men and 3% for women These figures were based on post mortem series Mr D H **CLARK** said that before puberty boys and girls had an equal incidence of peptic ulcer, but after puberty ulcer was many times more common in males 90% of women had a remission of ulcer symptoms during pregnancy, but symptoms always recurred Onset or aggravation of symptoms was common at the menopause

Dr A. R **CURRIE** drew attention to the association of peptic ulcer with islet-cell tumours of the pancreas The risk of malignancy in gastric ulcers was probably less than had previously been believed, it was estimated that only 4% of gastric cancers routinely examined had arisen from chronic peptic ulcers

Prof T F RODGER said that in many cases the onset of symptoms was associated with emotional upset Studies in the United States suggested that ulcer patients had intense unconscious dependency wishes An "ulcer type" was no longer recognised

Dr L D W SCOTT suggested that the association between peptic ulcer and coronary-artery disease might be explained by the *customary high fat* diet of ulcer patients Of 110 men admitted to his wards with myocardial infarction, 20 (18%) had peptic ulcers, of 89 controls with bronchial carcinoma 8 (9%) had ulcers

Dr S LAZARUS said that rest in bed was the most important single factor in medical care and increased the rate of healing of both gastric and duodenal ulcers, it was more valuable in hospital than at home Diet, milk drips, and drugs might relieve symptoms, but did not seem to influence the rate of healing of an ulcer

. Mr A P M FORREST said that, in view of the risk of malignancy, gastrectomy should always be performed for gastric ulcer In duodenal ulcer an attack on the acid-producing mechanism was essential Gastrectomy was *probably still the treatment* of choice, *but* where it was inadvisable (as in the patient with pulmonary tuberculosis, the female, the poor risk, and where it was technically hazardous) vagotomy, with pyloroplasty or gastro enterostomy, was suitable In gastric ulcer the Billroth-I gastrectomy was preferable, but in duodenal ulcer it carried a high rate of recurrence, and a Polya reconstruction was advisable

Mr W T IRVINE said that patients in the fourth and fifth decades were particularly liable to develop stomal ulcer This was a complication of gastric operations only when they were performed for peptic ulcer, it might appear many years after gastro-enterostomy but usually within three years after gastrectomy These ulcers had a particular tendency to penetrate Marginal ulceration following gastro-enterostomy was treated by gastric resection and reconstitution of the jejunum involved in the anastomosis, but for recurrent ulcer after gastrectomy a higher resection was usually the *treatment of choice Vagotomy might help patients* in this group

The post gastrectomy syndromes were described by Mr A N SMITH Their incidence was directly proportional to the amount of stomach removed The small capacity of the gastric remnant, increased rate of gastric emptying, reflux into the afferent loop, hypoglycæmia, jejunal distension, osmotic influences, alterations in blood volume, and disturbance of acid base balance had all been cited as possible causes of these syndromes He advocated a high protein and high-carbohydrate diet and eating meals dry, soups should be forbidden Potassium citrate, local anæsthesia, and ganglion blockers might relieve *symptoms*, in severe cases conversion to Billroth I gastrectomy gave good results

Mr A W KAY discussed the management of bleeding peptic ulcers and suggested that they were, in the first instance, amenable to medical treatment Operation was rarely advised for the initial bleeding, when the mortality was low, or for the long term recurrence which in all respects resembled an initial hæmorrhage On the other hand, surgery should always be considered in patients over the age of 50, as in this group the mortality rose steeply or when there was a history of a chronic ulcer, particularly if this was gastric An acute ulcer was unlikely *to cause fatal bleeding* Surgery was undoubtedly required where there was continuing or rapidly recurring hæmorrhage where there were added complications of the ulcer (perforation or stenosis), or where pain persisted after the initial bleeding At operation the presence of blood in the gastric aspirate and the level of blood in the gut were guides to the site of bleeding If no ulcer was palpable or visible and the bleeding was *coming from* the stomach, an acute ulcer was the most likely source The presence of an enlarged lymph node *at the origin of the left gastric* artery was suggestive of a gastric ulcer If no source of bleeding was apparent the stomach was not to be opened but a blind gastrectomy performed If examination of the excised specimen did not reveal the lesion causing the bleeding the gastric remnant was inspected and any lesion dealt with

Treatment of Carcinoma of Colon

Professor GOLIGHER said one would expect to save half the patients with carcinoma of the rectum Three quarters of the cases seen were operable Local fixation of the growth, as estimated on rectal examination, was a completely untrustworthy sign of inoperability Palliative resection should be performed wherever possible, $1^{1}/_{2}$–2 years of comfortable life might be obtained by the patient with liver metastases For growths below the peritoneal reflexion, abdominoperineal resection was indicated If the growth was in the upper third of the rectum, low anterior resection gave as good results and *maintained a continent anus Lesions* here would be more than 10 cm from the anal verge on sigmoidoscopy and just within reach of the palpating finger The only certain sign that the blood-supply to the anastomosis was adequate was arterial bleeding in the cut mesocolon or bowel If there was doubt as to the integrity of the anastomosis, a temporary transverse colostomy was advisable, an extraperitoneal drain was left in place for 7–8 days In acute obstruction due to cancer of the right colon, immediate resection and anastomosis was usually possible, if the ileocæcal valve was incompetent and the ileum distended it should be decompressed by catheter In obstructing lesions of the left colon, either transverse colostomy or cæcostomy would relieve the obstruction In obstructing lesions of the transverse colon, the colostomy should be placed next to the growth for the cancer and colostomy could be simultaneously excised later

Mr KERR said that, as cancer of the rectum rarely led to obstruction, a palliative colostomy should never be performed Radiotherapy was beneficial for perineal recurrence

Gastro-intestinal Hormones

Dr CARD said that the evidence for the presence of humoral factors in the intestinal tract of man was not good It was now possible to localise accurately and study the cells of origin of a hormone, by administering the appropriate antihormone, which caused a reaction in the [illegible] cells The blood supply to the stomach was enormous, 50 volumes of blood was required to produce 1 volume of 0 16 *M* HCl 0 004 µg of histamine per kg body weight per hour (a dose well within the physiological range) *by* constant intravenous infusion could induce acid gastric secretion He believed that gastrin was a histamine liberator The use of secretin was well established in the diagnosis of pancreatic disorders In relapsing pancreatitis the administration of morphine with secretin prevented a flow of pancreatic juice and reproduced the pain After sphincterotomy the test gave a good flow of pancreatic juice and no pain Recent reports had suggested that pancreozymin contained a gall bladder contracting substance Fat in the duodenum inhibited gastric motility and secretion by release of the hormone enterogastrone, which inhibited all types of gastric secretion and protected dogs against the development of peptic ulcer after the Mann Williamson operation Urogastrone, the excretory product of enterogastrone was known to inhibit histamine and induce gastric secretion in man

Mr H I TANKEL suggested that histamine could stimulate pancreatic secretion—an effect blocked by atropine Mr SMITH presented data which demonstrated that extracted gastrin liberated histamine in all tissues

In England Now

A Running Commentary by Peripatetic Correspondents

Now that the well-informed have disposed of the *Times's* Christmas tests of knowledge, they may care to try the menu of last Saturday's medical banquet in Amsterdam. The outside presented few difficulties:

Singulæ Dapes (it said) appositae in Epulis Sollemnibus Nonis Ianuarus MCMLVII propter Ephemeridem Neerlandicam pro Medicina centum annos vigentem.

But now we came to the essentials:

Promulsis cum cancro
Ius testudinis in calice
Vinum ex vinea aulica Wehlenensi MCMLIII
Summa solea more archimagiri
Solana tuberosa Britanno modo
Phasianus assus
Brassica salita ornata
Poma cocta mixta
Vinum ex vinea Beinæ MCMLIII
Casei selecti
Placenta ex ovis cocta glacie sub spuma latente
Vinum spumans siccum (Perrier Jouet)

It was about 20 to 1 when we adjourned for

Cafæum
Coniacum et liquores

feeling that the evening had been well begun.

* * *

Not far from the American border in this part of the world there used to be a place called Fort Whoop Up where American whisky traders ran trading-posts to sell liquor to Indians in Canada. This led to such lawlessness that a body of men known as the North West Mounted Police established itself in the same area under Colonel McLeod at a place that has become the town of Fort McLeod. Fort Whoop Up is now nothing but a Historic Site.

Times change. The N.W.M.P. has become the R.C.M.P. The provincial government has established trading-posts known as government liquor stores where any man who pays fifty cents for a permit can go and buy as much hard liquor as he likes, provided he pays for it and is not Indian. Gasoline in abundance from local oil-wells provides power to drive cars at high speeds, faster than the fastest horses of the days of Fort Whoop Up. By these means many casualties enter hospitals, and some go to the funeral parlours. Many cars are wrecked and prosecutions for "impaired" driving bring revenue to the government in addition to the profit from the liquor stores and the gasoline tax.

This whooping-it-up state of affairs is mildly endemic throughout the year, but about Christmas and New Year it used to become epidemic, until a few years ago when the Alberta Safety Council began to deal with it prophylactically. The council is helped by the newspapers and radio stations and their advertisers, commercial firms, motoring organisations, and the city police in Calgary. Here cars may be seen bearing curious bumper legends such as "Drive like Lightning, Crash like Thunder." Another jingle of the campaign is "Stay Alert, Stay Alive, Make it Coffee when you drive." Badges distributed to truck-drivers bear the motto, "No thanks, I drive a truck." A distillery advertises that "Men who think of Tomorrow practise Moderation Today."

The culmination of the campaign is at the peak of the epidemic. In Calgary since 1950 the police will, by request, drive you home on Christmas Eve and New Year's Eve if you lack sobriety but retain wisdom. The too convivial driver will be driven home, and his car will be driven home too if there is somebody to take charge of the keys. Otherwise the car will be parked overnight and may be claimed when the owner recovers. This duty is undertaken by unpaid volunteers of the police department, and no charge is made for their services. It is strictly understood that their attitude is one of sympathetic assistance, and that no action will be taken against the driver who asks for help and doesn't drive. But the most awful penalties are promised to him who is found to be "impaired" and driving. The year this service was started the number of accidents over Christmas and the New Year fell from 65 to 13 and has never risen above 12 since. Calgary's methods may be unorthodox but they seem to be effective.

* * *

Singing at work must be as old as man. The Hebridean woman churning milk, the Negro slave chopping wood, the sailor hauling in the mainsail, and the boatman with his Volga boat, were all employed in monotonous physical tasks rendered tolerable and even pleasurable by a sort of mass hypnosis. A happy custom, and we are the worse for losing this capacity to burst into an appropriate lyric when about our everyday chores. It is good news, therefore, that a Cobbleigh Committee is sitting at Widdicombe-in-the-Moor to select occupational songs for the medical profession.

Two Lovely Black Eyes is suggested for casualty officers, and *Dry Bones* for orthopædic surgeons. Cardiologists will trill *Boom, Why Does my Heart Go Boom* in close harmony between patients, and pædiatricians will take readily to *Sleep, Baby, Sleep*. This song was put forward first for anæsthetists, but *Two Sleepy People* was felt to be more appropriate. Of contemporary songs, *Shake Rattle and Roll* might suit the physiotherapists, and *Rock Around the Clock* the maternity department. The committee is not neglecting the Greater Medical Profession: medical statisticians will have the first 99 verses of *One Man Went to Mow*, and hospital administrators and home sister *You Can't do That There 'Ere*. For the rest of the nurses *Tea for Two* is suggested. For psycho analysts there was a wide range of choice. *My Dreams are Getting Better all the Time* was considered, but in the end the committee recommended the old song that goes *We've Been Together Now for Forty Years, and it Don't Seem a Day Too Much*.

* * *

The Medical Superintendent had thrown a Christmas party and was gazing out of the window with pride at a gigantic fir tree in the grounds which was blazing with coloured lamps. A visiting psychiatrist clapped him on the shoulder.

"I say, old boy, that's a terrific show; how did you get the lamps?"

"Oh, they are just replacements from the stores and we got the depressives to spray them with lacquer."

"Yes, but who foots the bill for the extra current?"

"There isn't any."

"How come?"

"Oh, we just replaced all the hundred watt bulbs in the nurses' home with twenty fives."

* * *

I believe an ancient word for physician meant "one who knows urine," and many old pictures of the physician show him holding up a vessel of urine to the light. My old chief used to start his round in the side-room where the urines of all his patients were displayed in conical glasses. All this seems to have gone now and urine has become a rare commodity. Nurses are tidier than ever and all specimens are sent quickly to the path. lab. or sluiced away. I no longer see urine but only typewritten slips of paper describing it.

* * *

I was driving along a quiet country lane on my morning round when a small car, driven by a woman, shot out of a side turning and came to a sudden stop alongside me. She gesticulated wildly and shouted "Pig!" I was somewhat taken aback at this and, feeling much aggrieved, I wound down my own window, shouted "And pig to you!" slammed into gear, and drove round the corner where, wandering in the road, was the largest pig I'd ever seen.

* * *

One of my junior colleagues preferred to avoid the contacts and the accuracy involved in claiming mileage. Now "they" won't give him petrol coupons. I have been trying to push his case, but

Fabius Cunctator
Sired my
Administrator

Letters to the Editor

FUTURE OF NURSING

SIR,—I should like to give complete support to Dr Ritchie Russell (Dec 15) The statement of policy from the Royal College of Nursing must surely have been formulated after a study of the report of the Nuffield Provincial Hospitals' Trust on "The Work of Nurses in Hospital Wards" (1953), yet its aims are in many ways out of harmony with this The report pointed out that those State registered nurses who remain in the hospitals spend their time in the main watching student nurses do the actual work And it is generally well known that few SRNs do in fact devote themselves ultimately to the techniques of nursing

The new proposals seem to increase these tendencies, so that one may justifiably ask what will be the object of becoming a trained nurse

Anyone who has recently visited hospitals in the United States will have noticed the *reductio ad absurdum* which the craving of nurses for academic status has created in that country In hospitals other than those staffed by nuns, the graduate nurses in charge of beds tend to sit majestically at desks outside their wards, doing the "office work" and making critical (though often pertinent) comments on such matters as the blood chemistry of their patients The real nursing is done either by orderlies or by the patients' relatives

In medicine the aim of most of us in qualifying is to practise our craft, very few of us become medical administrators or devote ourselves wholly to teaching So should it be in nursing

Finally, if the nurses and the doctors are in the future to belong to parallel services, what is to be the fate of the patient? Whose will be the ultimate responsibility for his care? Many of us have noticed with concern a growing lack of acceptance by senior members of the nursing profession that they belong to an auxiliary service which must be subordinate to the doctors, and which cannot possibly have an independent existence If the Royal College of Nursing made public acknowledgment of this fact, and used its influence to ensure that nurses in training are given the same opportunity to live their personal lives as is accorded to students in other spheres, nursing would have no lack of recruits

Radcliffe Infirmary
Oxford

RONALD MACBETH

SIR,—I would like to endorse the views put forward by Professor Vining and Mr Brian Watkin (Dec 29), and also to thank Professor Vining for his admirable statement of the complex range of duties for which nurses must now be trained

A further point which might be emphasised is the numerical importance of nurses in the National Health Service It must be recognised that senior members of the nursing staff, in both hospital and public health services, generally carry direct responsibility for the work of a greater number of people than the senior officer in any other section of the services Unless these leaders have good intelligence, a sound knowledge of the principles of administration, and the wisdom to deal with a wide range of human problems, wastage will be severely aggravated

The age of entry into training needs further consideration, but although it seems necessary to establish a minimum, should this be chronological age alone? The patient, male or female expects from the nurse a maternal attitude, and this is developed by girls at varying ages Some girls of 17 are more mature than others of 19 If an accurate assessment of maturity could be made, this would be more important than age in years

The pressing problem of the status of the State enrolled assistant nurse urgently demands attention and perhaps the easiest step towards improvement would be a change in title to "State enrolled nurse" It is regrettable that the Royal College of Nursing, in its otherwise valuable statement on policy, has not recognised the need for promotion. Team-work would offer more interesting duties to the S.E.A.N., but would this alone be sufficient to attract recruits in the numbers we require? Ambitions may well soar higher than providing "a much needed stable element in the team" Is there any reason why experienced assistant nurses should not become ward sisters in certain fields, particularly that of geriatrics, in which their reputation is so firmly established? They should be, at least, as good as the inexperienced and sometimes inadequately trained State registered nurse

Lastly, with regard to the vexed question of "common entry" versus two types of training, is Dr Ritchie Russell not aware of the generally accepted principle that students of widely different intellectual ability cannot be taught together? If they could, the 11+ examination and A B, and C streams in the schools would be superfluous If it is agreed that nursing has room for women of different levels of intelligence and academic ability it is surely reasonable to accept two streams, or types of training

I would like to allay some of Professor Vining's fears about picking "'high ups' at the start of training" Certainly a university course should not be a passport to high office It should only give a better preparation for leadership to the candidate who also develops the qualities of mind, personality, and character needed by the leader It may also be hoped that some of those who would have the advantage of a university course would choose to remain in the field, in close contact with patients, just as some of our most able members today remain as ward sisters, health visitors, and district nurses, instead of stepping into administration The influence of these women who have the ability for senior appointments, but choose the more practical aspects of nursing work, cannot be overestimated

Leeds

JOYCE M AKESTER

SIR,—We have long advocated a scheme of training like that suggested by Dr Ritchie Russell Its purpose is to encourage recruitment and to avoid on the one hand the wastage due to inability to pass the State examinations and on the other the alleged frustration of the more intellectual candidate

The assistant nurse scheme recognises and has proved the value of the "ordinary nurse," and it is surely absurd to speak of downgrading a nurse's status by teaching her the basic technique of nursing We consider that the minimum age of entry for hospital training should be reduced to 17, that candidates must have reached a reasonable standard of general education, and that the present assistant-nurse training and "assessment" should be taken by all candidates, and should lead to qualification as a "State registered assistant nurse" No difficulty should attach to postponement of the assessment in the case of the slower candidates, nor should there be any slur upon those who continue for the rest of their lives in this grade There should, however, be a grade of "senior assistant nurse," with higher pay, obtainable by promotion by those who have served for say ten years in a hospital

During the two years of basic training it will have become evident which nurses are fitted for advanced training These candidates, who should possess the General Certificate of Education or equivalent general educational qualification, should proceed to a third year of training and to an examination in the theory and practice of nursing to enable them to qualify as "State registered nurses" This training, in our opinion, should include a course in pharmacology, and State registered nurses should have the same duty as the pharmaci to question dosage No one should become a hospital staff nurse without this qualification, and no one should be appointed sister who has not had a minimum experience of one year as a staff nurse in either a general or a special hospital

For those of academic ability and inclination there is already a diploma of nursing obtainable at London

University This might be taken by aspirants to teaching or higher administrative posts Nursing, in our view, is a subject totally inappropriate to a university curriculum leading to a degree.

G M WAUCHOPE
C M OTTLEY

Hove Sussex.

SIR —Lest Dr Thomas Anderson should again be disappointed I hasten to write in support of his letter of last week.

For many years I have been personally concerned with the teaching and training of nurses in two very large mental-deficiency hospitals During that period I have seen the standard of nursing raised considerably, only to fall again The General Nursing Council are now the only examining body for mental nurses, and the preliminary examination of that body is quite inadequately related to the experience which a first-year student nurse gains in the wards The syllabus for that examination makes no mention of the nature of mental illness, or of mental defect, of the special needs of such patients, or of the reasons for the special methods used in nursing them On the other hand, the academic level required in anatomy, physiology, communal health, and bacteriology has been steadily raised

The number of female nurses who complete their training as mental or mental-deficiency nurses is quite inadequate, and the proportion of trained nurses has fallen to a dangerously low level

The Ministry of Health is now pushing forward a scheme for the instruction of ' nursing assistants "—clearly with a view to introducing a grade in mental nursing corresponding to the State enrolled assistant nurse The inefficient handling of mental patients can produce results which are very serious for the patient, and which raise serious difficulties in administration This official attempt to perpetuate the present shortage of trained staff can only result in a lowering of the standards of care and treatment available for mental patients

Like Dr Anderson I take the view that it is our duty, as the doctors responsible for the care of these patients, to protest, and to do whatever we can to impress upon the Minister of Health that nurses must work under the direction of doctors, and that senior medical staff in every branch of medicine should have a much greater influence in prescribing the standards of training and examination of the nurses who have the immediate care of patients

In conclusion, may I underline one of Dr Anderson s points ? What our hospitals need are far more ordinary nurses—i e , staff nurses, trained to undertake the routine care of patients efficiently From their ranks will emerge those capable, after further training of accepting the responsibilities of the higher nursing posts

Brockhall
Langho near Blackburn

D J ROSE

X RAYS AND LEUKÆMIA

SIR,—We appreciate the way in which Dr Rabinowitch (Dec 15) has clearly depicted the fundamental issue at stake—that is whether there is a threshold dose of radiation below which leukæmia in man is not induced Dr Rabinowitch weighs the evidence and concludes that such a threshold is likely to exist and that it may lie between 100 and 200r , in our view the present evidence is insufficient to justify this belief

The principal weakness in Dr Rabinowitch s argument is that he has not adequately taken into account the very large numbers of persons who need to be studied in order to establish the presence or absence of an effect from doses of radiation as low as those that may be received during the course of diagnostic radiology Thus on the assumption of a simple proportional relationship between dose and effect, a reasonable estimate is that a dose of 1r averaged over the red bone-marrow of the whole body would cause about 1 case of leukæmia annually in a population of 1,000,000 people Bearing in mind that in the general population, aged 15 years and over, the incidence of leukæmia is approximately 50 cases per 1,000,000 persons per year it can be shown that about 20,000 000 persons, each exposed to a mean marrow-dose of 1r in excess of that received by the general population, would probably have to be observed for a period of ten years before the excess of cases could be recognised. If the average marrow-dose were about 20r, a population as large as about 50,000 persons would need to be observed for the same period Even the latter project would be formidable but it is not impossible ; and we must face the fact that if this important problem is to be solved, projects may well have to be mounted on this scale

It is not perhaps generally realised that similar limiting conditions have also been found in the investigation of the incidence of radiation-induced gene mutations According to Muller, the lowest radiation dose level at which it has been possible to observe the excess of lethals resulting from the irradiation of drosophila sperm is 25r[1] Nevertheless, above this level the form of the relationship between dose and response is such that geneticists have postulated with considerable confidence that no threshold dose exists for the induction of gene mutations, and this postulate has been accepted in practice

With regard to Dr. Rabinowitch s specific arguments, we would make the following comments

(1) It is not to us, surprising that none of the children of the 205 women who were pregnant when they were exposed to the atomic explosion at Hiroshima have developed leukæmia In fact only 4 of the mothers were exposed at distances of under 1000 metres and 145 were 2000 metres or more from the hypocentre From data published by the United States authorities,[2] estimates can be made of the doses of prompt γ-radiation that would have been received by persons standing unprotected in the open at varying distances from the point of explosion. These suggest that the dose at 1000 metres would be not less than 1400r and at over 2000 metres it would be not more than about 8r[3] The dose resulting from such fallout as occurred in Hiroshima is not likely to have increased the total doses substantially above those resulting from the prompt radiation The fact that the women exposed at less than 1000 metres survived, indicates that they must have been heavily shielded from irradiation, presumably by buildings, as a dose of 1400r to the whole body would cause acute radiation death in all persons Many if not all, of the mothers exposed at greater distances would also have been shielded to some extent, so that on average these mothers, even those 2000 metres or more from the hypocentre, will have received appreciably smaller doses than those estimated above While, therefore, all these mothers, and their children may have suffered some increase in their probability of developing leukæmia, it is our view that the population exposed was far too small, relative to the doses received for it to be likely that even one case of leukæmia would have been subsequently observed either amongst the mothers or their children

(2) With regard to the general incidence of leukæmia among survivors in Hiroshima and Nagasaki, Dr Rabinowitch argues that no increase has occurred among persons exposed beyond 2000 metres and that doses of between 100 and 200r must have been received at this distance since many instances of ' radiation sickness ' have been reported Like many others interested in the problem we believe that such reports of radiation sickness should be treated with reserve It has already been pointed out that the available physical data suggest that survivors exposed at more than 2000 metres received doses

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[1] Muller H J Radiation Biology New York 1954, p 476
[2] Effects of Atomic Weapons New York 1950
[3] Medical Research Council Report Cmd 9780 H M. Stationery Office 1956 p 15

of not more than about 8r of prompt γ-radiation, and radiotherapeutic experience shows that whole-body doses of X rays of this order do not cause radiation sickness The most likely explanation of the reported instances of "radiation sickness" is that a feeling of malaise with some nausea, and even frank vomiting and diarrhœa, may occur in anyone subjected to sufficient physical and emotional stress However, the data on the ratio of the observed number of cases of leukæmia to the expected number at varying distances from the hypocentre among Hiroshima survivors show that there is, in fact, a steady fall from about 100 to 1 for those exposed at less than 1000 metres to about 1 5 to 1 for those between 2000 and 3000 metres and that the ratio is still above 1 to 1 (i e, 1 2 to 1) for those over 3000 metres[4] The numbers of cases are, however, too small to be able to conclude that the incidence has definitely been increased at these two latter distances The populations of survivors are estimated to be 30,350 and 37,350 persons respectively, and the data refer to an eight-year period of observation As has already been pointed out, a population of 50,000 persons exposed to a mean marrow dose of as much as 20r may well have to be observed for a period of ten years before any significant excess of cases of leukæmia can be recognised

(3) Dr Rabinowitch quotes our own preliminary data on the incidence of leukæmia in 13,352 patients treated with X rays for ankylosing spondylitis,[5] and points out that, whereas 35 cases of leukæmia were found in those patients who had received a maximum dose in the spinal marrow of 500r or more, only 2 were found among those who had received doses of less than 500r These data, however, should not be taken as evidence in favour of a threshold effect, for, if they are taken at their face value, it must be concluded that the number of cases observed at each level of dose is, in relation to the number of patients exposed, proportional to the dose received and hence the data tend rather to support the hypothesis that no threshold dose exists

(4) The data on radiation-induced leukæmia in animals are complex and the conclusions based on them can be applied to humans only with the greatest caution—if at all In the first place, there exist considerable species differences in susceptibility, and leukæmia is less easily induced in the dog, the guineapig, or the rat than it is in the mouse There now seems little doubt that man has a higher sensitivity to the induction of leukæmia than many other mammals Secondly, most animal observations have been made on mice, and Furth and Upton and other writers have now shown that in this animal 3 different forms of leukæmia may be induced—a thymic lymphoma, a non-thymic lymphoma, and a myeloid leukæmia The facility with which these various tumours are induced seems to depend on several factors apart from radiation, such as the breed of mouse, sex, age at the time of irradiation, hormonal state, &c Certainly, Furth and Upton did report that the combined incidence of both types of lymphoma in untreated ageing RF male mice was about equal to that in their group of male mice exposed to neutron irradiation, up to biologically equivalent doses of about 500r[6], but it is probably unwise to generalise from such observations to man—particularly since Furth and Upton reported an increase of myeloid leukæmia in their irradiated animals, and human radiation induced leukæmias are mainly of this variety Thirdly, it is only within the last year that the problem of the incidence of leukæmia in relation to low levels of radiation has assumed such importance Published animal experiments have not been designed to investigate this particular point, if they had been, the experimental designs would have been different and the numbers of animals used much greater

In conclusion, we should like to point out that leukæmia is only one of the delayed effects of irradiation It so happens that to date most attention has been paid to this effect, but there are undoubtedly others such as the production of other tumours, and there is also the possibility that there may be a general effect on the expectation of life, to which attention has been recently drawn by Shields Warren[7] Such effects may be additive, and the total risk run by a given individual after a given radiation dose will presumably not be fully described by his enhanced risk of developing leukæmia But whether it is proper to extrapolate from existing data and to estimate quantitatively the size of the very small effect to be anticipated with the low doses used in diagnostic radiology is uncertain It is evident that, in this era when the medical and industrial uses of atomic energy are expanding so rapidly, it is of basic importance to determine whether threshold doses for the induction of these delayed somatic effects exist

Group for Research into the
General Effects of Radiation,
Radiotherapy Institute,
Western General Hospital,
Edinburgh

W M COURT BROWN
RICHARD DOLL

HEAD INJURIES

SIR,—One has reason to believe that 80% of casualty cases are first seen at non teaching hospitals,[8] and that most of these hospitals are faced with the problems outlined in your leader of Dec 22 It is, in fact, a great credit to the casualty departments in this country that the mishaps you refer to are so few, when there is no clear policy that I have ever heard of for the disposal of head-injury cases brought in the first instance to outlying hospitals I have puzzled over it for many years and am little further on than when I started The only course one can adopt is to admit everything one possibly can and to hope that the inevitable piece of bad luck will land on some other hospital's doorstep

In deciding what to send on to the neurosurgical centre the situation is little better One cannot, in all fairness, send everything, and one seldom knows what proportion of those sent have profited by it I do not believe one should send head injuries merely because they are severe It may be, as we are told by the neurosurgeons, that patients with head injuries travel well, but many are moribund when they are first seen, and it is wrong that someone who is going to die should do so in an ambulance or soon after admission to a strange and sometimes distant hospital Not only is it wrong, but it may be said that the transfer precipitated the fatality, and it is hard to hold to a theoretical opinion in the face of an individual tragedy The casualty officer or the inpatient emergency surgeon is often faced with a dilemma—to risk the upset of these mishaps, or to hold onto a case which might profit by prompt transfer I find it very difficult to give a confident prognosis soon after a severe head injury, and the silent extradural hæmorrhage can deceive anyone Moreover, clinical judgment must be tempered by knowledge of transport and other resources because the disposal of accident cases is almost as much a geographical problem as a surgical one (My suggestions for improvement in this direction have been described as "semi military,"[9] but I do not know if this was intended as half a compliment or half a criticism)

The present development seems to be to put small neurosurgical "metastases" from the regional centres into suitable peripheral hospitals, as soon as the multiplication of neurosurgeons is adequate to staff them But how far is this to go? Do we aim at a head injury unit at every crossroads, and if so, how much will it cost and how long must we wait to get it?

It would, to my mind, be much more sensible, as well as much less expensive, to integrate and educate the resources at present available for selecting these cases and for carrying out such preliminary treatment as will help any later specialised procedures They are admitted to *our* wards or seen in *our* casualty-rooms We want to know, more precisely than we do at present, what type of case need not be transferred, what type it is useless to transfer, and, most particularly of all, what should guide us in deciding whether to send a case on, to ask a neurosurgeon out to see it, or to get on with it ourselves

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[4] Court Brown W M Doll R *Ibid* p 84

[5] *Ibid* p 87

[6] Furth J Upton A C Leukæmia Research London 1954 p 116

[7] Warren S *J Amer med Ass* 1956 162 464

[8] Lowden T G *Lancet* 1956 i 405

[9] Capener N *Ibid* 1956 ii 92

Neurosurgical units are busy, progressive institutions, but a new operation for cerebrospinal rhinorrhœa, or a post-mortem report on ruptured œsophagus (though I find them interesting enough) are of little practical value to us "on the periphery" We would welcome a clear lead from them on the points I have mentioned, covering a problem which (if your figures can be applied more generally) affects 50,000 Britons every year

Sunderland T. G Lowden

DANGEROUS CONTAMINANTS IN STORED BLOOD

Sir,—Apparently Dr Discombe, who wrote last week, infers from my letter that the contamination-rate in consequence of opening bottles of blood for cross-matching in hospital laboratories is 5 1% , but, for the reasons stated in my letter, this is not so Neither hospital pathologists nor transfusion-laboratory directors can help it if bottles of blood opened in their laboratories for cross-matching are again opened. but not used, in wards or operating-theatres Such opening is bound to increase the contamination-rate

As to pilot tubes, I have no desire to embark on a discussion on so controversial a matter except to say that pathologists and technicians having the necessary training can, and do, sample bottles of blood with very low contamination-rate Also, it has to be borne in mind that occasional bottles will be contaminated at phlebotomy In either event the contaminating organisms will probably always be non-pathogenic Provided the blood is used within the prescribed period of opening the bottle, and refrigeration of the blood is constant, no harm is likely to ensue in transfusion, as experience has abundantly shown Trouble from infection of blood is, of course, only too likely to arise from mishandling of blood after it has left the laboratory Without doubt the taking of samples of blood from bottles, and the cross matching of blood, should never be permitted by any persons—doctors or technicians—lacking the appropriate training and experience For obvious reasons the same rigid standards of aseptic technique in taking blood samples ought to apply to pilot tubes as to blood bottles

Regional Transfusion Centre
Phyd Lafar, near Cardiff R Drummond

Sir,—Dr Discombe states that bacterial contamination kills about 1 in 350,000 Dr Drummond (Dec 15) finds that 5 1% of entered bottles are contaminated Dr Discombe hesitates to enter the main bottle and relies on the pilot bottle for all his tests I consider that pilot bottles are reliable , but not all pathologists agree—they quote cases where the pilot bottle contained blood antigenically different to the contents of the main bottle One has to see their point of view There will be general agreement that it is undesirable to enter the main bottle unless some strong indication exists—e g , to give "packed" cells Even so contamination can be reduced to a minimum by using a long sterile steel needle for suction and a second needle guarded by an air-filter for the ingress of air Dr Discombe may get his figure of 1 in 350,000 from published statistics The objection here is that not all deaths from this cause are published , it is possible that some are not even suspected The procedure for establishing that death was due to contaminated blood can be quite difficult Even if the bottle of blood is removed during the course of the transfusion—without exposure to the air—and taken immediately to the laboratory, where tests are performed without delay, the blood still may have been contaminated at the time of use, and not at the time of taking from the donor or during storage

As blood escapes from the main bottle and enters the veins of the recipient, every volume of blood is replaced—while the blood is flowing—by an equal volume of air Strictly, this replacement air should be filtered Only too often it is not because the drip has stopped or slowed and someone finds that the rate of flow can be restored by removing the filter Possibly, also, the filter has become wet with blood, and constitutes a real obstacle It is sometimes possible to detect contamination of the blood in the main bottle by careful inspection (without removing the bung) The well-known line of hæmolysis at the junction of plasma and cells, the gas bubbles caught in the top layer of plasma, or the gas sometimes seen bubbling up through the cells into the plasma are all indications Once a bottle has been shaken it is difficult to detect contamination by inspection, in the absence of a bottle centrifuge, for which I should like to make a plea

Another useful sign is a loose bung This is a rare occurrence with modern equipment. but only a few years ago a loose bung was not very rare A loose bung allows contaminated air to be sucked into the main bottle while the contained blood from the donor is cooling from body-temperature down to 4°C A perfect bottle of blood from a donor after cooling should contain a slight negative pressure When the bottle is opened for actual use the absence of this negative pressure, or a slight positive pressure should make the user suspicious Such an occasion would justify the test recommended by Dr Aidin (Nov 17 and Dec 22) on the particular bottle under suspicion Desperately ill patients have more than one bottle of blood prepared , the transfusion can continue with another tested bottle while the one that behaved suspiciously while being opened is subjected to the procedure recommended by Dr Aidin

St Margaret's Hospital
Epping Essex Frank Marsh

ERADICATION OF TUBERCULOSIS

Sir,—Dr Beresford (Dec 22) draws attention to the incompleteness of notification of tuberculosis This defect is concisely illustrated by the 1500 cases each year whose tuberculosis is not known to public health authorities until revealed by death certification

The reasons for the failure to notify tuberculosis include

(*a*) Apathy on the part of doctors in hospitals

(*b*) Assumption that cases have been previously notified when in fact this is not so

(*c*) The view that the disease cannot ethically be disclosed to anyone except the person suffering from it

(*a*) It is understandable that those whose skill is concerned with the craft of treatment should overlook their menial duty of notification , but nevertheless, where courtesy fails it is the statutory duty of the medical officer of health to initiate proceedings against defaulting medical practitioners This duty is evaded

(*b*) The regulations require *every* medical practitioner who forms the opinion that a person is suffering from tuberculosis to notify the disease If he has grounds for believing that the case has already been notified, the medical practitioner diagnosing the diseases is *not* asked to refrain from notifying it

(*c*) We all tend to accept as an ethical necessity the practice of the mass radiography units of keeping confidential the names of those cases considered tuberculous , *but the fact* is that, when the director of a mass radiography unit forms the opinion from X-ray examination that a person is suffering from tuberculosis, his statutory duty is to notify the case to the medical officer of health

The value of notification lies not so much in its statistical use as in the help it gives in revealing tuberculosis among the contacts of the person notified

Dartford, Kent J H HUDSON

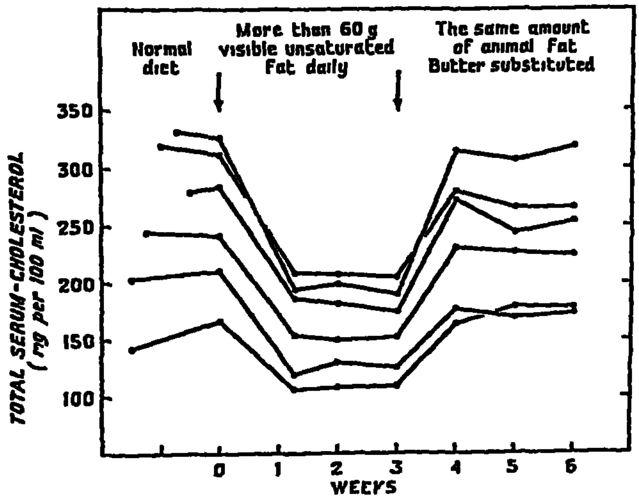
FATS AND DISEASE

SIR,—The reopening of the correspondence (Dec 8, p 1211) on your leader of April 28[1] demonstrates how widely this argument occupies medical thinking

Whilst Dr Gopalan confirms that sesame oil, which contains about 40% linoleic acid, lowers the serum-cholesterol level, Dr Gofman and his colleagues state that "the vegetable fat was not seen to have any specific lowering effect" It is important to realise that certain unsaturated fats seem to have not an absolute but only a relative lowering effect on the serum lipid level The workers at the Donner Laboratory say that there were *no significant differences in* S_f *0–20 lipoprotein content* during the two experimental periods when their subjects derived 8% of their calories from mixed fat or 43% of their calories from non-hydrogenated cottonseed oil But when the proportion of fat calories consisting of animal fats rose to 45% of the total daily caloric intake, the S_f 0–20 lipoprotein class was raised by 39% as compared with the period when approximately the same amount of fat was given (i e, 43%) but in the form of non hydrogenated cottonseed oil Thus there was a very definite difference in the S_f 0–20 lipoprotein class when approximately isocaloric amounts of vegetable and animal fats were compared (the carbohydrate intake being practically the same)

I have previously referred to some preliminary experiments[2] using pure corn oil and wheat germ oil for lowering the serum cholesterol level Meanwhile I had the opportunity of administering corn-oil products in a more palatable form[3]

The chart shows clearly that during the period of changing over to corn oil an immediate and substantial lowering of the serum-cholesterol proportional to the initial cholesterol level occurred When corn oil was replaced by fats of animal origin a rebound took place within a week's time The diet of these six patients was calorically not controlled The intake of visible animal fat was, however, limited to *about one teaspoonful* of butter daily on their toast at breakfast Unavoidably they obtained some further fats of animal origin in their food, which contained, besides unlimited amount of carbohydrates, at least 4 oz of lean meat, or 6 oz of lean fish, daily Hence their protein intake was adequate Wholemeal bread, plenty of fresh green vegetables, and fresh fruit were taken Tinned food was eliminated During the period of experiment the patients had incorporated into skim-milk and cheese, at least 60 g corn oil daily (which contains 55–60% of linoleic acid) and an adequate supply of vitamins



My experiments were of short duration, but I have since seen patients in Lund kept on a similar diet for many months, with a continuous lowering of the serum cholesterol level[4][5]

Though recognition of the cholesterol lowering effect of certain vegetable and fish oils is of great scientific importance, the application of any conclusion derived from it to a complex condition such as coronary atherosclerosis calls for great caution A generation ago Aschoff was already teaching that deposition of lipids in the intima of arteries cannot be expected under any mechanical condition unless hypercholesterolæmia is present Only under the impact of concerted post war research (discussed repeatedly in your columns during the past year[1][2][6–8]) it has been assumed "that any dietary factor that raises or lowers the level of β lipoproteins in the blood will also, by implication, raise or lower the liability to myocardial infarction"[1]

The most difficult aspect is that in a patient with moderate atherosclerosis a comparatively small plaque somewhere in the coronary tree may give rise to gross myocardial infarction, whilst patients with severe generalised atherosclerosis may escape a coronary catastrophe for a long time Coronary, but not generalised atherosclerosis has been prevented, or even made regressive, in animal experiments,[9] but this difference in the production of the atherosclerotic lesions has not so far been observed in man According to hospital statistics atheroma formation appears, if anything, to be no more extensive now than it was thirty to fifty years ago,[10] but the rapid increase of myocardial infarction in recent *decades is real*[11][12] *and, as a common* disease, it is new, not merely newly recognised[10]

For nearly a hundred years, under the impact of *Virchow's cellular pathology* and Pasteur's discoveries medical thinking was concentrated on finding one single causative factor of disease The concept of a multiple ætiology, rediscovered and applied to coronary heart disease, might explain some of the hazards linked with recent investigations Coronary heart disease encountered at the bedside is the end product of several processes developed through many years partly unnoticed, in which quite different stimuli, singly or together, lead to the same pathogenic response—hypercholesterolæmia In the past *I have discussed some of these* apparently not interconnected stimuli,[13] and have mentioned that on a fat-poor diet emotional stress may elevate the blood cholesterol level[14] May I add a few more points which were taken into consideration in the experiment represented in the chart?

In highly industrialised countries, where the greater part of the population is engaged in full time work in factories and offices, the tendency since the end of the first world war has been towards manipulating and processing food The food industry has become more and more efficient in the presentation of foodstuffs and also in improving their quality This 'improving' however, has many hidden pitfalls To mention one example we are rightly assured that the modern canning process is so effective that canned fruit or vegetables often have a higher ascorbic acid content than fresh fruit or vegetables stored for a long time But it has only recently become known that the pyridoxine content of canned or processed food may be reduced Nutritionists were seriously alarmed when Elvehjem found that American army combat rations used in Korea, consisting of a large variety of processed foods, were deficient in vitamin B_6 as judged by their effect on rhesus monkeys[15] Other much-praised army rations containing highly processed ham, pork meat, and eggs were inadequate for rats, but they could be made good by substitution with freshly processed similar food[16] Dr Sinclair has emphasised in your columns[6] the importance of the pyridoxal enzyme system in the intermediary metabolism with regard to the conversion of linoleic into arachidonic acid and also the importance of flour of high extraction-rate In order to prevent even marginal vitamin-B_6 deficiency, my patients received wholemeal bread, only fresh fruit and vegetables, and a generous supply of pyridoxine with their vitamins

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[1] *Lancet* 1956, i, 557
[2] Leitner, Z A *Ibid*, p 689
[3] Malmros, H Wigand, G *Minn Med* 1955 38 864
[4] Malmros, H Munke, A, Wigand, G *Conference on Atherosclerosis*, Basle 1956 (in the press)
[5] Malmros, H, Munke, A Wigand, G Second European Congress of Cardiology, Stockholm 1956 (in the press)
[6] Sinclair, H M *Lancet*, 1956 i 381
[7] Bronte-Stewart, B Antonis, A Eales, L, Brock, J F *Ibid* p 521
[8] Schroeder, H A *Ibid* p 1017
[9] Pick, R, Stamler, J Rodbard, S Katz, L N *Circulation* 1951 4 168
[10] Morris, J N *Lancet* 1951 i 1
[11] Ryle, J A Russell, W T *Brit Heart J* 1949 11, 370
[12] Martin, W J *Brit med J* 1956 i [illegible]
[13] Leitner, Z A *Proc R Soc Med* 1955 48 672
[14] Groen, J Tjiong, B K Kamminga, C E Willebrands, A F *Voeding* 1952 13 556

Another aspect of possible vitamin deficiency has to be considered if unsaturated fatty acids are given to patients for a longer time or permanently Already the discoverer of essential fatty acids found that during his experiments the vitamin-A stores in the experimental animals became depleted[17] Antagonistic effects of linoleic acid on carotenoids have been previously attributed to oxidation[18] As the normal adult liver carries a vitamin-A reserve sufficient for a year or longer[19] and our patients obtained at least 10 000 I U of vitamin A with their daily vitamin supply, no signs of deficiency could be detected during the short time of this experiment

The easy oxidability of unsaturated fatty acids is not necessarily heralded by a rancid pungent odour especially during the earlier stages when only the labile peroxides are involved There is now overwhelming evidence that the dietary intake of polyethenoid fatty acids seriously interferes with the metabolism of at least 15 species of farm and laboratory animals The exact mechanism of this metabolic disturbance is as yet unknown, but the action of the poly-unsaturated fatty acids—mainly present in marine oils—seems to affect the capacity of the tissues to utilise the potential free energy of the ingested food[20] The resulting pathological lesion affects the whole muscular system leading to a muscular dystrophy involving occasionally the myocardium with changes in the E C G , the extent of the lesions seems to vary in the different species of animals[21] Most of these "metabolic injuries" can apparently be prevented or corrected by the administration of α tocopherol[22] Vitamin E being the most powerful physiological antioxidant, will possibly prevent any oxidative rancidity in the intercellular metabolism even at the expense of its own destruction The possibility of precipitating vitamin-E deficiency by administering unsaturated fatty acids was considered during our experiments The corn oil used contained at the time of preparation about 108 mg vitamin E per 100 ml and this might have adequately protected my patients In future experiments of longer duration it would however be absolutely necessary to follow up the serum-tocopherol levels

In conclusion, there is every reason to believe that man is unable as yet to adapt himself quickly to the plentiful and sophisticated food offered to him wherever Western civilisation penetrates in force This type of nourishment, together with the Western way of life, uniformly raises the serum-cholesterol level independently of race These factors seem to be instrumental in producing early and extensive arterial changes and possibly altering the whole clotting mechanism Replacement of animal fats by certain oils containing essential fatty acids reduces the serum-lipid levels If this reduction could be maintained permanently a novel approach for the treatment (and more so for the prevention) of coronary atherosclerosis would have been gained There is urgent need for more extensive and coördinated research as inevitably there are some drawbacks connected with the rapid changing of long-established food habits No doubt new lines seem to have been opened to nutritional research, in which modern food industry is bound to take its part I completely agree with Schroeder,[9] however, that though it may still take a long time to prove the reversal of arterial lesions by lowering the blood-cholesterol level in man, we now have tools with which more extensive investigations can be undertaken without great risks or inconvenience to patients

London, W 1 Z A LEITNER

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15 Tappan D V, Elvehjem C A J Nutrit 1953 51 469
16 Tappan D V, Lewis U J, Methfessel A H, Elvehjem C A Ibid p 479
17 Burr G O Fed Proc 1942 1 224
18 Sherman W C J Nutrit 1941 22 153
19 Moore T Spec Rep Ser med Res Coun Lond no 264 1949 p 63
20 Blaxter K L Vitamina F Atti del terzo Congresso Internazionale Venezia 1955 p 622
21 Blaxter K L McGill R F Vet Rev Annot 1955 1 91
22 Blaxter K L Macdonald A M Lancet, 1956 ii 893

TOWARDS TELEVISION GASTROSCOPY

SIR,—In their most interesting letter of Dec 22 Prof Henry Wallman and Dr Bengt Rosengren report their trials with a midget television-camera assembly inserted into the stomach In Rheims Dr Dubois de Montreynaud is routinely demonstrating endoscopic views on closed-circuit television in black-and-white to visitors to his clinic He uses the Fourestier-Vulmiere-Gladu type of endoscope to project the field of view into a light-weight television camera developed for this purpose by Monsieur Minot While we must wait with interest to see which of these two teams first produces practicably useful colour-television images, I feel the French system preferable in principle, because it is sensible to keep high-voltage television equipment outside the patient's body

London W 1 BRIAN STANFORD

THE USE OF PLASMA

SIR,—In recent correspondence the relative merits and the cost of plasma and dextran have been discussed[1] Some observations concerning costs and also the capacity of these products to correct hæmostatic defects require further comment

To attach a theoretical price to a bottle of plasma is misleading and it is more useful to think in terms of actual expenditure in the conditions prevailing

Plasma can be prepared from outdated bank blood which has not been used for transfusion As the outdated blood is already available, and would otherwise be discarded, it has no intrinsic financial value, and the cost of plasma prepared from it is that of the processing If, however, more plasma is required than can be obtained by processing outdated bank blood then blood must be collected specially for the purpose, and this must be taken into account in assessing the cost of the extra plasma Whole blood has been priced variously at figures up to £2 per bottle , assuming a cost of 30s per bottle, the minimum cost of producing a 400 ml. unit of plasma (requiring 2 bottles of whole blood plus processing) is of the order of £3 10s

Dried plasma prepared from outdated bank blood immediately after the expiry date is a useful source of the stable clotting factors However, for the treatment of deficiencies of labile clotting factors (i e , antihæmophilic factor and labile factor [factor v]) fresh plasma prepared from specially collected

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1 Rainsford S G Lancet 1956 ii 849 995 1264 Wallace J Ibid p 945 Clarke P, Ibid p 995

Dr. Robert Fleig Library

blood is essential, and in view of the increasing quantities being used it is worth emphasising that this product costs at least £3 10s per 400 ml unit (Thus to maintain a hæmophiliac on three bottles a day costs £10 10s per day for the plasma alone)

To sum up, the following products are available

1	Whole blood	£2	per bottle
2	Plasma from outdated blood	under 10s	" "
3	Additional plasma from blood specially collected for the purpose	£3 10s	" "
4	Fresh plasma to provide labile clotting factors	£3 10s	" "
5	Dextran	£1	" "

It appears that outdated blood available from the transfusion centres could provide sufficient stored plasma for all peace time civilian needs, and therefore for civilian use the cost of plasma for routine use should be taken at the lower figure of under 10s

Under normal conditions up to 20% of blood collected is not used as whole blood and is available for conversion to plasma On this basis, the 1955 figures for blood collected in England and Wales indicate that about 80,000 bottles of plasma could be prepared from the outdated blood, and in fact this is approximately the amount manufactured The figure for dried plasma used in the same year is under 40,000, so a considerable surplus of the less expensive plasma is available

Regarding the clotting factors, Admiral Rainsford, in his second letter, states

> "Plasma recovered from stored blood or stored for any length of time in the liquid state has little or no hæmostatic properties and is known to produce hæmostatic defects —perhaps because of the large amount of citrate it contains "

It is true that plasma stored for three to six months at room-temperature, or treated with kaolin, is unsatisfactory as a source of clotting factors, but it is not widely thought to produce specific hæmostatic defects, nor does the presence of citrate cause an adverse reaction, except possibly in a very rapid massive transfusion

Further, dried plasma prepared directly from time expired blood is a useful therapeutic source of fibrinogen, and other stable clotting factors, although fresher plasma might be used in preference in a patient with a known deficiency Stefanini and Dameshek [2] state that plasma up to 20–30 days after collection can be used for the treatment of hypoprothrombinæmia, stable-factor (factor VII) deficiency, plasma-thromboplastin-component (Christmas factor) deficiency, plasma thromboplastin-antecedent deficiency, afibrinogenæmia, and fibrinogenopenia If such plasma is available, it should be used in the treatment of shocked patients, if there is a likelihood of a clotting-factor deficiency, rather than dextran, which itself tends to cause a coagulation defect In giving emergency treatment to patients with hæmorrhagic shock it should be remembered that such a clotting defect may already be present and a watch should be kept on clotting function In particular, fibrinogen deficiencies may arise in (*a*) various hæmorrhagic complications of pregnancy, (*b*) any condition involving very extensive tissue damage, whether through burning, injury, or surgical procedures

Caution has been advised in the use of large volumes of dextran,[3] and it has been suggested that for the time being it is best to limit the amount of dextran given to any one patient to one litre Stable liquid plasma freed from active hepatitis virus by storage at room temperature would provide a satisfactory alternative for patients with no sign of a clotting defect, but as Admiral Rainsford has pointed out, the problem of bacterial contamination has yet to be dealt with In the case of clear filtered, kaolin treated plasma, the contamination difficulty is less serious as the clarity of the final product is an indication of sterility However, before this product can be widely useful it is necessary to evolve a technique for kaolin treatment which will give a more stable product than that obtained by the original Maizels method[4] which remains clear for only a few months

To sum up, dextran and other plasma substitutes being free from the danger of serum hepatitis, are useful for the emergency treatment of oligæmic shock However, *in patients who require a large* transfusion, or who are likely to have a clotting-factor deficiency, blood or plasma are usually to be preferred, as their clinical value outweighs the danger from hepatitis

Regional Blood Transfusion
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Edinburgh, 3

DRUMMOND ELLIS

FIBRINOLYSIS AND ATHEROSCLEROSIS

SIR,—Will you permit some rather belated comments on Dr Astrup's review [5] *of the biological significance* of fibrinolysis ? There has been considerable discussion in the medical press over the revival by Duguid [6] of Rokitansky's hypothesis, advanced more than a hundred years ago, that atherosclerosis follows mural fibrin thrombosis Duguid's conclusions are based on his observations of thrombotic fibrin-layers which become altered and incorporated in the vessel wall to form atheromatous plaques His contention that this process of mural thrombosis is a recurring phenomenon, with successive fibrin deposits on the endothelium resulting in cumulative thickenings, is aided by my own concept presented in 1953, which serves as a theoretical basis for vascular alterations involving the endothelium [8]

I consider the inner or "endo endothelial" lining of the vessel wall to be a fine porous film of fibrin, produced and deposited on the layer of endothelial cells continually during life Disturbances in the physiological process which produce and maintain this fibrin coating throughout the vascular system are thought to lead to thrombosis or hæmorrhage Thus on the one hand increased production and deposition of fibrin, or decreased fibrinolysis, would result in thrombosis, while conversely reduced production and deposition of fibrin and increased fibrinolysis would result in hæmorrhage

Macfarlane and Biggs [9] were the first to describe increased fibrinolysis after strenuous exercise and after adrenaline injection and to emphasise its occurrence in anxiety states, thus suggesting that fibrinolytic activity is a physiological process According to Macfarlane [10] there is no destruction of fibrinogen in naturally induced fibrinolysis As there seems *to be normally* a steady fibrinolytic process, probably affecting primarily the endo endothelial lining, there must be a concomitant and continuous repair of this fibrin film, thus securing the integrity of the endothelial wall

There seems to be a highly intricate system of mechanisms which facilitate the formation of the fibrin film on the endothelial cells In the marginal plasmatic zone of Poiseuille, which is free of cellular elements practically no blood flows, thus permitting sufficient reaction time for the formation and deposition of non-gelated fibrin, as well as for fibrinolysis *The inter*endothelial spaces permit the infusion of tissue juice containing many factors which, upon mixture with the plasma, result in reactions concerned with fibrin formation and fibrinolysis Various *coagulation promoting* factors, present in tissue juice activate thrombin form its prothrombin complex and associated factors The steady infusion of minute quantities of heparin-like materials, released from the mast cells in the subendothelial and perivascular connective tissue, may not be enough to prevent the formation of fibrin particles, but, because of the antigeloplastic effect of heparin, aids in the prevention of vascular occlusion as well as in the maintenance of the fluidity of the blood We do not know what constitutes an intact endothelium, and it is not known whether the endothelial cells participate in fibrin formation and fibrinolysis—a field of study in which I am at present actively engaged

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[2] Stefanini M, Dameshek W The Hæmorrhagic Disorders New York 1955 p 2?6

[3] Mollison P L Blood Transfusion in Clinical Medicine Oxford, 1951 p 80

[4] Maizels M *Lancet* 1944 ii 20

[5] Astrup T *Ibid* 1956 ii 565

[6] Duguid J B *Ibid*, 1949 ii 925 *Ibid* 1954, i 891 *Brit med Bull* 1955 11, 36 *Practitioner* 1955 175 241

[7] Duguid J B Robertson W B *Lancet* 1955 i 525

[8] Copley A L *Abstr Comm 19th int physiol Congr* (Montreal) 1953 p 280 *Arch int Pharmacodyn* 1954 99 426 Thrombosis and Embolism First International Conference 1955 p 1?2 *Arztl Forsch* (in the press)

[9] Macfarlane R G Biggs R *Lancet* 1946 ii 862 *Blood* 1948 3 1167

[10] Macfarlane R G *C R 3rd Congr Soc int Europ Hemat* Rome 1951 p 719

In support of the concept of the endo endothelial fibrin film, recent observations are of interest Levene[11] examined the electron-microscopic structure of apparently normal aortic intima and found superficial fibres, obtained by scraping, indistinguishable from fibrin Even though some objections can be raised to Levene's conclusions (e g , the teased-off specimens do not provide exact knowledge as to their position in the intima, and the periodicity, which Levene gives as a criterion, may not entirely suffice to differentiate between collagen and fibrin), it cannot be stated with certainty that this protein film is not fibrin Finally, there are our findings on the hæmorrhagic effects of fibrinolysin (plasmin), and on the production of vascular purpura in guinea-pigs by guineapig antifibrin serum of rabbits[12] It is of interest that Kowalski and his associates[13] found, after streptokinase activation, greater fibrinolysis in the intima as compared to the other layers of human aorta and other human tissues

Astrup, too, contends that in the healthy organism small amounts of fibrin might be deposited on the walls of arteries However, his view appears to differ fundamentally from mine, since he limits this deposition to arteries, especially when strain causes tissue damage, and thinks that these deposits are removed by the fibrinolytic system as rapidly as they are formed In my view the continuous deposition and maintenance of the endo endothelial film takes place physiologically in all blood vessels throughout life

Moreover, the known occurrence of hæmorrhage due to an increase of fibrinolytic enzymes in the bloodstream cannot be explained merely by a fall in antiplasmin and the disappearance of fibrinogen as discussed by Astrup[14] It seems more likely that hæmorrhages are produced because the introduction of plasmin into the circulation, as I have shown, directly affects the vessel wall, and in particular the endo endothelial fibrin film This I consider also to be the explanation for hæmorrhage produced by an in-vivo coagulation defect or by the introduction of an anticoagulant into the bloodstream Some authors claim that heparin increases fibrinolysis, while Astrup found that it inhibits fibrinolysis Be that as it may, it is of interest that mast cell counts made in the vascular wall in atheromatous human aortas were found to be increased Sundberg[15] relates these findings to the fact that granules of the mast cells contain a heparin-like substance and to its effect on certain lipoproteins Another aspect which needs to be clarified is whether cholesterol and certain lipoproteins have a special affinity to fibrin surfaces

It is premature to reach any hard and fast conclusions about fibrin deposition, fibrinolysis, and atherosclerosis, but my concept of the new rôles of fibrin and fibrinolysis gives the findings of Duguid and his associates a physiological basis

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Paris

ALFRED L COPLEY

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[11] Levene C I *Lancet* 1955 ii 1216
[12] Copley, A L, Gélot B *Amer J Physiol* December 1956 (in the press)
[13] Kowalski F Kopec M Latallo Z, Roszkowski S Sendre N *Pol med Wkly* 1956 11 1536
[14] Astrup T *Blood* 1956 9 781
[15] Sundberg M *Acta path microbiol scand* 1955 suppl 107

SHORTAGE OF RADIOGRAPHERS

SIR,—I must deplore Dr G H Illingworth's views on radiographers (Jan 5)

My experience, previously as a qualified radiographer, and later as a doctor, persuades me there are no grounds for complacency regarding the average standard of radiography in this country I believe that consistently first class work is the exception, and where I have met it, it has invariably been done by radiographers who thoroughly understand what they are doing, and the apparatus with which they are doing it

To lower the standard of entrants to the profession, would, I think, be undesirable , but to lower the standard of teaching would be disastrous The former would be inevitable if, as Dr Illingworth seems to suggest, the best posts were reserved for selected male students If there are enough girls sufficiently foolish to train as radiographers under such circumstances, the standard of work to be expected from them must be abysmal

Incidentally, how would Dr Illingworth select his male students ?

Milford Chest Hospital
Godalming Surrey

W JOAN FERRABY

SIR,—I entirely disagree with Dr Illingworth There is widespread dissatisfaction among radiographers concerning their quite inadequate remuneration, the retiring age, and the terms for " on call " As a radiologist I agree wholeheartedly with their viewpoint

As regards superintendents, Dr Illingworth is seeing the problem from the point of view of the large teaching hospital In the majority of regional board hospitals, the radiologists are part-time and cannot attend to the details of organisation and the endless queries which need experienced handling, and the radiographer in charge, whether superintendent or in smaller hospitals senior in grade, has to carry a heavy responsibility, not only for the standard of work but for the care of the patients also I should not care to have the work in my department carried out by young girls of a lower educational standard with such inadequate training as is suggested Not all hospitals are within a short journey of the nearest manufacturer !

St Stephen s Hospital,
London S W 10

GRACE BATTEN
Consultant Radiologist and
Medical Superintendent.

SIR,—Concern about the inadequate remuneration is certainly not confined to a few male radiographers At a recent meeting of the North East London Radiographic Group more than 60% present were females and all expressed strong dissatisfaction with the recent award

All schools are permitted to admit students at the age of 17 and a number already do so No student, however, is allowed to come into contact with patients until the age of 17½, and the qualifying age remains at 20 This seems an eminently reasonable policy

The recently published Medical Research Council report on The Hazards to Man of Nuclear and Allied Radiations has indicated that the greatest radiation danger to the general population in peace time comes from diagnostic radiology Far from diminishing, diagnostic radiology will be used on an ever increasing scale if it is to continue playing a crucial part in the investigation of the patients It is essential therefore that measures to minimise the radiation hazards of diagnostic work be improved The person who will be primarily responsible in minimising these grave hazards should not only be versed in the art of positioning and correct exposure of films but have an understanding of the basic principles of physics and apparatus construction to make him/her a safe and understanding operator Surely " an intelligent girl of 17 or 18 with an aptitude for the work " will not be satisfied with being a mere push button and deprived of any possibility of deriving intelligent stimulation from her work

What sort of girl is going to take up radiography where there is no prospect of any intellectual satisfaction or any advancement in professional or financial status ?

Dr Illingworth suggests that the way out of our serious difficulties is to use the cheapest and least refractory labour force available and bring the whole profession down to the lowest common denominator This may be the easiest way but it is the least satisfactory It reflects an attitude of mind that is unfortunately too common in many walks of life today If his views prevail not only will a disservice be done to the profession of radiography but patients, medical staff, and not least radiologists themselves, will suffer

London, N 19 H M HARROTT

DIVERSION FOR THE PATIENT

SIR,—It is reported that background music will be played in order to calm patients undergoing obstetric operations under local anæsthesia Do doctors ever think of asking patients what they find helpful and comforting during such ordeals? And, quite apart from whether the patient finds music helpful, who is to decide what music shall be played? Some patients would want only the latest hit song by their favourite crooner, others might have Third Programme tastes

Surely in these days it is not beyond the bounds of possibility to have specially gifted women whose job would be, first to get to know the patient and her case, then to be at her side throughout her ordeal One is constantly meeting young mothers who complain that throughout their labour no one had time to speak a word of comfort or reassurance to them And this they remember long after they have forgotten their pains But I have yet to meet one who said "If only the radio had been on—or television"

Braunton Devon WINIFRED CUMMINGS

MYOPATHY IN SHEEP

SIR,—In your issue of Dec 29, Dr Bosanquet, Dr Daniel, and Mr Parry again mention the occurrence of vacuolated nerve cells in the medulla oblongata of sheep affected with scrapie, and they quote in full the opinion expressed by Dr Holman and myself[1] that "clinical symptoms suggestive of scrapie followed by microscopic discovery of vacuolated nerve cells in the medulla oblongata probably constitute sufficient evidence on which to base a positive diagnosis of the disease" We would like to state that we have found no evidence since these words were written to cause us to alter or to modify that opinion

Our conclusion was based on examination of 75 sheep affected with scrapie, 39 sheep dying of diseases other than scrapie, and 39 other sheep that were clinically healthy when slaughtered Two to six sections of the medulla were examined from each case, and the relationship of the presence of vacuolated cells to clinical scrapie gave a χ squared value of 155, with P less than 0 0001 We made it clear, however that the mere findings of vacuolated cells after death was not pathognomonic of the disease, because they were occasionally found in animals that had not shown clinical evidence of scrapie For this reason we emphasised the importance of observing the typical clinical symptoms in establishing a positive diagnosis We recognised then, as now, that very clinical cases of scrapie may show only a few vacuoles histologically, but in other cases vacuolation is far more extensive than we have ever seen in clinically healthy sheep killed for examination, or in sheep dying from other diseases An example of such a case was given in our paper, where 167 serial sections through the medulla gave a count of over 37,000 vacuolated cells

I have recently examined sections of the medulla oblongata from goats affected with scrapie, and here *again, as in sheep, I have no doubt that vacuolation of* nerve cells is characteristically associated with the disease This work is not yet complete, but counts of vacuolated cells made to date may be of interest

	Number of sections examined	*Total number of vacuolated nerve cells found*	*Range of number of vacuolated cells per section*
16 clinically healthy goats	592	8	0 to 1
16 scrapie affected goats	91	2279	2 to 69

These figures show a relationship between vacuolated nerve cells and scrapie that is obviously highly significant Dr Bosanquet and her colleagues have stated that *scrapie is essentially a myopathy* This may be correct but it does not alter the fact that vacuolated nerve cells occur in the medulla oblongata of many cases of scrapie in a concentration that far exceeds anything that has yet been recognised in any other disease of goats or sheep

With regard to your contributors' scepticism about the experimental transmission of scrapie, I would like to mention some recent experiences with goats

In 1954 I inoculated twelve goats from the Compton flock intracerebrally with 1 0 ml of a 10% brain emulsion from a sheep affected with scrapie All twelve animals developed the disease, the earliest symptoms being noted 15 months *after inoculation I then inoculated ten more goats* with brain emulsion from one of these animals, and to date only of these have developed the disease By contrast over 6 other goats have passed through this flock since 1949 without showing the slightest evidence of scrapie, myopathy, or any other nervous or muscular disability

This type of information has been accumulated over many years by other workers using sheep (notably at Moredun Institute, Edinburgh), and for me it constitutes evidence heavily in favour of scrapie being a disease that can be experimentally transmitted Control inoculation of sheep with brain material from clinically healthy sheep have never produced disease

In conclusion, I would like to say that we await with great interest the results of further researches by Dr

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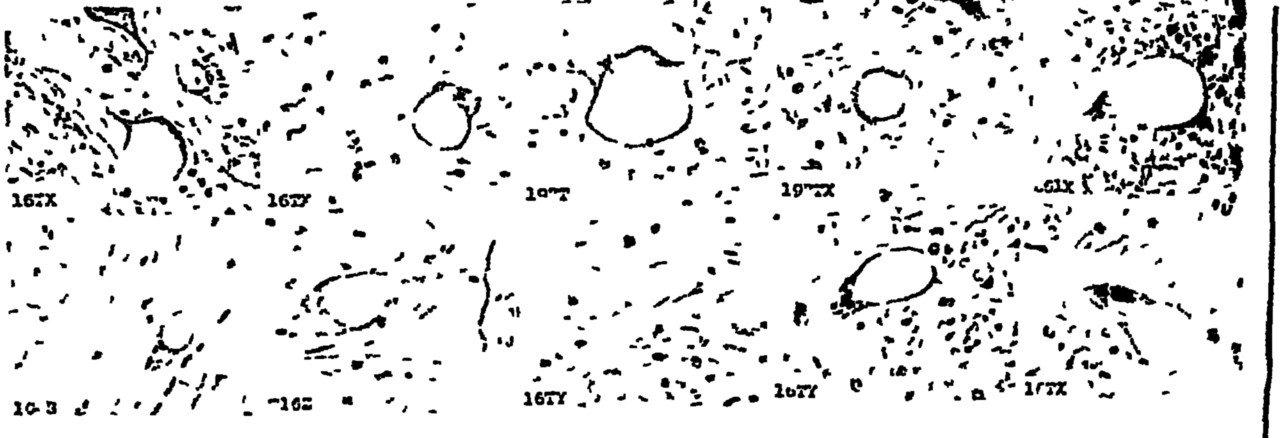
1 Holman H H Pattison I H *J comp Path* 1943 53 231



Bosanquet and her colleagues It may be that myopathy is the essential lesion in scrapie, and it is reassuring, therefore, that with such a wealth of natural, experimental, and control material readily available it will not be long before the relationship of myopathy to scrapie is established to the satisfaction of all concerned in the investigation of this odd disease

Agricultural Research Council
Field Station
Compton near Newbury, Berks I H PATTISON

THE Rh BLOOD-GROUPS

SIR,—Your editorial of July 21 criticises the tentative report of the American Medical Association's Committee on Medicolegal Problems because it recommends that "the C D-E notations for the Rh Hr types be discarded and that, in approved medicolegal reports, unless and until some other convention is agreed on, the original Rh-Hr nomenclature be retained as the sole nomenclature for this blood group system" This editorial is misleading since it contains serious errors of commission and omission, and, instead of citing scientific observations to support its position, it quotes "testimonials" from papers published almost a decade ago, and closes with four lines of poetry from *Ingoldsby Legends* which have no bearing on the scientific issues at stake

The issue of the *Journal of the American Medical Association* which contains the tentative report also contains an editorial requesting comments from workers in the field Since one of the arguments frequently offered by C D-E advocates is that "99% of workers prefer the C-D-E notations," it is noteworthy that approximately half the letters received in response to this request enthusiastically endorsed the position taken by the committee If it were true that C-D-E is preferred by the large majority, it would have been easy to obtain agreement by taking up the matter at the recent meetings of the International Society of Hematology in Boston, and it is significant that this opportunity was not used In fact, one year before the report was prepared by our committee, an effort was made to hold a meeting to discuss Rh Hr nomenclature, and, to avoid the possible charge of bias, a leading advocate of C-D-E was asked to act as chairman But the plans for this meeting were abandoned when Race and Fisher both declined an invitation to participate On the other hand, at a meeting of the International Society of Hematology held in Buffalo six years ago, a committee on Rh Hr nomenclature was formed of which I was not a member This committee introduced a resolution that the C-D-E notations be made international, but the motion was withdrawn when I pointed out that this was a problem to be settled not by vote but by work in the laboratory These facts are not commonly known, and were not mentioned in your inaccurate historical review Interested readers can find a detailed analysis of the scientific background in recent articles[1-3]

You said that Race and Sanger "note that only the C D E notation indicates which antigens and genes are present, and they are convinced that anti C and anti D are more rational names for antibodies than anti rh' and anti Rh_0" This is incorrect since, for example corresponding to the gene symbol r'^w, Fisher and Race use the "chromosome" symbol C^wdeF, which includes the letters d and F for antigens for which no testing sera exist, and at the same time conveniently omits the letter C (rh') for a factor present in agglutinogen rh'^w Yet this assertion and other similar mis statements in Race and Sanger's book have been quoted over and over in the literature[4] Moreover, the symbols C and D are not rational, since by assuming a one to-one correspondence between genes, antigens, and antibodies, no distinction is made between factors, agglutinogens, and genes This has resulted in numerous paradoxes,[5] and in medicolegal problems could cause mistakes which might result in a miscarriage of justice For example, the following represents a *hypothetical* case in terms of the Rh-Hr nomenclature

Blood of	Rh Hr type	
	Phenotype	Possible genotypes
Putative father	Rh_1rh	R^1r, R^1R^0, or R^0r
Mother	rh	rr
Child	Rh_0	R^0R^0 or R^0r

Obviously, the Rh Hr tests do not exclude paternity Yet in terms of the C-D E notations the same case might be reported as follows

Blood of	Most likely genotype
Putative father	CDe/cde
Mother	cde/cde
Child	cDe/cde

Such a report could mislead one into believing that the Rh-Hr tests exclude paternity That this danger is not merely theoretical can be seen from similar errors in published articles, caused by the use of the C-D E notations For example, the diagram of a pedigree in a recent paper[6] shows two women of genotype cDe/cde with children of a genotype CDe/–D–, combinations which would exclude the possibility of maternity!

The main arguments offered nowadays in defence of the C D E notations are that they are easier to "understand" and to teach Significantly, in the 1956 editions of the excellent books by Boyd and Mollison, the tables on the Rh-Hr types list reactions by antisera C, D, E, c, d, and e While such a simple symmetrical scheme is indeed easy to teach, it is unrealistic since it includes the anti d (Hr_0) which has not been found, but omits anti C^w (rh^w) and anti-f (hr) (Incidentally the books of Race and Sanger and of Kabat cite the "discovery" of d as confirmation of the Fisher hypothesis, but in the very next breath confess that the reports in question were almost surely based on faulty observation) Thus, the simplicity of the C D-E notations depends on distortion of scientific facts, whereas a good teacher never finds it necessary to distort in order to achieve simplification Authoritative simplified reviews can be found in many textbooks[7-12]

Certain correspondents who criticised the report insist that the Rh Hr nomenclature be dropped and the C-D-E notations be made international, but at the same time, somewhat inconsistently, urge that the so called "shorthand" symbols be retained These "shorthand" symbols, widely used by Fisher, Race, and other advocates of C D E, are merely minor modifications of the original Rh Hr nomenclature Thus, R_1R_2 is used as

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1 Wiener A S History of the rhesus blood types *J Hist Med* 1952 7 369
2 Wiener A S, Wexler I B Interpretation of blood group reactions with special reference to the serology and genetics of the Rh Hr types Novant Anni delle Leggi Mendeliane edited by L Gedda Rome 1956 p 147
3 Wiener A S Wexler, I B The Rh Hr types a complex problem in serology genetics and nomenclature Editorial, *Ann intern Med* 1956 45 725
4 Wiener A S The teaching of Rh nomenclature as the responsibility of directors of blood banks *Bull Amer Ass Blood Banks* 1956 9 104
5 Wiener A S The Rh Hr blood types a budget of paradoxes *J Forensic Med* 1955 2 224
6 Buchanan D I McIntyre J Consanguinity and two rare matings *Brit J Haemat* 1955 1 304
7 Colin E C Elements of Genetics New York 1956
8 Gradwohl R B H Clinical Laboratory Methods and Diagnosis St Louis 1956
9 Dorland W A N American Illustrated Medical Dictionary Philadelphia 1951
10 Schatkin S B Disputed Paternity Proceedings New York 1954
11 Gonzales T A, Vance M Helpern M, Umberger C J Legal Medicine Pathology and Toxicology New York 1954
12 Wiener A S Rh Hr Syllabus New York 1954 Stuttgart 1955 Naples 1956 Mexico City 1956

"shorthand" for CDe/cDE , but when the subscripts are converted into superscripts, as in the symbol R^1R^2 of the Rh-Hr nomenclature, the symbol apparently becomes unintelligible (cf pp 204 and 218 of Mollison's new book)

In conclusion, it must be pointed out that the A M A report was prepared by a fact finding committee In discharging its duties, this committee was compelled to exclude all material which it found to be incorrect or to lack experimental basis so that the charge of bias is inapplicable Readers who consult the references cited here will find that the problem of Rh-Hr nomenclature is dead scientifically The only problem remaining is one of education

Brooklyn, N Y , U S A   A S WIENER

SARCOIDOSIS

SIR,—In your leading article of Dec 29, you state that Nethercott and Strawbridge have presented important indirect evidence of the presence of tubercle bacilli in lesions of sarcoidosis Their evidence rests on the claim to have demonstrated α-ε-diaminopimelic acid (D A P) and mycolic acid in hydrolysates of biopsied tissues Dr Work (Dec 22) has dealt with the significance of D A P , and our observation of the presence of D A P in a scalene lymph node, which histologically appeared to be normal, adds point to her remarks This observation is not unexpected since this type of tissue, in the normal course of events, deals with debris from bacteria, many of which, as Dr Work stressed, contain D A P

Mycolic acid is much more specific to tubercle bacilli than is D A P , and its identification in tissues would be important, but the evidence for its presence is not very convincing

In the first place, although acid fastness could indicate mycolic acid, it is surely not justifiable on the basis of a staining reaction alone, to claim, as Nethercott and Strawbridge[1] do that mycolic acid was *identified* Apart from this, the authors have not specified in any detail the conditions of their acid fast tests, nor have they given any data for normal tissue extracts or for long chain fatty acids other than mycolic Though mycolic acid, either free or in certain of its compounds, is thought to be responsible for the acid fastness of tubercle bacilli, unless the test is carried out under carefully controlled conditions, it is possible to obtain positive results with lipids that do not contain mycolic acid For instance, we have recently tested on filter paper, samples of stearic acid, cholesterol and an extract of normal subcutaneous tissue hydrolysate, staining for 5 minutes with carbol fuchsin and washing for 30 minutes with acid alcohol Stearic acid gave an intense red spot whilst the others were of moderate intensity

The authors erroneously describe their solvent extracted material as "wax" Such substances could not survive prolonged heating with strong acid and their extract would consist predominantly of a mixture of long chain fatty acids derived from the fats of the tissue If mycolic acid were present it would almost certainly form only a very small proportion of the total and it is therefore rather difficult to see how mycolic acid can be distinguished in the infra red spectrum of this mixture, or why this spectrum should be so similar to that of wax C this is very rich in mycolic acid but also contains trehalose, which cannot possibly be present in the tissue extracts Infra red spectra give information regarding the functional groups present (OH NH, C=O &c) —for instance the peaks at 1725 cm^{-1} could correspond to the carbonyl groups of fatty acids It is not at all obvious from the spectra presented that a fatty acid is present which contains 88 carbon atoms—a feature which distinguishes mycolic acid from all other natural fatty acids In the absence of further data the similarity of the spectra tells us that similar functional groups are present in both specimens, which is to be expected since bacterial and animal lipids have many groups in common

It is to be hoped that the authors can clear up these queries Perhaps they have more data and intend to publish their results more fully elsewhere This would be welcome but for the present I think it advisable to accept their evidence for mycolic acid with some reserve

Canadian Red Cross Memorial Hospital
Taplow Maidenhead Berks   R CONSDEN

SIR,—In your leading article there occurs the sentence "D A P has been found in *Corynebacterium diphtheriæ* and *Mycobacterium tuberculosis*, but never in normal mammalian tissue" While this statement is true so far as it goes, it gives an incomplete and slightly misleading impression of the distribution of diaminopimelic acid (D A P) in bacteria and the use to which its occurrence in mammalian tissue could be put in diagnosis

D A P is widely distributed in micro organisms, as has been shown by Work and collaborators,[1 2] and our own work[3 4] indicates that the bulk of it is most probably in the cell wall of those species in which it occurs It is certainly present in the cell wall of species of Bacillus, Nocardia and Streptomyces, as well as in Mycobacterium and Corynebacterium, although absent from almost all gram positive cocci and it has also been found in the cell walls of a few strains of Salmonella, Shigella, Escherichia, and Pseudomonas[5 6]

Furthermore, since the bacterial cell wall is very insoluble, it may well persist for a considerable time in the tissues of a mammalian host A chronic infection involving only a few living organisms at any particular time might perhaps pile up a considerable store of material containing D A P , which could then be detected chromatographically On the other hand, persistence of bacterial cell-wall material in the animal body could well mean that D A P found in hydrolysates of tissues had merely accumulated from saprophytic organisms (for example non-pathogenic diphtheroids) and was not the end result of any pathological process In the latter case the finding of D A P in tissue hydrolysates would be very misleading unless its wide distribution among bacteria was borne in mind

The London Hospital
Medical College   C S CUMMINS
H HARRIS

CONGENITAL HYPERTHYROIDISM

SIR,—We were particularly interested in the account by Dr Lewis and Dr Macgregor, of congenital hyperthyroidism (Jan 5) because we have recently had a case almost identical in history and appearances, which was described at an Oxford regional pediatric meeting in December

In our case we decided not to give anti thyroid drugs, which might perhaps be harmful, in what was likely to be a transient condition due to maternal thyrotrophic hormone, and we endeavoured to deal with the child's excessive activity and hunger by steadily increasing the amount and strength of feeds, adding casein hydrolysate For four weeks the weight remained level, then the child began to gain, and the evidences of hyperthyroidism and the thyroid enlargement disappeared The child now seems to be thriving

These severe cases are rare, but there is the interesting possibility, suggested by Coccheri,[7] that the very much commoner syndromes of overactivity with feeding difficulty may sometimes be related to a minor degree of hyperthyroidism in the mother

J J KEMPTON
Reading   R A RATCLIFF

CUSHING'S SYNDROME WITH CARCINOMA OF BRONCHUS

SIR,—The article by Dr Harrison and his colleagues (Jan 5) is of great interest to me

A patient in this practice had an operation for ovarian carcinoma in 1938, and died in 1955 at the age of 46 from widespread secondary growths involving the abdomen thorax and other sites In the intervening years she had had radio therapy many times for secondaries with a remarkably good response

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1 Nethercott S E Strawbridge W G C Lancet 1956 ii 1132

1 Work E Dewey D L *J gen Microbiol* 1953 9 391
2 Hoare D S Work E *Ibid* 1956 15 xiii
3 Cummins C S Harris H *Ibid* 1956 14 583
4 Cummins C S Harris H *Ibid* 1956 15 ix
5 Salton M R J *Biochim Biophys Acta* 1953 10 512
6 Cummins C S Harris H Unpublished results
7 Coccheri P *Lattante* 1956 27 129

During the last year of her life she developed a well marked Cushing's syndrome. The records of her case were (as is usual) forwarded after her death to the executive council and are unfortunately not now available to me, but I have a vivid recollection of her. Hypertension (systolic over 200) and glycosuria developed, and she became very obese with a typical moon face. A profuse growth of hair with some pimples appeared on her face. Red striæ were inadvertently not looked for until a late stage in her illness when wasting had started, and they were not then observed.

The association of Cushing's syndrome with carcinoma may be more common than the published records would suggest. Doubtless the late stages of cancer are often observed only by us general practitioners. Confronted with a mystifying condition in these circumstances, we are unlikely to seek further specialist advice, without which we are unlikely to be venturesome enough to publish a record of the case.

Birmingham W. M. CHESNEY

Obituary

WILLIAM GEORGE CLARK

C.B.E., M.B. Glasg., F.R.C.P.E.

Dr. Clark, medical officer of health for Edinburgh from 1938 until 1953, died at his home in the city on Jan. 3 at the age of 68.

He was the son of William Clark, a civil and mining engineer, and he was educated in Glasgow. After graduating in medicine in 1910, he held resident appointments at the Glasgow Royal Infirmary, Belvidere Hospital, Glasgow, and Brook Hospital, London. During the 1914–18 war he served as a temporary surgeon in the Royal Navy. After he was demobilised he became an assistant medical officer at Woolwich Tuberculosis Dispensary. In 1920 he took the D.P.H. and joined the staff of the Glasgow health department, in which he rose to become senior deputy M.O.H. During his years in Glasgow he gained a reputation as an administrator and also gave much time and thought to his special interests of health education and the application of epidemiology to the practical issues of infectious disease. Later he made brilliant use of this experience in the sharp outbreak of smallpox in Edinburgh in 1942.

In 1935 Dr. Clark was appointed deputy to the medical officer of health for Edinburgh, and he succeeded him three years later. He was elected an M.R.C.P.E. in 1939, and became a fellow three years later. His distinguished service was recognised by his appointment as honorary physician to King George VI in 1945. When he retired in 1953 he was appointed C.B.E. in recognition of his organisation of the war-time health and casualty services in Edinburgh.

J. M. M. writes:

George Clark was a well known figure in the public health service of the United Kingdom for many years. He took a keen interest in the Society of Medical Officers of Health, and was elected its president in 1952. In his own domain he pursued a vigorous policy of prevention, and was never afraid of speaking his mind, either on immediate problems or in the wider councils of public health in the country generally. He was also a lively and successful teacher, exercising a great influence on generations of undergraduate and postgraduate students in the university, where he held the post of senior lecturer until his retirement in 1953.

In 1948 he became one of the original members of the Scottish Central Health Services Council, and he gave it his loyal service despite his outspoken criticisms of the Act and its operation. He had strong leanings towards the preventive side, which he felt was somewhat neglected. He was also an active member of the General Nursing Council, and took a great interest in the educational aspect of its work, with his continuing emphasis on prevention.

His many friends will remember him chiefly as a forceful, robust, and genial man. When something was said with which he disagreed, the big eyebrows would go up and he would look like a forbidding fortress. His first sentence in reply would emerge like a rocket. Then the eyebrows came down and he grinned happily. In support of his views, which were often strongly individualistic, he was a bonny fechter, but he never wounded a friendship. A large-hearted man.

Dr. Clark married in 1921 Gladys Catherine, daughter of C. H. Harrison, of Great Yarmouth. She survives him with one son, who is in the government service in Nigeria.

THOMAS ALEXANDER BRITTEN HARRIS

M.D. Melb., F.F.A. R.C.S., D.A.

Dr. Harris, senior anæsthetist and director of the department of anæsthetics at Guy's Hospital, died in London on Dec. 27 at the age of 59.

He was the son of a doctor who was a well-known political figure in Australia, and he graduated M.B. at Melbourne University in 1922. For several years he helped his father in general practice in a small community: this invaluable experience made him a good doctor. He came to this country as an anæsthetist at the West London Hospital. In 1935 he was appointed to the staff of Guy's Hospital, and his enthusiasm and search for knowledge soon made him well known to practically every member of the staff and school: when not teaching anæsthetics, he was picking the brains of the departments of physiology, pharmacology, or biochemistry. He taught anæsthetics in such a way that his students understood the mode of action of the drugs they used and became able to give a simple anæsthetic with confidence and safety. He also joined the staff of St. Peter's Hospital for Stone.

During the late war he served at Tidworth until 1942, when he was posted to India, where he became adviser in anæsthetics to Eastern Command with the rank of lieut.-colonel. One of his duties was to run intensive training-courses, and H. K. A. recalls that he ran them with "energy, conscientiousness, and scrupulous fairness to the candidates."

Whenever Tommy decided (he continues) that a candidate would not make the grade—and it was on his recommendation alone that an officer was or was not posted for anæsthetic duties after attending his course—he nearly always wrote me a personal letter wondering whether or not he was right. But after a month of intensive tuition from Tommy, there were few who did not make the grade and fewer still who subsequently did not prove in practice the soundness of his teaching. In the monthly intervals between courses he constantly toured the forward areas on the Assam and Arakan fronts, staying with the mobile surgical units and casualty clearing stations, watching them at work, and after his return to Calcutta, sending clear, concise, and, practical reports on what could and should be done to improve the anæsthetic service and equipment of these units. His energy was boundless. He wrote such an excellent statement of the case for a monetary grant for technical help in his research on the mode of action of anæsthetic drugs that he miraculously extracted it from G.H.Q. India, in spite of that august body's preoccupation with the war. Much of his book was planned and written in his small, comfortable, and always hospitable flat in Calcutta, where he was never happier than when entertaining his friends and colleagues. Despite his serious demeanour and his quiet and deliberate speech in the pleasant Australian accent which he never lost, Tommy was always gay and full of fun.

In 1948 he was elected F.F.A. R.C.S. In 1951 the first edition of his book *The Mode of Action of Anæsthetics* was published, and at the time of his death he was preparing a second edition. He was also studying the barbiturate antagonists, and he was making an extensive survey of the relationship between the use of muscle relaxants and anæsthetic mortality. For much of the time he worked too hard, and even after a coronary thrombosis had compelled him to rest for two months he refused to content himself with a less strenuous life.

W. S. McC., who in 1935 had faced the Guy's selection committee with Harris, writes:

The comparatively unknown Australian was appointed in open competition with Guy's men: it was a fortunate day for the hospital, for the hospital secured the lifetime devotion of a loyal and dynamic worker. He so identified himself with the hospital that he resented even mild criticism of Guy's and its traditions by an outsider. As an anæsthetist he was superb. Although not an imposing figure—he was short, and had not completely conquered a slight stutter—he conveyed to me and to his other patients a remarkable degree of confidence and assurance. For the surgeons he provided exemplary operating conditions and an atmosphere of tranquillity. In the years to come Tommy will be remembered as a man who had a "shorthand" for CDe/cDE, but when the subscripts are converted into superscripts, as in the symbol R^1R^2 of the Rh Hr nomenclature, the symbol apparently becomes unintelligible (cf pp 204 and 218 of Mollison's new book)

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6 Cummins C S Harris H Unpublished results
7 Cocchieri P *Lattante* 1956 27 129

During the last year of her life she developed a well-marked Cushing's syndrome The records of her case were (as is usual) forwarded after her death to the executive council and are unfortunately not now available to me but I have a vivid recollection of her Hypertension (systolic over 200) and glycosuria developed, and she became very obese with a typical moon face A profuse growth of hair with some pimples appeared on her face Red striæ were inadvertently not looked for until a late stage in her illness when wasting had started and they were not then observed

The association of Cushing's syndrome with carcinoma may be more common than the published records would suggest Doubtless the late stages of cancer are often observed only by us general practitioners Confronted with a mystifying condition in these circumstances we are unlikely to seek further specialist advice without which we are unlikely to be venturesome enough to publish a record of the case

Birmingham W M CHESNEY

Obituary

WILLIAM GEORGE CLARK

CBE, MB Glasg, FRCPE

Dr Clark, medical officer of health for Edinburgh from 1938 until 1953, died at his home in the city on Jan 3 at the age of 68

He was the son of William Clark, a civil and mining engineer and he was educated in Glasgow After graduating in medicine in 1910, he held resident appointments at the Glasgow Royal Infirmary, Belvidere Hospital, Glasgow, and Brook Hospital London During the 1914–18 war he served as a temporary surgeon in the Royal Navy After he was demobilised he became an assistant medical officer at Woolwich Tuberculosis Dispensary In 1920 he took the D P H and joined the staff of the Glasgow health department, in which he rose to become senior deputy M O H During his years in Glasgow he gained a reputation as an administrator and also gave much time and thought to his special interests of health education and the application of epidemiology to the practical issues of infectious disease Later he made brilliant use of this experience in the sharp outbreak of smallpox in Edinburgh in 1942

In 1935 Dr Clark was appointed deputy to the medical officer of health for Edinburgh, and he succeeded him three years later He was elected an M R C P E in 1939, and became a fellow three years later His distinguished service was recognised by his appointment as honorary physician to King George VI in 1945 When he retired in 1953 he was appointed C B E in recognition of his organisation of the war-time health and casualty services in Edinburgh

J M M writes

> George Clark was a well known figure in the public health service of the United Kingdom for many years He took a keen interest in the Society of Medical Officers of Health and was elected its president in 1952 In his own domain he pursued a vigorous policy of prevention and was never afraid of speaking his mind either on immediate problems or in the wider councils of public health in the country generally He was also a lively and successful teacher, exercising a great influence on generations of undergraduate and postgraduate students in the university, where he held the post of senior lecturer until his retirement in 1953
>
> In 1948 he became one of the original members of the Scottish Central Health Services Council and he gave it his loyal service despite his outspoken criticisms of the Act and its operation He had strong leanings towards the preventive side which he felt was somewhat neglected He was also an active member of the General Nursing Council and took a great interest in the educational aspect of its work with his continuing emphasis on prevention
>
> His many friends will remember him chiefly as a forceful robust and genial man When something was said with which he disagreed the big eyebrows would go up and he would look like a forbidding fortress His first sentence in reply would emerge like a rocket Then the eyebrows came down and he grinned happily In support of his views which were often strongly individualistic he was a bonny fechter but he never wounded a friendship A large hearted man

Dr Clark married in 1921 Gladys Catherine, daughter of C H Harrison of Great Yarmouth She survives him with one son who is in the government service in Nigeria

THOMAS ALEXANDER BRITTEN HARRIS

M D Melb, F F A R C S, D A

Dr Harris senior anæsthetist and director of the department of anæsthetics at Guy's Hospital, died in London on Dec 27 at the age of 59

He was the son of a doctor who was a well-known political figure in Australia and he graduated M B at Melbourne University in 1922 For several years he helped his father in general practice in a small community this invaluable experience made him a good doctor He came to this country as an anæsthetist at the West London Hospital In 1935 he was appointed to the staff of Guy's Hospital, and his enthusiasm and search for knowledge soon made him well known to practically every member of the staff and school when not teaching anæsthetics he was picking the brains of the departments of physiology, pharmacology, or biochemistry He taught anæsthetics in such a way that his students understood the mode of action of the drugs they used and became able to give a simple anæsthetic with confidence and safety He also joined the staff of St Peter's Hospital for Stone

During the late war he served at Tidworth until 1942 when he was posted to India, where he became adviser in anæsthetics to Eastern Command with the rank of lieut -colonel One of his duties was to run intensive training-courses, and H K A recalls that he ran them with " energy, conscientiousness, and scrupulous fairness to the candidates "

> Whenever Tommy decided (he continues) that a candidate would not make the grade—and it was on his recommendation alone that an officer was or was not posted for anæsthetic duties after attending his course—he nearly always wrote me a personal letter wondering whether or not he was right But, after a month of intensive tuition from Tommy, there were few who did not make the grade and fewer still who subsequently did not prove in practice the soundness of his teaching In the monthly intervals between courses he constantly toured the forward areas on the Assam and Arakan fronts, staying with the mobile surgical units and casualty clearing stations watching them at work, and after his return to Calcutta, sending clear, concise, and practical reports on what could and should be done to improve the anæsthetic service and equipment of these units His energy was boundless He wrote such an excellent statement of the case for a monetary grant for technical help in his research on the mode of action of anæsthetic drugs that he miraculously extracted it from G H Q India in spite of that august body's preoccupation with the war Much of his book was planned and written in his small, comfortable and always hospitable flat in Calcutta, where he was never happier than when entertaining his friends and colleagues Despite his serious demeanour and his quiet and deliberate speech in the pleasant Australian accent which he never lost, Tommy was always gay and full of fun

In 1948 he was elected F F A R C S In 1951 the first edition of his book *The Mode of Action of Anæsthetics* was published and at the time of his death he was preparing a second edition He was also studying the barbiturate antagonists, and he was making an extensive survey of the relationship between the use of muscle relaxants and anæsthetic mortality For much of the time he worked too hard, and even after a coronary thrombosis had compelled him to rest for two months he refused to content himself with a less strenuous life

W S McC who in 1935 had faced the Guy's selection committee with Harris writes

> The comparatively unknown Australian was appointed in open competition with Guy's men it was a fortunate day for the hospital for the hospital secured the lifetime devotion of a loyal and dynamic worker He so identified himself with the hospital that he resented even mild criticism of Guy's and its traditions by an outsider As an anæsthetist he was superb Although not an imposing figure—he was short and had not completely conquered a slight stutter—he conveyed to me and to his other patients a remarkable degree of confidence and assurance For the surgeons he provided exemplary operating conditions and an atmosphere of tranquillity In the years to come Tommy will be remembered as a man who had a

remarkable capacity for making friends. He was proud of his friends and valued their affection, but he had the courage to offer criticism and advice if he thought it would help them. Although forthright in his comments, his loyalty was constant.

Dr Harris leaves a widow and four sons. A memorial service was held in Guy's Chapel on Jan. 4.

GODFREY TAUNTON HEBERT
D.M. Oxfd, F.R.C.P.

FROM his appointment as physician in charge of the tuberculosis department at St Thomas's Hospital Dr Hebert retired with some regret in 1948 as the great promise of streptomycin began to show. Happily he lived to see modern chemotherapy make easier the way of his successors.

He was born in 1888, the son of a Kentish parson, and he was *educated at Harrow and Christ Church, Oxford*, where he got a first-class honours in physiology. He qualified from St Thomas's Hospital in 1913, and soon afterwards elected to make his career in tuberculosis. In 1920 he was appointed officer in charge of the Lambeth tuberculosis dispensary in St Thomas's Hospital and to the tuberculosis department of the hospital. He was responsible for the treatment of tuberculosis in a large district in south-west London, and by present-day standards had little help in dealing with a vast number of outpatients. With one assistant tuberculosis officer he was responsible for a large pneumothorax clinic. He was elected to the full staff of St Thomas's Hospital in 1927. During the late war his department suffered badly, but through these trying years he continued his full service, at times in very cramped quarters.

Dr Hebert was, according to the custom of his day, a tuberculosis officer and not a chest physician, but many other conditions passed through his hands for diagnosis. He always warned against woolliness in diagnosis, especially of chest films, and he "took a great delight in pulling his colleagues' legs by giving them tricky X rays." He was a former president of the Tuberculosis Association.

W. M. M. writes:

Dr Hebert's greatest interest was in the problems associated with pulmonary tuberculosis. He played a leading part in the development and acceptance of artificial pneumothorax therapy in England and his death severs another link with this important phase in the treatment of the disease. During the earlier years the interpretation of chest X-ray shadows was an ever-present topic for discussion—the significance of cavitation, the presence of fibrosis, and similar questions required answers which were not easily obtained. He loved such controversies and would delight, with a characteristic nod of his head, slight stutter, and a twinkle in his eye, to argue and tease and so illustrate the points of his teaching. His wide experience was invaluable to his assistants and students. Many house-physicians at St Thomas's served their apprenticeship in practical medicine as clinical assistants in his department. Their knowledge of chest disease and their skill in "needling" owed much to his clear and concise instruction.

In 1919 Dr Hebert married Miss Constance Tatton, who survives him with two daughters. *He died in* hospital in London on Jan. 4.

ERNEST THOMAS GASPEY
M.R.C.S.

Dr Gaspey, formerly medical superintendent of Tehidy Sanatorium, Cornwall, died on Jan. 1 at the age of 68. He should have qualified in Brussels where he was studying medicine when war began in 1914. The invasion of Belgium forced him to come to this country where he qualified in 1916. After the war he took up tuberculosis work and he held posts with the Welsh National Memorial Association and at sanatoriums at Montana and Matlock before he was appointed to Tehidy Sanatorium. C. S. writes: "While Gaspey was in Switzerland he met Spahlinger and observed his treatment of tuberculosis, and Gaspey's account of this was an interesting story. He was superintendent of Tehidy Sanatorium for many years until he retired three years ago. He had a remarkable faculty of remembering and being remembered by his ex-patients and there were few villages in Cornwall where he was not recognised and welcomed by someone for whom he had cared."

JAMES ROY OWEN
M.R.C.P.

Dr James Owen, senior honorary physician to the skin department of the Royal Northern Hospital, London, died on Dec. 28. He qualified from the Birmingham Medical School in 1920 and held house-appointments at the Queen's Hospital, Birmingham. Later he became first assistant to medical outpatients at the London Hospital and medical registrar at the Royal Cancer Hospital and the National Temperance Hospital. He took the M.R.C.P. in 1937, and after setting up in consultant practice joined the staff of the Hospital for Diseases of the Skin, Blackfriars. During the late war he was in charge of the medical division of an R.A.M.C. general hospital and he also acted as a blood-transfusion officer in the Emergency Medical Service. Besides his appointment at the Royal Northern, he was physician in charge of the skin department at Ashford County Hospital, and honorary physician for diseases of the skin at Hampstead General Hospital, Victoria Hospital for Children, and Queen Elizabeth Hospital for Children.

H. T. H. W. writes:

Those who knew James Owen in former years will remember him as a man of immaculate appearance and debonair charm. He had a passion for adventure and his past activities ranged from jumping by parachute to underwater exploration, with this was coupled a magnificent disregard for the trivialities of life. His essential kindliness endeared him to colleagues, nurses, and patients while his easy wit made him an excellent companion.

HERBERT FOWLIE
M.B. Aberd.

Dr Fowlie, who died at Aberdeen on Christmas Day at the age of 49, graduated M.B. at Aberdeen University in 1930 and, after house-appointments at Carlisle and experience of general practice in Appleby, settled in practice in that city in 1940.

A colleague writes:

By heredity and environment Hebbie Fowlie should have been a farmer, but he turned to medicine, *saying*, as he often did, that he "hadna the brains for farming." He soon became one of the busiest, best known, and best loved family doctors in Aberdeen. He was of great humanity and transparent honesty, of infinite patience when patience was needful, but of blistering *impatience* with *incompetence* or dishonesty. He made friends of all whom he met in his practice, on the golf course, or on his beloved shooting and fishing excursions. He was a wise and considerate colleague and the family doctor of a number of medical households including my own; he *paid us a visit only a few hours before his death*, and he left us all laughing, for his gaiety was infectious and wherever he went he left laughter and lightened hearts behind him. We, who were his patients, can say with pride and gratitude—"He was our doctor, aye he left us cheered."

Dr Fowlie leaves a widow, a daughter, and two sons.

Appointments

DOODY, P. J., M.B. N.U.I., D.I.H.: M.O., Wimbledon.
FRANCIS, A. J., M.D. Lond.: assistant pathologist (S.H.M.O.), St Peter's, St Paul's, and St Philip's Hospitals, London.
GRIFFITHS, J. A., M.D. Sheff., F.F.A. R.C.S., D.A.: consultant anæsthetist, United Sheffield Hospitals.
HALDANE, J. D., M.B. Edin., M.R.C.P.E., D.P.M.: deputy physician superintendent, Fife mental hospitals.
HUDSON, T. G., M.B. Belf., D.A.: assistant anæsthetist (S.H.M.O.) based on the Inverness hospitals.
SCOTT, O. L. S., M.B. Camb., M.R.C.P.: part-time consultant dermatologist, Charing Cross Hospital, London.

Colonial Appointments

BUCHANAN, G., F.R.C.S.E.: surgeon specialist, Western Nigeria.
EVANS, A. J., M.B. Lond., D.A.: senior specialist, Western Nigeria.
GRAHAM, J. L. T., L.R.C.P.E.: M.O., Northern Nigeria.
HAROBIWITS, A., M.B. Camb.: senior M.O., Kenya.
HAY, J. K., M.B. Aberd., D.I.H., D.T.M. & H.: senior M.O., sleeping sickness service, Northern Nigeria.
KALADIA, K. K., M.B. Bombay, D.T.M. & H.: M.O., Western Nigeria.
[illegible], I. A., M.R.C.S., D.I.H., D.D.M.S., Mauritius.
NUGENT, D. A. W., M.B. Madras, D.I.H., D.T.M. & H.: specialist malariologist, ministry of health, Gold Coast.
NWOKOLO, C., M.R.C.P.E.: specialist (physician), Eastern Nigeria.
ONWUMERE, R. J., M.R.C.S., D.O.: specialist (ophthalmology), Eastern Nigeria.
LARKINS, C. H., M.D., D.I.H.: senior radiologist, Jamaica.

The Birmingham Regional Hospital Board inform us that Dr W. G. A. Bigg, whose appointment as assistant psychiatrist to Shrewsbury group of hospitals we announced in our issue of Dec. 8, later withdrew from the appointment.

Notes and News

PATHOLOGICAL SPECIMENS BY POST

THE Post Office has expressed concern at the ineffective packing or sealing of some pathological specimens sent through the post If the material is infected or toxic, this may be hazardous for Post-Office workers, and, through contamination of other mail, for the general public Sometimes a patient is given a receptacle to send a specimen, but not told how to pack it, written instructions should always be given with containers The Post Office's instructions for packing such deleterious substances, which may be sent by letter post but not by parcel post, are as follows

> Any such liquid or substance must be enclosed in a receptacle, hermetically sealed or otherwise securely closed and this receptacle must itself be placed in a strong wooden or metal case (or other case which has been approved by the Post Office) in such a way that it cannot shift about, and with a sufficient quantity of some absorbent material (such as sawdust or cotton wool) so packed about the receptacle as absolutely to prevent any possible leakage from the package in the event of damage to the receptacle The packet so made up must be conspicuously marked "Fragile with Care" and bear the words "Pathological Specimen."

MEDICAL MEMBERSHIP OF HOSPITAL AUTHORITIES

THE Minister of Health has accepted the recommendation of the Guillebaud Committee that no more than a quarter of the members of regional hospital boards should be doctors In a circular to hospital authorities (H M [56] 111) he explains that in future he will observe this principle in appointing regional hospital boards, and asks that the boards shall do the same when appointing hospital management committees The Guillebaud Committee made no recommendation about the membership of boards of governors, and, as university nominees (who may be doctors) sit on these boards as well as representatives of the hospital medical staff, the Minister thinks it inappropriate to limit the proportion of medical members on these boards to a quarter of the total membership But he has asked R H B S when nominating their members to boards of governors to bear in mind "the desirability of securing a reasonable balance of lay representation"

MEDICAL CARE FOR AMERICAN SERVICEMEN'S DEPENDENTS

THE dependents of American Servicemen who live on or near military posts have by tradition been allowed to share the medical services available to their husbands and fathers In practice this has come to mean that no medical care is provided for those who probably need it most—the families of men serving overseas The Dependents Medical Act was passed last year by Congress to correct this anomaly When the Act was under discussion the Armed Services committees said that the Services could no longer compete with private industry for talented men, because industry offered so much more in benefits such as health insurance Under the Act the new scheme, which is popularly known as Medicare, came into force last month (*New York Times*, Dec 25, 1956) It provides hospital and medical care for the 800,000 dependents of Servicemen who do not live at military posts Hospital fees are being arranged through an insurance company, which is handling the business without profit, and through the Blue Cross a non profit organisation In all save two States doctors' fees will be handled by State medical associations Where a Service wife prefers to go to a civilian hospital the government will usually pay a substantial part of the costs

COUNTY CHARITIES

THE Welfare State has not wiped out the need for private charity but it has altered its purpose The widow can now rely on getting her dole from the post office, the orphan is sure of his schooling but both will still be grateful for some extra help—perhaps to buy more coal at Christmas, perhaps to eke out a scholarship which leaves little over for clothes or books Through the centuries almost every village has acquired some local trusts With the changing value of money some are today worth much less than their donors intended Others by fortunate investments have greatly increased their incomes A register of all this scattered well doing would be useful to many people and Dr I H C Clarke by listing *Charities in Kesteven* has provided what is thought to be the first county list Other medical officers of health may follow his example, for as he points out in his introduction, charities can be regarded as an instrument for the betterment of public health" The present state of honest but ineffective nescience is well shown by the last entry on his list under the heading "Unknown Charity"

> An income of 10*s* 8*d* p a is paid by the Charity Commissioners into the Midland Bank, where it is accumulating the balance being now a little over £9 Nothing appears to be known locally as to the origin or purpose of the Charity

By the end of 1957 surely some part of Kesteven will have put that £9 to good use

NEW MULTILINGUAL JOURNAL

Living Conditions and Health, a new quarterly journal sponsored by the World Congress of Doctors for the Study of Present day Living Conditions, appears in identical form in English, Chinese, French, German, Russian, and Spanish The English edition may be had from Dr A Ryle, the Caversham Centre, 25, Caversham Road, London, N W 5 (annual subscription 26*s*, single copies 7*s* 6*d*)

Royal College of Physicians of London

Dr D D Reid will give the Milroy lectures on Tuesday and Thursday, Feb 5 and 7, at 5 P M, at the college, Pall Mall East S W 1 He will speak on Environmental Factors in Respiratory Disease

Royal College of Surgeons of England

The Hunterian festival dinner will be held in the college on Thursday, Feb 14 The guests will include the Archbishop of Canterbury, the Lord Chancellor, the Minister of Education, and the Secretary of State for War Fellows and members may obtain tickets (£2 10*s*) from Mr W F Davis, deputy secretary of the college, Lincoln's Inn Fields, London, W C 2

International Congress of Therapeutics

This congress, which is sponsored by the International Union of Therapeutics, will be held at Utrecht from June 4 to 6 Further particulars may be had from the general secretary, Vondellaan 6, Utrecht, Holland

British Association of Plastic Surgeons

At a meeting of this association on Dec 14, with Mr Wilfred Hynes in the chair, Mr R P Osborne was elected president-elect and treasurer, and Mr C R McLaughlin hon secretary

Royal Appointment

Surgeon Captain Reginald Wear, R N V R, has been appointed an honorary physician to the Queen in succession to Surgeon Captain H M Willoughby

World Federation for Mental Health

Dr Margaret Mead, president of the federation, will give an address at County Hall, London, S E 1, on Friday, Feb 8, at 5 45 P M, on Mental Health in a Changing World Tickets (2*s* 6*d*) may be had from the National Association for Mental Health, 39, Queen Anne Street, W 1

Chronic Rheumatic Diseases

A course on this subject with lectures, ward rounds, and practical demonstrations, is being held at the rheumatism unit of St Stephen's Hospital, Fulham Road, London S W 10 on Saturday and Sunday, March 9 and 10 Further particulars can be had from the secretary, Fellowship of Postgraduate Medicine 60, Portland Place, W 1

Education of the Public regarding Cancer

The Central Council for Health Education is holding a conference on this subject at B M A House, London, W C 1 on Thursday, Jan 24, at 11 15 A M The conference is intended for chairmen of health committees, medical officers of health and their staff, members of hospital staffs, and others interested The speakers will include Mr R W Raven and Dr John Burton Further particulars may be had from the council Tavistock House North Tavistock Square, London W C 1

World Medical Association

The World Medical Association, founded in 1947, has as its first object "to promote closer ties among the national medical organisations and among the doctors of the world by personal contact and by all other means available" A British supporting group is to be formed, to stimulate interest in and provide financial support for, the association The inaugural meeting will be held at British Medical Association House Tavistock Square, London W C 1, at 3 30 P M on Tuesday Jan 29

British Overseas Airways Corporation

Dr Kenneth Bergin B O A C 's medical superintendent, Air Services, has been appointed to the post of chief medical officer to the corporation

Nuffield Dental Fellowships

One of the aims of these fellowships is to enable graduates in medicine and science to qualify themselves to undertake teaching and research on dental health and disease Further particulars will be found in our advertisement columns

Ageing and Old Age

A symposium on this subject, organised by the department of studies in psychological medicine of the University of Liverpool will be held on Saturday, March 23 The speakers will be Dr A Heron, Prof A B Semple, and Prof Martin Roth Further particulars can be had from Dr H Jarvie, 77 Bedford Street South, Liverpool 7

Royal Society of Health

The annual congress of this society is to be held at Folkestone from April 30 to May 3 For the first time it will include a section on hospitals over which Lord Inman chairman of Charing Cross Hospital, will preside The tercentenary of the death of William Harvey coincides with the congress, and Sir Arthur MacNalty, F R C P , will give a lecture on Harvey's influence on public health Further particulars may be had from the secretary of the society 90, Buckingham Palace Road, London, S W 1

Volunteers for Research on Common Cold

The Common Cold Research Unit at Harvard Hospital, Salisbury is starting its eleventh year with an appeal for more volunteers especially for the next two 10 day sessions, starting on Jan 15 and Jan 29 From now until the end of March some 100 volunteers are wanted, and there will be vacancies during the rest of the year for 400 to 500 Comfortable living quarters are provided, fares to and from Salisbury are paid up to a maximum of £3, and 3*s* a day pocket money is allowed Volunteers should be between 18 and 45 years of age and in normal health Further particulars may be had from the medical superintendent of the hospital

Committee on Public Health Engineering

The Institute of Sewage Purification the Institution of Municipal Engineers the Institution of Public Health Engineers the Institution of Water Engineers, the Royal Society of Health the Royal Institute of Public Health and Hygiene the Sanitary Inspectors' Association, and the Society of Medical Officers of Health have agreed to set up a coordinating committee to deal with problems in this field Sir Allen Daley, F R C P is the chairman and the secretary is Mr P Arthur Wells M SC (Royal Society of Health, 90, Buckingham Palace Road London, S W 1)

Medical Research Council

The council invite applications for the following fellowships for 1957–58

Rockefeller Travelling Fellowships —These fellowships are intended for graduates resident in this country who have had some training in research work in clinical medicine or surgery, or in some other branch of medical science and who are likely to profit by a period of work at a centre in the United States or elsewhere abroad before taking up appointments for higher teaching or research in the United Kingdom

Dorothy Temple Cross Fellowships in Tuberculosis —These fellowships offer special opportunities for study or research to British doctors who intend to devote themselves to the advancement by teaching or research of curative or preventive treatment of tuberculosis The fellowships will as a rule be awarded to candidates who wish to make their studies or inquiries elsewhere than in the United Kingdom

Alexander Pigott Wernher Fellowships in Ophthalmology and Otology —These fellowships are intended for doctors who are likely to profit by a period of work in ophthalmology or otology at a centre abroad before taking up positions for higher teaching and research in these branches of medical science The awards will normally be tenable for one year

All the fellowships provide for the payment of a maintenance allowance at the rate of £650 per annum for a single fellow or £900 per annum for a married fellow ($2700 and $3900 respectively if the fellowship is held in the United States) Allowances are made for travelling and other approved expenses Forms of application for these fellowships may be had from the secretary of the council 38 Old Queen Street London S W 1 with whom applications must be lodged by March 15 (March 31 for the Pigott Wernher fellowships)

Diary of the Week

JAN 13 TO 19

Monday, 14th

POSTGRADUATE MEDICAL SCHOOL OF LONDON Ducane Road W 12
4 P M Dr A C Dornhorst Pulmonary Physical Signs
INSTITUTE OF NEUROLOGY, National Hospital, Queen Square W C 1
5 30 P M Sir Rudolph Peters, F R S Biochemical Aspect of Vitamin B Group Disorders in Relation to the Central Nervous System

Tuesday, 15th

ROYAL COLLEGE OF PHYSICIANS OF LONDON, Pall Mall East London S W 1
5 P M Dr W D W Brooks Prevention of Tuberculosis (Marc Daniels lecture)
ROYAL SOCIETY OF MEDICINE 1 Wimpole Street W 1
8 P M *Pathology Epidemiology and Preventive Medicine* Dr B E Andrews, Dr J C McDonald Dr H G Pereira Dr R G Sommerville Adenovirus Infections
ST MARY'S HOSPITAL MEDICAL SCHOOL Paddington W 2
5 P M Prof L S Penrose, F R S Inheritance of Foetal Deformities
BRITISH POSTGRADUATE MEDICAL FEDERATION
5 30 P M (London School of Hygiene and Tropical Medicine Keppel Street, W C 1) Prof A J Lewis Social Psychiatry
INSTITUTE OF DERMATOLOGY, Lisle Street London, W C 2
5 30 P M Miss H C Hodges Conservative Radiotherapy

Wednesday, 16th

ROYAL SOCIETY OF MEDICINE
8 15 P M *General Practice* Dr A Robin Abel Mr C Naunton Morgan Piles
POSTGRADUATE MEDICAL SCHOOL OF LONDON
2 P M Prof G Payling Wright Cell Regeneration and Pathological Processes (Second of two lectures)
INSTITUTE OF DISEASES OF THE CHEST, Brompton S W 3
5 P M Dr E H Hudson Results of Prolonged Chemotherapy in Pulmonary Tuberculosis
INSTITUTE OF DERMATOLOGY
5 30 P M Dr Arthur Tickner Minerals in Skin Metabolism
EUGENICS SOCIETY
5 30 P M (Burlington House Piccadilly, W 1) Dr Barbara Simonds Twin Research in Tuberculosis
ROYAL MICROSCOPICAL SOCIETY, Tavistock House South W C 1
5 30 P M Mr J Smiles Fluorescence Microscopy (Presidential address)
ROYAL FACULTY OF PHYSICIANS AND SURGEONS OF GLASGOW 242 St Vincent Street Glasgow
5 P M Prof I Dahl Iversen Diagnosis and Treatment of Hyperplasias and Adenomas of the Adrenals (Welld lecture)

Thursday, 17th

ROYAL COLLEGE OF PHYSICIANS OF LONDON
5 P M Dr Raymond Daley Autonomic Nervous System in its Relation to Some Forms of Heart and Lung Dis
(First of two Goulstonian lectures)
ROYAL SOCIETY OF MEDICINE
4 45 P M *Dermatology* Dr R M B MacKenna Samuel Plumbe—the Forgotten Dermatologist
POSTGRADUATE MEDICAL SCHOOL OF LONDON
2 P M Mr D W C Northfield Tumours Involving the Floor of the Third Ventricle
BRITISH POSTGRADUATE MEDICAL FEDERATION
5 30 P M (London School of Hygiene and Tropical Medicine Keppel Street W C 1) Prof L G T Liddell F R S Cajal and Sherrington
INSTITUTE OF CHILD HEALTH
5 P M (Hospital for Sick Children Great Ormond Street W C 1) Prof C A Janeway (Boston) Resistance to Infection in the Child
ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE 26 Portland Place W 1
7 30 P M Prof P C C Garnham Prof C P Beattie, Dr J A B Cathie Mr R Lainson Toxoplasmosis
BRITISH INSTITUTE OF RADIOLOGY 32, Welbeck Street W 1
8 P M Dr John Pead (University of Otago) Prof Herman B Chase (Brown University U S A) Radiation Damage likely to be Involved in Tumour Regression
LIVERPOOL MEDICAL INSTITUTION 114 Mount Pleasant Liverpool
8 P M Prof C V Harrison Vascular Changes in Pulmonary Hypertension
ST ANDREWS UNIVERSITY Queen s College, Small s Wynd Dundee
5 P M Prof E J King D SC Enzymes in Clinical Investigati

Friday, 18th

ROYAL SOCIETY OF MEDICINE
5 P M *Pædiatrics* Professor Janeway Nephrosis
8 15 P M *Radiology* Mr H Jackson Burrows Prof L W Windeyer Dr J W Stewart Ankylosing Spondylitis
POSTGRADUATE MEDICAL SCHOOL OF LONDON
4 P M Prof Alexander Haddow Modern Views on Carcinogenesis
KING S COLLEGE HOSPITAL MEDICAL SCHOOL Denmark Hill S E 5
4 45 P M Dr Cuthbert Dukes Pathology and Treatment of Cancer of the Colon and Rectum (*Dorothy Platt lecture*)
YORKSHIRE SOCIETY OF ANÆSTHETISTS
8 30 P M (Leeds General Infirmary) Dr W M Shearer Steroid Anæsthesia

CEREBRAL ABSCESS IN CYANOTIC CONGENITAL HEART-DISEASE

MAURICE CAMPBELL
M A, D M Oxfd, F R C P

PHYSICIAN IN CHARGE OF THE CARDIAC DEPARTMENT, GUY'S HOSPITAL, PHYSICIAN, INSTITUTE OF CARDIOLOGY, LONDON

IN 1814, Farre described a cyanotic boy, aged 9, with Fallot's tetralogy and a brain abscess As early as 1880, Ballet thought there was an association between these two conditions and wrote " En résumé, coexistence d'une malformation du cœur et d'un absces du cerveau, tel est le trait d'union qui rapproche les unes des autres les six observations précédentes Faut il voir dans cette coexistence une relation étiologique entre les deux ordres de lésions ? " He thought so, because there was no other reason such as trauma or infection of the ear or nasal sinuses to explain the presence of the cerebral abscess

Ballet was describing the case of a large fronto parietal abscess in a boy of 15 where the two atria drained into the left ventricle and the small right ventricle could be reached only through a ventricular septal defect He found reports of five other cases, all of which had defects of the atrial or ventricular septa, sometimes with an overriding aorta so that, as he pointed out, the venous blood could easily become mixed with the arterial blood He concluded " Aussi bien pensons nous qu'on ne saurait expliquer par une pure coincidence le fait de 6 cas de malformations du cœur s'accompagnant d'absces du cerveau , que ce chiffre a son importance qui merite de fixer l'attention, et qu'il est logique d'admettre une relation étiologique entre les lesions précedentes "

As late as 1945, Robbins, reporting three cases among patients with Fallot's tetralogy, could find only twenty-three others, and only three where surgical treatment had been attempted Newton (1956), reporting seven cases from Birmingham, brought this total up to seventy-nine only Hence the following fifteen cases seem worth reporting

The Present Series

During the past 10 years, among our patients with cyanotic congenital heart disease (about eight hundred) we have seen fourteen with an abscess of the brain, of whom nine have died and five have recovered after surgical treatment We are including a fifteenth patient who after a sudden loss of consciousness and a right hemiplegia recovered with penicillin treatment only, because even if the diagnosis of brain abscess was incorrect the alternative of an infected embolism may help in understanding the cause of this association I saw them all for their heart condition but only some of them when they had a brain abscess This number of cases leaves little doubt that cerebral abscess occurs more often in patients with cyanotic congenital heart disease than in others A sixteenth acyanotic patient is dis ussed

These fifteen patients (ten male and five female) were between 3 and 25 years of age, and the age incidence was roughly the same as in our total number of patients In general, there is no difference in the sex-incidence

The Condition of the Heart

All the fifteen patients had central cyanosis with a right to left shunt (see tables I and II) eleven had Fallot's tetralogy , two had all the features of Fallot's tetralogy except that they had pulmonary atresia instead of stenosis, and two had an increased blood flow to the lungs and were diagnosed as having transposition of the aorta and pulmonary trunk Necropsy confirmed partial transposition in the last two, for in case 9 the aorta arose entirely from the right ventricle and in case 8 the pulmonary trunk arose from a rudimentary chamber of the left ventricle and there was a single atrium and a single atrio-ventricular valve One of the patients with Fallot's tetralogy had also situs inversus (case 15) and another had enough dextro-rotation to simulate dextrocardia (case 7) No patient had any evidence of subacute bacterial endocarditis

The Brain Abscess

Brain abscesses of all types are most often solitary and most often in the temporal lobe In abscesses associated with cyanotic heart-disease the former is true , but there is no high incidence in the temporal lobe, for this is due to the frequent association with middle ear disease

In our series, eleven patients had solitary abscesses One (case 3) had two abscesses in the temporal lobe and two others (cases 2 and 4) had multiple abscesses

The abscesses were widely scattered in two they were multiple and on both sides, in 4 on the right, and in 8 on the left side In the seventy nine cases collected by Newton (1956) they were equally distributed on the right and left sides and no lobe was affected much more frequently than the others The sites of the abscesses in our patients, excluding the two where they were multiple, were distributed as follows —3 frontal, 2 fronto parietal, 1 parietal, 1 fronto temporal, 2 temporal, and 3 occipital In most general series of brain abscesses apart from those with morbus cœruleus the parietal and occipital lobes are relatively uncommon sites

We are not discussing the symptomatology or treatment at length It may, however, be of interest to mention the more dramatic symptoms, for often these came with little warning and the period of headaches with increasing

TABLE I—PATIENTS WHO DIED WITH A CEREBRAL ABSCESS

Case	Sex and age at death	Condition of heart	Cerebral findings
1	F, 25	Fallot's tetralogy with severe infundibular and some valvular stenosis	Large abscess in posterior part of lt occipital lobe that had ruptured into lt lateral ventricle
2	M, 15	Fallot's tetralogy with low infundibular stenosis and small atrial septal defect	Multiple abscesses, lt temporal (15 mm diam), rt parietal (7 mm diam) and lt occipital (15 mm diam) tuberculous basal leptomeningitis
3	M, 12	Fallot's tetralogy with infundibular stenosis	Two large rt temporal lobe abscesses one of which had ruptured into 3rd ventricle
4	M, 6	Fallot s tetralogy with infundibular stenosis	Multiple abscesses Lt frontal, lt temporo-parietal rt frontal, rt fronto parietal rt temporo parietal (2) and rt cerebellar
5	M, 6	Fallot's tetralogy Successful subclavian pulmonary anastomosis 26 months before	Rt parietal lobe abscess Died after operation for abscess
6	M, 4	Atresia of a bicuspid pulmonary valve with other features of Fallot's tetralogy	Large abscess occupying most of lt frontal lobe, older postero medially and more recent antero-laterally
7	M, 3	Fallot's tetralogy with valvular stenosis aorta well over to right , dextro rotation simulating dextrocardia	Rt frontal abscess (2 cm diam) that had ruptured into rt and 3rd ventricles extensive basal meningitis
8	F 8	Transposition clinically at necropsy, single atrium, single atrio ventricular valve, pulmonary trunk from infundibular" chamber of left ventricle	Lt fronto temporal multilocular abscess 5 × 6 × 4 cm
9	M 6	Transposition clinically, at necropsy, aorta and pulmonary trunk both from right ventricle Large ventricular septal defect	Large solitary abscess (8 cm diam) in lt fronto-parietal lobe

TABLE II—PATIENTS WHO RECOVERED FROM A CEREBRAL ABSCESS *

Case	Sex and age (years)		Condition of heart	Cerebral findings
10	M	1	Fallot's tetralogy Some improvement after subclavian pulmonary anastomosis 3 months before	Rt posterior frontal region abscess Recovery after repeated aspiration
11	M	19	Fallot's tetralogy Successful subclavian pulmonary anastomosis 27 months before	Lt temporal lobe abscess Recovery after aspiration and operation
12	F	10	Fallot's tetralogy Successful subclavian pulmonary anastomosis 33 months before	Lt occipital lobe abscess Recovery after aspiration and operation
13	F	5	Fallot's tetralogy Successful subclavian pulmonary anastomosis 4 months before	Lt fronto parietal abscess Recovery after aspiration and operation
14	M	7	Pulmonary atresia with other features of Fallot's tetralogy	Lt occipital region abscess Recovery after repeated aspiration
15	F	12	Fallot's tetralogy and situs inversus Cardiac catheterisation 6 weeks before	Loss of consciousness with rt hemiplegia Cerebral abscess from septic embolism diagnosed recovery with penicillin only, but residual hemiplegia

* An additional patient has been seen since A girl aged 7 who had Fallot's tetralogy with stenosis that was thought to be infundibular seemed too well to advise operation But 18 months later she was admitted to hospital with meningeal signs cerebral irritation and papilloedema The diagnosis of a cerebral abscess in the left parietal region has been confirmed and she is being treated surgically

drowsiness and irritability—a period that is perhaps most characteristic of brain abscess secondary to infection from the middle ear or sinuses—was often short or not sufficiently noticeable to be recorded Only one patient, the boy with multiple abscesses, had a long pyrexial period and had been treated as having bacterial endocarditis before the correct diagnosis was made after his admission to Guy's Hospital necropsy confirmed the absence of bacterial endocarditis (case 4)

One patient had fits followed by a left hemiplegia (case 10), one had a right hemiplegia followed by fits (case 8), and another some clumsiness of the right hand followed by two Jacksonian fits (case 13) Three of them (cases 11, 12, and 14) and a fourth patient whose patent ductus arteriosus had been closed 28 months before (case 16) had homonymous hemianopia, two with abscesses in the occipital and two with abscesses in the temporal lobe In one the diagnosis was not made till the abscess had ruptured into the lateral ventricle (case 1)

Treatment

In several of the nine who died the abscess had been aspirated and one (case 5) had an open operation Of the six who recovered two had only repeated aspiration and antibiotics (cases 10 and 14) and three had an open operation as well (cases 11, 12, and 13) Only one—the unproved case 15—recovered with antibiotics only and she was left with persistent hemiplegia The other five made good recoveries though one (case 11) seems to have lost the exceptional energy and perseverance that he had shown since his Blalock operation two years earlier and another (case 12) had some residual organic symptoms in the right arm with a hysterical overlay due to psychological problems at home Three of the cases reported by Newton (1956) recovered after surgical treatment

Relationship to the Cardiac Operation

Of the nine patients who died, only one (case 5) had undergone an operation for his heart—a most successful subclavian pulmonary anastomosis 26 months before On the other hand four of the six who recovered from the brain abscess had undergone operations for the heart, with a good result in all but one, who was only somewhat improved No doubt they were under more regular observation and were perhaps more ready to seek advice at an early stage, but the symptoms that drew attention to the abscess were often so dramatic that this cannot have been of major importance and their improved condition after the heart operation must have helped in the recovery after the cerebral operation The other two who recovered were being considered for operation one had undergone angiocardiography 11 months before (case 14) and the other cardiac catheterisation 6 weeks before (case 15)

In this last case—the only one we have included when it was uncertain whether she had a brain abscess or an infected embolism, and where she recovered with antibiotics only—it seems probable that catheterisation was the indirect cause In two others (cases 10 and 13) the abscess was diagnosed 3 and 4 months after the operation for the heart and allowing for the time that an abscess may take to develop it seems probable that the operation was the indirect cause In the others, however, the abscess was diagnosed 26, 27, and 33 months after the operation and the patients had been in good health and greatly improved, so we think it unlikely that there was any connection (cases 5, 11, and 12) In the seven cases reported by Newton (1956) the abscess developed after a subclavian pulmonary anastomosis in two and after pulmonary valvotomy in a third

Possible Infections Elsewhere

In general, cerebral abscess arises from extension of infection (60–70%), especially from the ears, or through the blood stream Hæmatogenous abscesses may arise from bacterial endocarditis or other forms of septicæmia but most often from chronic suppuration in the chest especially from bronchiectasis and pulmonary abscess (25% of cases), but in about 10% they appear to arise from a source of infection that cannot be found or has cleared up in patients with morbus cœruleus, however, this last seems to be the common type

Most of our patients were free from signs of infection elsewhere None of them had bacterial endocarditis and none had any recognised chronic suppuration in the lungs None had clear evidence that the abscess was due to disease of the middle ear, though in one this was probable and in a second possible Thus in case 3 with two large abscesses in the temporal lobe, there was pus in the right mastoid but the dura was normal In case 1 there was a left otitis media, but the abscess was in the posterior part of the left occipital lobe and there appeared to be no connection In case 4, with multiple abscesses, there had been a right otitis media two years before, but nothing else was found

Although none of these patients had a cerebral abscess that was certainly attributable to middle ear disease we have seen a boy, aged 7 who has had a successful subclavian-pulmonary anastomosis for Fallot's tetralogy, and had made a good recovery after an operation 5 years before for a pneumococcal brain abscess that had followed directly on otitis media A boy, aged 4, with transposition of the aorta and pulmonary trunk and a ventricular septal defect died with a large abscess in the right temporal lobe following right otitis media A girl aged 1 year, with Fallot's tetralogy, had bilateral otitis media and died with lateral sinus thrombosis of some standing and with recent thrombosis of the superior sagittal sinus and other cerebral veins

Apart from those with proved cerebral abscesses, one other patient was suspected of this A girl, aged 9, with Fallot's tetralogy, developed symptoms 28 months after her Blalock operation, but was thought by Dr. McArdle to have cortical thrombophlebitis rather than an abscess she made an almost complete recovery with penicillin Untreated venous thrombosis of this type might, however, be a source of a subsequent abscess At least two other patients have died with meningitis during this same period, but neither had a necropsy and neither was thought to have a brain abscess In a boy, aged 11, with tricuspid atresia, the meningitis was thought to be tuberculous but the evidence was doubtful, and in a boy aged 11, probably with Fallot's tetralogy, it was meningococcal

Bacteriology

Little useful information can be gained from the bacteriology of the abscesses, for the notes are not very complete and represent the work of several different pathologists

Gram positive cocci were found in cases 3, 10, 12, and 14 In cases 5 and 16 there were non hæmolytic streptococci, and in the former they appeared to be aerobic and facultatively anaerobic Anaerobic streptococci were grown from the abscess at necropsy in cases 7 and 9 A coagulase positive staphylococcus was grown from the abscess at necropsy in case 8, and *Staphylococcus albus* under the same circumstances in case 1 In case 10 there was an aerobic actinomycete, and though this may seem unlikely it was isolated on culture from pus obtained at three separate aspirations In case 2 the abscesses were tuberculous In the twenty two cases of Newton (1956) where cultures were positive, the organisms were very varied and no one type predominated

Discussion

This series of cases and the number that have been reported in the past few years leave little doubt that Ballet's suggestion is correct and that cerebral abscess occurs more frequently in patients with cyanotic congenital heart-disease than in others Hanna (1941), Robbins (1945) and Gates et al (1947) found that there was a brain abscess in about 5% of all deaths of patients with congenital heart disease In our experience of patients with cyanotic congenital heart disease brain abscess is a greater hazard than bacterial endocarditis, though Gates et al (1947) found brain abscess in 4% and bacterial endocarditis in 7% We cannot recollect seeing any patient with acquired heart-disease, and we have seen only one with acyanotic congenital heart-disease, who has subsequently developed a cerebral abscess

In the seventy-nine cases of this association collected by Newton (1956) there was known to be a veno arterial shunt in at least 85%, an absence of any obvious primary infection in 70% and a distribution that did not show the usual predilection for the temporal lobe In the series of Maronde (1950) most of them had Fallot's tetralogy or related conditions, but several had ventricular septal defects only, where presumably the rising pressure on the right side had reversed the shunt In our experience fifteen of the sixteen patients have had a right-to-left shunt

In a 10 year series of necropsies Maronde (1950) found that 10% of all the patients with cerebral abscess had congenital heart disease In the Birmingham series of hæmatogenous brain abscesses Newton (1956) found that 10% had congenital heart disease, while in the general population he calculated that this was present in less than 0 1%

Of sixty-nine hæmatogenous brain abscesses at Birmingham (Newton 1956) and a hundred and four at the Mayo Clinic (Gates et al 1950) 45% were associated with lung infections and 10% with bacterial endocarditis and among these 55% only one had congenital heart-disease on the other hand, congenital heart disease was present in five of the forty eight with other primary infections and in four of the twenty seven with no known primary infection

This association between brain abscess and cyanotic congenital heart-disease seems well established and it is therefore interesting to discuss the reason

Bacteræmia and the Right to left Shunt

At first without much reflection I thought it could be explained by the fact that the right-to left shunt would allow bacteria present in the blood to reach the brain without passage through the lungs this assumes that the brain is less capable of dealing with them, though the action of the lungs in filtering off bacteria is now less generally accepted than it was Indeed, if this were an effective mechanism it would be difficult to explain why bicuspid aortic valves are unusually prone to develop bacterial endocarditis from chance bacteræmia (Osler 1886, 11 5% of all bicuspid aortic valves, Wauchope 1928) for this happens as a rule when there is no right-to left shunt

Furthermore, it is difficult to picture bacteria becoming lodged at any site, for they should be able to pass through the capillaries readily except perhaps in the case of coagulase positive staphylococci, which might collect and form an obstruction De Navasquez (1950) found that the intravenous injection of coagulase positive staphylococci regularly produced pyelonephritis in rabbits while several other organisms were unable to do so it is interesting that at least one of our patients (case 8) had such staphylococci in the brain abscess Also it has been found experimentally that it is difficult to produce cerebral abscess by the injection of bacteria into the blood-stream, and that local trauma or injury to the brain is generally necessary

It seems, therefore, that, in addition to the bacteria there must be some local factor, such as a thrombus or an embolus, leading to slowing of the capillary flow, but generally there is no evidence of a primary thrombus elsewhere

Paradoxical Embolism

Abbott et al (1923) thought that cerebral complications such as abscess or infarction were frequent in patients with congenital septal defects, and that these were generally embolic from a focus in the venous system Paradoxical embolism was reviewed by Thompson and Evans (1930) who gave some striking illustrations but had not much to say about cases where the right-to left shunt was a normal feature They thought that the rise of pressure on the right side of the heart following large or repeated pulmonary emboli was the main cause of a later embolism passing through a foramen ovale that could be forced open by the rise of pressure They also discussed this in relation to brain abscesses of a hundred and ninety-five cases there were twenty-two where the infection was thought to be blood-borne but here it did not seem to make much difference whether the foramen ovale was closed or not, and in more than half of them there were abscesses in the lungs

Classically paradoxical or crossed embolism is related to a patent foramen ovale or sometimes an atrial septal defect though, as Brown (1939) points out it also occurs with a right to left shunt and an overriding aorta, and may explain many cases of cerebral abscess The main argument against this is the absence of signs of a thrombosis from which the embolism may have come Such an infected embolism was suggested as the cause in our cases 15 and 16, but no primary thrombosis was recognised Nor has anyone suggested that systemic emboli elsewhere occur with unusual frequency in patients with morbus cœruleus This difficulty is not confined to cases of congenital heart disease and necropsy may show that a suspected thrombosis was in fact an embolism from an unrecognised thrombosis elsewhere

Emboli from the Lungs

An alternative explanation that discards any direct influence of the right to left shunt might be that the abscesses were due to emboli from the lungs for in these cyanotic cases there is generally a poor pulmonary blood flow and perhaps some tendency to pulmonary thrombosis The cases that follow quickly on surgical treatment might seem to support this for (especially after the early operations, where an undue proportion of these abscesses occurred) there were often some postoperative pulmonary complications, but the patients who later developed brain abscess showed no special incidence of these Even more important, necropsy has not shown any pathological changes in the lungs to support this explanation, either in our cases, or, so far as we know, in other reported cases In the column "primary focus" dealing with the seventy-nine reported cases, Newton (1956) included bronchitis three times but this was the only mention of any disease of the lung further, in seventy seven cases of hæmatogenous brain abscess (quoted in the Birmingham and Mayo Clinic series) that followed bronchiectasis, lung abscess, or empyema, there was not a single example of congenital heart disease

Secondary Infection of a Cerebral Thrombosis

Finally, in considering this series of cases, another explanation has come to seem increasingly likely—that the abscess is due to secondary infection of a cerebral thrombus This does not discard the concept of the importance of the right to-left shunt, for patients with such a shunt have anoxia and polycythæmia, often of extreme degree, and are therefore specially prone to cerebral thrombosis

Peacock (1866) thought that cerebral disturbance, resulting from the defective aeration of the blood, was one of the two most common causes of death in these patients Cerebral disturbance is still common, and is generally due to anoxæmia alone, but often, as Taussig (1947) has emphasised, there is also a cerebral thrombosis Berthrong and Sabistan (1951) found twenty-five examples of cerebral softening, ten with recent infarction, six with older changes, and nine with both, among a hundred and thirty-five necropsies of patients with cyanotic congenital heart disease These cerebral thrombi are generally arterial but one case of thrombophlebitis has been mentioned, and Barnett and Hyland (1953) have reported unsuspected thrombosis in the dural sinuses and cerebral veins in cases of heart failure, which might occur also in the presence of anoxæmia and polycythæmia

We have seen many examples of major arterial thrombosis three early patients developed hemiplegia just after subclavian-pulmonary anastomosis, and in several others this had happened earlier These large thrombi are not often, so far as we know, followed by infection or abscess, but if there are large thrombi there are likely to be smaller ones that might provide a damaged area where bacteria could settle and produce an abscess

Such damaged areas may also be the cause of epileptic fits, and this should be considered when patients are seen with epilepsy and morbus cœruleus Baker and Finnegan (1957) have emphasised that damaged areas in the brain, following embolism, are an important cause of epilepsy in patients with mitral stenosis

Secondary infection of a vascular thrombus would seem more likely in the early stages when there was a soft necrotic focus than later when it had become organised But some work of De Navasquez (1956) is interesting in this connection When pyelonephritis was induced in rabbits by the injection of coagulase positive staphylococci, most of them made a good recovery but were left with scattered scars in the kidney He found that in these rabbits, but not in others without these damaged areas, intravenous injection of gram negative bacteria could now cause serious pyelonephritis It is possible that old scarred areas in the brain may provide a site for the lodgment of bacteria and the development of an abscess, especially if, because of a right-to-left shunt, bacteria reach the brain in larger numbers than usual

Some of the cases where thrombosis was possible or certain will be described shortly The first two might have had an infected embolism or a thrombosis that quickly became infected The others illustrate the frequency of cerebral thrombosis

Case 15—A girl, aged 12, had Fallot's tetralogy with complete situs inversus Six weeks after an uneventful cardiac catheterisation she was admitted to hospital complaining of giddiness, and a disinclination to do things These symptoms had become worse the day before She was drowsy and resented interference, and had a temperature of 103°F, some infection of the gums and mouth, and a few petechial hæmorrhages, but no palpable spleen Next day she was more comatose and could not move her right arm and leg Lumbar puncture showed a cloudy fluid under increased pressure (270 mm of water), with 4750 cells per c mm, and 200 mg protein, and 685 mg chlorides, each per 100 ml Penicillin, 500,000 units 4 hourly, was continued for a month her temperature settled after 3 days, except for occasional spikes and the cell content, protein, and chlorides gradually returned to normal A cerebral abscess was suspected and she was transferred to Hill End Hospital for surgical treatment, but investigations there were inconclusive and it was thought that an infected cerebral embolism might have been the cause of her recent illness She was discharged with some recovery of the right leg but not much in the right hand Subsequently, after a successful operation for her heart, she has by hard work overcome most of the disability in her leg

Case 16—A girl, aged 12, had a patent ductus arteriosus This was closed and her heart became smaller (cardio thoracic ratio 61 to 54%) 28 months later she was admitted to hospital because she had been wakened by a severe headache vomiting and a stiff neck had followed and meningitis was suspected. Lumbar puncture 5 days later yielded a xanthochromic fluid with a protein content of 250 mg per 100 ml, and 100 white cells per c mm, mainly polymorphs 2 weeks later she was transferred to a neurosurgical centre and was found to have papillœdema and a left sided homonymous hemianopia without other localising signs There was some pyrexia and a palpable spleen, but no other evidence of bacterial endocarditis, and blood culture was negative there was no infection of the ears or of the paranasal sinuses An abscess in the right temporal lobe was aspirated and after this and penicillin treatment she improved and lost all her abnormal physical signs

The sudden onset of headache sufficient to waken her from sleep, followed by vomiting and stiffness of the neck, and the xanthochromic lumbar spinal fluid some 5 days later, were thought to suggest a cerebral vascular lesion, an embolic infarct having become infected so that the blood clot had become an abscess by the time of her operation, but no source for an embolism was found Her subsequent progress has been satisfactory

In case 9, no evidence of a vascular occlusion could be found to account for the left sided abscess and right hemiplegia, but 5 years before he had had a left hemiplegia and there was atrophy of the lower half of the middle of the right parietal lobe, involving the motor area and pre motor and post-motor cortex, part of the island of Reil, and the adjoining gyri of the upper temporal lobe this presumably accounted for his old left hemiplegia and must have been due to an old middle cerebral occlusion

A boy, aged 5 years, with a bilocular heart and severe pulmonary stenosis, was thought to have a cerebral abscess, but at necropsy there was a large area of softening in the left external capsule that had probably followed thrombosis some months earlier, and a much smaller area in the right frontal lobe that had been present only for days The older thrombotic area may have been present before his operation or may have followed this, and infection may have been prevented by the vigorous antibiotic treatment (case 9, Campbell and Forgacs 1953)

Two other patients, each with a single ventricle (cases 5 and 6, Campbell et al 1953) can be mentioned in one there was extensive thrombosis of the left vertebral artery extending along the posterior inferior cerebellar artery, and in the second a large area of cortical atrophy in the left temporoparietal region that may have followed thrombosis Our case 2, in addition to multiple abscesses, had some tuberculous arteritis and phlebitis that had led to an early ischæmic necrosis of the lateral aspect of the pons

These cases illustrate the tendency to cerebral thrombosis in patients with cyanotic heart-disease, and some of the abscesses may be due to secondary infection of such thrombi from bacteræmia

Summary and Conclusions

15 examples of cerebral abscess occurring in patients who were seen first for cyanotic congenital heart-disease have been described From these and from the others that have been reported, there is no doubt that a hæmatogenous brain abscess without any obvious primary infection occurs much more frequently in subjects with a right-to left shunt than in others

Reasons have been given for thinking that chance bacteria in the blood stream cannot provide the whole explanation even in the presence of a right-to-left shunt There is no evidence that these abscesses follow minor lung infections

Paradoxical embolism, perhaps the most widely accepted explanation, seems likely, for it would allow infected thrombi from systemic veins to pass readily to the cerebrum It probably accounts for some brain abscesses, but if it were the only cause there should be more cases with emboli elsewhere and more with evidence of the primary thrombus

We think that thrombosis in the cerebral vessels with secondary infection from chance bacteræmia is a frequent cause At first sight this seems to discard the hypothesis that the right-to left shunt is fundamentally important, but it does not, for patients with such a shunt are anoxæmic and polycythæmic and, therefore, prone to cerebral thrombosis, and in addition the right to left shunt makes it easier for bacteria to reach the cerebral circulation without passing through the lungs

We are most grateful to Sir Charles Symonds and to Dr S De Navasquez for helpful criticism of this paper We should like to thank many colleagues for their help with these patients—Sir Charles Symonds, Dr M J McArdle, and Mr Murray Falconer who have taken charge of those patients who have come under my care with a cerebral abscess Also, we should like to thank those who have written to us with details about the subsequent course of these patients Dr Thomas Anderson of Glasgow for case 1, Dr N S Clark and Dr J Watt of Aberdeen for case 6, Mr D Simpson and Dr M Zambellas of Oxford for case 7, Dr R C B Pugh of Great Ormond Street for case 9, the staff of Oldchurch County Hospital for case 10, and the late Mr C A Calvert of Belfast for case 16

My friend Dr Heim de Balsac has kindly informed me that Gilbert Ballet was Professor of Medicine of Paris he published more than two hundred papers, but many of these were of neurological subjects and only two or three on congenital heart disease

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URINARY TRACT INFECTION IN A MALE UROLOGICAL WARD

WITH SPECIAL REFERENCE TO THE MODE OF INFECTION

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During routine examination of urine from male urological patients in the genito urinary ward of the hospital, infection was found to be frequent We therefore decided to investigate (1) the incidence and (2) the mode of infection

Two possible modes of infection were suggested —namely, auto-infection (by the patient's intestinal flora) and cross-infection If auto-infection were common, the organisms found in the urine should also be found in the fæces (Since they were mostly antibiotic resistant, they would presumably have appeared in the intestine after the patient's admission to hospital) If cross-infection were to blame, the organisms should be recoverable from sites from which they could be transmitted to patients Both these possibilities were examined

Material and Methods

The series comprised 80 unselected patients—35 with benign prostatic hyperplasia, 7 with carcinoma of the prostate, 10 with other urinary-tract neoplasms, 9 with urinary-tract calculi, and 19 with miscellaneous urological conditions Patients were included in the series if the whole of their stay in the ward fell within the period of investigation and was not less than seven days Only patients passing urine containing both pus cells and bacteria were regarded as infected

Examination of Urine

Urine was collected once or twice a week either from an indwelling catheter or as a " mid stream " specimen Wet preparations and gram stained films of the centrifuged deposit were examined Samples of uncentrifuged urine were cultured aerobically on blood agar and MacConkey agar plates for eighteen hours at 37°C

Identification of Species

Species other than *Staphylococcus pyogenes*, *Streptococcus fæcalis*, *Pseudomonas pyocyanea*, and those of *Enterobacter* genera (*Bergey's Manual* 1948) were isolated so rarely that they are disregarded here Typing was done whenever possible, to help identify strains of probably common origin

Staph pyogenes, *Strep fæcalis*, and *Ps pyocyanea* were identified in the usual way Strains of *Staph pyogenes* were confirmed as such by a slide coagulase test and were phage typed Strains of the other two species were not typed

Enterobacter genera were provisionally identified by the laboratory's routine range of biochemical tests representative strains (excluding *Proteus* species) were investigated more fully by Dr Ørskov, of the Statens Seruminstitut, Copenhagen, using biochemical tests, and were classified as *Escherichia coli*, *Esch freundii* (*Citrobacter*), *Cloaca*, *Klebsiella*, or *Providence* (Kauffmann 1951) Strains of *Esch coli* were identified serologically by their O antigens, and *Klebsiella* by their capsule types (capsule swelling reaction) A few strains not examined by Dr Ørskov are referred to as "coliform bacilli"

The four species of *Proteus* were identified biochemically One organism frequently isolated in this investigation resembled *Pr vulgaris* but did not produce indole after eighteen hours' incubation, it is referred to as *Pr vulgaris* (indole negative) Few of the strains of any proteus species swarmed readily However, in the case of *Pr mirabilis* it was possible to compare certain strains by the Dienes phenomenon Dienes (1946) observed that, when two different swarming strains of *Proteus* converge a narrow line of demarcation remains between the advancing edges of the cultures Kriller (1953) has shown that, with few exceptions, there is no such

TABLE I—INCIDENCE OF URINARY INFECTION IN RELATION TO DIAGNOSIS AND SURGICAL PROCEDURES

Diagnosis	No of cases	Uninfected throughout	Became infected in hospital				Already infected on admission
				Infection followed*			
		No of cases	No of cases	Catheterisation (indwelling)	Instrumentation	Operation	No of cases
Benign prostatic hyperplasia	35	2	22	16	0	2	13 (2)
Carcinoma of prostate	7	4	2	1	1	0	2 (1)
Other urological conditions	38	16	11	2	6	3	11
Neoplasms	10	3	6				1
Calculi	9	3	2				4
Miscellaneous	19	10	3				6
Total	80	22	35	19	7	5	26 (3)

Figures in parentheses = readmissions counted twice

* Data not available for 4 patients with benign prostatic hyperplasia

demarcation between antigenically identical strains, particularly if the flagellar antigens are the same A line of demarcation appears if the antigenic structure is different

Drug sensitivity Tests

The sensitivity of nearly all the strains was tested against streptomycin, chloramphenicol, chlortetracycline (aureomycin), and oxytetracycline (terramycin) by a ditch plate technique Sulphonamide sensitivity was tested on laked horse blood agar containing sulphathiazole (10 mg per 100 ml of agar) *Staph pyogenes* and *Strep fæcalis* were also tested on ditch plates for their sensitivity to penicillin and erythromycin, and *Enterobacter* species and *Ps pyocyanea* for their sensitivity to polymyxin The Oxford staphylococcus was used as control organism for all sensitivity tests except polymyxin, where a sensitive strain of *Esch coli* was used

Incidence of Infection

The clinical diagnosis and the stage at which patients became infected are presented in table I

Of 35 patients with benign prostatic hyperplasia, 2 remained uninfected, 22 became infected in hospital, and 11 were already infected on admission

Of 7 patients with carcinoma of the prostate 4 remained uninfected, 2 became infected, and 1 was already infected on admission

Of 38 patients in the third (miscellaneous) group 16 remained uninfected, 11 became infected, and 11 were already infected on admission

Nearly all the patients who became infected in hospital showed infection within a few days of the insertion of an indwelling catheter or other instrumentation, and before operation

Evidence of Cross-infection

The bacteriological findings provide strong evidence of cross infection In view of the high proportion of patients who became infected after admission, special attention was directed towards organisms acquired in the ward Table II lists all the organisms isolated from patients who became infected after admission, and also the additional organisms acquired in hospital by patients already infected on admission The table shows the number of patients infected by each species, and, where typing was done, the number of patients infected by the most commonly occurring strain The drug sensitivity is also given. Table III deals in a similar way with organisms isolated from the first specimens of urine from patients already infected on admission No strain of typed species was isolated from more than one patient in this group

Evidence of cross infection among patients infected in hospital is seen in the following organisms *Staph pyogenes*, with 11 of 22 patients infected by the same phage-type, *Klebsiella*, with 7 of 9 patients infected by the same strain (i e, being of the same capsule type), *Pr mirabilis*, with the same strain from 8 of 11 patients when tested by the Dienes phenomenon * Further supporting evidence of cross infection is provided by the incidence of infection by *Providence, Pr vulgaris* (indole negative), and *Esch freundii* one strain (identified by its biochemical and sensitivity pattern) of each species infected 17, 14, and 4 patients respectively These organisms are very rarely found in urinary infections elsewhere in the hospital In the present series they were isolated only from the urine of patients infected after admission

In all, 38 of the 58 patients infected in hospital were infected by the predominant strain of one or more of these species

In contrast to these patients, the strains of *Esch coli* infecting the 8 patients on admission were each of a different O antigenic type The strain subsequently isolated from the single patient infected by *Esch coli* after admission was one of these types

The drug sensitivity (table II) was characteristically that of hospital infection Organisms which were naturally sensitive were commonly resistant to penicillin, streptomycin, and sulphathiazole, the drugs most often used in the ward These resistant organisms were isolated from patients before any chemotherapy was given With *Staph pyogenes* 25 of 28 strains were resistant to penicillin,

TABLE II—URINARY ORGANISMS ACQUIRED IN HOSPITAL AND THEIR DRUG SENSITIVITY

Organism	No of patients infected	No of patients with commonest strain	Penicillin			Erythromycin			Streptomycin			Chloramphenicol			Chlortetracycline			Oxytetracycline			Polymyxin		Sulphathiazole	
			S	P	R	S	P	R	S	P	R	S	P	R	S	P	R	S	P	R	S	R	S	R
Staph pyogenes	22*	11	3	0	25	26	0	0	5	0	24	26	0	3	22	0	4	23	0	6			5	21
Strep fæcalis	23*		0	22	6	20	2	0	0	2	26	26	0	2	11	0	15	11	1	16			0	28
Esch coli	1								1	0	0	1	0	0	0	1	0	0	1	0	1	0	0	1
Esch freundii	4	4							0	0	4	4	0	0	0	4	0	0	1	0	4	0	0	4
Klebsiella	9	7							1	0	8	9	0	0	0	9	0	1	8	0	9	0	1	8
Providence	17	17							0	0	17	0	0	17	0	0	17	0	0	17	0	17	0	17
Pr vulgaris I +ve	3								0	0	3	0	0	3	0	0	3	0	0	3	0	3	0	3
Pr vulgaris I -ve	14	14							0	0	11	0	0	14	0	11	0	0	11	0	0	14	0	14
Pr mirabilis	20*	8†							0	0	22	18	2	4	0	1	19	0	13	10	0	14	0	14
Pr morgani	6								3	0	2	5	0	1	0	2	3	0	1	1	0	6	0	6
Pr rettgeri	14								0	0	14	0	0	11	0	0	14	0	0	14	0	11	0	14
Ps pyocyanea	11								0	3	7	0	0	10	0	0	8	0	0	1	10	0	2	8

* Some patients carried more than 1 strain † Strains from only 11 patients were typed I +ve I -ve indole positive indole negative
S, sensitive P partly sensitive but less sensitive than Oxford *Staphylococcus* R resistant

TABLE III—URINARY ORGANISMS PRESENT ON ADMISSION AND THEIR DRUG SENSITIVITY

Organism	No of patients infected	Penicillin			Erythromycin			Streptomycin			Chloramphenicol			Chlortetracycline			Oxytetracycline			Polymyxin		Sulphathiazole	
		S	P	R	S	P	R	S	P	R	S	P	R	S	P	R	S	P	R	S	R	S	R
Staph pyogenes	2	0	0	1	1	0	0	0	0	1	1	0	0	1	0	0	1	0	0			0	1
Strep faecalis	5	0	4	0	2	1	0	1	1	3	5	0	0	2	0	2	3	0	2			0	5
Klebsiella	1							1	0	0	1	0	0	0	0	0	1	0	0	0	0	0	1
Esch coli	8							8	0	0	6	2	0	0	6	2	0	8	0	8	0	6	1
Cloaca	2							1	0	1	2	0	0	0	1	1	1	1	0	2	0	1	1
"Coliform bacilli"	4							2	0	0	2	0	0	0	0	1	0	2	0	0	1	0	2
Pr mirabilis	2							0	0	2	2	0	0	0	0	0	0	0	2	0	0	0	2
Pr morgani	2							1	0	1	0	0	2	0	0	1	0	0	2	0	1	1	1
Pr rettgeri	4							0	0	4	0	0	4	0	0	4	0	0	4	0	4	0	4
Ps pyocyanea	2							2	0	0	2	0	0	2	0	0	1	1	0	2	0	1	1

S sensitive　　P partly sensitive but less sensitive than the Oxford *Staphylococcus*　　R resistant

24 of 29 strains were resistant to streptomycin, and 24 of 29 strains were resistant to sulphathiazole A similar picture was seen with *Pr vulgaris*, *Pr mirabilis*, *Klebsiella*, and *Esch freundii* in relation to streptomycin and sulphathiazole, organisms naturally sensitive to both drugs In contrast the strains of *Esch coli* isolated from patients infected on admission were sensitive

Evidence of Auto-infection

It has already been pointed out that, since most of the infecting organisms were antibiotic-resistant, if auto-infection took place it must be by organisms appearing in the intestines after admission to hospital This could happen as a result either of antibiotic therapy or of the ingestion of such organisms The finding of the same strains in many patients indicates that they were cross infected by some route Therefore if auto infection took place in these patients it was subsequent to the ingestion of the infecting organisms and not due to chemotherapy In other patients, where we were unable to establish evidence of cross infection, either of these mechanisms was possible In both groups, however, if auto infection took place, the species infecting the urinary tract should be recoverable from the fæces

TABLE IV—INCIDENCE OF URINARY ORGANISMS IN FÆCES OF 29 PATIENTS INFECTED WITH STREPTOMYCIN-RESISTANT BACTERIA

Organism	Urine	Fæces†				
	No of patients infected*	Before infection			During infection	
		Positive	Negative	Not tested	Positive	Negative
Staph pyogenes	9	0	6	3	0	3
Esch freundii	2	0	1	1	1	0
Klebsiella	3	0	2	1	0	1
Providence	9	0	2	7	0	7
Pr vulgaris indole positive	2	0	2	0	0	0
Pr vulgaris indole negative	6	0	5	1	0	1
Pr mirabilis	6	2	3	1	2	0
Pr morgani	2	0	2	0	0	0
Pr rettgeri	14	1	8	5	0	5
Ps pyocyanea	5	0	3	2	0	2

* 22 patients were infected by more than one organism
† 2–4 specimens per patient the inoculum count for each specimen being 10^6–10^7 organisms

From two to four samples of fæces from 41 unselected patients were examined quantitatively Samples were homogenised in saline solution and several dilutions plated on blood agar and MacConkey's agar Since most of the urinary organisms were streptomycin resistant, the heavier inocula were also plated on the same media to which streptomycin (50 µg per ml of agar) had been added The quantity of fæces used was increased during the investigation to very thick inocula containing 3 mg of fæces The total viable aerobic organisms, excluding streptococci, were counted and the number of them in the heaviest inoculum was estimated Organisms causing urinary infection were counted on the streptomycin-containing plates Organisms were identified as described above

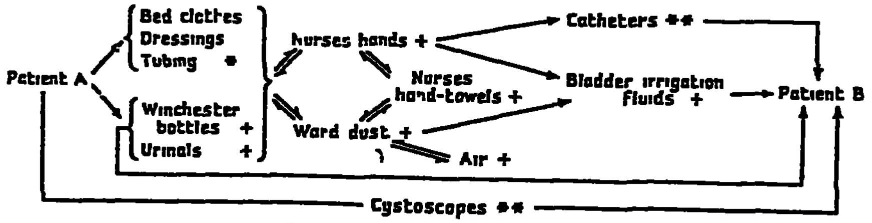
Data from 29 patients with streptomycin-resistant urinary infections are presented in table IV, which shows that, in nearly all instances (representing 23 patients), urinary strains were absent from any fæcal samples taken either before urinary infection developed or on the same day as the first infected specimen of urine was found In 3 cases species causing urinary infection were recovered from the fæces before urinary infection developed, constituting 0 001%, 0 9%, and 2% of the total flora In a further 3 cases the proportion was 1 in 3 × 10^5, 0 15%, and 6% of the flora of the first samples, these being taken on the same day as the first infected urine The remaining 12 patients were not infected with streptomycin resistant organisms—in no case were streptomycin-resistant organisms found in the fæces Thus the fæces of 35 of 41 patients did not yield streptomycin-resistant organisms The possibility of a few cases of auto infection remains

It will be seen from table IV that there were no *Esch coli* infections If auto infection were a common mode of infection, one would expect a high incidence of infection by this intestinal organism

These results provide strong evidence that the bacteria causing urinary infection could seldom have been derived from the patient's intestinal tract Presumably, therefore they were exogenously acquired

Potential Routes of Cross-infection

Possible routes of cross-infection are indicated in the accompanying figure Bacteriological studies were made on the following Winchester bottles used for collecting urine from patients with indwelling catheters, urinals ready for re use, nurses' communal hand-towels, nurses' hands, solutions used for bladder irrigations, catheters, cystoscopes; air, and ward dust Table V shows that the same species as isolated from patients' urine were recovered from all these sites except catheters and cystoscopes



Possible routes of cross-infection

* tubing leading from catheter to Winchester bottles, ** tests made and no urinary organisms isolated, + tests made and urinary strains isolated

TABLE V—URINARY ORGANISMS RECOVERED FROM POTENTIAL SOURCES OF CROSS-INFECTION

Source	*Staph pyogenes*	*Strep fæcalis*	*Escherichia*		*Klebsiella*	*Providence*	*Proteus*				*Ps pyocyanea*
			coli	*freundii*			*vulgaris* (indole–ve)	*mirabilis*	*morgani*	*rettgeri*	
Winchester bottles	–	+	–	–	–	–	–	–	–	–	–
Urinals	–	+	–	–	–	–	+	+	+	–	–
Nurses ward hand towels	–	+	–	–	–	+	–	+	–	–	–
Nurses' hands	–	+	–	–	–	–	–	+	–	–	–
Bladder irrigation fluids*	–	+	–	–	–	–	+	+	–	–	–
Catheters	–	–		–	–	–	–	–	–	–	–
Cystoscopes	–	–	–	–	–	–	–	–	–	–	–
Air	+†	+	–	–	+†	–	–	+	+	–	–
Ward dust	+	+	+	–	+	+	+	+	–	+	–

* Lactose fermenting "coliform bacilli" not of types isolated from urine were also recovered

† The commonest air type was the same as the commonest urine type

Winchester Bottles

When these were in use, a rubber-tubing extension from the catheter hung free in the bottle, which was not stoppered The bottles were treated routinely before re-use by rinsing out with water followed by the addition of 10 ml of toluene as antiseptic

To each of six Winchester bottles ready for routine use 2 litres of nutrient broth were added, and the bottles were incubated for eighteen hours at 37°C From two of the six bottles *Strep fæcalis* was recovered It was concluded that the treatment of the bottles was inadequate for sterilisation

It was considered that organisms present in a contaminated Winchester bottle, or those gaining access to it from the air, might multiply in the collected urine and reach the bladder by growth up the drainage tubing To test this hypothesis several mock bladder-drainage systems were set up in the laboratory

The bladders were represented by laboratory aspirator bottles, the outlet of each of which was connected to a rubber catheter and tubing which drained into a Winchester bottle One litre of urine was poured into the aspirator, which was then sterilised Several Winchester bottles containing broth were artificially contaminated with various combinations of urinary infecting strains of *Staph pyogenes*, *Strep fæcalis*, *Esch coli*, *Providence*, and 3 *Proteus* species They were incubated till a perceptible but light growth was obtained and were then washed out several times with water, and 10 ml of toluene was added Four feet of rubber tubing, similar to that used in the ward, hung from each aspirator containing urine into an infected Winchester bottle A flow of urine from the aspirator was started and was controlled to flow intermittently for twenty four hours to simulate natural conditions

When Winchester bottles were infected with *Staph pyogenes* and *Strep fæcalis* these organisms were recovered from both the Winchester bottles and the aspirators When Winchester bottles were infected with gram-negative bacilli, none of these species was recovered from either the Winchester or the aspirator bottles We concluded that gram-negative bacilli were destroyed by the routine treatment given to the Winchester bottles, but that gram-positive cocci survive and can ascend to the bladder

Urinals

Broth was pipetted into twelve glass urinals which had been rinsed out in water after use and awaited reissue to patients The urinals were then plugged and incubated for eighteen hours at 37°C

Nurses' Communal Hand-towels

Several towels in use were immersed in broth in large flasks, which were then incubated

Nurses' Hands

Sterile finger-stalls moistened with nutrient broth were worn on the index, middle, and ring fingers of the right hand for thirty minutes they were then removed and the inside was rinsed with broth, which was then cultured When they were worn by nurses on routine ward duties, they yielded organisms of all the species listed in table v except *Esch coli* When they were put on after the routine "wash-up" before irrigating the bladder, *Staph pyogenes* (a urinary infecting type) was recovered as well as an antigenic type of *Esch coli* not previously isolated

Contamination of the nurses' hands during bedmaking was also investigated For this experiment the nurse first "scrubbed up" for five minutes and then dried her hands on a sterile towel Culture of the fingers at this stage proved sterile After "scrubbing up" and drying once more she did the routine bedmaking round At its conclusion a repeat finger-culture yielded one of the urinary strains of *Esch coli* together with other non-urinary type organisms

The results of these tests indicate that the nurses carried on their hands a representative range of organisms that infect the urinary tract, and that these organisms could be recovered even after the hands had been prepared for a bladder irrigation

Bladder-irrigation Fluids

As species of organisms that infect the urinary tract were isolated from the hands of nurses on various occasions, it seemed possible that the fluids used for bladder irrigation might be contaminated from this source Cultures of samples of such fluids from loaded syringes immediately before injection into patients yielded pathogenic species on 18 of 27 occasions (table vi) Cultures from the stock bottles of commonly used fluids (saline solution, 1 1000 mercury oxycyanide, and 1 1000 silver nitrate) were sterile, but samples of distilled water used as diluent, taken from stock bottles and sterile bowls on the trolley in use, yielded *Strep fæcalis* and *Staph pyogenes* on several occasions The organisms recovered from fluid in syringes included additional species acquired during later stages of preparation for the irrigation These may possibly have been derived from the environment, but the nurses' hands seems a more probable source

Catheters

Seven catheters (Tiemann and Foley types used in the ward) were cultured in broth after routine sterilisation by immersion in boiling water for three minutes No urinary species was recovered

Cystoscopes

The sheaths of three cystoscopes were each totally immersed in broth cultures of a representative range of urinary organisms The cystoscopes were then replaced

TABLE VI—URINARY ORGANISMS RECOVERED FROM FLUIDS FROM BLADDER IRRIGATION SYRINGES IMMEDIATELY BEFORE USE

Bladder washout fluid	No of tests	No of tests yielding pathogenic species	No of tests in which each pathogenic species was isolated					
			Staph pyogenes	*Strep fæcalis*	"Coliform bacilli"	*Pr mirabilis*	*Pr vulgaris* (indole neg)	*Ps pyocyanea*
Physiological saline solution	4	3	1	2	0	0	1†	1
1 2×10^4 silver nitrate	6	4	2*	0	0	1†	2†	0
1 2×10^4 mercury oxycyanide	17	11	2*	11	2	0	0	0

* Same phage type as that isolated from operation wounds of 4 patients in ward

† Urinary type

in their metal containers and immersed in boiling water for two and a half minutes After this each cystoscope was immersed in sterile broth and incubated overnight No urinary species was recovered

In view of the negative findings in the cases of catheters and cystoscopes, *syringes* used for bladder irrigation and sterilised by immersion in boiling water were not investigated

Air and Dust

A Bourdillon slit-sampler was operated non-quantitatively in the ward during bedmaking In addition, containers holding erythromycin broth were exposed in the ward to facilitate the recovery of gram-negative organisms

Floor sweepings were collected with sterile brush and pan They were cultured in nutrient broth and also, to facilitate the recovery of gram-negative bacilli, on this occasion in bacitracin broth

The findings are shown in table v

The strains of *Staph pyogenes, Esch coli, Klebsiella,* and *Pr mirabilis* obtained from these various sources were typed and proved identical with the urine strains, except that coliform bacilli and strains of *Staph pyogenes* isolated from bladder irrigation fluids were not of any urinary types Strains of *Staph pyogenes,* however, isolated from fluids diluted ready for two irrigations on one day and two on another day, were of two types isolated from the operation wounds of several patients The identification of *Esch freundii, Providence, Pr vulgaris* (indole-negative) and *Pr rettgeri* as urinary infecting strains was based on biochemical data and drug sensitivity Other organisms were not typed

Discussion

That urinary infection is common in urological wards, particularly among prostatectomy cases, is well recognised, but the mode of infection is less certain Auto-infection has been suggested by Hjort and Sletvold (1945), Kimmelman et al (1951), and Story (1954) Story found that 64 of 119 patients with *Proteus* infection of the urinary tract carried a rectal strain which, on the basis of the Dienes phenomenon, was identical with their urinary strain However, as he pointed out, the urinary infection was already established when the rectal specimen was taken It seems to us that perineal and anal contamination could readily lead to the recovery of *Proteus* from a rectal swab culture, particularly since Story used a technique which would yield organisms present only in very small numbers

Most of the infecting species encountered are intestinal organisms, but in our investigation the infections acquired in this ward seem to have been mainly due to transfer of organisms from one patient to another and not to transfer from the patient's own intestinal tract

Published reports of cross infection of the urinary tract are few Ørskov (1952, 1954) reports findings similar to our own in a study of *Klebsiella* infections of the urinary tract The same strain was often isolated from patients in the same ward, and this strain was recovered from various sites in the ward

Our investigation of the possible sources of cross infection shows that the ward dust and the air are a permanent reservoir of species that infect the urinary tract (This state of affairs has long been realised in connection with other types of cross infection) Also infection may pass from one patient to another via the Winchester bottles used to collect urine from patients with indwelling catheters and possibly via the urinals

In a urological ward some degree of contamination of the nurses' hands seems more or less inevitable, but such contamination is clearly an important cause of cross infection The risk with some procedures (e g, bladder irrigation) is obvious, but incidental procedures, such as reconnecting the drain tube when it has been detached from the catheter might equally transfer organisms to the patient

Procedures in this ward are to be altered in the light of our findings, and the incidence of infection will be estimated again after they have been introduced

Cross-infection of the urinary tract has a special significance now that an increasing proportion of hospital strains of bacteria are resistant to antibiotics

Summary

An investigation of urinary-tract infection in 80 unselected patients in a male urological ward is reported

Of 35 patients with benign prostatic hyperplasia 22 became infected in hospital Of the remaining 45 patients, with various urological conditions, 13 became infected in hospital

Two possible modes of infection were investigated —auto-infection from the patient's intestine and cross-infection

There was little evidence of auto infection Samples of fæces from 41 patients were examined quantitatively for urinary organisms, excluding streptococci, using media containing streptomycin since nearly all the infecting strains were streptomycin-resistant No urinary infecting organisms were isolated from any samples from 23 of 29 patients infected with streptomycin-resistant organisms or from the 12 other patients investigated The possibility remains of occasional cases of auto infection

There was conclusive evidence of cross-infection in a high proportion of the patients Of 58 infected patients 38 were infected by strains of organisms recovered also from other patients The numbers of patients infected by the predominant strain of each species were *Staph pyogenes* (11), *Esch freundii* (4), *Klebsiella* (7), *Providence* (17), and an indole-negative strain of *Pr vulgaris* (14), and strains of *Pr mirabilis* from 8 of 11 patients were the same type

The drug sensitivity was characteristic of that found in hospital infections Resistant strains were isolated from patients who had been infected after admission but before any chemotherapy was given In contrast, strains of *Esch coli* recovered from patients already infected at admission were sensitive and were all of different serological types

A number of potential sources of cross infection investigated yielded one or more urinary infecting strains—Winchester bottles used for collecting urine from patients with indwelling catheters, urinals, nurses' ward hand-towels, nurses' hands, fluids from bladder-irrigation syringes immediately before use, air, and dust Boilable catheters and cystoscopes gave negative results

Mock bladder drainage systems were set up in the laboratory and both *Staph pyogenes* and *Strep fæcalis* (but not gram-negative bacilli) survived the routine chemical disinfection treatment given to Winchester bottles and ascended from these along sterile tubing to the "bladder" against a flow of sterile urine

We are deeply indebted to Dr William Hayes for his continued help and advice and to Lord Stamp and Mr Ralph Shackman for their interest and encouragement We should like to thank the nurses of the urological ward for their willing coöperation Dr F Ørskov, of the Statens Seruminstitut, Copenhagen, kindly examined the strains of *Enterobacter* species, and Dr R E O Williams, of the Staphylococcus Reference Laboratory, Colindale, typed the strains of *Staph pyogenes*

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LONG-TERM EFFECT OF DRIED THYROID ON SERUM-LIPOPROTEIN AND SERUM-CHOLESTEROL LEVELS

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FORMERLY PSYCHIATRIC RESIDENTS

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IT has previously been reported by Strisower et al (1954, 1955) that dried thyroid exerts a profound influence on low-density serum lipoprotein and serum cholesterol levels

Strisower et al (1954) reported the effect of 650 mg of dried thyroid substance administered daily for about ten weeks, in each of 11 cases on this dosage of thyroid the levels of cholesterol and of S_f 0–12 and S_f 12–20 lipoprotein in the serum fell considerably throughout the treatment with thyroid , The levels of S_f 20–100 and S_f 100–400 lipoprotein did not fall so uniformly during thyroid treatment That study was designed to test the response to a very high dosage of thyroid The discovery that all patients respond to a high dosage of thyroid by a fall in serum lipoprotein and serum-cholesterol levels led to the study of the response to lower doses of thyroid

A long term study was therefore initiated, starting with a dosage of 195 mg daily Strisower et al (1955) have reported the results of thirty weeks' administration of this dosage of thyroid A considerable fall in the levels of S_f 0–12, and S_f 12–20 lipoprotein and cholesterol in the serum was observed initially on this dosage in 50 patients , but, in spite of continued administration of thyroid, the great majority of patients showed an apparent "escape" phenomenon the lipoprotein and cholesterol levels, maximally depressed at three weeks after the start of thyroid treatment, gradually returned towards the pre treatment values until, at thirty weeks, they were almost up to the pre treatment values

The hypothesis was advanced that this "escape" phenomenon was, in all likelihood, due to a gradual cessation of production of endogenous thyroid hormone, with the result that the amount of thyroid hormone available daily to the patient after thirty weeks' administration of dried thyroid 195 mg daily was not appreciably above the amount of hormone available before such treatment It was expected that, if the dosage of dried thyroid were increased sufficiently, a point would be reached where the sum of endogenous and exogenous thyroid hormone would exceed that produced daily before such treatment, and that the lipoprotein and cholesterol levels in the serum would remain low

This concept has been tested now by extending the original treatment period of thirty weeks' thyroid 195 mg daily to include two additional periods thirty-nine weeks' thyroid 260 mg daily, and thirty six weeks' thyroid 325 mg daily These studies are reported here

Materials and Methods

Sixty schizophrenic patients at Stockton State Hospital were chosen for the experiment So far as could be determined, these patients were physically and metabolically normal There were thirty females aged 27–56 (mean 39 6) and thirty males aged 25–57 (mean 40 3) The only selection used in constituting the group was that each patient's mental status made both leave and discharge from the hospital during the experiment very unlikely *

Two important requirements of an experiment to test the efficacy of a drug such as dried thyroid in lowering the serum-lipoprotein levels are met by using chronic mental patients (1) a stable diet, such as that of an institution, because it is well known that alterations in the diet exert profound effects on the levels and distribution of lipoproteins (Glazier et al 1954, Gofman et al 1954, Nichols et al 1956) , and (2) assurance that the drug is taken consistently by each patient

Two samples of blood were taken for estimating the lipoprotein and cholesterol levels before the administration of dried thyroid At the same time body weight blood-pressure, and pulse rate were recorded Treatment with dried thyroid was begun in twenty patients (ten male and ten female) in each of three succeeding weeks Samples of blood were taken on the same staggered schedule at three-week intervals during the first two periods of the experiment and later at six-week intervals, body weight, blood pressure, and pulse rate being recorded at the time that each sample of blood was taken The lipoprotein and cholesterol levels in the serum were measured by techniques previously described by de Lalla and Gofman (1954) and Colman and McPhee (1956) The treatment with dried thyroid was deliberately started at different times so that blood sampling would also be done in different weeks to minimise the effect of any small technical variations in the estimation of serum lipoproteins and serum cholesterol

The dosage of dried thyroid was maintained at 195 mg daily for an initial period of thirty weeks, followed by 260 mg daily for thirty-nine weeks and 325 mg daily for thirty-six weeks

The patients were followed up for twenty-seven weeks after the treatment had been stopped, samples of blood being taken and body-weight, blood-pressure, and pulse-rate being recorded at three, six, twelve, and twenty seven weeks after the end of treatment

Of the original sixty patients thirty nine completed the course of thyroid The twenty-one who did not complete the course are accounted for as follows

(1) Six patients were transferred to a different ward for active psychiatry There was no indication that the thyroid had made the transfer necessary

(2) One patient was transferred to a surgical ward for hæmorrhoidectomy

(3) Two patients refused to allow further samples of blood to be taken

(4) Six patients left the hospital

(5) Four patients lost so much weight that, in view of possible thyrotoxic effects, they were excluded from the experiment

(6) Two patients showed increased agitation, which, although probably not due to thyroid treatment, led to their exclusion from the experiment

Results

The mean changes in the levels of the four classes of low density lipoproteins (S_f 0–12, S_f 12–20, S_f 20–100, S_f 100–400) and of cholesterol in the serum of the thirty nine patients who completed the course of treatment are shown in fig 1 From the data plotted in fig 1 and significance tests the following results can be deduced

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* This experiment was begun in June, 1953, before the common use of such therapeutic agents as reserpine and chlorpromazine At no time in the course of this entire study were such agents administered to any of the patients in this group

(1) *Serum cholesterol*

After three weeks on thyroid 195 mg daily there was a significant ($p<0.01$) fall in the mean level of serum-cholesterol from an initial value of 216 mg per 100 ml to 157 mg per 100 ml Thereafter the mean serum-cholesterol level rose progressively toward the pre-treatment value From twenty-four to thirty weeks after the start of treatment with thyroid 195 mg daily the serum cholesterol level was 210 mg per 100 ml, which does not differ significantly from the initial value when the dosage was increased to 260 mg daily, a significant progressive fall of the serum cholesterol level was observed (mean 184–200 mg per 100 ml throughout most of the treatment with 260 mg daily) Towards the end of the thirty-nine weeks on 260 mg daily and in the first fourteen weeks on 325 mg daily the serum cholesterol level tended to rise

At this stage of the experiment the question arose whether there was real evidence for some "escape" from the effect of the thyroid, or whether the patients were receiving less than the full dosage of 325 mg daily The ward attendants were then re-impressed with the need for very careful attention to administration of the full dosage of the thyroid each day to every patient and were constantly reminded of this throughout the remainder of the experiment After these discussions with the attendants the serum-cholesterol level fell progressively and remained low (mean 195 mg per 100 ml) throughout the remaining twenty-two weeks on 325 mg daily Thus, during treatment with 325 mg daily, when there was reasonable assurance that the patients received the full dose, there was no evidence of an "escape" phenomenon from the effect of thyroid on the serum-cholesterol level

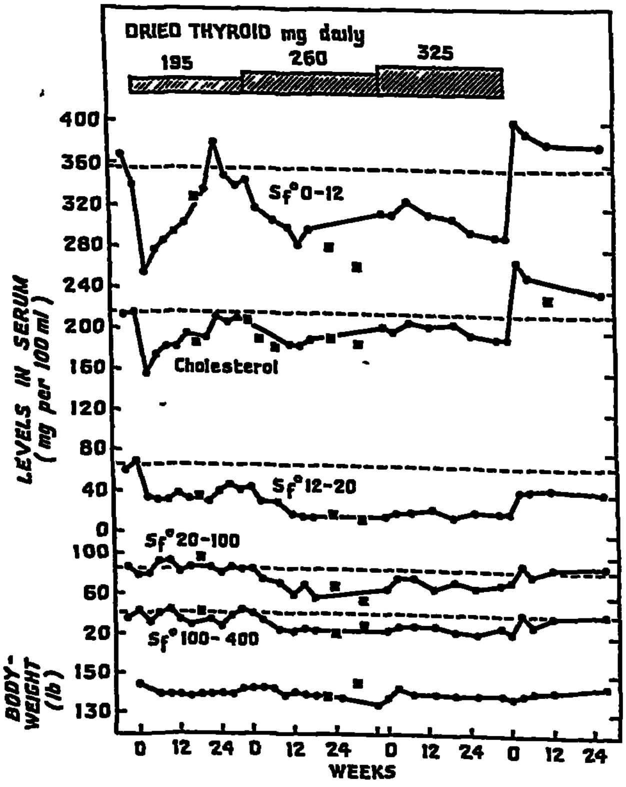

Fig 1—Levels of cholesterol and S_f 0–12 S_f 12–20 S_f 20–100 and S_f 100–400 lipoproteins in serum and body-weights during treatment with dried thyroid 195 mg 260 mg and 325 mg daily and during follow up Interrupted lines means of two pre-treatment readings circular plotting-points means of 30 or more samples square plotting points means of less than 30 samples

Three weeks after the administration of thyroid 325 mg daily had been stopped the serum-cholesterol rose quickly to 269 mg per 100 ml Thereafter it fell gradually to 235 mg per 100 ml and stayed there for the last fifteen weeks of the follow-up

(2) *S_f 0–12 Lipoproteins*

The behaviour of the level of the S_f 0–12 lipoproteins in the serum was roughly the same as that of the serum-cholesterol level On thyroid 195 mg daily the level of the S_f 0–12 lipoproteins fell sharply for three weeks, from its initial value of 354 mg per 100 ml to 256 mg per 100 ml, and then gradually returned to its pre-treatment value at the end of the thirtieth week on 195 mg daily Under treatment with 260 mg daily the mean level of S_f 0–12 lipoproteins fell progressively to about 306 mg per 100 ml The rising trend in the last part of the treatment with 260 mg daily and the first part of the treatment with 325 mg daily corresponded to that observed for the serum-cholesterol level

As with the serum cholesterol level, after the attendants had been warned to make sure that the full doses were given, the levels of S_f 0–12 lipoproteins fell, and remained low at a mean value of 294 mg per 100 ml throughout the rest of the treatment with 325 mg daily No evidence of an "escape" phenomenon was noted

Three weeks after thyroid medication had been stopped, the level of the S_f 0–12 lipoproteins rose quickly to 403 mg per 100 ml and then gradually dropped and stayed at 378 mg per 100 ml twenty seven weeks after the end of treatment

(3) *S_f 12–20 Lipoproteins*

The level of S_f 12–20 lipoproteins fell from 76 mg per 100 ml to 44 mg per 100 ml on the administration of thyroid 195 mg daily In contrast to the levels of S_f 0–12 lipoproteins and cholesterol, the level of S_f 12–20 lipoproteins did not tend to rise under treatment with 195 mg daily, except for a slight increase in the last nine weeks However, even with this increase the levels remained significantly below the pre treatment value When the daily dosage of thyroid was increased to 260 mg the levels of S_f 12–20 lipoproteins dropped further to about 25–30 mg per 100 ml and stayed there for the rest of the treatment with 260 mg daily and throughout the treatment with 325 mg daily

When the thyroid treatment was stopped, there was a significant rise to 52 mg per 100 ml but no rebound above the initial levels During the remainder of the twenty seven weeks' follow-up the level of the S_f 12–20 lipoproteins remained unchanged at 52 mg per 100 ml

(4) *S_f 20–100 and S_f 100–400 Lipoproteins*

In contrast with the findings for cholesterol and the S_f 0–12 and S_f 12–20 lipoproteins, neither the S_f 20–100 nor the S_f 100–400 lipoproteins showed any significant change in mean level during treatment with thyroid 195 mg daily When the dosage was increased to 260 mg daily, the mean levels of both S_f 20–100 and S_f 100–400 lipoproteins gradually fell and remained low during the rest of the treatment with 260 mg and throughout the treatment with 325 mg The level of the S_f 20–100 lipoproteins dropped from an initial mean value of 83 mg per 100 ml to a mean value of 60–70 mg per 100 ml during treatment with 260 mg and with 325 mg The level of the S_f 100–400 lipoproteins was 39 mg per 100 ml initially The mean level of the S_f 100–400 lipoproteins dropped to about 25 mg per 100 ml during treatment with 260 mg and with 325 mg

When the thyroid treatment was stopped, the levels of both the S_f 20–100 and the S_f 100–400 lipoproteins rose within three weeks to the pre-treatment values and stayed there throughout the twenty seven weeks follow up

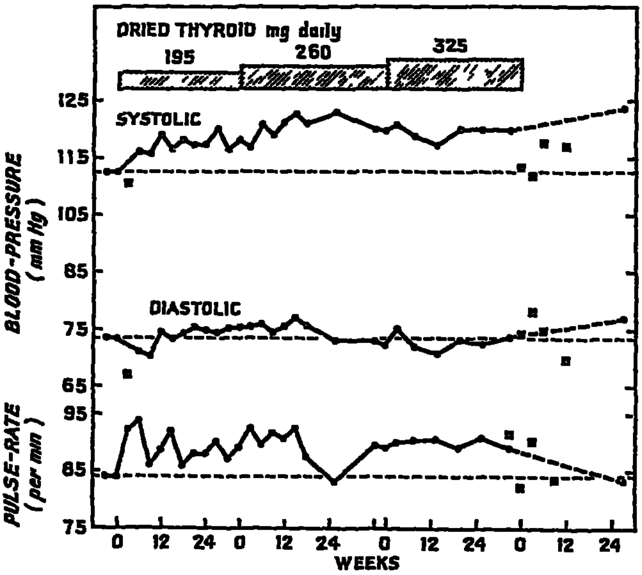

Fig 2—Pulse rate and systolic and diastolic blood pressures during treatment with dried thyroid 195 mg, 260 mg, and 325 mg daily and during follow up Interrupted lines, means of two pre-treatment readings, circular plotting points, means of 30 or more samples, square plotting points means of less than 30 samples

(5) *Body weight*

During the first six weeks' treatment with 195 mg daily the mean body-weight decreased from 145 lb to 140 lb Thereafter, throughout all three periods of treatment (195 mg, 260 mg, and 325 mg daily) the mean weight remained at 140 lb except for oscillations of ±3 lb Fig 1 certainly does not suggest that continued negative caloric balance (and hence continued weight loss) is necessary to produce and maintain falls in the levels of lipoproteins and cholesterol in the serum After the thyroid treatment had been stopped, the body-weight gradually returned to its pre treatment value of 145 lb during the twenty seven weeks' follow-up

(6) *Blood pressure and Pulse rate*

The mean changes in pulse-rate and systolic and diastolic blood-pressure under the different dosages are shown in fig 2

The pulse rate increased from an initial mean value of 84 to an average of about 90 during the entire period on dried thyroid at the three dosages of 195 mg, 260 mg, and 325 mg daily When the thyroid treatment had been stopped, the pulse rate returned to its pre-treatment value

The systolic blood pressure rose gradually from a mean pre treatment level of 112 mm Hg to an average of about 120 mm Hg during treatment with 260 mg and 325 mg daily It remained at 120 mm Hg during the follow-up

The diastolic blood-pressure kept its mean value of 74 mm Hg during the entire period on thyroid and during the follow up The greatest changes observed were ±4 mm Hg

Discussion

The long-term study of the administration of dried thyroid in successive dosages of 195 mg, 260 mg, and 325 mg daily shows that it is possible to produce and maintain depression of the levels of cholesterol and S_f° 0-12, S_f 12-20, S_f 20-100, and S_f 100-400 lipoproteins in the serum The "escape" phenomenon, expressed as a rise in lipoprotein and cholesterol levels, in spite of the continued administration of thyroid 195 mg daily, was previously attributed by us to diminished production of endogenous thyroid hormone As a corollary we predicted that the "escape" phenomenon would be prevented by increasing the dosage of dried thyroid The periods of administration of 260 mg and 325 mg of thyroid showed no "escape" phenomenon Hence the results in these periods support the concept that diminished production of endogenous thyroid hormone was indeed responsible for the "escape" phenomenon observed on a dosage of 195 mg The rebound in levels to values above the initial values on the cessation of thyroid treatment provides further evidence of diminished production of endogenous thyroid hormone Immediately after the thyroid treatment has been stopped—i e, the exogenous supply of thyroid has been withdrawn—if the endogenous production of thyroid has diminished, the immediately available supply of thyroid hormone is less than it was before treatment Therefore the levels should rise above the pre-treatment values As the endogenous supply of thyroid hormone increases, the lipoprotein levels should gradually fall towards the pre-treatment values This was precisely what happened in the later part of the follow-up

In three of the thirty-nine cases the levels of S_f 0-12 lipoproteins in the follow up period still remained more than 25% above the pre-treatment value, even twenty seven weeks after the end of treatment with thyroid In the absence of other reasons for such a rise the possibility must be considered that reversal of inhibition of the thyroid gland is extremely slow or will not take place at all Such slowly reversible or irreversible inhibition of the thyroid gland does not appear to be of any serious consequence, because substitution therapy is readily available in the form of dried thyroid

As one aspect of the effort to understand metabolic factors that might influence the response to dried thyroid, the fall of the serum-lipoprotein level in relation to its pre treatment value was assessed in the patients studied For this purpose the patients were ranked according to the initial levels of the several classes of lipoproteins in their serum and then according to the falls in level of those lipoproteins by the end of the thirty six weeks' treatment with thyroid 325 mg daily From table I it is clear that, whatever lipoprotein is used to rank the patients, the higher the initial level of lipoproteins the greater is its subsequent fall The net effect of therapy with thyroid is to decrease the variability, or range of values, of each class of lipoproteins within the group under study One possible interpretation of this observation is that, in patients with high lipoprotein levels, there is a relative deficiency of that thyroid function which controls lipoproteins

It is possible that the control of metabolism and the control of lipoproteins are two separate functions of the

TABLE I—CHANGE IN LEVELS OF LIPOPROTEINS IN SERUM UNDER TREATMENT WITH DRIED THYROID

Lipoproteins	Initial level (mg per 100 ml)		No of cases	Level at end of treatment (mg per 100 ml)	Change in level (mg per 100 ml)
	Range	Mean			
S_f 0–400	Above 650	721	10	480	−241
	500–650	586	16	458	−128
	Below 500	380	13	333	−47
S_f 0–12	Above 400	437	16	340	−97
	300–400	350	15	295	−55
	Below 300	218	8	184	−34
S_f° 12–20	Above 100	145	8	47	−98
	50–100	76	17	29	−47
	Below 50	37	14	23	−14
S_f° 20–100	Above 100	120	13	94	−26
	70–100	81	10	73	−8
	Below 70	54	16	54	0
S_f 100–400	Above 50	88	10	45	−43
	25–50	36	10	21	−15
	Below 25	16	19	13	−3

TABLE II—EFFECT OF DRIED THYROID ON MEAN ATHEROGENIC-INDEX VALUES (UNITS)

Initial	After 30 weeks' thyroid 195 mg	After 39 weeks' thyroid 260 mg	After 36 weeks thyroid 325 mg
70 0	65 7	51 0	52 0

thyroid gland. Goolden (1956) reports that tetraiodothyroacetic acid given to a euthyroid person lowered the plasma cholesterol level without decreasing the body-weight, and Trotter (1956) reports that tri-iodothyroacetic acid lowered the blood-cholesterol level in three euthyroid patients without significantly altering the basal metabolic rate THE LANCET (1956) commented that these newer compounds showed promise of being able to lower the blood-cholesterol level without causing unwanted side effects

Our own observations indicate that considerable caution should be used in setting apart these new thyroid-active substances as being different in their action from dried thyroid, because we find that dried thyroid produces a well-marked effect on the serum lipids in many patients without significantly altering the body-weight Thus, in the present series, eighteen patients lost only 5 lb or less of body-weight in a hundred and two weeks of study, and eight of these actually gained weight In all of them the lipoprotein level was significantly lowered as a result of the administration of dried thyroid In these eighteen patients the mean change in body-weight was + 3 1 lb, and the mean fall in level of S_f 0–400 lipoproteins 41 mg per 100 ml

TABLE III—CHANGES IN MEAN ATHEROGENIC-INDEX VALUES (UNITS) AFTER TREATMENT WITH DRIED THYROID

Initial	After 30 weeks thyroid 195 mg	After 39 weeks' thyroid 260 mg	After 36 weeks' thyroid 325 mg
In 10 patients with highest S_f 0–400 lipoprotein level			
94 1	84 6	62 0	64 0
In 10 patients with lowest S_f 0–400 lipoprotein level			
43 0	46 5	39 9	37 1

Furthermore, fig 1 shows that, from the last part of treatment with 195 mg daily and throughout treatment with 260 mg and with 325 mg daily, there was practically no alteration in weight in any of the patients, although the serum-lipoprotein and serum-cholesterol levels fell during this period In addition, in a separate study of patients with the S_f 0–12 hyperlipoproteinæmia characteristic of xanthoma tendinosum, it was commonly observed that the lipoprotein level fell considerably without loss of body-weight and often with a gain in weight (Gofman et al 1957) We therefore consider that unwanted side effects—e g, weight loss—need not arise in treatment with dried thyroid Therefore if any of the recently studied active compounds produced by the thyroid gland act separately on the lipids and on metabolism to a greater extent than does dried thyroid the demonstration of this fact requires a carefully controlled comparison of the various substances

One field where the effect of dried thyroid on lipoprotein and cholesterol levels is of especial interest is arteriosclerosis especially coronary arteriosclerosis and its sequel, coronary heart-disease Gofman et al (1953) have shown that there is a positive association of the serum levels of the S_f 0–12, S_f 12–20 S_f 20–100 and S_f 100–400 lipoproteins with clinical coronary heart-disease A composite measure called the atherogenic index (A I) value† represents the best combination of the lipoprotein levels in distinguishing patients with overt coronary disease from clinically healthy persons Since raised A I values are associated with increased risk of clinical coronary heart-disease, one reasonable approach to prophylaxis of coronary heart-disease is by trying to reduce raised A I values The effect of dried thyroid in lowering lipoprotein levels and keeping them low suggests its possible application for this purpose The data of fig 1 can be calculated on the basis of A I response to dried thyroid These results are presented in table II

The decrease in A I value during treatment with thyroid 260 mg and with 325 mg is considerable Table I shows that, as already stated, the higher the initial lipoprotein level the greater is the fall in response to thyroid The A I response in the ten patients with the highest initial level of S_f 0–400 lipoproteins is compared with that in the ten patients with the lowest initial level of S_f 0–400 lipoproteins in table III

It is clear that the patients with the highest initial levels showed a considerable decrease of A I value in response to thyroid administration, this decrease should indicate a smaller risk of clinical coronary heart-disease The patients with the lowest initial levels showed a much smaller decrease of A I value, both actual and proportional, their risk of developing clinical coronary heart-disease is already small and is only slightly decreased further by treatment with thyroid From the point of view of possible prophylaxis of coronary heart-disease the much greater effect of thyroid on raised A I values than on low ones is especially useful because it is precisely the patients with high A I values who most need prophylactic lowering of their A I values

Summary

Dried thyroid 260 mg daily and 325 mg daily produces a sustained fall in the levels of S_f 0–12 S_f 12–20, S_f 20–100, and S_f 100–400 lipoproteins and of cholesterol in the serum

The higher the initial level of lipoproteins the greater is the fall in that level under such treatment

"Escape" phenomena, previously observed on thyroid 195 mg daily, were not observed with higher dosages

The large falls in atherogenic index values for patients with high initial atherogenic index values suggest that dried thyroid is worthy of consideration as a prophylactic agent against coronary heart disease

We gratefully acknowledge the assistance of Minnie Adams, Ellen Davis, John Sanders, and the other ward personnel of Stockton State Hospital for administering the dried thyroid, for measuring blood pressures, pulse rates, and body weights, and for drawing the samples of blood We also thank the technical workers at Donner Laboratory for ultracentrifugal analyses, and Alice McPhee, of the Donner Laboratory, for all the serum cholesterol analyses The dried thyroid was supplied by the Armour Laboratories, Kankakee, Illinois This work was partly supported by the United States Atomic Energy Commission, the Albert and Mary Lasker Foundation Inc, and Wyeth Laboratories, Inc, Philadelphia, Pennsylvania

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†Atherogenic index (A.I) = 0 1 (S_f 0–12) + 0·175 (S_f 12–400)

THE INFLUENCE OF TRIIODOTHYROACETIC ACID ON THE CIRCULATING LIPIDS AND LIPOPROTEINS IN EUTHYROID MEN WITH CORONARY DISEASE

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It has now been established beyond reasonable doubt that the circulating cholesterol, the cholesterol/phospholipid ratio, and the proportion of cholesterol which is attached to β lipoprotein are all raised in coronary disease (Morrison et al 1948, Gertler et al 1950, Barr et al 1951, Steiner et al 1952, Nikkila 1953, Oliver and Boyd 1953, Rosenberg et al 1954 Oliver and Boyd 1955) But it has not yet been established in man that correction of the abnormal pattern of circulating lipids and lipoproteins will retard the atherosclerotic process or decrease the tendency to thrombosis Hence any compound which lowers the levels of cholesterol and β lipoprotein cholesterol in the plasma requires consideration

It has been known for many years that thyroid extract lowers the plasma cholesterol and plasma phospholipid levels in hypothyroid and euthyroid subjects and at the same time increases their metabolic requirements (Lévy and Lévy 1931, Turner and Steiner 1939, Gildea et al 1939) More recently it has been shown that thyroxine reduces the β lipoprotein fraction (Malmros and Swahn 1953) Triiodothyroacetic acid (triac), an acetic acid analogue of triiodothyronine first synthesised by Pitt Rivers (1953), also lowers the plasma cholesterol, but in small doses it may not produce a concomitant rise in the basal metabolic rate (B M R) (Lerman and Pitt-Rivers 1955) A similar lowering of the plasma cholesterol without any rise in the B M R has been observed in euthyroid subjects after larger doses of triac (Trotter 1956) and after small doses of triiodothyronine (Oliver and Boyd 1956, Boyd and Oliver 1957)

In general, thyroid derivatives are not suitable for administration to patients with coronary disease, because they may increase metabolic requirements enough to provoke angina and to reduce exercise tolerance, but a derivative which decreases the plasma cholesterol without apparently increasing metabolic requirements has obvious potentialities

Methods

The subjects were twelve hypercholesterolæmic men between the ages of 33 and 49 (mean 42) who had experienced classical myocardial infarction, confirmed electrocardiographically, more than 9 months before the clinical trial of triiodothyroacetic acid All the men had returned to their usual full time occupations, and none of them were off work during the trial or in the 3 months preceding it

The plasma cholesterol was estimated by the Sperry Schoenheimer procedure modified by Sperry and Webb (1950) , the plasma phospholipids were estimated by the method of Allen (1940) , and the distribution of cholesterol between the α and β lipoproteins was estimated by filter paper zone electrophoresis with subsequent elution of cholesterol (Boyd 1954) The B M R was determined on a standard Benedict Roth apparatus by the linear formula of Aub and DuBois (1917) All the men were admitted to hospital for two nights for this purpose, the B M R being determined on two consecutive mornings Electrocardiography was done before the administration of triac, with every change in its dosage and after the end of the course From the start of the course the men attended weekly between 9 A M and 10 A M for withdrawal of blood and recording their weight

Results

Small Dosage

To six men triac was administered orally in divided and increasing doses from 0 5 mg to 4 0 mg daily for 95 days (fig 1). There was no significant change in the levels of the circulating lipids and lipoproteins until 3 0 mg was given daily

At the end of the course, when 4 0 mg had been given daily for 10 days, the mean plasma cholesterol had fallen by 21%, but the mean cholesterol/phospholipid ratio was not significantly altered The proportion of cholesterol attached to β-lipoprotein had fallen by 26% and the proportion attached to α-lipoprotein had risen by 46% There was no loss of weight, and the mean B M R of the six men was not significantly altered the mean readings before the course were +1% and -5% and at the end of the course +1% and –3% There was no significant change in the electrocardiograms during or after the course

In two of the six men the B M R had risen by the end of the course In one of them the B M R rose by 20% and this rise was associated with a fall of 15% in the plasma cholesterol and of 19% in the β lipoprotein cholesterol In the other man the B M R rose by 13% and this rise was associated with a fall of 29% in the plasma cholesterol and of 29% in the β lipoprotein cholesterol This man complained of decreased exercise tolerance and of about three attacks of effort angina daily , previously he had only had angina once or twice weekly on strenuous exertion This increase in the incidence of angina necessitated recourse to glyceryl trinitrate, which he had not required for 3 years

In another man, who previously had excellent exercise tolerance and no angina, the B M R fell during the course

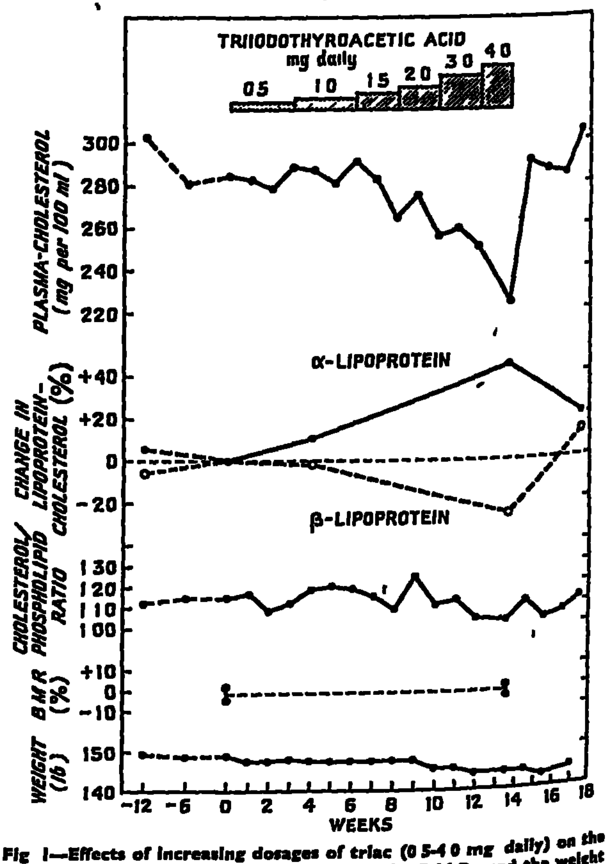

Fig 1—Effects of increasing dosages of triac (0 5-4 0 mg daily) on the plasma levels of lipids and lipoproteins, the B M R , and the weight of six euthyroid men with coronary disease

of triac, but he developed classical angina of effort twice or three times each day, his plasma cholesterol had fallen by 13% and his β-lipoprotein cholesterol by 15%.

When triac was withdrawn, both of these men experienced rapid regression of their symptoms, and they now have little angina or impairment of exercise-tolerance.

Large Dosage

To six men triac was administered orally in divided and increasing doses from 3·0 mg. to 5·0 mg. daily for 3 months (fig. 2).

After 3·0 mg. had been administered daily for 1 month, the mean plasma cholesterol had fallen by 4% and the mean cholesterol/phospholipid ratio by 12%. After the administration of 4·0 mg. daily for a week the plasma-cholesterol had fallen by a further 10% (making a total fall of 14%) and the cholesterol/phospholipid by a further 8% (making a total fall of 20%). After the administration of 4·0 mg. daily for 2 weeks the β-lipoprotein cholesterol had fallen by 12% and the α-lipoprotein cholesterol had risen by 15%. During the subsequent 2 weeks, when the men received 4·0 mg. daily, the plasma cholesterol and the cholesterol/phospholipid ratio rose to control values or higher.

When 5·0 mg. was administered daily for a month, there was a further slight fall in the plasma cholesterol, but this was much less impressive than the original fall at the beginning of the course of triac with the 3·0 mg. dosage. At the end of the administration of 5·0 mg. of triac daily for a month, the proportions of cholesterol attached to α- and β-lipoproteins had returned to control values. When triac was withdrawn, there were rebound rises in the plasma-cholesterol and in the cholesterol/phospholipid ratio.

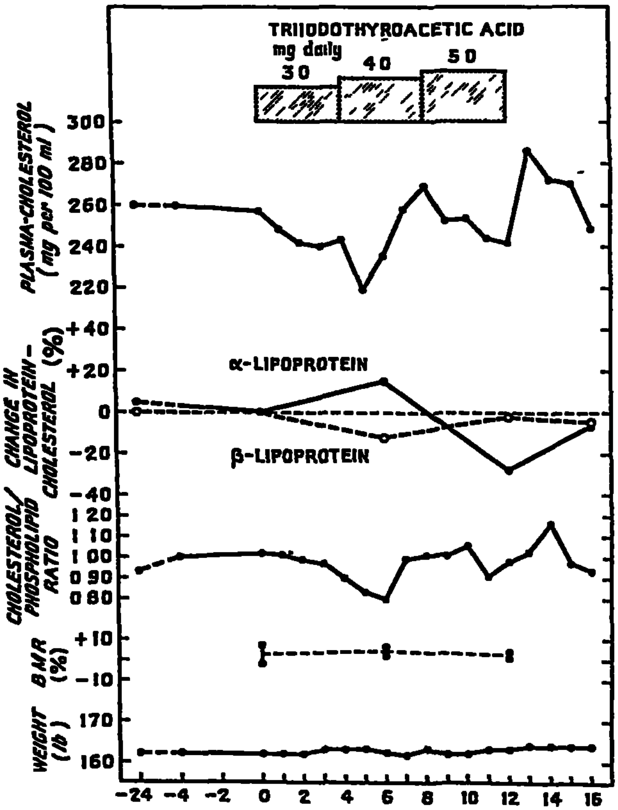

Fig. 2—Effects of increasing doses of triac (3·0-5·0 mg. daily) on the plasma levels of lipids and lipoproteins, the B.M.R., and the weight of six euthyroid men with coronary disease.

There was no loss of weight, and the B.M.R. of these six men was not significantly altered; the mean readings before the course were +7% and −2%, after 6 weeks on triac they were +7% and +2%, and at the end of the course they were +4% and +2%. There was no significant change in the electrocardiograms during or after the course. In one of the six men exercise-tolerance was less, as shown by more angina and breathlessness on exertion.

Discussion

In euthyroid men with coronary disease triiodothyroacetic acid (triac) lowered the plasma cholesterol, the cholesterol/phospholipid ratio, and the proportion of cholesterol attached to β-lipoprotein without raising the basal metabolic rate. The dosage of triac that will produce this dissociation varies from patient to patient, but the optimum is usually 3–4 mg. daily—i.e., six or eight times what is required by hypothyroid patients (Boyd and Oliver 1957).

In three out of twelve men the normally good exercise-tolerance was reduced, and angina developed or was greatly aggravated. In one of these three triac raised the B.M.R., and the reduction of exercise-tolerance is therefore not surprising. In the other two the B.M.R. did not change, yet their exercise-tolerance certainly diminished as was evident from our previous observation of the patients for several years.

It has been shown that the administration of triac to euthyroid and to hypothyroid rats increases the oxygen uptake of heart tissue to a greater extent than that of liver, skeletal muscle, and kidney (Barker and Lewis 1956, Boyd and Oliver 1957). It has been suggested that triac may increase the oxygen requirements of the myocardium without causing any observable increase in the B.M.R. (Boyd and Oliver 1957). It is possible therefore, that the dissociation of its action on the circulating lipids and lipoproteins from any effect on the B.M.R. is more apparent than real; it may depend partly on inadequacy of the B.M.R. to reflect a selective increase in the oxygen requirements of a comparatively small tissue.

Fig. 2 shows that depression of the plasma cholesterol could not be maintained over long periods even when the dosage of triac was increased. In this graded study a comparatively large dosage (such as 5 mg. daily) was no more effective than a smaller one. Moreover such large dosage may be undesirable in some patients because it may induce angina more readily.

Summary and Conclusions

In euthyroid hypercholesterolæmic men with coronary disease triiodothyroacetic acid (triac) lowered the plasma cholesterol, and cholesterol/phospholipid ratio, and the β-lipoprotein cholesterol without raising the basal metabolic rate.

After a course of triac two out of twelve men developed angina of effort, and their exercise tolerance was decreased even though their basal metabolic rates were not raised.

The fall in the plasma cholesterol level could not be maintained for long even by increasing the dosage of triac.

It is concluded that triac may not prove suitable for the long term control of hypercholesterolæmia in patients with clinical coronary disease.

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ROVSING'S OPERATION FOR POLYCYSTIC KIDNEY

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SINCE Rovsing described his operation in 1911, little has been written about the results obtained Most of the series have been published in the United States, but neither there nor in Britain is the value of the operation widely recognised Apparently most surgeons try it once or twice and then abandon it because the mortality-rate is high This is easy to explain Uræmia is not relieved, and indeed may be fatally aggravated by, Rovsing's operation Hence the surgeons who try it as a last resort in patients deteriorating in spite of medical treatment, are likely to be disappointed On the other hand, those who use it in earlier cases are often more favourably impressed

Catrill and Fish (1941) operated on 23 of their 58 cases with 2 deaths They found that the results were poor when the kidneys were failing

Rathbun (1942) claims that hæmaturia is particularly likely to benefit from Rovsing's operation, and quotes an interesting misadventure leading to nephrectomy

Newman (1950) reviews the literature and observes that all authors claim good results from surgery in polycystic disease, he reports 24 cases treated by operation and maintains that considerable benefit may be expected for pain and bleeding, but not for renal function

Goldstein (1951) treated 18 patients conservatively and 18 by his own operation He claims to have doubled their expectation of life and to have improved their general health by reducing the severity of symptoms

I have been tapping polycystic kidneys for twenty-five years, and have operated on nearly half the patients I have seen I should now recommend surgery for a much higher proportion

Methods

Preoperative Care —Anæmia and disturbances of blood-chemistry should be corrected as far as possible Infection should be treated by the appropriate drug, but streptomycin should never be given to a patient with polycystic kidneys, 3 cases of vestibular destruction have been seen from quite short courses

The Operation —It is strongly recommended that only one kidney be tapped at a time The second can be tapped after fourteen days in fairly fit patients, but in advanced cases some months should be allowed

The patient is placed face-down with a pillow under the chest Edebohl's incision is used The advantage of this is that, when a further tapping is required, the usual curved lumbar approach can be used for the front of the kidney and no scar tissue will be present to make difficulties

The peritoneum, which extends very far posteriorly with the colon over these large kidneys, should be carefully freed towards the front The posterior and postero lateral cysts are punctured, or rather slit, with a small knife (diathermy is not favoured), and, as the kidney shrinks, more and more cysts come into view To avoid shock, the operation should not be prolonged

The ilio inguinal nerve should be protected otherwise there may be postoperative pain The wound is drained for about six days and rarely breaks down

Results

I have operated on 18 patients with polycystic kidneys

There were two postoperative deaths One patient (case 5) died suddenly a week after operation, with a blood-urea of 230 mg per 100 ml In the other (case 14) a biopsy specimen of the polycystic liver was taken at a physician's request To control the bleeding took a long time, she became shocked and soon died

Both were very advanced cases, but in the light of present knowledge they should not have died In case 5 the operation should have been delayed and the man's condition further improved, in case 14 the liver biopsy should have been avoided

This series does not include patients operated on during the war whose notes are lost and who have not been followed up As there was no death after operation in those cases, the mortality-rate in my experience is less than 2 in 18 In most published series it appears to be just under 10% for advanced cases

Of the 16 surviving patients, symptoms were relieved or improved in 15, the other (case 7) had no symptoms but satisfactorily withstood a prostatectomy a month after operation

6 patients were relieved of pain and 5 of bleeding, in 3 renal function improved temporarily 2 with infection were improved

Hypertension is a symptom for which improvement is not usually claimed, yet 8 of these 16 cases had benefit It was often dramatic with relief of headache and papillœdema, though most relapsed after three or four years Such a relief is surely worth achieving

The results are summarised in tables I and II

Illustrative Cases

Case 1 —The right kidney was tapped in 1933 and no further deterioration was observed on that side for over 11 years, but the left kidney continued to deteriorate and was tapped in 1944 The patient is alive and well 23 years after the first operation

Case 2 —A woman of 26 had her right kidney operated on in 1937 The preoperative X rays report reads "Gross enlargement lower pole of right kidney Pelvis and calyces displaced upwards and stretched over this swelling Ureter displaced inwards General excretion rate is good"

Intravenous pyelography was repeated in 1956, and Dr Blewett, who did not know the history, reported "Both kidneys are secreting a good concentration but the pelves were not completely filled Both are large and, so far as is shown, the outline of the left is consistent with a large cyst polycystic kidney The right one, although the pelvis is large, shows no characteristic cystic impression but may be of a small cyst type" In other words, the radiologist could not be sure that the right kidney (on which we had operated) was cystic, whereas the untreated left kidney was enormous

Clinically the right kidney (which was tapped) is only just palpable, whereas the left is very large and knobbly This supports the suggestion that the tapped cysts do not re form

Case 11 —A priest, aged 43, was in extreme hypertensive heart failure in 1951 His blood pressure was 205/120 mm Hg and his blood urea 58 mg per 100 ml A bilateral Rovsing operation was performed as a life saving measure A month later his blood pressure was 156/104 and the blood urea 28 mg

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Atrial fibrillation ceased and he went back to work There was some relapse by 1953 blood pressure 180/120, blood-urea 78 mg A further tapping of the left side allowed another return to work He relapsed again in 1956 and died in uræmia There is no doubt that this patient's life was usefully prolonged for five years

DISCUSSION

Some benefit from cyst-puncture can be expected for various symptoms

Hypertension —There is a quite remarkable fall in blood-pressure, which relieves hypertensive heart-failure and may persist for some years, it is impossible to anticipate which cases will improve, but on the whole the higher the blood-pressure, the more likely the improvement

Pain may be relieved by considerable reduction in the size of the vast swellings, several pints of fluid being removed

TABLE I—PATIENTS AGED OVER 30

Case	Sex	Age (years) at first operation	Blood-pressure (mm Hg)	Blood-urea (mg per 100 ml)	Operation	Date	Remarks	Survival after first operation (years to date)
4	F	43	160/120 170/100 135/85	35 25	Bilateral Repeat left	1945 1951 1956	Pain relieved Vast decrease in left kidney Well and working	11
5	M	43	190/120	146	Left	1948	Preoperative anæmia (hæmoglobin 54%) Blood urea 230 mg after operation	Died after operation
6	M	37	132/90	68	Right Left	1945 1946	Well after operation Died of coronary thrombosis	1½
7	M	70	200/100	39	Left	1943	Blood urea 33 mg after operation Successful Harris prostatectomy a month later	Untraced
10	M	47	180/120 190/110	190 155	Left- Right	1952 (Jan) 1952 (June)	Hæmaturia and salt taste in mouth relieved completely Blood urea rose then fell Return of uræmic symptoms in 1953	2
11	M	43	205/120 180/120	58 74	Bilateral Repeat left	1951 1953	Hypertensive heart failure After first operation B P fell to 125/95 Much improvement (see text)	5
12	M	49	180/110	34	Left	1953	B P fell to 150/90 after operation Hæmatoma had to be evacuated Second side not done Hæmaturia less	Untraced
13	M	38	175/110 180/120 200/120	43 52	Left Right	1953 1954 1956	B P fell to 135/100 after first operation Well except for ilio inguinal pain Hæmaturia less	3
14	F	58	210/130	112	Right		See text	Died after operation
15	M	77	140/75		Left	1954	Bleeding and pain improved Infection not affected	2
16	M	43	190/130 200/140	68	Right (May) Left (June) Right (Aug 1) Left (Aug 22)	1954 1956	After first operation B P fell to 120/90 General improvement 20 oz aspirated from each side	2
17	F	50	250/150 210/110	101	Left Right	1955 1956	Feels 'vastly improved Put on 2 stone in weight	1
18	F	43	240/120 170/100	80 50	Right Left	1955 1956 1957	 No headaches even without reserpine Symptom free	1

TABLE II—PATIENTS AGED UNDER 30

Case	Sex	Age (years) at first operation	Blood pressure (mm Hg)	Blood-urea (mg per 100 ml)	Operation	Date	Remarks	Survival after first operation (years to date)
1	F	23	140/[illegible] 120/80	40 60	Right Left	1933 1944 1956	Pain relieved completely (see text) Now alive and well	23
2	F	26	170/100	32	Right	1937 1956	Now alive and well Pain relieved completely (see text)	19
3	F	(26) 36	160/104	84	Right (Nov) Left (Dec)	1938 1948	Great benefit Lived life to the full till her death in 1951 (see text)	3
8	F	29	146/98	73 42	Left (March) Right (May)	1948 1950	Was very well in 1951 Pain relieved	5 (untraced since 1953)
9	F	27	170/120 174/116 148/90 170/104		Left Right	1952 1953 1955 1956	Much improved headaches gone Pyelography showed improved secretion	4

Hæmaturia is relieved in some cases

Psychological benefit may be considerable in that at least some treatment is being tried

Renal Function—Deterioration may be prevented, especially in young patients, if the tapped cysts fail to regrow, for it takes some years for the tiny untapped cysts to grow big enough to press on the functioning tissue and damage it Improvement probably derives from removal of pressure on the secreting tissue

Nearly all cases, however, show some immediate post operative deterioration of function I have always attributed this to falling blood-pressure from shock, anæmia, absorption of toxic matter, infection, or even œdema (from the trauma of tapping) temporarily increasing the pressure on surviving nephrons However, Patton and Bricker (1954), found evidence that cystic nephrons may serve as functioning units I have seen (case 17) fluid under great pressure in the cysts in a patient thought to have obstruction due to a ureteric stone, which may be evidence that they were secreting urine Damage to these cystic but functioning nephrons must therefore be justified by at least comparable relief to the normal renal parenchyma

From this and my own experience, I feel sure that it is unjustifiable to operate on both kidneys simultaneously

Late uræmic cases benefit least, the risk of the operation is greater and relief is likely to be short lived In patients without uræmia, however, the prevention of deterioration is, in my opinion, most valuable Young patients seem to do best The one young patient who has died, delayed her operation from 1938 until 1948, and although she had great benefit and lived a full life until her death in 1951, I feel sure that if she had had the operation 10 years earlier, before the blood-urea reached 84, she would have had more kidney tissue to preserve and would have been alive today It is interesting to note that all the patients under 30 were female 4 of them were discovered at antenatal clinics, and the 5th presented with malignant hypertension

No case of polycystic disease in infancy is included, the process is so advanced that expectation of life is negligible In my opinion this disease may have a different pathology

It is hoped that this brief account will stimulate interest in the operation and encourage practitioners to recommend surgery for patients with polycystic disease early enough for them to benefit

Summary

18 patients have had Rovsing's operation Apart from 2 who died soon after operation, all patients have had benefit in one way or another

Expectation of life may be increased when operation is undertaken early In 2 patients benefit from unilateral tapping was compared with the contralateral deterioration after 11 and 19 years respectively Relief from pain and hæmaturia and temporary relief of hypertension can be expected

Renal function is always lowered for a short time, after recovery it is unlikely to improve further, but deterioration is delayed The delay is most marked when there is most kidney to preserve This is an important feature in patients treated early, who are the ones most likely to benefit

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EFFECTS OF SOME ANALGESIC DRUGS USED IN CHILDBIRTH

WITH SPECIAL REFERENCE TO VARIATION IN RESPIRATORY-MINUTE VOLUME OF THE NEWBORN

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THE comparative inaccessibility of the fœtus prevents detailed observation of the effects on it of analgesics given to the mother during labour, but the respiratory centre of the fœtus in utero is very susceptible to the depressant action of pain relieving drugs, and this depression may be obvious in the infant at birth Many studies have been made of the anoxic newborn, and the degrees of asphyxia classified Nevertheless, we felt that a more detailed investigation of the reactions of the newborn infant's respiratory system to frequently used analgesics would be worth while

Preliminary Survey

A preliminary study was made of alteration in the respiratory minute volume of the newborn infant in response to various analgesics administered to the mother during labour The minute volume was recorded with a trip spirometer described by Donald and Lord (1953) Since an apparatus involving the use of a face mask can annoy and stimulate an infant and promote accumulation of carbon dioxide beneath the mask, the recordings considered were those made by quiet infants over a period of not more than a minute and a half The minute volumes obtained in this series were larger than those recorded by Cross (1949) with a plethysmograph but our results were intended as a measure of comparison and not a physiological standard

During the preliminary investigation the newborn infants were divided into ten groups according to combinations of drugs given to the mother during labour Table I shows the variation of mean minute volumes according to the type of analgesia used The four smallest minute volumes followed the administration of pethidine, but other factors, particularly age and weight, may affect the minute volume and, if the babies had been

TABLE I—MEAN MINUTE VOLUMES IN RELATION TO TYPES OF ANALGESIC

Type of analgesia	No of infants	Mean minute vol (c cm)	S D	S E M
Pethidine	15	893 7	101 2	104
Peth gas air	205	907 2	315 8	21 2
Peth scop gas air	34	1014 4	284 6	48 8
Peth gas oxygen	7	1024 0	381 5	144 2
Peth trichloroethylene	20	1150 5	562 7	125 8
Controls	38	1092 8	401 6	74 9
Gas air	565	1111 8	419 9	17 7
Iso propyl chloride	9	1370 2	328 2	109 4
Gas oxygen	7	1137 6	441 6	166 9
Trichloroethylene	24	1198 7	287 3	58 6

S D, standard deviation   S E M, standard error of mean selected in some way, could be the cause of the apparent effect of pethidine

Each of these four groups was therefore divided into sixteen subgroups—four age-groups and four weight-groups less than 6½ lb , 6½–7½ lb , 7½–8½ lb , and more than 8½ lb

In the gas-and-air group (565 cases) was found a significant increase, apparently linear, of the minute volume with greater body-weight This increase was estimated at 124 9 c cm for each 1 lb increase of weight and was the same for each age-group

To compare the groups, the observations were corrected to 7½ lb (the mean body-weight in the gas-and-air group), the value of 124 9 c cm being used for each 1 lb increase of body-weight The mean values of the corrected figures for each age-group in six of the groups are shown in table II

An analysis of variance showed that the difference in the mean minute volumes of the pethidine and non-pethidine groups was statistically significant at the 1% level The other factors showed no significance We may therefore conclude that pethidine has a depressant effect on the minute volume of the newborn infant The amount of the decrease in minute volume when pethidine is used appears to be about 10–15% and is being examined further

TABLE II—MEAN MINUTE VOLUMES (C CM) BY AGE GROUPS AND ANALGESICS

Age (hr)	Gas and air		Trichloroethylene		No other drugs	
	With pethidine	Without pethidine	With pethidine	Without pethidine	With pethidine	Without pethidine
0–1	947	1252	581	1217	627	1159
>1–10	930	1002	900	1276	961	1116
>10–20	1012	1115	1251	1182	813	962
>20	1209	1288	1477	1155	863	1411
Mean	1024 3	1164 2	1077 2	1207 5	815 0	1162 0

Levallorphan

Since pethidine appears to diminish the minute volume, it was suggested that an antagonist to it might be used with advantage, therefore the effects of levallorphan with pethidine were studied

Levallorphan tartrate or (—) 3-hydroxy-N-allylmorphinan tartrate differs chemically from levorphan tartrate or (—) 3-hydroxy-N-methylmorphinan tartrate only by the substitution of an allyl group for the methyl group at the nitrogen atom Whereas levorphan exerts an analgesic action like that of morphine levallorphan does not, nor does it behave in other respects like morphine In small doses (0 5–1 0 mg) levallorphan relieves respiratory depression Large doses are required to inhibit other typical effects of morphine, including analgesia The following points require special consideration when it is used during labour (1) its prophylactic value against depression of respiration in the newborn , (2) its effects on other central side effects of drugs of the morphine group (i e , nausea and vomiting) , and (3) its effects on the degree of analgesia The dosage proposed by American workers, after research on animals and some preliminary work on man, is 1 mg of levallorphan to 200 mg of pethidine

Preliminary trials to establish whether levallorphan diminished the analgesia produced by pethidine involved 19 deliveries in two groups of alternate treatments

Group 1 the mother received pethidine only , and levallorphan was given to the infant if asphyxiated

Group 2 pethidine was given when required and about an hour before delivery levallorphan was injected intramuscularly After three or four cases levallorphan was given three quarters to one hour after pethidine In no case did the analgesia appear to be impaired by the levallorphan.

TABLE III—DEGREE OF ANALGESIA ACCORDING TO MOTHERS AND OBSERVERS OPINIONS

Group	Degree of analgesia		
	Very good	Good	Fair
1	3 (*30%*)	7 (*70%*)	0
2	4 (*44%*)	4 (*44%*)	1 (*11%*)

Sufficient pethidine (150–400 mg) was given to promote a very satisfactory analgesia, and the distribution was fairly even in both groups, as was the time relationship to delivery. Gas-and-air was given to the mother as required The degree of relief was judged during labour, immediately after delivery, and again on the following day (table III)

There were 8 (80%) anoxic infants in group 1 and 2 (22%) in group 2, the difference being significant at the 5% level 5 in group 1 responded without levallorphan The remaining 3 were severely affected but responded within a half to one minute after the injection of levallorphan 0 25 mg into the umbilical vein , they became active and cried within two minutes and showed no tendency to relapse The anoxic infants in group 2 responded to minimal treatment

This pilot experiment helped in the planning of the main survey It will be seen that the patients studied in the pilot experiment received larger doses of pethidine

Main Survey

508 cases were studied Three groups were established

Group A pethidine and gas-and-air (177 cases)

Group B pethidine, levallorphan, and gas and air (178 cases)

Group C methylpentynol ('Oblivon ') and gas and air (120 cases) Subgroup C2 was created by patients who required pethidine in addition to methylpentynol (33 cases)

The administration of the various drugs, according to a table of random numbers, was as follows :

Group A intramuscular pethidine 150 mg initially and 100 mg when required , gas and air when required

Group B pethidine 150 mg and levallorphan 1 mg given in the same syringe Subsequent doses were pethidine 100 mg. and levallorphan 0 5 mg Gas and air as in group A

Group C Oblivon elixir ' 6 drachms orally with water If the patient vomited within ten minutes, draught was repeated immediately Subsequent doses of 3 or 6 drachms as required Gas and air was administered In 33 cases pethidine 150 mg was given

Groups A and B are reviewed together (table IV) and group C separately

GROUPS A AND B

Anoxia in Newborn

There were 6 severely anoxic newborn infants in group A All were subjected to endotracheal intubation

TABLE IV—TYPES OF DELIVERIES INCIDENCE OF ANOXIA IN NEWBORN, AND RELIEF OF PAIN

—	Group A		Group B	
	Primigravidæ	Multiparæ	Primigravidæ	Multiparæ
Deliveries	78	99	83	95
Normal deliveries	65	97	83	95
Forceps deliveries	11 (*14%*)	1 (*1%*)	5 (*6%*)	0
Cæsarean sections	2 (*2 5%*)	1 (*1%*)	0	0
Postmaturity	9 (*11 5%*)	13 (*13%*)	3 (*3 6%*)	15 (*15 8%*)
Prematurity	9 (*11 5%*)	5 (*5%*)	5 (*6%*)	5 (*5 2%*)
Anoxia at birth				
Severe	2 (*2 5%*)	4 (*4 1%*)	0	0
Moderate	4 (*5 0%*)	6 (*6%*)	6 (*7 2%*)	1 (*1 1%*)
Mild	8 (*10%*)	3 (*3%*)	10 (*12%*)	5 (*5 2%*)
Stillbirth	1 (*1%*)	0	0	0
Relief from pain				
Good	124 (*70%*)		134 (*75 2%*)	
Fair	42 (*23 7%*)		36 (*20 2%*)	
Poor	8 (*4 5%*)		8 (*4 4%*)	

Abnormal factors associated with the delivery were cæsarean section, forceps delivery in 2 cases, and prematurity in 1 infant In the moderately affected infants such complications as cæsarean section, forceps delivery, cord tight round the neck, and antepartum hæmorrhage occurred in equal proportions in both groups

It is difficult to assess relief of pain, because the personal element interferes with impartial judgment But by having only one person to question patients the day after their deliveries, one can estimate fairly consistently the degree of analgesia produced by pethidine and by pethidine with levallorphan (table IV) Group B showed slightly more analgesia, which fact, though possibly not significant, confirms that levallorphan 1 mg to pethidine 150 mg did not impair the analgesic value of the pethidine Some of the nurses said that levallorphan appeared to make the patient drowsier

TABLE V—INCIDENCE OF ANOXIA IN RELATION TO TIME OF ADMINISTRATION OF PETHIDINE

Time of giving single dose of pethidine 150 mg	No of deliveries	No of anoxic infants
Group A		
Within 3¹/₄ hr of delivery	107	10 (*9 3 %*)
More than 3¹/₄ hr before delivery	49	11 (*22 4 %*)
Group B		
Within 3¹/₄ hr of delivery	104	9 (*8 6 %*)
More than 3¹/₄ hr before delivery	42	7 (*16 6 %*)

The distribution of the amount of pethidine in the two groups did not differ much

The higher incidence of anoxia in the infants was in the group where the mother received the pethidine more than three and a quarter hours before delivery (table V), which fact is rather unexpected These cases were uncomplicated by anæsthesia, and only a mixture of nitrous oxide and air was given in addition to the pethidine

Minute Volume of Newborn

Satisfactory records were made of the minute volumes of 419 newborn infants in six groups according to the analgesics received by the mother during labour Delivery was uncomplicated by anæsthesia, and the three-and-a-quarter hour limit is purely arbitrary The groups are as follows

A1 pethidine (P), last dose less than three and a quarter hours before delivery

A2 pethidine (P), last dose more than three and a quarter hours before delivery

B1 pethidine and levallorphan (P L) less than three and a quarter hours before delivery

B2 pethidine and levallorphan (P L), last dose more than three and a quarter hours before delivery

C1 methylpentynol (M)

C2 methylpentynol and pethidine (M P)

The age distribution was about the same in each group

The mean weight of all the babies whose minute volumes were recorded was 7 34 lb , the mean weights in each group being as follows

A1 (P)	A2 (P)	B1 (P L)	B2 (P L)	C1 (M)	C2 (M P)
7 27	7 57	7 22	7 48	7 44	7 10

Thus the groups are comparable for age and weight, and we may therefore compare their minute volumes

In any one group the distribution of minute volumes was decidedly skew, so the groups are probably best compared by using the logarithms of the minute volumes instead of the actual volumes The accompanying figure shows the distribution of the minute volumes on a logarithmic scale in each group, there are no great differences in the distributions, although perhaps there may be a difference between the groups C1 and C2

Table VI gives the mean logarithm of the minute volumes of each group and the geometric mean of the minute volumes (The geometric mean is the antilog of the mean logarithm of minute volumes) The geometric mean cannot be compared with the more usual arithmetic mean but is probably more useful in the present case as a measure of the middle minute volume of each group, as roughly half the babies have minute volumes greater than the geometric mean, and half less

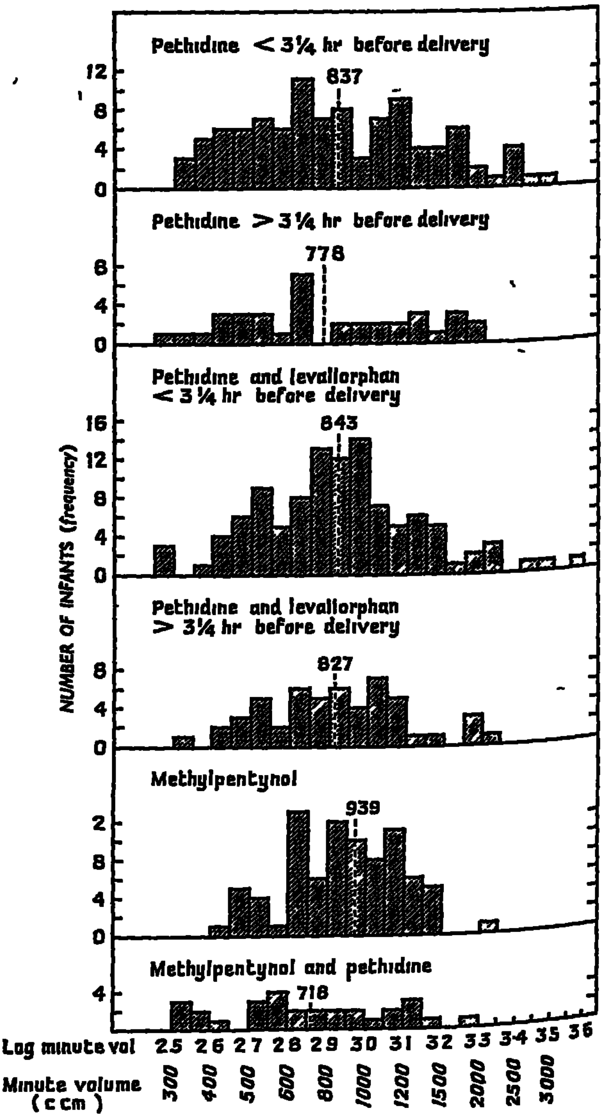
TABLE VI—MEAN LOGARITHMS AND GEOMETRIC MEANS OF MINUTE VOLUMES BY TYPE OF ANALGESIC

Group	A1 (P)	A2 (P)	B1 (P L)	B2 (P L)	C1 (M)	C2 (MP)
Mean log	2 923	2 891	2 926	2 917	2 973	2 856
Geometric mean	837	778	843	827	939	718

Although the groups are comparable for age and weight and the minute volumes can thus be compared without correcting for these factors, it is of interest to examine their effects

The actual minute volume is used here, rather than the log minute volume as in the previous section, because, although the logarithm is better on statistical grounds, the actual minute volume enables comparison to be made with previous work

The relationship between the minute volume and body-weight was found for each group and each age



Distribution of minute volumes of newborn infants on logarithmic scale (geometric mean given) group, the mean increase of minute volume being 118.2 c.cm. for each increase of 1 lb. in weight. This compares with 124.9 c.cm. found from 565 babies in a previous survey, the difference being insignificant.

The mean minute volumes (corrected for weight) for each group and age-group are given in table VII.

TABLE VII—MEAN MINUTE VOLUME CORRECTED FOR WEIGHT FOR EACH ANALGESIC GROUP AND AGE GROUP

Age (hr.)	Mean minute volume (c.cm.) (corrected for weight)					
	A1 (P.)	A2 (P.)	B1 (P.L.)	B2 (P.L.)	C1 (M.)	C2 (M.P.)
0–1	1147	1089	1013	1007	1072	1010
1–2	946	910	1055	764	1047	803
2–3	812	564	836	733	853	589
3–4	595	802	721	651	694	367
4–10	805	646	793	828	998	527
1–10	818	740	916	771	907	676

Approximate analyses of variance of groups A and B in table VII show:

(1) There is no evidence that, when pethidine is used, the addition of levallorphan has any effect on the minute volume.

(2) There is a significant difference between the minute volumes at different ages. The data suggest that the minute volume is high immediately after birth, declining to a minimum at about three to four hours, and thereafter increasing.

Methylpentynol

The use of methylpentynol in labour has been studied clinically by Bourne (1954). Our observations agree with his conclusion that it diminishes the stress of labour.

Methylpentynol is highly selective in its action, relieving apprehension and acting as a sedative but exerting no antispasmodic or analgesic action. In cases of overdosage both nikethamide and methylamphetamine hydrochloride given intravenously have proved to be satisfactory restoratives. Experiments on rats have shown that about 20% of the methylpentynol given was in adipose, muscle, and liver tissue while the rats were still under its hypnotic influence. No residual products were found in the tissues when the clinical effects had worn off. Methylpentynol is not incompatible with any other drug. When it is given with barbiturates, there is a summation of the effects of both drugs.

GROUP C

The results obtained in group C are set out in table VIII. The pethidine 150 mg. in group C2 was given when the mother appeared to need more relief than the methylpentynol and gas and air sequence would produce.

The incidence of analgesia and some side effects produced by methylpentynol alone on the mother were as follows:

Relief from pain		
Good	*Fair*	*Poor*
38 (31.0%)	37 (30.8%)	45 (37.5%)

Drowsiness	48 (40.0%)
Euphoria	34 (28.0%)
Amnesia	4 (3.3%)
Dizziness	2 (1.6%)
Vomiting within 10 minutes of receiving drug	11 (9.1%)

Methylpentynol given in early labour appeared to accentuate the analgesic effect of pethidine and of gas-and-air given at a later stage of labour.

In group C1 the anoxia in 2 newborn infants was associated with a forceps delivery for persistent occipito-posterior presentation and with a premature infant weighing 2 lb.

The infants with mild anoxia in group C1 recovered with the minimum of extra attention.

The stillbirth in group C1 is difficult to explain, because the fœtal heart sounds disappeared about fifteen minutes before delivery, more than two hours after the administration of 6 drachms of methylpentynol. Since methylpentynol is excreted in about an hour it is unlikely to have played any part in the death of the fœtus.

Comparison of the minute volumes in groups C1 and C2 in table VIII shows that the mean minute volume in the group where pethidine was used was significantly smaller than in the group where pethidine was not used.

Conclusions

Comparisons of the minute volumes of newborn infants indicate that pethidine given to the mother during labour leads to diminished respiratory activity in the baby for some hours after birth.

The levallorphan-pethidine and pethidine groups in the main survey showed no statistical significant difference between the minute volumes in the two groups.

The effect of the levallorphan was more noticeable in the pilot experiment, where the amounts of pethidine given to the mothers were greater than in the main survey, and the incidence of anoxia in the newborn was less in the levallorphan-pethidine group; here the difference is significant at the 5% level.

We suggest that, if similar doses of pethidine had been given in the larger trial, the value of the levallorphan would have been reflected in larger minute volumes of the infants in the levallorphan-pethidine group. Alternatively, an increase in the amount of levallorphan per 200 mg. of pethidine might have produced more positive results. Levallorphan does not diminish the analgesic effect of pethidine, and clinical observations show that it may enhance the sedation produced by pethidine.

Methylpentynol appears to have only a moderately depressant effect on the minute volume, compared with the gas-and-air group in table II. It can be concluded that methylpentynol can be of value during labour to produce a sense of relaxation and drowsiness in a small proportion of cases (about 40% of those reviewed here) and to augment the analgesic action of other drugs given later in labour.

TABLE VIII—RESULTS IN MOTHERS GIVEN METHYLPENTYNOL AND THOSE GIVEN METHYLPENTYNOL AND PETHIDINE

—	Group C1 (methylpentynol)		Group C2 (methylpentynol and pethidine)	
	Primigravidæ	Multiparæ	Primigravidæ	Multiparæ
No. of cases	37	83	18	15
Normal deliveries	36	82	14	15
Forceps deliveries	1 (2.7%)	1 (1.2%)	4 (22.2%)	0
Postmaturity	2 (5.4%)	6 (7.2%)	1 (5.5%)	2 (13.3%)
Prematurity	2 (5.4%)	9 (10.8%)	0	0
Anoxia at birth				
Severe	0	0	0	0
Moderate	2 (5.4%)	2 (2.4%)	4 (22.2%)	2 (13.3%)
Mild	5 (13.5%)	1 (1.2%)	0	0
Stillbirth	1 (2.7%)	0	0	0
Relief from pain				
Good	80 (66.6%)		24 (72.7%)	
Fair	30 (25.0%)		7 (21.2%)	
Poor	10 (8.3%)		2 (6.1%)	

Summary

The alteration in the minute volume of the newborn in response to various analgesics administered to the mother during labour was studied.

The mean minute volume of 565 newborn infants in the gas-and-air group was compared with that of 205 babies in the pethidine/gas-and-air group. Pethidine apparently reduced the volume by 10–15%.

The action of levallorphan as an antagonist to pethidine was studied. The mean minute volume of 177 newborn babies of the pethidine/gas-and-air group was compared with that of 178 infants of the pethidine/levallorphan/gas-and-air group. There was no significant increase in the mean minute volume in the latter group.

Methylpentynol was administered to 153 patients in labour: 120 receiving methylpentynol and gas and air, and 33 methylpentynol, pethidine, and gas and air. Of the former group 66.6% experienced satisfactory relief, of the latter 72.7%. The mean minute volume of the newborn infants in the group in which pethidine was used was significantly lower than in the methylpentynol/gas-and air group

We wish to thank Prof McClure Browne, the board of governors of the Hammersmith, West London, and St Mark's Hospitals, and the matron of Hammersmith Hospital for their interest and cooperation, and the midwifery staff of the labour ward for their help during the trials Prof Ian Donald helped immeasurably by lending the trip spirometer for which we are most grateful to him Roche Products Ltd supplied the levallorphan, and British Schering Ltd the 'Oblivon' Finally, we wish to acknowledge with gratitude the monetary help given to one of us (H R) by the National Birthday Trust Fund, without whose assistance this work could not have been done

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INHIBITION OF GASTRIC EMPTYING AND SECRETION IN PATIENTS WITH DUODENAL ULCER

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GASTRIC hypersecretion of acid and pepsin is common in patients with duodenal ulcer, and there is a strong tradition that such patients often show unduly rapid gastric emptying (Hurst and Stewart 1929) I report here experiments designed to determine whether failure of one of the mechanisms which normally inhibit gastric activity can explain part or all of the gastric hyperfunction in patients with duodenal ulcers

Although the plan of the experiments is simple it is best explained in terms of a concrete example Suppose that, under conditions which produce minimal inhibition of gastric emptying, subject A empties 400 ml of a test-meal from his stomach whereas subject B empties only 200 ml, and that, on retesting these subjects with a meal which powerfully inhibits gastric emptying, subject A empties 100 ml and subject B also empties 100 ml It may reasonably be concluded that subject A has the more effective inhibitory mechanism braking gastric emptying, and that the ratio of the uninhibited rate of emptying to the inhibited rate may be used to assess the degree of its effectiveness

Earlier experiments had shown that a saline solution containing 100 m eq of sodium chloride per litre left the stomach very rapidly and could be regarded as a minimal stimulus to the duodenal osmoreceptors whose activity slows gastric emptying (Hunt 1956) To provide an index of the rate of minimally inhibited gastric emptying such a test-meal was used In the second test a solution containing 100 g of glucose per litre provided a powerful stimulus to the duodenal osmoreceptors which slow gastric emptying Gastric secretion is usually inhibited by the same conditions as inhibit emptying, therefore a comparison of the ratios of the secretory responses to these two meals was also used to assess the effectiveness of the mechanism inhibiting gastric secretion

The work described here leads to the conclusion that rapid gastric emptying is not generally characteristic of patients with duodenal ulcer, but that such patients do, in response to test-meals, secrete about twice as much acid and pepsin as do healthy persons The mechanism which inhibits gastric secretion and emptying in response to glucose has not been found to be defective in patients with duodenal ulcer

Methods

Control studies were made on 27 healthy students The patients with a diagnosis of duodenal ulcer without pyloric stenosis were under treatment in the medical and surgical wards of the hospital After the stomach had been washed out, two test-meals were given by tube on separate days one of 750 ml of saline solution containing 100 m eq of sodium chloride per litre, and one of 750 ml of glucose solution (100 g per litre), both of which contained the dye phenol red as a marker Ten minutes after the saline solution was given and thirty minutes after the glucose solution was given, the whole of the gastric contents was recovered The concentrations of phenol red, acid, chloride, and pepsin were determined in the recovered gastric contents From these data and corresponding data on the meal before ingestion the amounts of acid, chloride, and pepsin secreted were calculated (Hunt 1954) The data for the test-meals containing glucose have already been reported as a control for studies on the influence of hydrochloric acid on gastric secretion and emptying in 16 patients (Hunt 1957) Because there was a technical failure in estimating the secretory response to one of the saline meals, comparisons of secretion are based in this paper on 17 tests in 15 patients with duodenal ulcer

TABLE I—MEAN VOLUMES OF MEAL AND OF GASTRIC CONTENTS AFTER TEST MEALS OF SALINE AND OF GLUCOSE SOLUTION

—	27 healthy people	16 patients with duodenal ulcer (18 tests)
Volume of gastric contents 10 min after saline meal (ml)	408 ±29	370 ±31
Volume of saline meal remaining at 10 min (ml)	361 ±27	322 ±26
Volume of gastric contents at 30 min after glucose solution (ml)	566 ± 9	542 ±21
Volume of glucose solution remaining at 30 min (ml)	489 ± 9	439 ±23

The figures after the means are the standard errors of the means

Results

Gastric Emptying

Table I shows that there is no significant difference between the healthy people and the patients with duodenal ulcers in their rate of gastric emptying of saline meals If gastric emptying of glucose solution is assessed from the mean data for volume of gastric contents remaining at thirty minutes, there is no significant difference between the healthy people and the patients with duodenal ulcers The table also shows that the patients with duodenal ulcer had a mean volume of meal remaining in the stomach 50 ml less than that found in the healthy people, but this difference is too small to be considered clinically significant

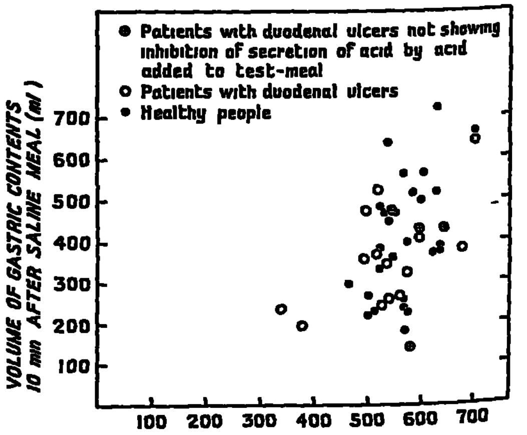

Fig I—Relation between volume of gastric contents 10 minutes after a saline meal and 30 minutes after a meal of glucose solution (100 g per litre)

The data on gastric emptying are given in more detail in fig 1, in which the individual values for the volumes of the gastric contents with saline meals have been plotted against the corresponding values for the volumes of gastric contents with meals containing glucose. It will be seen that the points for the patients and the healthy people are freely intermixed. Moreover, the high standard error of the mean volume of the gastric contents for the patients with duodenal ulcer after the meal of glucose solution will be seen to be largely attributable to two points.

It may be concluded that a duodenal ulcer is not associated with any characteristic emptying of these test-meals. There is no evidence of general defective operation of the duodenal brake in patients with ulcer which would have been indicated in fig 1 by the points for patients with duodenal ulcers lying to the left of those for healthy people.

Gastric Secretion

The mean data on the gastric secretion for two test-meals are shown in table II, which shows that, although in response to both types of meal the patients with duodenal ulcer secreted about twice as much acid, chloride, and pepsin as did the normal subjects, the ratios of the mean response to meals containing glucose to the mean response to saline meals are nearly equal for the healthy people and the patients with duodenal ulcers.

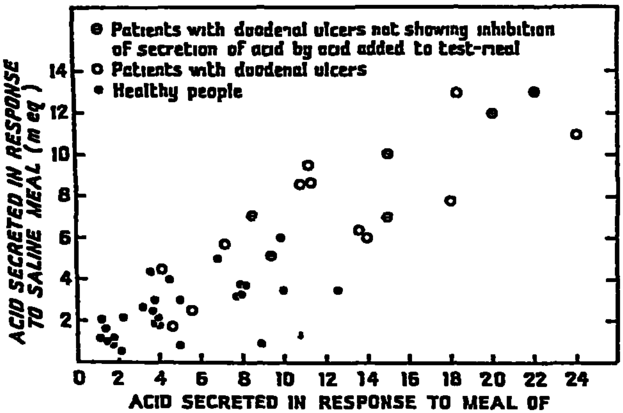

Fig 2—Relation between secretory response to saline meal in 10 minutes and to a meal of glucose (100 g per litre) in 30 minutes

The data on the secretion of acid are given in more detail in fig 2, in which the amount of acid secreted in response to the meal containing glucose has been plotted against the amount of acid secreted with the saline meal for each person.

Although many of the patients with duodenal ulcers secreted more acid than did the healthy people, there is nothing to suggest that, relative to their response to saline meals, the patients secreted more acid in response to solutions of glucose than did the healthy people. 6 of these patients were found not to respond to the addition of hydrochloric acid to test meals by an inhibition of the secretion of acid (Hunt 1957). Their data are specially marked in fig 2 but do not stand out from those of the other people.

It may be tentatively concluded that the two inhibitory mechanisms, that responding to glucose and that responding to acid, have at least one component which is not common—possibly the duodenal receptors.

Because the gastric mucosa produces at least two secretions, one containing acid and the other containing bicarbonate, the measured output of acid is not necessarily a good index of the secretion of acid which is partly neutralised by the bicarbonate of the non-parietal secretions. For this reason the secretory responses are shown in table II in terms of the hypothetical parietal and non-parietal secretions (Hollander 1938, Fisher and Hunt 1950). It will be seen that the data confirm the remainder of table II in that the patients with duodenal ulcers secreted about twice as much parietal component as did the healthy people.

TABLE II—MEAN GASTRIC SECRETION IN RESPONSE TO MEALS OF SALINE AND TO GLUCOSE SOLUTION

—	27 healthy people	15 patients with duodenal ulcer (17 tests)
Outputs in response to saline meal in 10 min		
H⁺ (m eq)	2.6 ± 0.3	6.8 ± 0.8
Cl⁻ (m eq)	7.8 ± 0.5	13.2 ± 1.5
Pepsin (units)	3600 ± 250	8000 ± 1700
Parietal component (ml.)	25.4 ± 1.8	50.6 ± 5.3
Non parietal secretions (ml)	30.0 ± 2.0	34.2 ± 5.7
Outputs in response to meal of glucose solution in 30 min		
H⁺ (m.eq)	5.1 ± 0.6	12.5 ± 1.7
Cl⁻ (m.eq)	8.4 ± 0.7	19.1 ± 2.0
Pepsin (units)	6300 ± 870	11 400 ± 2000
Parietal component (ml.)	36.7 ± 3.8	87.8 ± 11.7
Non parietal secretions (ml)	18.5 ± 1.8	35.8 ± 3.4

The figures after the means are the standard errors of the means

Discussion

The maximal emptying power of the stomach in healthy people and patients with duodenal ulcers without stenosis has been assessed by using test-meals of saline solution which empty very rapidly (Hunt 1956). There is nothing in the data obtained to establish that the maximal emptying power is greater in the patients than in the healthy people.

As an alternative cause of the rapid gastric emptying which is believed to be common in patients with duodenal ulcer, it might be suggested that the power of the duodenal mechanism which slows gastric emptying may be defective, but it has not been possible to demonstrate this with glucose or with acid (Hunt 1957) as the stimulus to the duodenal brake.

It is not surprising that a cause of rapid gastric emptying in patients with duodenal ulcer has not been discovered, because it has not even been possible to demonstrate that rapid gastric emptying is specially common in such patients. This finding is confirmed by Brooks et al (1950), in whose experiments the volume of the saline test-meal was 100 ml compared with 750 ml in the present experiments. Hence it appears that the failure to demonstrate rapid gastric emptying with these two meals of widely different type in patients with duodenal ulcer cannot be explained as arising from the use of an unsuitable volume of meal.

The absence of any convincing evidence of abnormal gastric emptying stands in striking contrast to the gastric hypersecretion found in the patients with duodenal ulcer in response to saline meals and to meals containing glucose. However, the hypersecretion cannot be explained by any defect in the inhibitory mechanism which responds to glucose, although such a failure has been demonstrated in response to acid added to test-meals in 6 of these 16 patients (Hunt 1957). This latter finding clearly suggests that the inhibitory mechanisms operated by acid and glucose are separable.

It seems probable that the hypersecretion of acid and pepsin by patients with duodenal ulcer can be largely explained by an increased number of parietal and peptic cells in the stomachs of such patients (Guiss and Stewart 1948, Meyers 1948, Hunt 1950, Card 1952, Cox 1952, Hunt and Kay 1954). This conclusion should direct attention to the importance of the tonic action of the vagus in maintaining the integrity of the mucosa (Oberhelman and Dragstedt 1948), because vagotomy decreased the secretory response to histamine which is currently believed to act on the parietal cells.

The anterior lobe of the pituitary gland (Kyle and Welbourn 1956) may also influence the population of cells, because there is pronounced gastric hyposecretion in patients with atrophy of the pituitary gland

There is also, in some patients with duodenal ulcer, a deficiency in the mechanism which reduces gastric secretion in response to a rising acidity of the gastric contents (Shay 1944, Hunt 1957), the receptors mainly operating from the duodenum but also possibly from the antrum (Woodward et al 1954)

Summary

Saline test-meals and test-meals containing glucose were given to 27 healthy people and 16 male patients with duodenal ulcer

There was no convincing evidence of unduly rapid emptying of either of these meals by the patients with duodenal ulcer

The secretory response to these two test-meals (measured as amounts of acid, chloride, and pepsin) by patients with duodenal ulcer was about twice that of the healthy people

In patients with duodenal ulcer there was no evidence of any abnormality in the mechanism which regulates gastric emptying and secretion in response to changes in the osmotic pressure of the duodenal contents produced by glucose

It is a pleasure to thank many clinical colleagues for permission to investigate their patients with duodenal ulcers, the patients themselves, and the students who cooperated in these studies I am indebted to the Society of Apothecaries for the award of the Gillson scholarship, out of which part of the expenses of this research were defrayed

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MANUAL ARTIFICIAL RESPIRATION IN THE SITTING POSTURE

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If a patient stops breathing while sitting in a chair (e g , at the dentist's), it is necessary to move the patient from the chair to the floor to apply any of the current methods of artificial respiration This may cause injury and loses valuable time It is also possible that a person might stop breathing in a confined space without any possibility of lying down in an extended position—e g , in railway accidents and in bombed buildings

A new method of manual artificial respiration has therefore been devised for treating apnoeic patients in the sitting posture

Technique

Both inspiration and expiration are actively produced by this method by the operator stationed either in front of or beside the patient

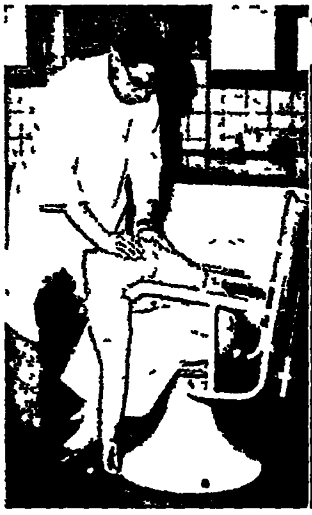

Fig 1—Expiration

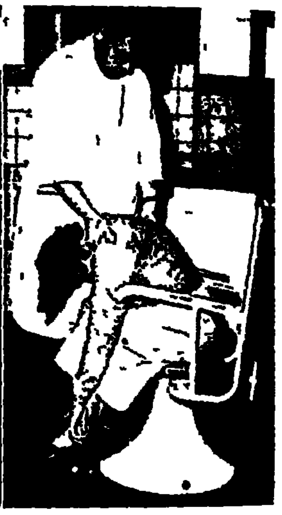

Fig 2—Inspiration

Expiration

The patient's body is flexed in such a way as to bring the head and trunk close to the legs The flexion is increased by pressing on the patient's back (figs 1 and 3) This manœuvre both compresses the abdominal contents, thus forcing the diaphragm upwards, and decreases the capacity of the thorax

Inspiration

The operator stops pressing on the back, so that the thorax will expand passively and reach its resting position, in which inspiration starts Inspiration is increased by lifting the upper part of the body, thereby decompressing the abdominal contents and allowing the diaphragm to descend

The method of lifting the upper part of the body depends on the position of the operator An operator standing in front of the patient can lift the upper part of the body by placing his hands one in front of each shoulder An operator standing to the right of the patient can lift the upper part of the body by placing his right hand on the patient's left shoulder and his left hand in the patient's right axilla (figs 2 and 4)

If the lifting is done in such a way that the patient's spine is extended slightly, the depth of inspiration will be increased by the resulting increase in the capacity of the thorax

Artificial expiration and inspiration are applied thus alternately about 12–15 times a minute

Experimental Trial

In 6 patients who underwent an operation under general anæsthesia, and who gave permission for special investigations to be made, the tidal air produced by this method of artificial respiration was measured immediately after the operation During the application of the method the patients respired atmospheric air not enriched with oxygen All the patients were endotracheally intubated, and an airtight fit between the catheter and the trachea was ensured by the use of an inflated cuff The free end of the tube was so connected that the inspired air and the expired air were kept separate The expired air was passed through a gas meter, with which it was possible to measure the tidal air with an accuracy within at least 50 c cm

The apnœa was produced by intravenous suxamethonium iodide, and the application of artificial respiration was interrupted several times to make sure that apnœa was still present Usually, 75 mg of suxamethonium iodide was sufficient to induce apnœa, and 15–30 mg a minute to maintain it, and the trials usually lasted 10–15 minutes on each person

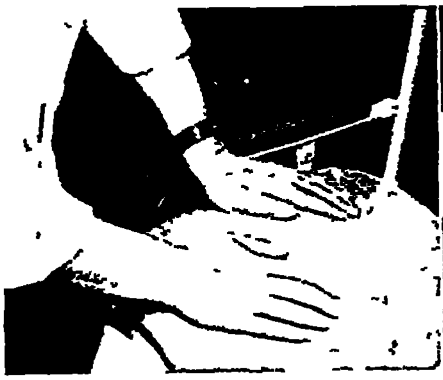

Fig 3—Expiration

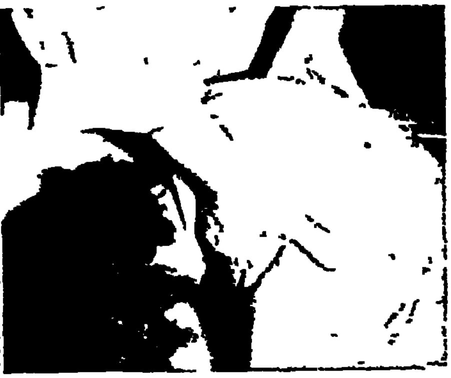

Fig 4—Inspiration.

The patients were kept unconscious with intravenous thiopentone No complications occurred, and no patient showed signs of oxygen lack during or after the trial.

During the application of artificial respiration the values of different variations in the method were compared—e g, lifting of both shoulders, lifting of one shoulder alone (with slight rotation of the upper part of the body), "high" compared with "low" lifting of the upper part of the body, no lifting at all (only intermittent pressure on the back being used), flexion of the body with and without pressure from the legs, and the use of two operators instead of only one

The amount of physical effort required by the operator and the technical difficulty in applying the method were also estimated

The results are shown in the accompanying table The air exchange per respiration was 300–1200 c cm, depending on how the method was applied The table shows that the volume of tidal air was about the same as in current methods of artificial respiration applied to patients lying down in an extended position

The air exchange was 500–1000 c cm per respiration when the method was applied by one person alone The air exchange was not significantly increased when two persons simultaneously applied the method Also it did not seem to matter whether, during flexion, pressure from the legs against the thorax was used or not, or to what height the upper part of the body was lifted Lifting the trunk just a little way off the legs seemed to suffice It also seemed to be unimportant how the lifting was done, but lifting both shoulders produced a slightly greater air exchange than lifting one shoulder only

The patients were maximally relaxed (curarised) during the trials so the results were obtained under the most unfavourable conditions for applying manual artificial respiration During apnoea patients often retain some tonicity of the muscles, which might make the air exchange greater and the method more easy to apply, but in any case the method is not particularly tiring to apply

No preparation is required, therefore this method of artificial respiration can be applied immediately There is no technical difficulty in applying it, therefore an untrained onlooker may take over its application without any other training than just watching it being applied for a few seconds

COMPARISON OF METHODS OF ARTIFICIAL RESPIRATION

Case no	Sex	Age (yr)	Body weight (kg)	Height (cm)	Air exchange in different variations of sitting method (c cm)	Average air exchange in standard method (c cm)
1	F	28			800–1000	About 800
2	M	27	67	164	550–1200	" 1000
3	F	44	79	[illegible]	300–700	450
4	F	51	[illegible]	162	300–700	500
5	M	55	60	170	400–1000	650
6	F	11	50	162	450–700	550

The patient's position in this method appears optimal for maintaining the air-way free because the tongue automatically moves forwards, or can easily be made to do so, because any fluid contents of the mouth and the pharynx will move forwards out of the mouth, and because the mouth cannot be obstructed by the application of the method

During the intermittent flexion of the body the abdominal viscera press not only on the diaphragm but also on the vena cava, thus possibly helping to pump the blood towards the heart

Summary

A new method of manual artificial respiration is described

It consists in alternate flexion of the upper part of the body against the knees of the patient and subsequent extension

Experimental trials on curarised patients showed that an effective exchange of air was produced by this method

The patient's position during the application of the method maintains a free air-way and avoids aspiration

The method is very simple and can be learnt in a few seconds

This method of artificial respiration is useful for patients who become apnoeic while sitting (e g, at the dentist's) and where the patient cannot be put lying down in an extended position

REGRESSION OF SECONDARY CARCINOMA AFTER HORMONE THERAPY

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THE following cases are presented in the hope that similar trials will be made of the methods outlined They are two cases of cancer, the first of the breast, the second of the œsophagus secondary to an epithelioma of the finger What makes them worth reporting is that case 1 survived for five years despite recurrence of metastases after surgical removal of the primary growth, and case 2 recovered to the extent of being able to drive his car for six months after he had appeared moribund

The method of treatment was evolved after I had treated three previous cases of cancer of the breast which had recurred after surgical removal In two of these cases stilbœstrol 15 mg daily was injected and in the third case testosterone propionate 25 mg daily was injected In all three cases there was some initial regression of secondaries, but all three patients died of diffuse secondaries with ascites I then decided to try, in the next case that presented (case 1), the effect of combining œstrogen with androgen therapy This was given in the form of 'Mixogen' (Organon) tablets These appeared to be more effective than either androgen or œstrogen alone, but their effect was also temporary Injections of gonadotropic hormone—'Pregnyl' (Organon)—were then given and were wholly successful in causing regression of the metastases This patient is alive and well after five and a half years

Case 2 was therefore also treated with pregnyl injections, with the temporary but dramatic improvement already mentioned, the patient being able to swallow solid food again as well as to drive his car

Case-reports

Case 1 —A woman, aged 59, was seen on March 10, 1951, with two months' history of a lump in her right breast I referred her to a surgeon, who described the growth as a late stage II carcinoma and amputated the breast on March 22 Histologically the growth was an intraduct carcinoma which in parts had become frankly scirrhous The wound healed well, and the patient was given a course of intensive deep X rays in the following June, consisting of six daily irradiations There was a severe reaction, with some eczematisation of the chest wall She later developed severe myxœdema The reaction subsided, and she remained well until January, 1952, when she developed severe pain in both thighs and legs, chiefly in the right thigh She was considered to have a secondary deposit and had a further course of six irradiations This did not relieve her pain She had now developed the classical symptoms of deficient eyebrows, swollen and coarsened features, thin hair, and a low pitched croaking voice She was put on thyroid gr $^{1}/_{2}$ t d s, together with stilbœstrol 15 mg t d s At this time her general condition was poor and she had lost weight, was bedfast, vomited not infrequently, and was intolerant of the stilbœstrol, which was reduced to 15 mg daily She was maintained free from pain with either methadone ('Physeptone') or pethidine and was given quinalbarbitone ('Seconal') sodium gr $1^{1}/_{2}$ at night The pain became less with the stilbœstrol for four to six weeks and then began to worsen again

At this time her general condition was poor, and she was totally confined to bed again and was feeble and confused Mixogen 1 tablet t d s was substituted for the stilbœstrol *She held her own rather than improved* After six weeks' treatment with mixogen, in December, 1952, she began to bleed per vaginam fairly heavily, despite her age (61) The tablets of mixogen were reduced to one daily, and she was maintained on these until February, 1953, when she began to complain of severe pain in her right shoulder and neck The posterior fold of the right axilla began to swell and ulcerate, and she developed a typical fungating secondary deposit, which became offensive, requiring daily toilet by the district nurse The patient became disoriented and ran a swinging temperature of 101–102°F at night

It was then that pregnyl injections were begun She was started with 100 rat units daily After two days the dosage was stepped up to 1000 rat units daily and kept at this level for a week The patient appeared to be sick because of the injections, and the dose was reduced to 750 rat units daily At first one mixogen tablet was given daily with the pregnyl, but after a week the pregnyl was given alone At the start of the treatment with pregnyl the patient was considered to be in the final stages of cancer, and morphine analogues were given freely After a month of injections, however, the fungating mass had disappeared The patient has almost complete amnesia for this period The injections were stopped after six weeks Two weeks later she developed a severe pain in the region of the distribution of the 6th and 7th cervical nerves on movement, and the pain became so bad that she was referred to hospital During this time she had a further course of pregnyl injections, which lasted three months At hospital she was fitted with a plastic collar, which she wore for four months The second course of pregnyl consisted of injections of 500 rat units each thrice weekly During this period she steadily gained strength She has had no injections of pregnyl since, and is now very well but has to be maintained on thyroid

Case 2 —A tall spare man, aged 66, who had had chronic bronchitis and emphysema for years His blood pressure was 220/110 For ten years he had had, on the little finger of his right hand, a wart which, after being knocked about August, 1954, broke down and ulcerated He kept a leather finger stall on this wound until, visiting him one day, I questioned him about this bandage, whereupon he displayed the finger, which appeared to have an epithelioma over the knuckle of the first joint I referred him to a dermatologist, who confirmed the diagnosis and, rejecting my suggestion that the finger be amputated, prescribed a radium collar There was, unfortunately, some delay in admitting him to hospital, but he was admitted in October, 1954, treated, and discharged at the beginning of November The local condition apparently healed but almost from the time of his coming home the patient had difficulty in swallowing, and this dysphagia steadily increased until he could take only sips of fluid, and he rapidly wasted and became cachectic His general condition now was poor, he had lost more than a stone in weight and was obviously failing rapidly He had a profound aversion to hospital, and there was *little I could do but call* out a consultant to decide whether he had indeed a carcinoma of the œsophagus This was done, and the patient was taken into hospital for a barium swallow This upset him very much because he could not swallow the barium, which regurgitated, he was also upset by the hospital routine When his wife visited him in hospital she was so upset by his rapidly worsening condition that she insisted on my getting him out of hospital immediately so that he could, as she said, die at home

This was accordingly done, and pregnyl injections were begun immediately Enemas were given to clear his loaded bowel After two weeks of daily injections of 500 rat units he began to swallow more easily, and the nausea lessened On his return from hospital he was so weak that he could scarcely move in bed, his dysphagia was almost complete, and he was incontinent Now he could take a fair amount of fluid in small sips He was given injections of pregnyl 750 rat units thrice weekly, and his capacity to swallow improved until, at the end of a month, he was taking two pints daily of meaty fluids (Armour's peptone, 'Bovril,' and similar fluids) About this *time it seemed reasonable to decide whether or not he* had a carcinoma of the œsophagus, and Mr J A Aylwin was called in consultation to decide whether it was possible to pass an œsophagoscope Since the patient resolutely refused to become an inpatient, Mr Aylwin took him in for the day only, passed the œsophagoscope, and took a biopsy specimen, which proved the presence of a squamous epithelioma of the œsophagus The patient steadily improved to the point that he could go out for walks on his farm and drive his car alone, and for six months he could swallow solids again About October, 1955, his condition began to deteriorate He was still getting injections of pregnyl but was very intolerant of them, they gave him a severe headache and made him go partially blind for a while For a time he refused point blank to have them, and it was only by telling him that he had a cancer that I could continue the treatment He died on Jan 10, 1956, having had about a year after he had been brought home to die

Discussion

Hormone therapy in inoperable or recurrent breast cancer is established, since Loeser (1940) initiated treatment with testosterone It was followed up by Adair and Herrmann (1946), among others, who have confirmed its temporary benefit Haddow et al (1944), Nathanson (1947), and Stoll and Ellis (1953) attempted to depress pituitary function by giving massive doses of œstrogen to inhibit ovarian secretion Huggins (1952), working on the assumption that the suprarenal glands may secrete a hormone which reactivates tumour growth, was the first to do bilateral adrenalectomy and oophorectomy, and Cade (1955), among others, reported favourable results of this combined operation in late carcinoma of the breast

The procedure outlined above has the merit of simplicity, but injections of *gonadotropic hormone* are not without danger The patient may become very intolerant of the injections, which probably have an inhibiting effect on the pituitary gland and cause it to atrophy, just as injections of insulin may cause atrophy of the islets of Langerhans

Though a five-year period of freedom from secondaries is not necessarily synonymous with recovery, the unusual feature of case 1 is that, despite *the clear and* successive emergence of secondaries throughout nearly two years, there seems to be no reason to doubt that the succeeding three and a half years' freedom from secondaries is due to the treatment she has had The growth was fairly advanced to begin with and had all the stigmata of a fatal carcinoma, yet the patient has survived and done well. Whether this degree of recovery is due to stilbœstrol, mixogen, or pregnyl, or a mixture of all three, at least it gives some sort of lead for further investigation

Although case 2 died, the remarkable if comparatively short-lived improvement suggests two things (1) cancers other than those of the breast and the prostate gland may be susceptible to hormone therapy, and (2) the effect of the pregnyl injection appeared to be equivalent to that of a surgical operation, for in both cases there appeared to be an equal degree of regression of the growth followed in 1 case by recurrence and death

Summary

Two cases are presented of cancer one of mammary carcinoma involving axillary lymph nodes, and one of constricting carcinoma of the œsophagus The first patient is alive and well five and a half years after operation despite recurrences The second patient improved temporarily after treatment with pregnyl but subsequently died

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VAGITUS UTERINUS

CRYING IN UTERO

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THE word "vagitus" is derived from the Latin *vagire*, to squall, and is used by many writers including Pliny, Virgil, Quintilian, and Ovid, nearly always alluding to the cry of the newborn The historical background has been well reviewed by Ryder (1943), who found 122 well authenticated cases up to 1943 He surmises that physicians in the Middle Ages were loth to report cases for fear of religious persecution One might add that any midwife associated with such events might even have been accused of witchcraft

Case-history

A primipara, in good health throughout pregnancy, was admitted at term to Victoria Hospital Sidmouth, at 1 P M on Sept 10, 1952 The membranes had ruptured but no pains had been felt Even after castor oil an enema and then oxytocin, progress was slow The os was fully dilated at 8 45 A M on Sept 13 when a breech presentation was discovered The second stage was very long apparently because the legs were extended

At 2 30 P M, under nitrous oxide, oxygen, and ether, a deep episiotomy was done and a hand passed into the uterus to bring down a leg During this manœuvre a baby s cry was heard quite clear and coming from the mother s abdomen Dr Gibbens whose case this was describes it as a clear remote cry very like a baby crying in the next room but close below our heads It was heard by all three doctors present There was no other baby in the labour ward The sister was out of the labour ward at the time and on her return a few few moments later she was told that she had missed the chance of hearing a baby cry in utero However at that moment the baby gave another cry clearly audible to all in the room, and I had time to put my ear on the mother s abdomen and confirm beyond any doubt that it was the unborn baby that was crying in utero

Both legs were brought down and the aftercoming head extracted with forceps somewhat more rapidly than is usual because it was felt that the baby might drown in its own liquor He weighed 7 lb 2 oz and was a little limp at birth but he cried well after the air-passages had been cleared

The first stage lasted about sixteen hours, the second six, and the third one The child is now 4 years old and thriving

Discussion

Authenticity —Probably no one who has heard the cry can doubt its reality To dismiss it as merely a cry during the act of birth is absurd since in many cases the patient was not even in labour, and in the present case, as in Jackson's (1943) the head was in the fundus uteri There is no need to invoke "a vibrating fold of mucous membrane" suggested by some authors quoted in the *British Medical Journal* (1912)

In the light of Barcroft's (1946) famous work on fœtal respiration the occurrence of vagitus is more easily understood and need not surprise us As Barclay, Franklin, and Prichard (1944), whose studies were based on fœtal lambs have put it "the first breath of life is the culmination of over a hundred days of intra-uterine rehearsal and preparation" It is perhaps surprising that premature respiration does not occur more often

Conditions —Kitzmiller and Mitchell (1942) say that three conditions should be fulfilled

(*a*) The membranes must have ruptured

(*b*) There must be some operative manipulation or asphyxia to stimulate the infant

(*c*) Air must enter the uterus

In Parviainen s case (1949) the cry was heard during the version of twins, and in Morton s (1924), during the application of forceps Crotty and Kuehnle (1948) had a somewhat similar episode with twins and prolapse of the cord when using caudal analgesia

In Fraser's case (1943) a whimper was heard while the mother was being washed, and made louder by "gentle external prodding" An air-bubble was demonstrable in utero by percussion and a splash Labour started thirty hours later, the child died after three hours In Field's (1943) case, air could be heard being sucked in through a Drew Smythe catheter during induction A cry was then heard, but labour did not start for fifty-four hours After delivery expression of the placenta was accompanied by expulsion of air from the vagina The baby cried at birth

Clinical Features —In the cases published, the child's cry is often strikingly loud, and usually heard by all present, not least the mother (Mitchell 1944) In one of the cases described by Brodhead (1914) it was even heard by another woman in an adjoining room In Allard s case (1912) the nurse referring to the unborn infant, remarked with true Gallic insight, "*On voit bien qu'il s ennuie, il pleure*" The mother asked her husband what it was that made such a noise!

It is remarkable that the child is often none the worse even though labour may not start for many hours as in Field s case One might suppose that the child would probably drown in utero but this rarely happens Stoeckel (1938) says that 8 out of 58 (14%) were stillborn Ryder's figure is 21 out of 112 (19%), which he attributes to over-hasty manœuvres to deliver the baby Ryder's view is probably correct, and in our case efforts to deliver the baby were undoubtedly unduly hurried, because we then knew less about the subject

Little has been recorded about the extent of aeration of the lungs even in fatal cases Presumably it is patchy, leaving a vital amount of lung tissue to expand in the ordinary way after birth, otherwise one would expect a higher mortality from drowning.

Summary

A case of vagitus uterinus is described and the literature reviewed. Birth trauma from over-hasty attempts to deliver the baby is a bigger danger than drowning in utero.

I am greatly indebted to Dr. Gerald Gibbens, of Sidmouth, for his collaboration and notes on the case.

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Preliminary Communication

SENILE CONFUSION AND THE BLOOD-SUGAR LEVEL

In elderly diabetics with cerebral arteriosclerosis the biochemical and clinical findings do not always tally.[1] In 3 of the 5 cases recorded here, attacks clinically resembling those of hypoglycæmia were associated with a relatively high blood-sugar; and in 4 of these 5 cases mental deterioration was arrested or reversed when hyperglycæmia was deliberately permitted.

CASE-HISTORIES

Case 1.—A retired nurse, aged 89, had diabetes mellitus recognised in 1948. On Jan. 29, 1951, her pre-lunch blood sugar was 200 mg. per 100 ml.,[2] with glycosuria. Next day, because of a mild respiratory infection and mild mental confusion, her daily dose of 30 units of insulin (protamine zinc and soluble) was supplemented by 20 units of soluble with 100 g. glucose. On Feb. 1 confusion proceeded to coma, with bilateral extensor plantar responses. Despite glycosuria and a raised blood sugar (it proved to be 160 mg. per 100 ml.), clinical hypoglycæmia was diagnosed, and striking improvement followed administration of glucose (100 g. by Ryle's tube and intravenous infusion of glucose and physiological saline solution). Withdrawal of her insulin did not produce ketosis, and her condition—general and mental—improved so much that during the next few months she pottered round the ward, taking a great interest in the nursing. In October, 1951, she was again put on insulin (12 units protamine zinc) and her condition remained satisfactory; but her activities dwindled until she died in 1955 of bronchopneumonia following fracture of a femur. Necropsy showed generalised arteriosclerosis but no additional pancreatic or other lesion.

Case 2.—A widow of 70, who was very alert, was admitted with symptoms of diabetes mellitus and ulcers of her legs due to pemphigus vulgaris. Her blood sugar after breakfast was 641 mg. per 100 ml. She was given a diet low in carbohydrate, and increasing doses of insulin. Alarming torpor developed twice and on both occasions was relieved by oral glucose, though on the first the blood sugar had been 265 mg. per 100 ml. She died soon afterwards with aspiration pneumonia. Necropsy showed cerebral and other arteriosclerosis and a small flabby pancreas.

Case 3.—A housewife aged 74, who had been given insulin (20 units of soluble and protamine zinc daily) for four months for diabetes, was admitted after a behaviour change; she had twice tried to set fire to the house. She was uncooperative and confused, but her normal mental state returned at once when she was given intravenous and oral glucose, though the blood sugar before treatment had been 315 mg. per 100 ml. No more insulin was given and her general condition improved though the blood sugar remained around 500 mg. Nine months later she died from pulmonary oedema after infarction of the right cerebral hemisphere. Necropsy showed generalised arteriosclerosis and a decrease in pancreatic islet tissue.

Case 4.—A spinster aged 62 had had diabetes for four years treated by diet and soluble insulin, 60 units daily in divided doses. She was transferred to hospital from a welfare home with a gangrenous ulcer of her right leg, where the pulses were absent from the foot. The same diet and insulin dosage were continued. Three weeks later she had an episode of giddiness and incoherent babbling which was attributed to a minor cerebrovascular accident in the right hemisphere. For several weeks she was incontinent and miserable and did not speak. Her mid-morning blood sugar at this time was about 180 mg. per 100 ml. Insulin was withdrawn and carbohydrate restricted; her corresponding blood sugar increased to over 320 mg. Gradually she became more alert and continent, and it was found that she was supplementing her diet with sweets, which she insisted that she needed; she was persuaded to accept extra dietary starch instead. Nine months after admission she was so much better that operation for her cataract was deemed worth while. She continued to improve and was active till she was immobilised by a patch of gangrene which made amputation necessary.

Case 5.—A spinster of 62 had behaved oddly since a cerebrovascular accident four months earlier. She had been given insulin for a short period for mild diabetes. Her condition was static and she was admitted to hospital, making agitated gestures and unintelligible sounds. Preprandial blood sugars were below 200 mg. per 100 ml. Her carbohydrate intake was increased till the corresponding blood sugars were over 400 mg. Within a week she began to respond to encouragement and she was able increasingly to make herself understood. Finer movements returned to both hands. This very satisfactory progress has been maintained up to the time of writing.

DISCUSSION

In cases 1–3, disturbance of consciousness typical of hypoglycæmia and responding to glucose was seen at capillary blood sugar levels of 160, 265, and 315 mg. per 100 ml. It is unlikely that the blood-sugar was lower shortly before these determinations (e.g., in case 1 an extra 100 g. of glucose had been given at 8 A.M. on the day of her attack) or that glucose relieved cerebral oedema from some other cause. Transient cerebral anoxia is difficult to exclude absolutely, but there was no apparent cause for it. Fabrykant and Bruger[3] pointed out that the clinical symptoms recognised as the hypoglycæmic reaction are merely an expression of disturbed brain function which is common to many reactions including cerebral anoxia.[4] Focal cerebral disturbance associated with and following hypoglycæmia has been clearly described.[5] It has recently been emphasised that the surest confirmation of the hypoglycæmic nature of an attack lies in its response to glucose[1]; and, though Post[6] refers to relief of non-specific senile confusional states by the infusion of glucose, he says that the reason for it is not clear.

Himwich[7] attributes the infrequency of hypoglycæmic reaction in babies with subnormal blood-sugars to a lower local metabolic requirement than in adults, and, referring to this, Fabrykant and Bruger[3] suggest an opposite state of affairs in adults, where, with normal blood sugar values, the supply of sugar to the brain may be less than is needed. What may be more important in the former is the relatively high cerebral blood-flow early in life[8] which will ensure adequate glucose delivery despite the low concentration. This state of affairs contrasts strongly with that governed by the precarious cerebral circulation of the aged arteriosclerotic subject.[9] Himwich[10] elsewhere has shown that oxygen utilisation in the brain depends on an adequate supply of glucose, the mediation of insulin not being required in this situation.

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[1] *Lancet*, 1956, i, 618.
[2] All glucose determinations were made according to the method of Folin and Wu, using capillary blood.
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These case histories suggest that in the elderly diabetic with arteriosclerosis, and consequently reduced blood-flow, cerebral metabolism may become adapted to a supply of glucose in higher concentration than normal, and may be disturbed (in some cases irremediably) by reduction of the blood-sugar to normal. It is as though glucose in supernormal concentration may permit a higher level of cerebral metabolism, albeit perilously, than the reduced cerebral blood flow (and therefore oxygen supply) can otherwise support. Thus, though hyperglycæmia may do harm in other parts of the body, the optimal blood-sugar level in the *brain* of the arteriosclerotic diabetic may be higher than normal, and this will often be an overriding therapeutic consideration. The potential danger of aiming at chemical normality[11] is nowhere greater.

Cumulative cerebral disorganisation can take place without definite episodes as a result of slight but repeated or long continued deficiency of glucose in the brain. The trend of events in cases 1, 3, and 4 suggests that in the elderly arteriosclerotic diabetic this may happen with a normal or even a high level of blood-sugar, and that such mental deterioration may be reversed by letting the blood sugar rise. In case 5 advantage was taken of the patient's mild diabetes to ensure a hyperglycæmic state which appeared to improve recovery from a cerebrovascular accident. Ketosis must of course be avoided.

We might expect hyperglycæmia to improve cerebral metabolism similarly in the non-diabetic patient with reduced cerebral blood flow, and we have ourselves obtained encouraging though temporary clinical improvement, substantiated by electro encephalographic record, with continuous intravenous infusion of glucose in non-diabetic cases of senile confusion. We delivered directly into the great veins, by 'Polythene' tubing, 3 or more litres, according to circulatory or renal fluid tolerance, of 10% glucose in the twenty four hours. 3 litres a day is more than Post recommends, but other workers[12] have found that this rate and concentration produce no significant dehydration.

This measure may help in cerebral disturbance associated with short lived hypoxic states of remediable circulatory or respiratory origin. Oral administration of equivalent amounts of carbohydrate to non-diabetic subjects with arteriopathic mental change has been less promising, probably because it has not produced sustained hyperglycæmia. When one wants to maintain a high blood sugar for longer than can reasonably be done by continuous glucose infusion, it would be rational to use glucagon, corticosterone, or even somatotrophic hormone; work on these lines is planned.

My thanks are due to Lord Amulree for his encouragement and help and for permission to publish the cases, and to the laboratory staff of University College Hospital, London, for the blood sugar estimations.

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Reviews of Books

An Outline of Bacteriology and Immunity

RONALD HARE, M.D., professor of bacteriology in the University of London, and honorary consulting bacteriologist at St Thomas's Hospital. London: Longmans, Green. 1956. Pp. 418. 35s.

ONE difficulty about teaching bacteriology to medical students is that the wider implications of the subject are often lost by emphasis on the diagnostic methods. The precise identification of bacteria and viruses is extremely important, but easy familiarity with all the technical processes is beyond the scope of an undergraduate training in medicine. Nevertheless this aspect is precisely that on which students and teachers alike are inclined to concentrate—the student because his textbooks emphasise it, the teacher because it is his daily work. In fact, the important thing is that the student should gain a clear idea of how infection spreads and of how the human body can be helped to resist the invasion of disease-producing *microbes*.

Professor Hare has done a real service by writing a book for students that is neither too long nor too costly but gives its greatest emphasis to such important subjects as virus diseases, epidemiology, and immunity. The chapters on immunity offer a particularly clear and interesting presentation of a subject that students often find difficult; chapter 6, on the host-parasite relationship, is notable for its wide range and stimulating approach. The illustrations are well above average quality for books of this kind. Students who use Professor Hare's text will be well able to meet their examiners and will gain some idea of what attracted their teachers to bacteriology. Altogether the book may be warmly commended.

Lymphatics, Lymph and Lymphoid Tissue

2nd ed. **JOSEPH MENDEL YOFFEY**, M.D., F.R.C.S., professor of anatomy, University of Bristol; **FREDERICK COLIN COURTICE**, D.PHIL., D.SC., F.R.A.C.P., director, Kanematsu Memorial Institute of Pathology, Sydney Hospital, Sydney. London: Edward Arnold. 1956. Pp. 510. 60s.

THIS volume is the third in succession to C. K. Drinker and M. E. Field's *Lymphatics, Lymph and Tissue Fluid*. The new edition is based on wide reading and the authors' own experiments.

The use of isotopes has confirmed and slightly extended previous knowledge about electrolyte exchanges through capillary membranes. Radioactive colloids have provided clues to the passage of particles through the bronchial tree, and electrophoresis has given more detailed information of the proteins and lipoproteins in lymph. Experiments with the war gases have extended knowledge of altered capillary permeability. Many knotty problems are still with us—for example, the hypothetical pores in vascular and lymphatic endothelium through which particles are able to pass. Some will deplore the continued use of the phrase "tissue space" for intercellular substance. Credit should be given, but is not, to W. H. Gaskell (*Ludwig's Arbeiten*, 1876, 11, 43) for resolving the puzzle of the opening of lymphatic channels in *œdema* when hydrostatic pressure outside them is greater than within. Discussion of the state of affairs in local urticarial and angioneurotic œdema would be welcome.

The intractable problem of the function of lymphocytes is discussed very fully. Since the view now finds support that plasma cells rather than lymphocytes are a source of antibodies, the lymphocyte is again left without apparent function. The reasonable opinion is adopted here that lymphocytes are important not for what they do but for what they develop into. On morphological grounds and making use of quantitative data the conclusion is reached that lymphocytes are continuously supplied to marrow. Only thus is it possible to account for the numerical output of red and white blood corpuscles, for which inadequate numbers of primitive blast cells are found in marrow. Lymphocytes, micromyeloblasts, and pro erythroblasts are here regarded as morphologically *indistinguishable*. This unitarian view of the origin of blood cells will enliven many old controversies

The Physiology and Biochemistry of Lactation

S J Folley, d sc, ph d, f r s, head of the physiology department, National Institute for Research in Dairying, Shinfield, Reading, Berks Edinburgh Oliver & Boyd 1956 Pp 153 18s 6d

This book is substantially a translation of the original French edition which was based, with little alteration, on a series of lectures given by Dr Folley at the Collège de France in 1953 It is the first work in English devoted to the subject of lactation Dr Folley and his co-workers, by their chemical and metabolic studies, are responsible for much progress in this subject

The book deals first with factors in the normal development of the glands postnatally and goes on to consider the initiation of milk secretion Dr Folley contends that development and lactogenesis are a response to the action of more than one hormone and that the endocrine glands supply a complex and delicately balanced dynamic equilibrium which may centre round the anterior pituitary and also depend on central nervous activity Only in the presence of this equilibrium is the whole process of lactation possible This argument is developed in the section on initiation and inhibition of milk production There is good evidence in man and animals that oestrogen and progesterone act synergistically in these processes and that the end result—initiation or inhibition—is determined by the absolute and relative amounts of these substances released In chapter 3, dealing with the maintenance of lactation, or galactopoiesis, it is pointed out that until we know the mechanism of this we cannot know whether hypogalactia is due to failure of lactogenesis or of galactopoiesis Dr Folley next surveys the mechanism of suckling and milking and the neuro endocrine control of the myoepithelial cells, then in the last two chapters deals with the biosynthesis of the solid constituents of milk This last section brings out interesting species differences thus, non ruminants can easily utilise glucose for the synthesis of fats, whereas ruminants such as the sheep must start from acetate From this it follows that the importance to milk formation of hormones such as insulin varies from species to species

This is an important and useful book

Lesions of the Cervical Intervertebral Disc

R Glen Spurling, m d, professor of neurosurgery, University of Louisville, Kentucky Springfield, Ill Charles C Thomas Oxford Blackwell Scientific Publications 1956 Pp 134 36s

Professor Spurling describes this monograph as an account of his personal philosophy and practice on the subject of cervical-disc lesions, but it also contains a very comprehensive account of the anatomy, pathology, and clinical features of protrusions in this region

The diagnosis and localisation of the lesion is fully considered and effectively illustrated There is a detailed description of the technique of cervical myelography, but the accompanying radiographs are far from convincing The indications for, and the results of, surgical treatment of cervical disc lesions are based on a personal series of 197 private cases, of which 61 were treated surgically The results of both conservative and operative treatment are analysed, and there is an excellent account of the surgical procedures

The book, which is attractively written and beautifully produced, is a worthy companion to Dr Spurling's earlier monograph on lumbar-disc lesions

Freud and His Time

Fritz Wittels, m d, *formerly instructor at the* New York Psychoanalytic Institute London Peter Owen 1956 Pp 451 42s

The publisher does not indicate on the title page or elsewhere that this book was first published twenty years ago, but the reader becomes aware that the world for which the author was writing is not the one we live in It is difficult to see any central theme in the book it begins with Goethe's influence on Freud, it ends with a chapter entitled Einstein and Freud which discusses masochism in Indian philosophy, sadism and masochism in civilisation, 'our hurt narcissism," and the rights of man As a commentary on the Freudian doctrine, the book is too discursive to command contemporary attention

Tredgold's Textbook of Mental Deficiency (9th ed London Baillière, Tindall, & Cox 1956 Pp 480 40s)—First written in 1908 by the late A F Tredgold, this became and has remained, the standard English work on the subject In the past half century Tredgold's views on the neuropathic diathesis and the major influence of heredity in mental defect have been accepted rather uncritically, and consequently little attention was paid until recently *to social and* environmental causes or to the distinction in children between mental defect and mental disorder Dr R F Tredgold and Dr *Kenneth Soddy* have now rewritten much of the book The classical clinical descriptions have been retained, but a new chapter on Disorders of Relationship Formation contains interesting case histories which show the distinction between psychosis and amentia in childhood The book, nevertheless is in a difficult transitional stage, the old and the new material being separated by a generation Some of the illustrations are rather dated, and the rather sketchy drawings of abnormal brain cells should be replaced by photomicrographs The chapter on pathology would benefit from the inclusion of more modern material The omission of the chapter on the law relating to mental deficiency, because of impending changes, may leave the reader with an impression that feeblemindedness is a definite entity irrespective of its legal definition The same applies to the lack of a chapter on mental testing and its problems We hope that for the tenth edition the rewriting of this important work will be completed

New Inventions

A NEW SUPPORT FOR THE BOYLE-DAVIS GAG

This support fulfils the requirements of simplicity and ease of adjustment It may be made in any small workshop from materials usually available It consists of a length of $^{3}/_{16}$-inch steel rod bent to the shape shown (fig 1), the legs are 50 cm long, and the top cross piece 5 cm long A small stud is welded on to the cross piece *and angled slightly* A leather strap, with the usual holes enlarged and multiplied if necessary, completes the support The ordinary buckle of the strap is used to accommodate the hooked end of the Boyle-Davis gag Stability is ensured if the legs of the support are pressed close to the patient's shoulders and directed slightly backwards (fig 2) The length of the support enables it to be used for both adults and children

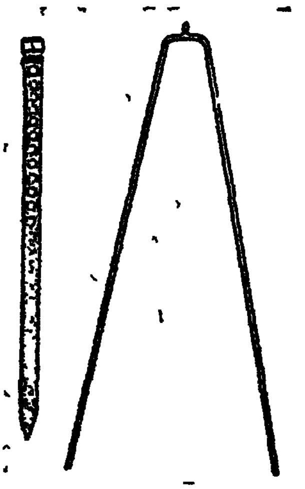

Fig 1

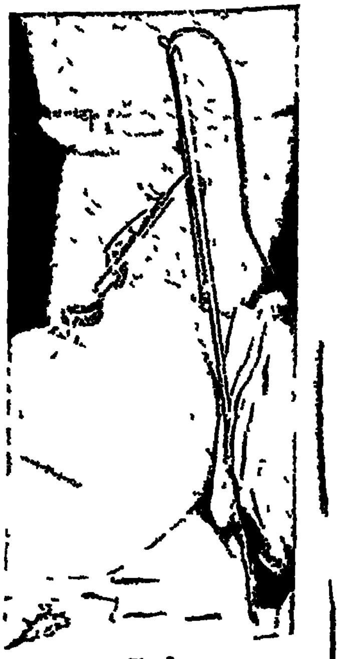

Fig 2

I wish to thank the Director-General of Medical Services, Royal Air Force, for permission to publish, and Warrant Officer W J Salzer, chief radiographer, for the photographs

Royal Air Force Hospital,
Wegberg, *Germany*

A J Merrifield
m b Lond, f f a r c s

THE LANCET

LONDON SATURDAY, JAN. 19, 1957

Coronary Disease, Serum-lipids, and Thyroid Hormones

THREE months ago there appeared an account of one of the most ambitious cooperative experiments ever devised[1] Organised by two committees of the United States National Advisory Heart Council, it was designed to examine the value of serum-lipid estimations in predicting clinical coronary-artery disease, and one type of lipid measured was the serum total-cholesterol It is well known that patients with clinical evidence of coronary-artery disease have, on the average, higher serum-levels of cholesterol than do unaffected persons of the same age and sex—a fact which has been demonstrated in many parts of the world, including Britain[2] In all such studies the clinical manifestations preceded the serum-cholesterol estimation, and it remained arguable that the raised serum-cholesterol might have been in some way a result of myocardial infarction rather than a cause of the underlying atherosclerosis Moreover, in these retrospective surveys, there has always been a large amount of overlap between the serum-cholesterol levels of the control and atherosclerotic groups, and this has led to many attempts to measure lipids by more refined methods Since serum total cholesterol showed a definite, but imperfect, correlation with atherosclerosis, it seemed a reasonable guess that some fraction might show a closer correlation Cholesterol is carried in serum in lipoprotein complexes, and these were fractionated by one of three methods Thus, RUSS et al[3] used Cohn fractionation, and (among many others) OLIVER and BOYD[4] used paper electrophoresis, in order to separate α and β lipoproteins In both instances serum-β-lipoprotein levels tended to be higher in those who had had a coronary infarct The difference between the two groups was possibly a little greater than when total cholesterol alone was estimated but even so there was a great deal of overlapping The third method of lipoprotein analysis was devised by GOFMAN and his colleagues[5] in the Donner Laboratory of the University of California The essential feature of their technique has been the use of the analytical ultracentrifuge, with control of the density of the medium by addition of salt solutions Under these conditions lipoproteins tend to float to the surface, according to their density and can thus be graded by their position in the tube To describe the results obtained by this technique the Donner group devised a new notation of Svedberg flotation (S_f) units Statistical analysis of a large series of patients with coronary disease and comparison with controls[6] showed that the S_f 12–20 group of lipoproteins was most closely associated with clinical manifestations Later work at the Donner Laboratory[7] led to technical modifications involving a change of scale to correct for the effects of concentration on flotation rates which had not been appreciated before Thus corrected, the "standard flotation-rates" are measured in S_f units From the revised values an "atherogenic index" (A.I.) was calculated in which the values for several flotation classes were combined in specified proportions to give a single figure

The combined committees of the National Advisory Heart Council (on which the Donner group was represented) set out to investigate these claims, and to determine whether serum-lipid levels were capable of predicting the onset of clinical coronary-artery disease It was an enormous undertaking four laboratories in different parts of the United States cooperated in some 15 000 serum-lipid analyses About two years were spent in securing agreement between the analytical results in the four laboratories Discrepancies in the values for serum total-cholesterol levels seem to have caused more trouble than the results of the more elaborate ultracentrifuge work. 4914 men aged 40–59 were then selected in different parts of the country, they had undergone a rigorous examination and been pronounced normal These men were followed for from one to two years, and during this time clinical evidence of disease of the coronary arteries developed in 82 of them The doctors who assessed their clinical state had no knowledge of the serum-lipid values In three of the laboratories it was agreed that the serum total-cholesterol level, on the whole gave better predictions of the likelihood of developing clinical manifestations of coronary-artery disease than either the S_f 12–20 or the S_f 20–100 lipoprotein classes but the Donner group were not able to accept this finding, and they state their reasons in an appendix to the main report It is a pity that this vast project, carefully planned and conscientiously executed, should end in a sort of stalemate over the interpretation of the results To the outside observer it seems evident that both serum-cholesterol and various figures derived from ultracentrifuge analysis have some value in assessing liability to overt coronary disease, but they do not predict the fate of an individual with any certainty Since the experts cannot decide which method is the most helpful in this respect it is reasonable to conclude that there is probably little to choose between them, save that S_f measurements require the very expensive ultracentrifuge and so are possible in only a few laboratories

There is no doubt that the serum-lipids are abnormal in some people who will shortly have a cardiac infarct or show other signs of coronary atherosclerosis At first sight, it seems an obvious precaution to try to lower the serum-lipid level in the hope of preventing or postponing these events, and various attempts have been made, using, for example, sitosterol, unsaturated fatty acids, or stilbœstrol **Oliver** and **Boyd**[8] have lately given evidence of the way in which certain hormones can influence cholesterol and lipid metabolism, and Professor **Gofman** and his colleagues, in an article on p 120, now amplify their suggestion[9] that thyroid extract might profitably be used in this way They gave it to 60 schizophrenic patients for a hundred and five weeks, starting with 3 grains and gradually increasing to 5 grains daily If they were using *U S P* dried thyroid, these doses would be equivalent to 6 and 10 grains daily of *B P* dried thyroid 39 patients completed this strenuous course (which seems to confirm the view that schizophrenics are unusually resistant to thyroid) There was an undoubted decrease in serum-cholesterol levels and in the level of all the S_f fractions measured and the atherogenic index fell considerably These changes persisted throughout the long experimental period, and there was no tendency to "escape," as had been observed by **Gofman** et al in an earlier experiment with a fixed dose of thyroid extract This supports their contention that, in experiments like this, it is necessary to make gradual increases in dose In the early stages the patient's own thyroid gland is adding substantially to the exogenous material, later the gland is inhibited, and any action is due entirely to the outside supply The biggest falls in total cholesterol and lipoprotein fractions and in the atherogenic index were observed in those patients who had the highest initial levels As the result of their inquiries, Professor **Gofman** and his associates suggest that thyroid extract is worth considering as a prophylatic agent against coronary heart-disease

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[1] *Circulation* 1956 14 691

[2] Oliver M F Boyd G S *Brit Heart J* 1953 15 387 see leading article *Lancet* 1955 ii 1123

[3] Russ E M Eder, H A Barr D P *Amer J Med* 1951 11 468

[4] Oliver M F Boyd G S *Brit Heart J* 1955 17 299

[5] Gofman J W Lindgren F Elliott H Mantz W Hewitt J Strisower, B Herring V *Science* 1950, 111 166

[6] Jones H B Gofman J W Lindgren F Lyon T P Graham, D M. Strisower, B Nichols A V *Amer J Med* 1951 11 358

[7] Glazier F Tamplin A Strisower B de Lalla O *Physiol Rev* 1954 34 [illegible]

An obvious disadvantage of thyroid extract is its capacity to raise the basal metabolic rate (B M R) as the serum-cholesterol level falls The work of the heart would thus be increased and patients whose coronary arteries were already narrowed might be much worse The observations of **Lerman** and **Pitt-Rivers**[10] pointed to a possible line of escape from this dilemma in 2 cases of myxœdema, treatment with the acetic-acid analogue of triiodothyronine (triac) produced a substantial fall in blood-cholesterol without detectable change in the B M R These results raised hopes that triac might control the blood-cholesterol level in euthyroid subjects without adding to the burden on the heart A tentative trial by **Trotter**[11] showed that it was sometimes feasible, by carefully grading the dose of triac, to lower the blood-cholesterol of patients with coronary disease without materially increasing the B M R On p 124 Dr **Oliver** and Dr **Boyd** describe further experiences with triac They confirmed that with suitable graded doses the blood-cholesterol could often be reduced (though it later tended to "escape") without increasing the B M R But in 2 of their atherosclerotic patients attacks of angina developed although the B M R did not increase This suggested to them that triac might increase cardiac metabolism, even without an increase in total metabolism as reflected by the B M R It seems, therefore, that triac is not likely to be any more or less useful than other forms of thyroid hormone for this purpose Other chemical variants of the thyroxine molecule may have more desirable properties, but the present evidence suggests that if this type of prophylaxis is to be contemplated at all, ordinary thyroid extract is probably better than any other preparation

The Donner Laboratory group have no doubt already set out to determine whether the administration of dried thyroid extract does actually prevent the clinical signs of coronary-artery disease, and many people will be wondering whether similar large trials should be started in this country The balance of evidence suggests that the results would be unlikely to justify the enormous effort involved There are two ways in which such a trial might be conducted

(1) A large number of healthy men of a susceptible age-group could be selected and half of them given thyroid extract The difficulty here would be mainly one of scale, for though the accumulated morbidity and mortality from coronary-artery disease is high, the annual attack-rate is relatively low It would be necessary, therefore, to observe an enormous population for a fairly short time, or a smaller population for a longer period In either case it would be hard to ensure that the thyroid extract was, in fact, being taken regularly

(2) Patients known to have coronary-artery disease could be given thyroid extract to see whether it would prevent further episodes of coronary insufficiency This plan would be easier, but it would call for very careful clinical observation, because thyroid extract may aggravate the symptoms of angina This type of experiment implies that thyroid extract has something of a curative as well as a prophylactic action in atherosclerosis

The effort needed to launch and sustain either type of trial on an adequate scale would be justified if there seemed a reasonable prospect of helpful results, but at present the picture is not encouraging In the first place, it is still far from certain that a raised level of either cholesterol or any other lipid in the serum is a direct cause of atherosclerosis or coronary infarction Certainly there is some connection, but in view of the relatively poor correlation in individuals between the biochemical and clinical events, as recorded by the two American committees, it may well turn out to be a second-order or indirect relationship Though it is probably a good thing to lower serum-lipid levels, there are several other ways of doing so (for example, changes in the diet) which would be safer than large doses of thyroid extract to a patient whose coronary arteries are already damaged Nevertheless, further news of research along these lines will be eagerly awaited

Reflux Œsophagitis

Normality is precariously balanced at the junction of stomach and œsophagus, if one thing goes wrong, other difficulties ensue, and achalasia of the cardia illustrates the point Surgical relief is often followed by œsophagitis, and in the experience of **Brewer** et al,[1] in New York, œsophagitis is commoner after operations which interfere with the junction, such as cardioplasty or œsophagogastrostomy Of 15 patients treated thus for achalasia, 11 ultimately had œsopha gitis, some with stricture as compared with 2 out of 13 treated by Heller's myotomy alone (follow-up was however shorter in the myotomy group) Reflux of gastric contents into the œsophagus after distortion or destruction of the cardia is thought to be the cause of failure, and yet SWEET,[2] who used in 21 patients a form of œsophagoplasty[3] similar to the cardioplasty performed at the New York Hospital found only 4 whose symptoms were not relieved in a follow-up period of three to twelve years, stricture developed in only 2 patients in this group, and 2 required gastric resection for hæmorrhage due to gastritis SWEET, however, recognises two forms of achalasia one in which an atrophic muscle layer is present in 75% of cases and which is suitable for the plastic operation, and another in which there is thickening due to hypertrophy of the circular muscle-fibres and which is curable by Heller's myotomy Already one of the causes of difficulty and confusion is apparent—namely, terminology—for what SWEET calls œsophagoplasty includes a longitudinal incision, sewn up again "circumferentially," or transversely, "the lower limit of which must be at or just distal to the cardia"[3], though it is not implied in the terminology, disturbance of the cardia must take place and may give rise to reflux WOLF et al[4] have indicated the further confusion that arises from the terms "peptic œsophagitis" and "peptic ulcer of the œsophagus" and, though they have tried to adhere to the classification derived from the work of ALLISON and of BARRETT, they have added yet another term—"marginal œsophagogastric ulceration" Meanwhile, MARCHAND has pointed out that there is nothing specific about the irritant which produces the symptoms of regurgitation dyspepsia, the reflux of gastric contents may contain irritants, in the form of acid, bile, products of partial digestion, and pepsin itself[5] In MARCHAND's view it is the persistence of reflux that leads to œsophagitis, "peptic" therefore seems an inappropriate prefix, and "reflux œsophagitis" is preferable since it is more inclusive

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[8] Oliver, M F Boyd G S *Lancet* 1956, ii, 1273
[9] See *Ibid*, 1956 i 896
[10] Lerman J, Pitt Rivers R *J clin Endocrin* 1955 15 653
[11] Trotter, W R *Lancet* 1956, i, 885

[1] Brewer McH S, Barnes, W A, Redo S F *Ann Surg* 1956 144 823

Another result of MARCHAND's work has been further to dispel the *idée fixe* that associates hiatus hernia with œsophagitis Though the two commonly occur together it is not always so, many changes can promote regurgitation and doubtless they act together in a complex way Rise in intra abdominal pressure is one, MARCHAND found that 182 of 250 pregnant women who were interviewed one week before delivery had had heartburn during pregnancy, though only 3 had had this symptom before All symptoms ceased after delivery, and in 20 of 78 primigravidæ heartburn was relieved during the final month, presumably by the descent of the fœtal head This is not to deny that hiatus hernia may be seen and can perhaps develop during pregnancy, though MARCHAND was unable to find a single case among the 14 patients with severe symptoms who agreed to X-ray examination with barium GORBACH and REID,[6] however, demonstrated a hernia radiologically in 31 out of 50 antenatal patients with heartburn, nausea, vomiting, or hæmatemesis

One fact does seem to be clear—namely, that œsophagitis, except in the extremely rare case,[7] is due to regurgitation Furthermore, surgical interference with the cardia can lead to reflux, and many other conditions may so alter the anatomy and physiology of the œsophagus and cardia as to create incontinence Less emphasis is now being placed on the diaphragmatic pinchcock described by ALLISON,[8] and more on the possibility of intrinsic sphincteric action Recent experiments by BRAASCH and ELLIS[9] point to the œsophagogastric junction itself as the important site in maintaining gastro-œsophageal continence, for cardioplasty, œsophagogastrectomy, or œsophagocardio-myotomy in dogs was followed by œsophagitis just as often when the new œsophagogastric junction was placed in the thorax as when it was in the abdomen when, however, the junction was maintained intact but a short length of abdominal œsophagus produced, no œsophagitis developed within the segment now below the diaphragm and no longer safeguarded by its supposed pinchcock Indeed LYONS et al[10] go so far as to consider that the presence of an internal sphincter is established, though they do not think that it alone is responsible for continence Nevertheless, in man the diaphragm may play some part in the maintenance of the œsophagogastric angle and thus affect continence in a rather less direct way than is implied by the pinchcock hypothesis

Since the œsophagogastric junction must inevitably be disturbed by a resection or any plastic operation in that area, devices must be found to protect the œsophagus from reflux MERENDINO and DILLARD[11] used a method of jejunal interposition based on animal experiments which showed that the interposed section of jejunum suffered in no way from contact with gastric contents, and if it was sufficiently long it prevented reflux into the œsophagus above it The results of this operation were encouraging, though follow-up has so far been short Longer observations are those of WANGENSTEEN[12] who seven years ago first exploited the idea of partial gastrectomy for œsophageal stricture Though it was originally based on the association of œsophageal stricture with gastric or duodenal ulcer,[13] the operation has since been used by WANGENSTEEN in the absence of gastric or duodenal disorders, on the ground that rapid emptying of the stomach from below will minimise regurgitation of gastric contents, which are themselves less irritant as a result of the resection In 18 patients observed for periods of up to sixteen years after operation, the dysphagia completely disappeared or substantially improved In 7 the stricture was associated with hiatus hernia, in 4 there was no other abnormality, and in the other 7 a duodenal or gastric ulcer was present In all but 3, subtotal gastrectomy was performed the œsophageal lumen subsequently increased and this change persisted In another patient who failed to respond the stricture was due not to reflux but to swallowing a corrosive

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[2] Sweet, R H New Engl J Med 1956 254 87
[3] Sweet R H Surg Clin N Amer 1947 27, 1128
[4] Wolf B S Marshak R H Som M L Winkelstein A *Gastroenterology* 1955 29 744
[5] Marchand P *Brit J Surg* 1955 42 504
[6] Gorbach A C Reid D E *New Engl J Med* 1956 255, 517
[7] Achenbach H Lynch J P Dwight, R W *Ibid*, p 456
[8] Allison P R *Thorax*, 1948 3 20, *Surg Gynec Obstet* 1951 92 419
[9] Braasch J W Ellis F H *Surgery* 1956, 39 901
[10] Lyons W S, Ellis F H, Olsen A M *Proc Mayo Clin* 1956 31 605
[11] Merendino K A Dillard D H *Ann Surg* 1955 142 486.
[12] Maclean L D Wangensteen O H *Surg Gynec Obstet* 1956, 103 ,
[13] Wangensteen, O H, Leven N L *Ibid* 1949, 88 560

The Search for Tuberculosis

In those countries with the most complex social and industrial structures, the emphasis in case-finding in pulmonary tuberculosis gradually shifted from mere routine follow-up of contacts to mass X-ray surveys, but lately there has been a swing back to detailed and painstaking Mantoux-testing whenever possible On the whole, mass X-ray surveys are of limited value, and they are certainly rather expensive in man-power and money But many such surveys have been made of highly selected groups, such as hospital patients, old people, prison populations, people in social class v, and "Skid Row" victims, among whom a high prevalence of tuberculosis might be expected Other groups may have a high susceptibility to the disease—school-leavers, students, and nurses And there are also the food-handlers, child-minders, and school-teachers who may act as reservoirs of infection Surveys of all these groups, however, can form an impression only of the amount of disease discoverable at the time of the survey and they can give but little account of the social and economic background of the individuals and their families It was left to **Cochrane** and his colleagues,[1] during a study of the prevalence of a number of common diseases in an industrial community in the Rhondda, to try to assess the attack-rate for pulmonary tuberculosis The success of their initial survey and the subsequent follow-up was attributed in part to certain local conditions, such as the closely defined population and the ever-present threat of pneumoconiosis among the men, and it was thought that it might be more difficult to do the same thing with equal success in other areas and among other populations **Cochrane**, **Miall**, and **Clarke**[2] now report the results of a chest X-ray survey in an agricultural community in the Vale of Glamorgan, which was chosen for three reasons country-dwellers were reputed to be healthy, the results would provide a norm for future comparisons, and it was near the Rhondda Fach The population was defined as those aged 5 or over in July, 1955 An X-ray examination of the chest was made in 2688 (94%) out of 2880 males and 2697 (95%) out of 2841 females These striking figures for the Vale are a little better than those for the second Rhondda Fach survey and are apparently the best recorded anywhere for a voluntary chest X-ray survey The over-all prevalence of tuberculosis was low, and when the figures were compared with the results of the Rhondda survey the difference was much greater for females (0 7 per 1000 as against 6 7 per 1000) than for males (1 5 and 4 6 per 1000) But it is clear that the smaller difference for males is explained by the similar prevalence among elderly men in the two areas The yield of previously unknown infectious cases was 0 9 per 1000 in the Vale, compared with 2 2 per 1000 in the Rhondda

Springett[3] has shown that the radiological attack-rate for tuberculosis of reinfection type is similar in the two sexes and largely confined to young adults A difference in attack rate between the two areas over a period of time would account for the difference in the prevalence of clinically significant tuberculosis at the younger ages, but it cannot explain the similar prevalence among the older men in the two areas **Cochrane** et al[2] incline to the view that population densities are important in the Rhondda there are 4 7 persons per acre, but in the Vale the figure is 0 5 Overcrowding is much less important because the indices are nearly identical (Rhondda 0 7, Vale approximately 0 7) There is also evidence, from a study of a selected cohort, that in fact the attack rate is falling in the Vale

Whole-community surveys of this kind are very valuable, and there is useful guidance to be had from examining the methods which gave such highly successful results **Cochrane** et al did not attempt a "fast tempo" survey, such as the survey carried out in Bootle last winter and described on p 153 Their first step was to take an accurate census, and this in itself was probably the best propaganda weapon, then they visited at home those who did not come of their own accord, and finally the team never aimed to do anything beyond their capability We hope that the lessons learnt in the Rhondda and the Vale will be applied in other parts of the world, especially in those black areas where tuberculosis is still a very common disease

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1 Cochrane, A L, Cox J G, Jarman, T F *Brit med J* 1952 ii 843

2 Cochrane A L, Miall, W E, Clarke, W G *Tubercle, Lond* 1956 37, 417

3 Springett V H *Brit med J* 1951, ii 144

Annotations

SOIL, FOOD, AND HEALTH

Before the war Boyd Orr[1] showed that, even in our own prosperous country, millions of people were not getting enough of certain foods Their diet was in many respects deficient in quantity, and this remains true for a large proportion of mankind But nutrition may also be unsound when food-supplies are abundant, and attention is now being paid (1) to damage done by taking certain foods in excess of need, and (2) to the possibility that modern methods of producing and processing foods may damage their quality In agriculture the use of fertilisers to produce larger crops might conceivably alter the biological value of these crops for man and animals, and, fearing that the health of the soil, on which all crops depend, may be impaired by chemical treatment, some people are now demanding an agricultural counter-revolution—urging a return to the traditional methods by which the soil was kept in good heart almost wholly by the use of animal and vegetable waste, applied as manure and compost Without committing themselves so far as this, many think it important that we should at least know what we are doing, and that the advantages and disadvantages of "natural" and "artificial" soil treatment, and the nutritional value of their products, should be compared by all the scientific means at our disposal, and in asking for support of such a comparison on its experimental farms at Haughley the Soil Association has readily obtained from 400 members of the medical and dental profession their signature to the declaration published on p 152

To most agriculturists the suggestion that farmers should again do without fertilisers seems unrealistic They admit, of course, that, in some parts of the world the land has been kept fertile for hundreds and even thousands of years by systematically returning to it all crop residues, dung, and domestic waste, and by resting it periodically under grass But this can happen, they say, only where production is not too intensive, where the

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1 Food, Health, and Income London 1936

population is relatively sparse and evenly distributed, and where the soil is not naturally deficient in some essential mineral The changes in our social and sanitary habits, and the very great increase in population throughout the world, have inevitably changed the picture, if only because much of the manurial residue which used to find its way back to the land is now carried as sewage to the sea No amount of composting can now fully restore to farms the products which move out of them in the form of crops and livestock consumed at a distance , nor can the use of natural organic manures alone supply the trace elements which are deficient in the soils of considerable areas of the world's surface, such as parts of agricultural Australia (In the United States it is estimated that if all the readily available garbage and organic wastes were made into compost it would probably not provide more than 5–10% of the elements needed to keep the soil in a satisfactory state of production) As to the biological value of the product, it is agreed that any manurial system which alters the proportion of the leaf, stem, and flowering parts of a plant will affect the ratios of the individual proteins, and perhaps the concentration of free amino acids and non-protein-bound amino-acids , but we are told that no evidence of imbalance of amino acids, or adverse effect on proteins, attributable to the use of fertilisers, has yet been detected As regards the vitamin content of crops, the changes measured are said to be relatively small, but may be beneficial rather than otherwise for example, there is reason to think that, when the nitrogen content of wheat is raised, its content of vitamin B_1 will rise too Possible changes of this kind in the chemical constitution of particular plants are, of course, different from the change in the constitution of an animal's diet that may take place when pasture is improved Some farmers and veterinarians think that certain of the so called metabolic diseases of cattle (e g , acetonæmia, lactation tetany, and bloat) and enterotoxæmia in sheep, are on the increase, and that this is a result of growing more grass with the aid of fertilisers , and few would deny the possibility that excess of nitrogenous material, and deficiency of roughage, could be harmful Though they do not think that this risk should deter farmers from trying to get a maximum yield from their land, or from continuing the grassland improvement demanded by present economic conditions, agricultural authorities agree that the effect of such improvement must ultimately be judged by the condition of the animals for which it is done Their emphasis on production does not necessarily mean that the need for complementary investigation is ignored or neglected

The same is true of research on soil and on soil plant-animal relationships, on which work is being done in many countries ; and it would be wrong to suppose that the Soil Association is the only body interested in the "integrity and biological quality" of nutrient materials The association's objection to what is being done under official auspices is that the purpose of such investigations is mainly technological (the utilisation of what is known) rather than ecological (the exploration of relationships that are still unknown)—that they seek know-how rather than fundamental knowledge

> " Official experimental work, which is itself based on science fragmented into subjects and sub subjects though nowadays better coördinated than formerly, usually begins by fragmenting the material or problem it is investigating in order to examine weigh and measure components At a later stage equipped with the knowledge it has gained it selects and reassembles components, discarding some and introducing new ones until some formula is achieved which can be tested against other formulæ or material again by quantitative measurement
>
> The result as it finally emerges as a fertilizer prescription seeds mixture or animal ration or perhaps some chemical spray or additive may appear to work it may offer a short term cash profit to farmers But the procedure can reveal little about living Nature which is ill-adapted to survive such dissection Indeed, it can be said to substitute the technologists' 'know how for that of Nature, with the not infrequent outcome that factors ignored or brushed aside as being of only academic interest later give rise to fresh problems It may, by artifice, achieve synthesis , but it neither studies nor fosters *symbiosis*, that 'living together' process which is the key to relationships between soil, plants, animals and humans "[2]

Looking at agriculture in this way, the association argues that the conventional experiments with small plots of land are insufficient , they can never be more than detached fragments , and comparisons of different methods cannot be justified unless they are made on a farming scale The Haughley experiment, which started in 1940 and was taken over by the association in 1948, is described as " the only farm-scale experiment devoted to the scientific study of ecological aspects of farming —the relationships that develop between soil, plant and animal under controlled and observed conditions " The association, which might more easily have confined itself to spreading its gospel, deserves praise for devoting so much of its resources to an attempt to collect valid evidence Sir Cecil Oakes, as chairman of Haughley Research Farms speaks of a change not only in other people's opinion of the venture but " also, imperceptibly, in our own outlook , we are determined to conduct the research on such sound farming lines, with the best scientific advice obtainable, that any results which we can offer to the world will be acceptable as the products of true research "[2]

Therein lies the strength of the appeal now made for financial support for the Haughley experiment Its weakness lies in the difficulty of the investigation To the agricultural expert it may seem that the kind of measurements made are not going to yield satisfying evidence Can the previous treatment of the land be " largely written off," as is suggested ? Can the comparison between the two dairy-herds, as selected and reared, be really valid ? Some hold not only that this particular experiment, even if extended, can never produce the evidence needed, but also that to prove or disprove, by experiment, the thesis of the Organic Movement is virtually impossible

> To get the required results (writes one critic) " several generations of men, women and children living under comparable environmental conditions, would have to be fed on food derived from organic farming or mixed farming , and the farms would have to start from a common virgin or organic ' basis, with similar soil types and water tables."

To the medical observer it may seem either that the present experiment, though imperfect, is worth backing and perhaps improving , or that the agricultural research authorities would be well advised to design something better on the same lines Or he may think that the science of nutrition, and its many institutions, are now so advanced as not to need the stimulus of pressure from outside enthusiasts But at least he will agree that the subject deserves thought and that, in our present concern with the quantity of foodstuffs eaten, the possibility of their changing in quality should not be forgotten

TRIBUTE TO A PSYCHIATRIST

PSYCHIATRY, like other branches of social science offers many examples of personalities who are said to have " lived before their time " The reason usually given for the failure of ideas and reforms to survive their originators is that the public was not yet ready for them The outstanding work of Conolly and Tuke, for example, was recognised by contemporaries but failed to take firm root , it became instead the subject of repeated rediscovery Indeed, respect for the mentally sick, which was the keynote of their teaching, was until quite recently little more than an ideal and a slogan One of the main obstacles to the public understanding of psychiatry has been the mental hospital itself, for, though it occupied the centre of the field, it was geographically and spiritually isolated from the community it aimed to serve Reform within the hospitals was certainly needed, but it was not at first recognised that this largely depended on the development of external services It was necessary to show the public what psychiatry had to offer Only in this way could early treatment be secured, the need for admission to hospital prevented, and overcrowding reduced

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[2] The Haughley Experiment *Journal of the Soil Association* October 1956

It may truly be said of Dr T P Rees that by his work outside Warlingham Park Hospital he made internal reforms possible in fact by teaching the public he created his own time The future of psychiatry depends on prevention, and mental health, like any other social reform, needs promotion, which can be achieved only by contact with society Dr Rees's contributions to mental hospital management are internationally accepted His concepts of the therapeutic community, respect for the individual patient, and the need for team-work among the staff have set the standard for British mental hospitals But it is significant that recognition of his work has come not only from within the medical profession but from the people of Croydon In conferring on Dr Rees the honorary freedom of their borough its citizens have shown their appreciation of the man and also their understanding of the worth of the community psychiatry he has practised

THE PLIGHT OF HOSPITAL PHARMACY

New salary scales have lately been announced[1] for hospital pharmacists, but, so far from attracting recruits to sustain a service on the point of collapse, they are likely to discourage newcomers still further because they compare so unfavourably with salaries in other branches of pharmacy and in the technical colleges and universities, and with those of other hospital staff, especially biochemists, physicists, and supplies officers The seriousness of the situation is illustrated by what has just happened in the Portsmouth hospitals,[2] where it has proved impossible to fill two vacancies in an establishment of nine pharmacists Advertisements produced no replies, and the group secretary sees worse to come because he expects that the hospitals will lose the staff they already have to new pharmaceutical factories in the district He made it plain that pressure on the overburdened staff was resulting in serious dangers

For several years hospitals have been losing many of their best pharmacists to retail and manufacturing pharmacy The new Burnham scale salaries for teachers in the schools of pharmacy are now likely to cause a further drift of better-qualified pharmacists away from the hospitals An assistant lecturer's pay is now considerably better than that of a pharmacist in the basic grade and roughly equivalent to that of a senior pharmacist, and a lecturer's salary is better than that of the highest grade of non teaching hospital pharmacist The salary of a senior lecturer is now approximately the same as that of the chief pharmacist of the largest teaching hospitals, and that of the head of department of one of the colleges of advanced technology is much above anything that the most fortunate teaching hospital pharmacist can expect from all sources even after many years' service Yet the qualifications, the type of knowledge, and the ability required of the chief pharmacist of a large non-teaching hospital, and the responsibility he shoulders, are comparable to those of a senior lecturer, and the same can be said of the chief pharmacist of a teaching hospital when compared with the head of department in a college

There has long been difficulty in filling posts in the basic grade of pharmacists, and this has extended in the past few years to senior staff and to chief pharmacists, even to those in the teaching hospitals Not long ago the chief pharmacist of one of the big London teaching hospitals resigned to join a pharmaceutical firm In addition to his higher pharmaceutical qualification, he had an honours degree in physiology with biochemistry as a major subject, and he could have earned a much higher salary as a biochemist In fact, any honours graduate pharmacist who has taken chemistry and pharmacology as finals subjects would do well to enter the hospital service as a biochemist rather than a pharmacist Several have already done so and some colleges are now advising their graduates of this possibility

Successive Ministers of Health have expressed their concern at the state of hospital pharmacy and their anxiety to see pharmacists of the right calibre as chief pharmacists, but they have done little or nothing to attract staff of the right type The increases of the past few years have barely met the rise in the cost of living and have not kept pace with increases in comparable professions The Whitley Council negotiations seem unable to resolve the problem The staff side, in putting forward a reasoned and moderate claim, pointed out that the last increase had not attracted new recruits into the service, and that there was a 27% deficiency of establishment in a representative sample of 187 hospitals In spite of convincing figures comparing pharmacists' pay with other rates in the N H S, all that was conceded was roughly a cost of-living increase Such experiences will convince many people that the Whitley Council is not used by the Ministry of Health as a negotiating machine and that it has become a method of dictating what salaries shall be.

The Whitley Councils have been criticised for the rigidity which bars hospital authorities from making special scales for posts of unusual responsibility—and this objection applies particularly in hospital pharmacy For example, to assess the chief pharmacist's *salary, hospitals are allowed from 1 to 40* points, but many hospitals, by this method of scoring, can raise double this number of points and yet their pharmacist's salary is the same as if they had only 40 Moreover, many pharmacists have been doing the work of group pharmacist since 1948 without extra remuneration, and a group duties allowance has not yet been made Elsewhere in the hospital service, biochemists and physicists already have a "special grade" of £1900 per annum above the normal "top grade," and hospital authorities have power to make higher scales in exceptional circumstances Consultants have merit awards, the new Burnham scales allow for special responsibility allowances for teachers in schools of pharmacy, whereby a graduate can command a much higher salary than a non graduate, and in the hospital service a catering officer with a dietitian's certificate gets an extra £40 a year Yet the request for a rise in the pharmacists' higher qualification allowance from £25 to £50 was refused in the recent claim It is not surprising that few graduate pharmacists enter the hospital service

The pharmaceutical work of the hospitals is at present being maintained by a dwindling nucleus of established staff, some of whom are too old to embark on another career, by those who want a few years' hospital experience before passing to other branches of pharmacy, and by locums, many of whom are temporary visitors from the Commonwealth, and some of whom have little hospital experience, yet are often employed for months on end at salaries greater than those of established pharmacists who have given the hospitals many years of valuable service. The cumulative damage of the past ten years' losses is becoming increasingly obvious. Patients and nurses are having to wait longer for drugs, mistakes are commoner than ever before, and there is a general attitude of discontent in the hospital pharmaceutical service. Unless prompt action is taken to raise hospital pharmacy to an attractive career, as recommended by the Linstead report, the service will soon collapse. As we said[3] of the radiographers' situation, the new salary scales will do little to put things right.

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[1] H M (57)3 and P H circular no 21

[2] *Portsmouth Evening News* Jan 4, 1957

PLEURAL BIOPSY

THE unusual causes of "pleurisy with effusion" are fairly easily diagnosed at an early stage,[4] but the common causes are often hard to differentiate rapidly. It has become the custom to consider the condition tuberculous in the young and to suspect malignant disease in older patients, and to wait until the results of repeated tests (which may never become positive) or the clinical course decide the issue. With the changing habits of disease, however, tuberculosis is now appearing more often in older patients[5] and malignant disease more often in the young. An early diagnosis is thus much more important and, as a result, standard methods of investigation are becoming more accurate. In the effusions eventually believed to be tuberculous, it has been shown[6] that the number of positive results is greatly increased by using much larger amounts of the pleural fluid and clot for the bacteriological tests. The methods of searching for malignant cells have also been improved, both by the examination of smears[7] and by histological section of the sediment though sometimes the cells are too disrupted for either method. But even so these methods may be time consuming and still give no definite results in a fair proportion of cases.

Before the days of chemotherapy for tuberculosis it was too risky to undertake even minor chest operations in patients who might have active tuberculosis, but it is now possible to remove a biopsy specimen by thoracotomy and examine the tissue histologically. At first,[8] [9] this operation required a thoracic surgeon in an operating-theatre, positive pressure anæsthesia, and the removal of fluid and air by catheter before the wound was closed, but it enabled the pleura[10] to be observed and a piece of tissue about 1 5 × 3 cm to be removed for examination.[11] Now, Breckler and his colleagues[12] have modified the procedure to remove only a small portion of pleura by special forceps. They point out that though the pleura may be thin and glistening, it may still be involved by granulomatous disease. Even if pneumothorax does result, suction by catheter can be started immediately and no harm is done. An even simpler technique is described by Heller et al[13] (and also used independently by De Francis et al[14] and Katz et al[15]), consisting of needle biopsy, as for biopsy of the liver and kidney. The advantages are that it can easily be repeated in another site if the first result is equivocal, and the risk to the patient is negligible.

These new methods have enabled a much quicker diagnosis to be made in many cases of pleurisy with effusion, not only between tuberculosis and malignancy but also in several of the more unusual causes. At the same time, no specific cause could be found in some cases: some showed non specific fibrosis of the pleura after sulphonamide-treated pneumonia, trauma, or lung infarct, and a few other conditions were not diagnosed at all but were kept under observation until the condition cleared up. In this last group it was very useful not to have to embark on a full course of antituberculous treatment.

In another way these observations are helping towards an understanding of tuberculous pleurisy. In most of the recorded series the finding of tuberculosis by biopsy was sometimes as definite when culture from the pleural fluid was negative as when it was positive and negative biopsies were never associated with positive cultures. The implication is that there is widespread tuberculous granulation tissue throughout the pleural cavity when the tubercle bacillus is the cause of the pleurisy and that it is not a question of collateral effusion or hypersensitivity. This point requires much more evidence to be in any way final although Stead and his colleagues,[16] who examined tissue removed at decortication from 24 patients with pleural effusion suspected of being tuberculous, found evidence of tuberculosis in only 15—thus emphasising the frequency of non-tuberculous effusions.

THE REFUGEES

WITH more arrivals in prospect, we may soon have exhausted the £390 put at our disposal for the relief of Hungarian doctors in this country. We should be very glad to have further contributions—as many as possible, however small—from readers.

Of forty odd Hungarian doctors that have so far arrived in this country, perhaps a third have friends or relations here who are housing them and doing what they can. Of the others the majority are temporarily accommodated in medical households, but two at least have rented rooms and are living on their own. Some six or eight have gained hospital appointments.

Possibly half these doctors have decided to emigrate, if they can, usually because they believe that overseas the openings are greater or they will establish themselves more quickly. Except for the lucky few who know English, each one needs urgently to learn our language, for until he does so he cannot resume his professional work.

The *Lancet* fund is being used for three main purposes: first, to help clothe the doctors and their families, some of whom arrived with only the clothes they wore; secondly, to provide for small expenses and to help meet other immediate needs, including the need for prompt tuition in English (through the purchase of special long playing gramophone records which may be had on loan from this office[17]), and thirdly to help maintain the two who are living for the time being in lodgings supported otherwise only by grants from the National Assistance Fund.

These doctors want above all to work and pay their own way, and in their present dispiriting period of dependence and uncertainty they deserve well of their more secure colleagues. Contributions intended for them may be sent to the Editor of *The Lancet* and marked Hungarian Doctors' Fund.

DR JOHN MCGRATH, consulting State pathologist for Eire and professor of pathology and bacteriology at University College, Dublin, died on Jan 11.

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[3] See *Lancet* 1956 ii 1296

[4] Pagel W Simmonds F A H, Macdonald N Pulmonary Tuberculosis London 1953 p 354

[5] Robertson R F *Brit med J* 1952 i 133

[6] Close H G *Lancet* 1946 i 193

[7] Papanicolaou G N Atlas of Exfoliative Cytology London 1954 and suppl. 1956 Plate series F & F 1

[8] Klassen K P Andrews A J Curtis G *Arch Surg* 1949 59 694

[9] Sutliff W D, Hughes F Rice M L *Dis Chest* 1954 26 551

[10] Lloyd M S *Quart Bull Sea View Hosp* 1953 14 128

[11] Small M J Landman M *J Amer med Ass* 1955 158 907

[12] Breckler I A Hoffman M C Hill H F Hensler N M Hukill P B *New Engl J Med* 1956 255 690

[13] Heller P Kellow W F Chomet B *Ibid* p 684

[14] De Francis N Klosk F Albano F *Ibid* 1955 252 948

[15] Katz S Donohoe P Mathews M J 15th Veterans Administration Army Navy Conference Missouri 1956

[16] Stead W W Eichenholz A Stauss H K *Amer Rev Tuberc* 1955 71 473

[17] See *Lancet* Jan 12 1957 p 88

Special Articles

UNMARRIED PARENTHOOD*

ECOLOGICAL ASPECTS

CYRIL GREENLAND

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OF every 1000 children born in 1954 in Scotland 45 were illegitimate. This was a considerable improvement over the previous ten years, but an illegitimacy-rate of even 4·5% remains a cold statistical fact tending to conceal rather than to reveal the wide variety of situations in which a baby is born to parents not married to each other.

The illegitimate child starts life with considerable handicaps. His chances of death are 70% higher than those of the legitimate child. The infant mortality rate among legitimate children in 1953 was 30 per 1000 live births compared with 51 per 1000 illegitimate children. This means that 212 of the 4177 children born in Scotland to unmarried mothers did not live a year. Many of the survivors face a host of new hazards—social, emotional, medical, moral, and legal.

Faced with these problems those who care about the suffering of little children have a healthy desire to understand and eventually to overcome the grave disadvantage with which the illegitimate child starts life. This is one of the principal aims of the Scottish Council for the Unmarried Mother and her Child.

My present aim is to describe briefly some of the known characteristics of unmarried parenthood and the environmental setting in which illegitimacy may be regarded as a major problem—the geographical factors in illegitimacy, the relative influences of religion, and the ages and civil status of unmarried parents.

As regards the wider aspects of illegitimacy, which are beyond my present scope, I suggest that further consideration might profitably be given to the prevailing cultural and economic factors. For example, Dr. J. R. Rees, director of the World Federation for Mental Health, who visited Latin America in 1954, reported that 75% of the children of Peru were illegitimate (Rees 1954). This he attributed not, as one might expect, to some widespread and deep-seated Peruvian neurosis but, among other circumstances, to the high cost of getting married in that country.

TABLE I—BIRTH OF FIRST CHILD WITH DURATION OF MARRIAGE 8 MONTHS OR LESS

(From Table 12, Annual Report of the Registrar General for Scotland 1953)

Age (yr.)	Total	Under 8 mos.
16–19	2688	1750 (65·1%)
20–24	13,937	3404 (24·4%)
25–29	9399	967 (10·1%)
30–34	3921	316 (8·06%)
35–39	1329	133 (10·0%)
40–44	314	42 (12·3%)
45–49	23	
All ages	31,611	6612 (20·9%)

Distribution of Illegitimacy

It is particularly important to consider the social and moral climate in which illegitimacy prevails. In Scotland (table I) 6612 (20·9%)—roughly 1 in every 5—of the women giving birth to a first baby in 1953 had been married for less than nine months. In the 16–19 age group 65%, and of the women aged 20–24 years 24%, were pregnant when they married.

Table II shows that a similar situation prevailed in England and Wales.

These figures only hint at the real incidence of premarital sexual intercourse, and suggest that premarital chastity is the exception rather than the rule at present.

Glass and Grebenik (1955) claim that conception before marriage is associated with high fertility. In their group of most fertile women 25–30% gave birth to a live child before they had been married 8½ months. "In such circumstances," these workers state, "prenuptial conception cannot be regarded as abnormal."

It is therefore no longer possible to regard the unmarried mother as necessarily less stable or less moral than her married sister when the only difference may be her very much higher fertility.

Geographical Factors

In 1890 the incidence of illegitimacy in Scotland was calculated to be 7·5% of all births (Lamond 1892). This incidence was twice as high in southern rural and in the north-eastern rural counties. The lowest incidence of illegitimacy was in the densely populated counties of Lanark and Renfrew.

Sixty-three years later almost exactly the same situation prevailed (fig. 1). In 1953, over the whole of Scotland, the rate of illegitimacy was 4·6% of live births. Illegitimacy was highest in the counties of Wigtown in the south-west and of Caithness and Banff in the north-east. The lowest incidence is still to be found in and around Lanark, Renfrew, and, especially, Selkirk.

TABLE II—BIRTH OF FIRST CHILD WITH DURATION OF MARRIAGE 8 MONTHS OR LESS

(From Table LL, The Registrar General's Statistical Review of England and Wales for the Year 1953)

Age (yr.)	Total	Under 8 mos.
16–19	22,137	15,372 (69·4%)
20–24	111,614	25,515 (22·9%)
25–29	74,917	6050 (8·1%)
30–34	28,825	1921 (6·6%)
35–39	8643	550 (6·3%)
40–44	1980	125 (6·2%)
45–49	122	9 (7·3%)
All ages	251,187	49,504 (19·7%)

In an attempt to explain this curious fact I studied the population structure over the whole of Britain and Ireland. I assumed that the risk of illegitimacy was greater in some counties than in others because of an imbalance of the sexes. If, for example, a population consisted of 100 single women of marriageable age and only 50 men, the risk of illegitimacy would be greater than in a county where the position was reversed.

Fig. 2 shows the counties with a surplus of men and those with a surplus of women of reproductive age. Contrary to popular belief, there are few areas where nubile women outnumber single men. In Scotland the counties of Aberdeen and Angus in the north, and Peebles, Lanark, and Renfrew in the south-west, have an apparent excess of unmarried women. Peeblesshire, which has the highest surplus of single women, has a fairly low illegitimacy rate. Aberdeen and Angus, on the other hand, have a surplus of unmarried women as well as a rate of illegitimacy above the average.

The methods used in making these estimates are relatively crude. But in spite of this the evidence is sufficient to indicate that there is no absolute relationship between a surplus of unmarried women and a high illegitimacy-rate. It still remains a mystery why the illegitimacy rate in Wigtownshire (15%) is three times as high as the average for Scotland (4·6%) when single men aged 15–44 (3783) outnumber single women (2566) by roughly 3 to 2 (table III).

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* An address given in May, 1956, at the annual conference, in Glasgow, of the Scottish Council for the Unmarried Mother and her Child.

Religious Denomination

The study of the geographical distribution of illegitimacy in Britain also permitted a comparison to be made between Eire, predominantly Roman Catholic, and northern Ireland, predominantly Protestant The Roman Catholics comprise well over 90% of the population of Eire, and about 34% of the population of Northern Ireland

TABLE III—AGE DISTRIBUTION OF SINGLE MEN AND WOMEN IN WIGTOWNSHIRE

(From Table 11 of the 1951 Census Report)

Age (yr)	Single men	Single women
15–19	1415	1064
20–24	1110	568
25–29	540	326
30–34	289	221
35–39	222	189
40–44	207	198
	3783	2566
Widow/widower and divorced	56	116
Total unmarried	3839	2682

TABLE IV—POPULATION, BIRTH RATE, AND PERCENTAGE OF ILLEGITIMATE BIRTHS IN EIRE AND NORTHERN IRELAND

—	Population*	Birth rate†	Percentage of illegitimate births‡
Eire	2,960,593	21·1	2·5
Northern Ireland	1,370,709	20·9	2·8

* 1951 census
† Per 1000 population 1953
‡ Per cent of live births 1953

Illegitimate births represent 2·5% of live births in Eire and 2·8% in Northern Ireland (table IV) This appears to indicate that factors other than religion are responsible for the low incidence of illegitimacy in these countries

A comparison of the relevant data for other mainly Catholic and mainly Protestant countries reveals an incidence of illegitimacy of 3·4% in Italy and 5·2% in Spain In the Netherlands the percentage was 1·5%, in Norway 4·1%, and in England and Wales 5·1% Therefore the differences in the incidence of illegitimacy between Catholic and Protestant countries are hardly significant

Age of Unmarried Mother at Maternity

A composite picture of the unmarried mother, according to popular imagination, would reveal a drab pathetic-looking girl in her early teens or a brassy young madam in her middle twenties This sort of picture, however, does not accord with the facts The Registrar-General's statistics (table V) showing the age of mothers at maternity reveal that, of all those aged less than 20, 1 in 5 is unmarried, but, except these and the 25–29 age-group, the percentage distribution of maternity cases in the different age-groups are about the same for legitimate and for illegitimate births The difference in the 25–29 age-group (21·6% illegitimate, 32% legitimate) is probably due to the fact that, with the widespread practice of birth control in marriage, conception is delayed and the peak of fertility not reached until the age of 25–29, whereas, for unmarried mothers, the peak age for fertility is 20–24

The impression that, for the most part, unmarried mothers are relatively young is to some extent explained by the survey undertaken by the Church of England Moral Welfare Council (1954) This revealed that 3543 of 7057 applicants (more than 52%) were aged less than

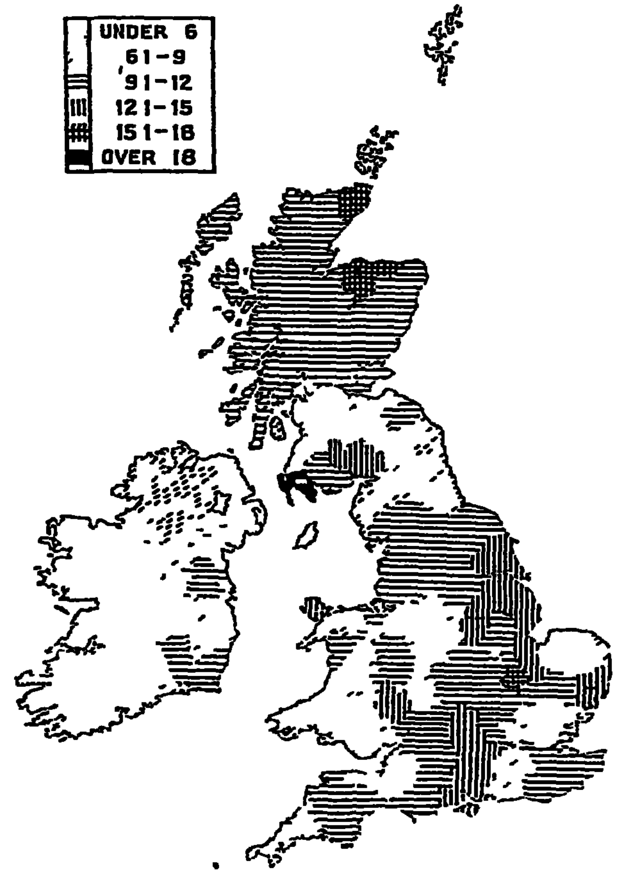

Fig 1—Number of illegitimate births in 1953, per 1000 unmarried women aged 15–44

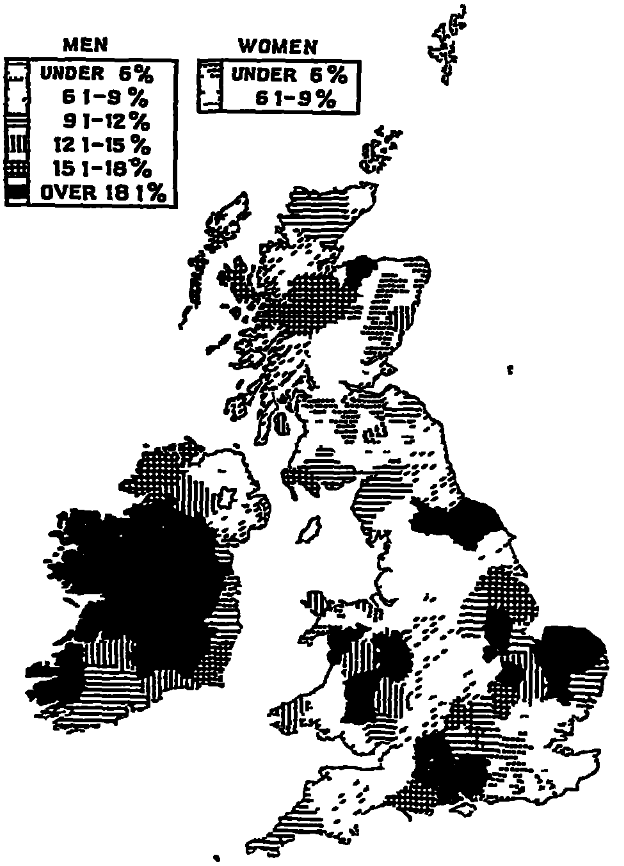

Fig 2—Surplus of unmarried adults aged 16–44 in 1953 excess expressed as percentage of total for both sexes

TABLE V—AGE OF MOTHER AT MATERNITY

(From Table AA, Registrar General's Statistical Review of England and Wales, 1953)

Age of mother (yr)	Legitimate	Illegitimate
	Total	Total
Under 20	25 058 (*3 8%*)	5359 (*16 5%*)
20–24	185,106 (*28 5%*)	9659 (*29 7%*)
25–29	209 669 (*32 1%*)	7028 (*21 6%*)
30–34	144,779 (*22 2%*)	5860 (*18 0%*)
35–39	65,253 (*10 0%*)	3215 (*10 0%*)
40–44	20 603 (*3 1%*)	1291 (*4 0%*)
45–49	1381 (*0 2%*)	87 (*0 2%*)
50 and over	20 (*0 003*%)	4 (*0 01*%)
All ages	651,869	32,503

22 Of the 3436 unmarried mothers dealt with by the National Council for the Unmarried Mother and her Child in 1953 (unpublished) 48 8% were aged less than 22

This is confirmed by my own unpublished findings in more than 11,000 requests for advice in 1953, of which 662 (6%) related to "illegitimate births and pregnancies" About 60% of those giving information were aged less than 22

These facts indicate that it is usually the younger unmarried mother who needs and seeks the help of moral-welfare agencies It is therefore extremely important to recognise that the young woman who comes for help has additional problems to those of the older unmarried mothers Failure to make the important distinction between unmarried mothers who seek the help of a specialised welfare agency and those who do not tends to vitiate the findings in otherwise useful case studies On common sense grounds alone it must be assumed that the girl who overcomes her difficulties with the loving support of her own family and friends is likely to have a vastly different psychology to the unhappy pregnant girl rejected by her family and left to face her troubles as best she can

In considering the problems of unmarried parenthood it cannot be emphasised too strongly that, apart from the unmarried mothers aged less than 20, who represent 1 in every 5 maternities, and, to a lesser extent, those aged 25–29, who represent 1 in every 30 maternities, the age distribution of mothers is about the same for legitimate and for illegitimate maternities Most of those who seek the help of specialised welfare agencies are aged less than 24 and therefore can be regarded as having very special difficulties, which often include the broken home and mental instability

Civil Status of Unmarried Parents

There is relatively little reliable information about the civil status of unmarried parents Apart from the single girl who becomes pregnant after brief sexual contact with a casual acquaintance, there are those who are betrothed but cannot marry the girl whose fiancé is unexpectedly posted overseas, and the girl whose lover may be a married man waiting for a divorce There are also the particularly tragic situations of the married woman who becomes pregnant by a man other than her husband, and the widow who, often as a result of loneliness and misery, enters into an undesirable sexual relationship

The Church of England Moral Welfare Council (1954) reported that 6006 (84 3%) of 7194 mothers were single, 903 (12 3%) were married, 180 (2 2%) divorced, and 105 (1 2%) widowed In my unpublished study of the "advice column" 68% were single, 16% married, 1 6% divorced, and 3 3% widows In 11 1% of cases civil status was not stated

The Registrar-General's reports unfortunately do not distinguish between the child born to a single woman and the child (possibly one of several) born to parents who live together in a permanent relationship although not legally married to each other An equally grave omission in these reports is the complete lack of information about the putative father

In the Church of England Moral Welfare Council's (1954) survey of 4880 cases available for analysis 1698 (35%) of the putative fathers were married men This proportion is amply confirmed by the finding that, of the 3436 cases dealt with by the National Council for the Unmarried Mother and her Child, about 48% of the putative fathers were married This helps to explain the lack of relationship between figs 1 and 2 showing the geographical distribution of illegitimacy and counties with a surplus of single men and women

The fact that probably more than a third of putative fathers are married men, who are therefore not free to marry, is of considerable significance in assessing the value of current theories regarding illegitimacy It is important also to appreciate the extent to which illegitimate children are born to parents who, although living together in a more or less stable home, are not married to each other

Spence et al (1954) reported an illegitimacy rate of *58 7 per 1000 at Newcastle upon Tyne Less than half* of these infants were first babies, and the mothers' age distribution differed very little from that of mothers giving birth to legitimate babies The explanation was that many of the second and third infants were born to parents living in established, if unofficial, families, 27 (30%) of the children alive at the end of the study were living with both parents as members of unofficial families

Nisbet (1954) reported that, of 200 illegitimate births inquired into by the Kilmarnock health department, the number of mothers cohabiting was 60 (30%)

It therefore seems reasonable to assume that about 1 in every *3* illegitimate births are to women, probably in older age groups, cohabiting in a more or less permanent relationship Although it is impossible to make any accurate estimate, probably most of these women have more than one child by the same father

TABLE VI—ILLEGITIMATE BIRTHS AND SOCIAL CLASS

(From Table 28, Registrar-General for Scotland Report 1954)

Social class	1	2	3	4	5	Not stated
Total live births	3509	9341	49,041	14,372	11 871	1614
Total illegitimate live births	3	132	994	1089	345	4
Percentage	0 08	1 40	2 02	7 50	2 90	0 24

Cooper (1955) emphasises that, although 34 of the 55 illegitimate children referred to by Spence et al (1954) were living more or less stably with their parents, in 32 cases the conditions of living were most unsatisfactory *10 children belonged to problem families, 12* were in severely overcrowded homes, and 14 lived in dwellings classed as unfit for human habitation There is little evidence to suggest how far this sordid picture is common to all cohabiting parents It is, however, probably true that the habit of living together without the sanction of marriage is common among problem families, the sort that give rise to many of the insoluble social difficulties of a large city

An opportunity to test Cooper's (1955) impression was presented by the 1954 Annual Report of the Registrar General for Scotland, which classifies live births by social class, the age of the mother, and the number of previous children (*table* VI) *Illegitimacy is rare in social* classes 1 and 2, the professional and intermediate occupations, and uncommon in class 5, the unskilled, where most of the problem families would be grouped Illegitimacy is commonest in class 4, partly skilled workers The same class distribution occurs for illegitimate stillbirths Thus suggests that the sordid conditions described by Cooper (1955) are probably not common to the majority of illegitimate children, at least in Scotland Unfortunately this valuable table is not included in the England and Wales report

Two other facts are also of importance (1) divorce, which would have enabled at least some of these parents to marry each other, was not until fairly recently (Legal Aid and Advice Act, 1949) available to those with limited means, and (2) efficient contraception is used far more frequently among the upper social classes (Lewis-Faning 1949), this may tend to reduce the number of illegitimate maternities among the higher income groups

Abortion

Similarly, although it is exceedingly difficult to prove, it is also possible that abortion is practised more commonly among women in the higher social classes The extent of abortion in Britain was officially estimated as 110,000–150,000 every year The report of the Inter-departmental Committee on Abortion, 1939, states (p 107)

> "Although by far the greater number of criminal abortions undoubtedly occur among married women, there is reason to suppose that the proportion of pregnant unmarried women who undergo criminal abortion is higher than the proportion of pregnant married women who resort to it"

Young (1954), in the U S A, states that "very few unmarried mothers apparently consider the possibility of abortions" Since this is contrary to experience in this country, I obtained, with the kind assistance of Mrs Alice Jenkins, of the Abortion Law Reform Society, a fairly authoritative statement on the incidence of abortion among single women in the United States The Planned Parenthood Federation of America stated "that a conservative estimate of criminal abortions in the United States is 330,000, roughly a thousand a day," and "unmarried girls are reported to consist of 10 per cent of the abortionists' clientele" According to this estimate about 100 criminal abortions are done each day in the U S A on single women As Young (1954) recognises the girl who procures an abortion does not present as an unmarried mother, and her psychological picture would be different

Discussion

The data presented here, however, do not appear to support the view that unmarried mothers as a whole, apart from having conceived out of marriage, differ in important respects from other women of the same age and social class If there is a difference it is in their relatively higher reproductive capacity, which has a physical as well as a psychological basis

I could discover no evidence to support Young's (1954) conclusion that "in the majority of cases the unmarried mother wants a baby, specifically an out-of-wedlock baby without a husband" The fact that at least a third of the putative fathers are married does not necessarily indicate a widespread desire to avoid marriage Many unmarried parents marry as soon as they are free to do so In 1953 there were in England and Wales 2369 and in Scotland 469 re-registrations of births under the Legitimacy Acts The Church of England Moral Welfare Council's (1954) survey showed that within a year the mother had married the "putative father" in 299 (3 6%) cases and "another man" in 119 (1 4%) cases

It is evident that not enough is yet known about unmarried parenthood for the formulation of considered theories or generalisations about it Nor are the unmarried mothers or putative fathers a homogeneous group of people with special social and psychological characteristics in common The greatest need at present is for further detailed studies of them

Apart from the vital considerations of the health and welfare of mother and child the investment of public funds on preventive work and research would eventually considerably reduce public expenditure In 1953 the National Assistance Board found that more than 20,000 unmarried mothers received allowances amounting to £2,359,000 yearly—a subsidy from public funds of £2 5s a week for each mother

The already influential work of the National Council for the Unmarried Mother and her Child and the welfare work of the non-sectarian religious organisations, such as the Church of England Moral Welfare Council, should receive official recognition and financial support In cooperation with these agencies medical officers of health and Universities should be encouraged to undertake well planned and coördinated research A useful approach might be to finance experienced social workers with anthropological training so that they could take up several years' residence in selected areas where the illegitimate birth-rate is traditionally high This would enable them to obtain first-hand and intimate knowledge of the operation and influences of the particular cultural patterns By establishing herself as a member of the community the research-worker, together with the health visitors, could better safeguard the health and welfare of mother and child and direct the attention of the community towards appropriate preventive measures

Conclusion

I have tried to bring together here some of the facts which provide the foundation for discussing unmarried parenthood

Most of the vital pieces of this jig-saw puzzle are missing, and only a very few of the available pieces fit together Accordingly there is a natural impulse to ignore the facts and to retreat into the comfort of our own prejudices and fancies, where we can conveniently fashion the facts to suit our personal needs But the problem will still be there and, although we may not see it, children will continue to die needlessly, many of those who survive will be miserable, and the unmarried mother will suffer for our indulgences as well as her own The aim to save these children so that they may live without a sense of guilt and shame will best be served when we face the facts and understand their meaning better

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ODONTOLOGICAL CENTENARY

In October 1856, the 'memorialists' a small group of ardent, pioneer practitioners in dental surgery, led by John Tomes, who had failed to win the support of the Royal College of Surgeons for their repeated demands, met in Old Burlington Street and founded the Odontological Society of London On Jan 5, 1857, they held their first formal meeting of the society which some fifty years later, as the section of odontology, became one of the founder sections of the Royal Society of Medicine

The centenary of the founding of the Odontological Society was celebrated on Jan 4 by a dinner at the Royal College of Surgeons, under the chairmanship of Mr J A S Wright, president of the section of odontology, when Miss Patricia Hornsby Smith parliamentary secretary to the Ministry of Health was the principal guest

In a speech proposing the health of the section, Sir Zachary Cope spoke of the founders' persistent, far sighted, and eventually successful efforts to establish dental education on a firm and independent basis and dental surgery as a specialisation in its own right

SOIL, FOOD, AND HEALTH

A Public Declaration

THE following statement has been sponsored by medical and dental members of the council of the Soil Association (8f, Hyde Park Mansions, Marylebone Road, London, N W 1) and has been signed by more than four hundred members of the medical and dental professions The signatories include general practitioners, consultants, medical officers of health, and university professors

THE TEXT

In 1939 the Local Medical and Panel Committee of the County of Cheshire, representing some six hundred general practitioners, issued a Medical Testament[1] This testament, in our considered opinion, ranks as a historic document It declared forthrightly that, whilst good progress had been made towards the second objective of the National Health Insurance Act of 1911, in so far as postponement of death could be regarded as evidence of the cure of sickness, no such progress could be observed in the attainment of the first objective—presumably of at least equal importance—the prevention of sickness It affirmed that the basis of such prevention was essentially nutritional, its signatories stating that their daily work brought them repeatedly to the same point "This illness results from a lifetime of wrong nutrition"

MEDICAL SIGNIFICANCE OF THE ORGANIC MOVEMENT

The Medical Testament was an inspiration to many forward looking people, in particular Sir Albert Howard and Lady Eve Balfour, pioneers of what has come to be known as the Organic Movement It confirmed and enlarged their own experiences in the field of agriculture and constituted a notable contribution to the thesis for which the movement stands and for which considerable support has been gained in many different parts of the world in the last ten years

This thesis is, basically, the concept of organic wholeness applied to the vital relationships between soil, plant, animal and man, with special reference to health It envisages health as a positive process which is profoundly influenced by the interdependence of all life, primarily through the medium of nutrition It postulates, therefore, that the key science is the somewhat neglected one of ecology—the study of the relationships between living creatures and between such creatures and their environment

In all these respects the Organic Movement represents a marked departure from the present trend towards the increasing fragmentation of science, the piecemeal application of science through technology as expediency dictates, and the unceasing struggle to deal with the ever changing manifestations of individual diseases, whether in plants, animals, or humans On the other hand, its tenets are in keeping with the definition of health propounded by the World Health Organisation—namely, "a complete physical, mental and social well-being, and not merely the absence of disease or infirmity"[2]

Moreover, the concept of nutrition as a flow of nutrient materials from the soil through plants and animals to humans has been strongly reinforced by recent researches in the field of human metabolism These, by the use of isotopes to trace the passage of food constituents through the body, have demonstrated that all human tissues undergo constant renewal

It follows that the integrity and biological quality of the nutrient materials used for this renewal are of first rate importance to health; and that the extent to which they are influenced by agricultural practices becomes a matter of great practical significance to the medical and dental professions Yet, so far as we are aware, the only scientific studies hitherto attempted in this field are those being conducted at the Haughley Research Farms in Suffolk These are maintained by the Soil Association as a purely voluntary effort to enlarge our stock of knowledge, independently of State aid or commercial patronage

The Haughley experiment is designed to investigate and compare, on a farm scale—and therefore on a realistic basis—the cumulative effects of three contrasted types of soil management on (1) the fertility of the land, (2) the nutritional quality of its produce, and (3) the health and productivity of farm animals fed continuously and exclusively on that produce

There are three sections or "farms," side by side on land of similar type, managed as follows

(*a*) An "organic" section of 75 acres on which fertility is maintained by leys (temporary pastures) and compost made from its own animal manure and vegetable wastes—i e, it is self contained

(*b*) A "mixed" section of 75 acres on which fertility is maintained by leys and its own animal manure, supplemented by "artificial" chemical fertilisers—i e, similar to orthodox farming practice

(*c*) A "stockless" section of 32 acres treated with chemical fertilisers only, and green manuring—i e, it represents the purely chemical concept of soil fertility

Since 1947 the "organic" and "mixed" sections have each maintained its own herd of Guernsey dairy cattle (the third-generation heifers bred on the farm are not yet coming into milk) and its own flock of poultry, the foundation animals and birds having been carefully selected from common stocks by independent experts

Having first been laid out (as regards soil management) in 1940, this experiment has the unique advantage of having undergone a preparatory period long enough to permit previous treatment of the land to be largely written off and subsequent cumulative effects to develop With this prepared material as a starting-point, scientific studies were begun in 1952 under the direction of Mr R F Milton, PH D These, which have gradually been extended in scope, include

(1) Detailed chemical and physical analysis of soil samples taken monthly from each field, including some trace mineral analyses

(2) Detailed analysis (including some vitamin assessment) of the field produce and of the milk and eggs

(3) Close observation of the health and behaviour of the farm animals

Results to date indicate[3]

(*a*) That there are very considerable fluctuations (which would not of course be shown by the usual annual sampling) in the levels of available plant nutrients according to the season and the system of management

(*b*) That in terms of nitrogen and humus contents—a fair measure of soil fertility—the "organic" section is improving while the other two sections are deteriorating

(*c*) That there are changes in soil structure, attributable to systems of management, which may well become significant in effect

(*d*) That the recovery, through crops, of the plant nutrients applied as fertilisers to the "mixed" and "stockless" sections is extremely low

(*e*) That the dry matter content of crops on the "organic" section tends to be higher than that of crops on the other two sections

(*f*) That the dairy herd on the "organic" section yields consistently more milk, with a higher solids content, than does the herd on the "mixed" section, and has so far shown a better breeding record

(*g*) That there is preliminary evidence of lower vitamin and trace elements in the produce from the "mixed" and "stockless" sections than in that from the "organic" section

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[1] Cheshire Panel Committee Medical Testament Nutrition Soil Fertility, and the National Health *Brit med J* 1939 i, suppl p 157

[2] From the first of the Nine Principles of the World Health Organisation

[3] Summarised reports 1952, 1953, 1954 are available from the Soil Association

DECLARATION

We, the undersigned medical and dental practitioners, desire to reaffirm the conviction expressed by the Cheshire Panel Committee regarding the intimate connection between nutrition and health

We deplore the fact that, in the seventeen years that have elapsed since the publication of the Medical Testament so little has been done to implement the avowed intention of the National Health Service Act, 1946, in regard to the prevention of disease the more especially in view of the steadily increasing incidence of degenerative diseases, which contrasts markedly with the mastery achieved over infectious and inflammatory diseases

We would draw attention to the fact that during this period, we and a growing number of professional colleagues, together with many veterinarians farmers, horticulturists, and others, concerned with the health of livestock and crops, have become increasingly aware of the fundamental importance of the relationships between soil plants, animals, and man

We believe that the task of preventing disease is best envisaged as the enhancement of positive health and that, in this task, nutritional research should play a leading part

We believe further, that any such research which fails to take into consideration the soil on which the food is grown, and the farming practices involved, must be accounted incomplete This belief is in no way modified by the fact that much food is subjected to chemical and mechanical treatment after it leaves the land, flour being an outstanding example Such treatment also is of deep concern to us, though it cannot be discussed here We would, however, observe that it may well depress still further any reduction in food values that may be attributable to current agricultural practices

We would urge, therefore, that any research designed to discover which methods of soil management result in the highest food values should receive our professional support, and that such research should be both comprehensive in scope and of long term—extending over several decades rather than years

We note that apparently the only such research at present in progress is that being conducted at the Haughley Research Farms already mentioned and consider that it would be a tragedy if this one experiment, with its prepared material, were to be brought to a premature end—as seems only too possible—for lack of public interest and support It has now reached a stage at which its further extension, especially on the scientific side, should yield an increasing dividend of knowledge, but the enthusiasm of the Organic Movement, which has already accomplished so much, cannot be expected to undertake unaided the heavy financial commitment involved

In support of these contentions we would cite Sir John Charles who, in his 1952 annual report as chief medical officer, Ministry of Health,[4] referred to the uncharted fields exploration of which would surely reduce the burden of the curative services and who called for research into the causation of the so called chronic diseases Sir John referred also to the activities of the Medical Research Council indicating that the fields of research lying open to the investigators would not be narrowly limited

We would cite also the chief medical officer for the Department of Health for Scotland who in his 1955 annual report,[5] states that "at later ages the increasing threats of coronary thrombosis and cardiovascular disease, and of cancer of the lung, especially in males, maintained their position as major health problems in which no clear lines of medical attack have yet emerged"

In our view the recent suggestion of the importance of the essential fatty acids to the circulatory and nervous systems and to the carcinoma barrier points to the kind of knowledge which is becoming essential to us as practitioners

We therefore, call upon those responsible for the finance initiation, and guidance of medical research to consider the urgent need for ecological research, linking the basic approach to human nutrition with the origins of human food and, in particular, to assist the one experiment already in progress in this field

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[4] Annual Report of the Ministry of Health for 1952 Part II p 17 H.M. Stationery Office 1953

Annual Report of the Chief Medical Officer Department of Health for Scotland, for 1955 H M Stationery Office 1956

Medicine and the Law

A Missed Fracture

A WOMAN of 82 fell at an old people's home The doctor at the home, and the casualty officer at the hospital to which she was sent, both diagnosed a fractured arm, but failed to diagnose a fractured hip She was sent back to the home and died some days later At the inquest[1] the casualty officer said that he had not made a very thorough examination He knew she had been examined by a doctor at the home The coroner criticised him, saying that it would be as well if casualty officers "carried out their duties with a completeness the public has a right to expect"

Public Health

Miniature-radiography Survey in Bootle

IN the winter of 1955–56, an intensive survey was undertaken in Bootle by the Liverpool Regional Hospital Board's mass-radiography service[2] The object was to determine the extent of the reservoir of tuberculosis

One mobile unit was used continuously and two others occasionally each unit worked independently All streets were visited systematically, there was one open session each week for doctors' cases, volunteers, and contacts, factories offices, and schools were visited Before and during the survey a propaganda campaign was carried on Leaflets were displayed in public offices and cinemas and distributed in schools, the local newspapers carried advertisements, the film *Also Coming Shortly* was shown in the cinemas, talks were given to women's organisations, loudspeakers were used, and members of the Women's Voluntary Services canvassed from door to door, explaining the campaign and offering to act as baby-sitters while mothers were being radiographed

Bootle contains about 61,000 people over the age of 11, in the survey 22,340 were examined, including 13 901 residents of Bootle Many of the population work in Liverpool and could not be examined The response of industry was about the same as in 1954, nearly all eligible school children attended the open sessions started well, but fewer and fewer volunteers attended partly because they preferred to wait for the street sessions the street sessions started well, but attendances fell in bad weather and around Christmas On the whole, the response was much better than in 1954, and might have been better still if the survey had been held in summer if the site for the open session had been more convenient, and especially if two mobile units had been used exclusively for the street examinations early in the survey, leaving the school and office examinations till later This sequence was recommended after a similar survey in Salford[3] Efforts to follow those who failed to attend for further examination were not very successful

In the survey 32 people were found to have tuberculosis that needed immediate treatment, and 580 to have tuberculosis that was suspected, healed or needed clinic supervision The number of Bootle residents in the street-to-street group found to have tuberculosis needing immediate treatment or close clinic supervision represented 4 92 per 1000 people examined 12 patients with carcinoma, 98 with bronchiectasis, and 332 with cardiac abnormalities were found

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[1] *Manchester Guardian* Jan 4

[2] Liverpool Regional Hospital Board an Intensive Mass Radiography Survey carried out in the county borough of Bootle By T R ROBERTSON and J A RUSHWORTH

[3] See *Lancet* 1954 ii 1172

Many of the tuberculous had not been examined before and many had unilateral disease It is concluded that "the method of street to street and house to house survey has proved its value as a case-finding method"

Statistical Review of England and Wales

In part I of his Statistical Review for 1955[1] the Registrar-General records the detailed statistics of deaths from all causes and notifications of infectious diseases in that year, by age, sex, area of residence, and time of year

Deaths—The death rate of 11 7 per 1000 living was the highest since 1951, but the rate was lower in 1955 than in 1954 for all age groups except 5–19, 55–64 (where the rate was unchanged), and 65 and over

Deaths in early life—The stillbirth-rate (23 per 1000 total live and still births) was the same as in every year since 1948, except for 1953 when it dropped to 22 The infant mortality rate of 24 9 per 1000 related live births was the lowest ever recorded in this country The Northern region and Wales had the highest infant mortality rates (31), while the Eastern, South Western, and London and South Eastern regions had the lowest (21)

Tuberculosis—Deaths from tuberculosis (all forms) numbered 6492 in 1955 compared with 7897 in 1954 Since 1949 deaths from tuberculosis have declined by more than two thirds

Cancer—Compared with 1954, there was an increase of 941 in deaths from cancer of the lung, which formed 31% of all male deaths from cancer but only 6% of female deaths from cancer

Coronary heart disease—Deaths attributed to this cause have risen by almost 50% since 1949, reaching 44,256 for men and 26,341 for women in 1955

Bronchitis and pneumonia—The number of deaths certified as due to pneumonia was practically equal for the two sexes, but more than twice as many men as women died from bronchitis (19,294 males and 9499 females), of these, 16,519 male and 6607 female deaths were assigned to chronic bronchitis

A New Way With Chilled Meat

The idea of transporting beef carcases from abroad at temperatures high enough to avoid freezing the carcase and yet low enough to retard microbacterial growth has always been attractive As long ago as 1875 chilled beef was shipped across the North Atlantic the artificial cooling being applied at first by ice and thereafter by mechanical refrigeration The Argentine became Britain's main source of imported meat, for the sea journey took only fifteen days compared with some thirty days from Australia

The biggest difficulty in exporting chilled meat from Australia was that during the voyage mould developed on the surface of the meat, and for many years Australian beef imported to Britain had to be consigned in the hard-frozen state Many attempts were made to avert the development of mould on chilled meat during long voyages formaldehyde was tried but was eventually forbidden as constituting a danger to public health, but more recently it has been shown that the storage life of chilled beef is considerably prolonged if the atmosphere in the ship's hold contains about 10% of carbon dioxide—a method that has been used commercially

The arrival in Liverpool recently of the first shipment of Australian chilled beef kept fresh by ultraviolet rays has created considerable interest, for the cooling chambers of any ship can be fitted quickly and cheaply with the necessary apparatus Hitherto ultraviolet light has proved fairly effective in sterilising air, but less effective in the case of food because of its negligible penetrating power The opinion of the meat trade and of the consumer as to the quality of chilled beef so imported will be awaited with interest

In England Now

A Running Commentary by Peripatetic Correspondents

THE postman, whose sample-laden calls are causing distress and inducing black thoughts about the drug trade on Saturday mornings (*Lancet*, Jan 5, p 44), can be troublesome on other days of the week to those who work, as I do, in the second-floor front of an old London house and resent every foot-poundal expended in climbing the stairs And so can other people delivering goods But there is a remedy Buy from a fishing-tackle shop a wooden reel, 10–12 yd. of no 6 square-plaited flax line (20 lb breaking strain), and a small leaden weight Fix a spare front-door key to the end of the line with the weight threaded on an inch or so above it and a strong spring paper-clip riding loosely above that When the bell peals, and/or the knocker bangs, lower away, meantime engaging the caller in conversation from above By the time he has realised where the voice comes from the key is dangling at his hand at lock-level He then opens the door, disengages the key, and deposits the parcel on the floor while I reel in If a signature is required the book (or document) is fixed to the line by the paper clip In the absence of a supply of tiny parachutes a further "reel out" and "reel in" is needed, but the improved technique which comes with practice makes this task both agreeable and quickly executed In the spring, when the vine burgeons on the first-floor balcony, I plan to have a proper "spinning" rod (small) lest entanglements threaten our local blackbird's autumn food supply I will think of my peripatetic colleague at breakfast time on Saturdays, which is only fair, since I am a medical consultant to a firm of pharmaceutical manufacturers which doesn't post samples on a Friday—at least I don't think it does

* * *

A letter addressed to me at the "Royal Informary" called out some pleasing overtones I was not sure whether a delicate compliment was being paid to our skill in teaching, or whether a snook was being cocked at our disciplinary ward-sisters But my chief once again displayed his realism by suggesting that an informary was a place where forms were filled in At any rate we all felt in better form, and after all even Shakespeare and Freud scorned not the pun

* * *

In future, when people suggest that in technology and science we lag behind our cousins in the United States, I shall take comfort in the story of the gallant New Jersey firemen and their struggle to insert a fire alarm through a 730 ft pipe The pipe pursues an awkward twisting course beneath the New Jersey Turnpike, on one side of the highway lie the Lafayette Estates (a new housing scheme), on the other the Woodbridge fire-station The Woodbridge firemen, conscious of their responsibilities for these new residents, are anxious to connect the estate with the fire-station Oblivious, or perhaps suspicious, of the march of science, they have turned for help to the animal kingdom By means of a light harness they attached a piece of string to a rat and urged the rodent into the pipe But though eight rats have now entered the pipe none has emerged at the other end After brief explorations six have returned to base two, it is feared, have died in an S-bend Anxious to give the rats every help and encouragement, the firemen next procured a pet mongoose to keep them company The mongoose, Pop by name, seems to be an infuriating animal While acting as pace-maker he scuttled gaily through the whole length of the pipe But when he too was provided with harness and offered the responsibility of a length of string he never penetrated deeper than 300 feet

In their troubles the firemen have had the sympathy and interest of what the *New York Times* (Jan 6) describes as "an aroused public" It is true that some experts, such as the assistant dean of the Brooklyn Polytechnic Institute and the head of the department of civil engineering at the Massachusetts Institute of Technology, have tamely suggested such gadgets as an electric mouse or a ball under pressure But other citizens have shown more imagination Mrs Richard Fondiller, for instance, suggested that a large beetle with butter on its nose would follow the scent of the butter through the pipe (This method she says was successfully used, according to a classical tale, for transmission of a rope to a prisoner in a high tower) Artie Gildener (aged 14) proposed, rather unkindly, that a bottle of ammonia should be opened near the end of the pipe after a rat has entered Another kindlier but anonymous man suggested toasting cheese at the exit

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[1] Registrar General's Statistical Review of England and Wales 1955 Part I Tables Medical H M Stationery Office, 1957 Pp 373 12s 6d

I don't know what the firemen are going to do, but I shouldn't be surprised if some of them are out looking for beetles

* * *

The jargon used by music critics is not in the same class as that of wine-tasters, but it is sometimes unsettling The other Sunday, relaxing from the busy immunisation programme of the previous week, I tuned in to *Music Magazine*, and immediately learned that a symphony by Stravinsky was built round a "germ theme" Moreover, this germ theme, I was told, consisted of B C G repeated frequently An extract was then injected intra-aurally, with a multiple-puncture technique In the circumstances there was surprisingly little local discomfort, but my composure was gone The therapeutic value of music is well known, but its prophylactic virtues are obviously fraught with controversy

* * *

He is an old man of 81 and very thin I asked whether he had been losing weight "I don't rightly know, but I *think* I must have When they gave me a bath yesterday I floated"

* * *

DEATH IN THE THEATRE

So this is death,
And God's white angels stand around the bed
Angels One at my feet, one at my head,
And two And two How does the rhyme go on ?
Angels But were they angels, Luke and John ?
Why are they wearing masks ? When did I die ?
I can't draw breath
" Just go on breathing, ' who said that, and why ?
Why must I breathe, why, now that I am dead ?

Thus the patient,
Waking a moment from premedication
But not long sentient

A stranger entered
Angels indeed ? Mock angels to his eyes,
In baggy booted amateur disguise,
Whose backs, in place of wings,
Revealed a row of clumsily tied strings
And gaps And other gaps the stranger
Impartially observed, glancing behind
Façades into recesses of each mind
Trivial, self centred,
Earthbound expressions of exasperation
Hidden behind masks ignored the danger
Of unseen observation

The anæsthetist
Was thinking, we'll not finish off this list
By lunch time , nothing left to eat
But tepid scraps A houseman cursed the heat
A nurse was thinking deeply of injustices,
The surgeon of œsophageal varices
(Routine appendicectomies are waste of time)

Time ? Twenty minutes past the hour ,
The angels are passing over Make haste
Hush
And the mock angels thoughts were quieted,
Stilled by the silence of the silent rush
Of unseen wings A pulse flickered rioted
and ceased
The sombre silence stiflingly increased ,
None dared draw breath

Only the stranger
Watched with delight, ironical and mild
Death smiled

Letters to the Editor

THE FUTURE OF NURSING

SIR,—It was with real regret that many nurses read Dr Thomas Anderson's letter (Jan 5), though perhaps we can exercise some measure of understanding when we remember that his main experience of nurses and nursing has been in the field of infectious diseases—a field now rightly regarded as part of a comprehensive nursing education

In the experience of many nurses, medical men can be divided into two broad categories (*a*) those who regard nurses as their colleagues in rendering service to the patients , and (*b*) those who regard nurses as the handmaidens of the doctor, requiring only that they know (preferably from him) how things are done and never inquiring why they should be done in this way The first category is anxious to help nurses establish and maintain standards of patient care, realising that the nurse who knows both how and why is a better all round nurse and colleague The second category looks at nursing and nurses from one angle

The shortage of woman-power, the increased need for nurses in a national health service, and the very large number of callings now open to women, means that nurses are drawn from all socio economic levels with various degrees of intellectual capacity and differing educational background Inevitably, we are going to recruit more and more of the girls who only want to know how, as opposed to those who want to know how and why and who will form the leaders in the profession This latter group must be given a preparation which will enable them to exercise more than adequate supervision so that the patient comes to no harm If this is what Dr Anderson calls "officer class," then we do not quarrel , after all, we do not attempt to run the Services without officers, so why do we think it is possible to do so in nursing ? Perhaps Dr Anderson thinks of the doctors as the officers, and of the nurses as the other ranks

The letter goes on to say that nurses should develop along the "line of the needs of the doctor and of the needs of the public whom we both serve" Do the majority of doctors really accept this ? Medicine is diagnosis and therapeutics, but nursing has a unique function

> "The nurse is temporarily the consciousness of the unconscious, the love of life for the suicidal, the leg or arm of the amputee the eyes of the newly blind We do not do *to* patients as if we were their custodians, nor do we do *for* them as if they were our dependents We do *with* them leading them on to increasing self direction '

The nurse renders her service to the patient, not to the doctor

In so far as the *examinations are concerned*, they are the responsibility of the General Nursing Council, and, if Dr Anderson wants to find fault with them, he should register his protest in the right quarter

His recent experience with the sister tutor seems to have surprised him, but it would not have surprised a nurse What makes Dr Anderson think that he or the chest physician sees things from the point of view of the social worker or the occupational therapist ? Social work, occupational therapy, and nursing are all professions in their own right with disciplines and skills which play no part in the curriculum of the medical student

Finally, may I add that the *Lancet* Commission on Nursing was not set up to "allow the medical profession to redefine the kind of nurse this country requires" The nursing profession is quite capable of doing this, and would regard any other profession laying down its standards and its code of ethics as little short of impertinence

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MARGARET C N LAMB
Education Officer

SIR,—I have read with interest the correspondence following your annotation (Nov 24), having myself trained as a nurse before starting on a medical career

The statement of policy of the Royal College of Nursing reiterates the problem of providing enough nursing care of a high standard in the country's curative and preventive services, but their answer appears unrealistic and in some ways regressive They envisage a horizontal expansion to equip enough people to do the nursing, and a vertical expansion to provide teachers and leaders The result would be a hierarchy rather than a "team" Admission to training for each grade is to be based on "qualitative selection including entrance tests and assessment of individual capacity" It is said to be hard to select medical students, then surely to choose (at the age of 18) embryo leaders and teachers for a vocational profession will be even harder A profession offering opportunities for advancement is surely more attractive than one which offers only the chance of selection to some grade, especially when the grade may bear the title "assistant nurse" Would it not be better to give all nursing candidates a short basic training in the care of patients after which they could either remain practical nurses or take more advanced courses in special nursing ward management, teaching, or administration ? This scheme would do away with the invidious distinction between hospitals suitable for training S R N s and those suitable only for training assistant nurses An "officer class" which has not risen from the ranks may not understand the problems of those who provide the daily nursing care

The R C N report makes no mention of less drastic changes which might increase what they call nurse power Educated girls will not choose a profession in which they are cut off from a normal cultural and social life, as are student nurses, by the irregular and unpredictable hours of work The shift system as tried successfully during the war can be the answer to this problem, for, properly organised, it gives predictable off duty without detriment to the standard of nursing care

The R C N give no reason for the categoric statement that no one under 18 should be included in the nursing team In support of Dr Ritchie Russell's contention that most girls are ready for hospital work at 17, it may be mentioned that fifteen years ago some general training schools did accept student nurses at 17 (and perhaps they still do) The professional life of nurses is usually short, being terminated by marriage, and the year gained by an earlier start would do much to relieve the shortage

The problem of the supply of nurses is one not simply of recruitment but also of preventing wastage Any profession mainly staffed by women must be realistic enough to accept and cater for marriage and motherhood if it is not going to lose some of its most valuable recruits A recent advertisement, for a responsible person to look after two children and to do light housework part-time was answered by 3 S R N s and 2 nurses on the supplementary register All said they would like to nurse if they could find suitable posts, now that they had homes and families With imagination and a less rigid approach, surely these mature women could be used in the nursing services

Cardiff JULIA FOURMAN

SIR,—It is obvious from this correspondence that there is a pressing need for nurses and doctors to meet and discuss problems common to them both on an equal footing It is as ridiculous to say that a nurse must always be subordinate to a doctor as it would be to suggest that she should always act independently of a doctor The care of patients is a far more complex problem than the carrying out of doctor's orders, and nurses, or at least some nurses, must be trained to meet the wider concept of total care of the patient

How many doctors would wish to be responsible for the way a ward sister runs her ward ? Or for the training of nurses in the art of nursing ? These are not properly the functions of a doctor, any more than venepuncture and taking the blood pressure are properly the functions of a nurse But if doctors are willing to allow competent nurses to carry out such things, can they expect them to regard themselves as wholly subordinate ?

Nursing, in the sense of caring for the sick, can be quite independent of medical care it can be good, bad, or indifferent, so that the patient can be well treated medically but badly nursed Similarly, the patient can be well nursed but inadequately treated Indeed, one of the criticisms of nursing today is that nurses are carrying out so many "treatments" that they have no time to devote to nursing This criticism only applies at the bedside, however, and at the bedside care can be carried out, under the direction of trained people, by those with little basic training It can be adequate, but it need not be we must not allow ourselves to be persuaded that sick people can be well nursed by untrained or partly trained or unintelligent people An intelligent well taught person can do everything better than a stupid or untaught one, and this applies to nursing no less than to any other job

So far from lowering our standards of basic training, they should be raised, teaching must be improved so that everyone who wishes to learn and is capable of learning does so, training must be organised so that trainees learn what they need when they need it, and at their own pace With regard to the qualified nurse, it is becoming increasingly obvious that basic nursing training is not sufficient to enable anyone to take higher posts without further specialised preparation This applies from the ward sister level upwards Now there is no *reason whatever why such preparation* cannot be at university level, the arts of administration, of teaching, of organisation, the knowledge of psychology, of personal relationships, of educational methods, can all be learnt at a university Tutors are trained in this way and there is no reason at all why ward sisters and matrons should not be In fact, I would go further and say that they must be if, in future, hospitals are going to be places where sick people get better, and if the wider needs of the health services of the community are to be met

The old pernicious practice of promoting people simply because they had given ten or twenty years' service must certainly go, and go quickly Long years of idling away time in the same job, doing the same things year after year, is not experience, nor does it teach anyone anything Nurses in future must move about more, think more, do more, and be prepared to undergo further education in preparation for higher posts, and doctors must realise that in the higher posts they will find men and women they can regard as useful and reliable colleagues fully able to realise the responsibilities we must all share in the future health of the community

Doctors who are interested in nurse-training would be well advised to read and study carefully the proposed new syllabus of the G N C for mental-nurse training They will find here a curriculum that offers opportunities for a basic training within the capacity of any normally intelligent and interested person, yet capable of providing a foundation on which further studies can be built—a curriculum which can turn out trained nurses able to care well for sick people, yet also suitably prepared for gaining further knowledge at a higher level

It is surprising that doctors should consider themselves in a position to criticise nurse education Many nurses could make pertinent criticisms of medical education, except that they do not consider they have any right to do so. Perhaps what is really needed is a freer exchange of opinion and ideas on both sides; if the participants did not benefit, the likelihood is that the patients might.

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UNA V. BUDGE
Sister Tutor

RETURN TO PLANNING

SIR,—Your leading article of Jan. 5 contains a statement that cannot be allowed to pass unchallenged. You say "... while a salaried service would abolish financial competition altogether." Surely this is quite untrue. Would you say that there is no financial competition to reach high rank in the Army or Navy—or, for that matter, in our own profession among members or those seeking membership of hospital staffs where payment is in the main by salary, with the possible addition of Merit Awards?

There are, of course, many other possibilities to be considered; but if there is to be a "return to planning," which is the title of your article, the idea of a salaried service cannot be summarily dismissed on the grounds you state. The precise opposite is the truth. One of the great advantages of payment by salary is that it could offer the best possible type of financial competition in that the reward could be based on the quality of the work done rather than on the number of patients on a doctor's list—two things that so often compete in inverse proportion.

A few years ago[1] you were good enough to publish my views as to how a salaried service might provide a solution to our problems. Very briefly, one visualised general practice in the National Health Service organised in groups working from health centres, some members of each group adopting special interests and their salaries mounting to match their special skill, qualifications, and experience. In the higher grades these should certainly conform to those paid to members of hospital staffs. Vacancies in the service would be filled by a system of advertisement and application supported by testimonials. Advancement would depend on the judgment of professional colleagues instead of, as at present, the chance of popular favour or density of population.

This indeed would present a most radical change and a complete break from the past. It would offer a new prospect to those joining the profession and might help to solve our registrar problem. One feels, therefore, that young men should have a greater voice in our counsels, and planning should not almost entirely be in the hands of the elderly who have in the main retired from practice.

I am acutely aware of the many difficulties and dangers that such an idea would present and the intense opposition it would arouse. Nevertheless one must surely admit that far from abolishing competition for financial and professional advancement it would foster it in an extreme degree and this is one of the greatest points in its favour.

Plymouth

W. A. LISTER

THE Rh BLOOD-GROUPS

SIR,—Dr. Wiener, in his letter last week, again demands not only the retention of his Rh-Hr nomenclature but also the abolition of the far more convenient CDE terminology. While nobody could deny the value of Dr. Wiener's work in this field, he is now rather in the position of a Chinese philosopher who has written a great work in the language he knows best and stubbornly opposes its translation into Western languages, arguing that it is up to the Western countries not only to learn Chinese, but to abandon their own languages in favour of it.

Dr. Wiener takes you to task for "serious errors of commission and omission" in your editorial, but the "evidence" he himself produces will not stand examination. His method of arranging it by comparing dissimilar tables can equally well be used in reverse. One takes phenotype and all possible genotypes for one's own system but only the "most likely genotype" for one's opponent's. Thus:

Blood	*Most likely genotype*
Putative father's	R^1r
Mother's	rr
Child's	R^0r

Such a report could mislead one into believing that the Rh-Hr tests exclude paternity. Yet in the CDE notation the same case might be reported as follows:

Blood	*Phenotype*	*Possible genotypes*
Putative father's	CcDee	CDe/cde, CDe/cDe, cDe/Cde
Mother's	ccddee	cde/cde
Child's	ccDee	cDe/cDe, cDe/cde

Obviously the CDE tests do not exclude paternity. If Dr. Wiener is going to omit the word "possible" before "genotype" he is going to find paradoxes everywhere. The -D- pedigrees quoted could have been expressed equally misleadingly in Rh-Hr notation, and could have shown mothers of genotype R^0r having children of genotype $R^1\mathfrak{R}$. In both these examples it is possible to "prove" by Dr. Wiener's own reasoning the superiority of the CDE system.

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J. W. NICHOLAS

UNILATERAL ELECTRO-SHOCK

SIR,—Not to harm (*primum non nocere*) is a cardinal maxim forcibly brought to mind by electro-shock treatment. It has prompted me to try the effect of applying electrodes to one side of the head only.

The dominant side of the brain was avoided as a precaution against possible damage to the speech area. The shock was therefore administered on the right side of the head in right-handed persons and on the left in the left-handed. To limit the area exposed to direct stimulation, the electrodes were placed on the scalp over the precentral (motor) gyrus in about its middle third (i.e., Brodman's area 4b) or lower (area 4c).

The smallest response has been a slight upward movement of the contralateral eyebrow; the next a contraction of the contralateral muscles of the face as a whole. In other cases the head was turned to the side opposite to the site of the shock and the contralateral platysma muscle contracted; in others still, the convulsive movement involved the contralateral arm and even the leg.

Sometimes, despite the limited area of stimulation, the convulsion would spread to the whole body. Nevertheless the muscular response was in general more restricted and milder than in trans cerebral shock.

Practical points worth noting are:

(1) A small sand pillow is placed beside the head on the side opposite that on which the shock is to be given. Though as a rule the turn of the head is barely perceptible, there may be a jerk. In any case, support is needed to withstand the slight pressure of the electrodes.

(2) For the headgear, the standard horseshoe shaped plastic holder may be broken in the middle for greater freedom of placement.

(3) 'Cambridge Electrode Jelly' is rubbed into the hairy scalp at two selected points—about an inch apart—in preparation for placing the electrodes. The electrode pads, soaked in saline, are squeezed beforehand so that the saline does not run.

A muscular relaxant (suxethonium bromide, 'Brevedil E') and an anæsthetic (thiopentone) are used in the accepted manner.

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[1] *Lancet*, 1951, ii, 876.

Where the muscular contraction is limited to a flicker of half the face, the risk of fracture of spine or limb is eliminated, and even when the fit has involved a limb or limbs there has been no obvious damage Breathing was resumed far more quickly than after the standard bilateral shock—perhaps because the diaphragmatic area was missed altogether or because only half the diaphragm contracted As anatomically the thoracic representation in the brain lies higher up, in Brodman's area 4a, the pulse often remained full and regular In the most favourable cases, the cerebral representation of the abdominal cavity should be missed, with less risk of abdominal complications

Patients awoke within a few minutes of the shock Many became lucid and orientated very quickly, and those who had previously been puzzled by retrograde amnesia following bilateral electro shock seemed delighted by the extent of their memory of events just before unilateral shock The patients soon became ambulant and, in many cases, cheerful Recovery room activities took much-less nursing time for the group of patients as a whole and the ward resumed its normal appearance much more quickly

In over 100 shocks, the only hazard noted as peculiar to the unilateral method has been slight singeing of the hair where the saline on the electrode pads has run or where a bridge of jelly has contaminated the hair between the pads

Clinical results, so far, appear to justify continuing with the method of unilateral electro shock

Deva Hospital, Chester ISAAC FROST

DANGEROUS CONTAMINANTS IN STORED BLOOD

SIR,—It is no use Dr Discombe saying (Jan 5) "I maintain that the safest procedure is to use pilot bottles and to refrain from entering the main bottle until it is actually to be used" and thinking he has thereby solved all the problems of blood transfusion My department cross matches about three thousand bottles of blood each year, and that experience might lead me to be as dogmatic as Dr Discombe and maintain that pilot bottles are useless and misleading and should not be permitted

In practice neither statement would stand up to examination in detail, and arguments such as those used by Dr Discombe will do nothing to make transfusion safer All we can do is to establish the general principle that transfusion is a hazardous procedure and that therefore each laboratory must devise a method of providing blood that reduces the hazards to a minimum if they cannot be abolished. My own view is that to do this involves taking all samples for cross matching from the bottle that is to be infused, that whatever appropriate tests can be done in the time available should be done, and that all this must be done by trained staff who are doing enough of it to remain trained and expert

In such circumstances Dr Discombe's conclusion from Dr Drummond's figures that 5 1% of entered bottles are contaminated in hospital laboratories must be wrong In this laboratory all blood is looked at for gross contamination by examining a film of the sample that is being used for cross-matching, and at the same time, and all bottles that have been entered and are to be re used are re entered and cultured My technicians would not agree with, and Dr Discombe's can hardly be complimented by, the suggestion that a few minutes spent on examining a film renders them liable to make a mistake in ABO grouping In any case contamination is so rare that one might be tempted to accept Dr Discombe's dictum and neglect the procedure, but we do not because we are prepared to take all steps we can to reduce the hazards

We believe we have seen more deaths after transfusion from clinical misjudgment as to the need for that procedure than from bacterial contamination or serological incompatibility Wise and restrained use of blood by clinicians and a good system of laboratory control by trained personnel (only), including bacteriological examinations and no pilot tubes, and we are doing the best we can

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NEUROTIC PARENTS

SIR,—I have read Dr J G Howells's article on Day Foster-Care and the Nursery (Dec 15) with the same interest as all his previous excellent publications Such work is indeed rare among children's psychiatrists, whose daily routine usually prevents research But this very lack of parallel investigation should make us the more careful about accepting too readily the apparent implications of a pilot experiment and rejecting the pioneer work of J Bowlby and others which has led to a healthy change of attitude in child welfare workers throughout the world If, as Dr Howells mentions, the Report of the Children's Department for 1955 shows that only 1 in every 200 children is now in institutional care, this is due very largely to the drastic change of policy inspired by Bowlby's report on Maternal Care and Mental Health Howells's work is an antidote to uncritical acceptance of the theory of maternal deprivation, but it is less contradictory to Bowlby's researches than it appears It seems to me that he has, in fact, unwittingly confirmed what Bowlby teaches by showing[1] how separation from the mother was longer among the 37 neurotic children than among the healthy ones, and that a father can prevent nervous symptoms in a child by acting as (in Bowlby's sense) a mother substitute His observation that, because of poor substitute mothering, hospital admission is the most traumatic experience for children supports Bowlby's views rather than his own insistence on the benefits of day foster care Furthermore, the value of Bowlby's work lies in the prevention of affectionless and chronic neurotic adolescents and adults, and not, as Howells and Layng[2] imply, in any claim that maternal deprivation causes maladjustment in childhood itself Bowlby has never failed to emphasise the need for removing the child from an emotionally unhealthy home, but he has emphasised how harmful separation from parents can be It would be wrong, I think, to weaken belief in our present tendency to keep families together, and to encourage even "unwanting harsh, rejecting and hurtful parents" to seek substitute care too readily in every case we should first try by intensive psychiatric social work or the help of a family service unit, to change their attitude

Bowlby's work remains unchallenged and proves that satisfactory adult affectionate social relationships can be learnt in infancy only through one's love relationship with one's own mother As Dr Howells says, substitute care must supply "warm mothering," and "many well intentioned people drawn to child care" lack the ability to supply this Even more serious, and surprisingly often overlooked, is the persistent insecurity of any child "in care," because of continual changes of personnel and the ever possible rejection by a foster parent The real parents, even if they refuse to acknowledge the child and stay bodily away, remain to him all his life "my father and my mother" Are we not overstating the damaging effect of a neurotic home when we form our views on our rather limited child psychiatric experience? Hardly any family is without

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1 Howells, J G, Layng J *Med Offr*, 1956, 95 345

2 Howells, J G, Layng, J *Lancet*, 1955, ii 285

its skeleton, yet history testifies to the existence, throughout the centuries, of vast numbers of successful and stable adults

Child Guidance Unit
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A K **Graf**

ENURESIS

SIR,—I was much interested in the article by Dr L A Nichols (Dec 29) He has said nothing to change my view that in these cases the personal influence of the doctor is one of the most important factors Certain of his theoretical and practical statements I feel are incorrect May I offer a few comments and criticisms ?

(i) It must be accepted that enuresis is socially undesirable This statement may seem trite, but in my experience it is all too common to hear that a doctor has said "Don't worry, mother, my own son had it until he was 14" Furthermore, loss of bladder control is not thought abnormal in all societies for example, Margaret Mead[1] tells us "When an infant urinates, or defecates, the person holding it will jerk it quickly to one side to prevent soiling his or her own person This jerk interrupts the normal course of excretion and angers the child In later life the Arapesh have notably low sphincter control, and regard its loss as the normal concomitant of any highly charged situation"

(ii) Arnold Gesell and his colleagues[2] have described the natural history of bladder control and pointed out that "the whole problem of bladder control is so charged with developmental factors in normal as well as deviated children, that they should have primary consideration both in interpretation and in treatment The culture is inclined to be too meddlesome and too emotional "

(iii) The causes of enuresis have often been examined Stockwell and Smith[3] found a psychological cause in 50% of the cases, and of these 88% were improved or cured by psychiatric help, including environmental changes A further 37% were ascribed to physiological variations of neuromuscular function This group is the one that would respond best to renewed habit training and the use of drugs The remaining 13% had some organic basis for their enuresis This is in my view abnormally high It is the general consensus of opinion that urological lesions are found in perhaps 5–7% of children with enuresis Therefore Donald Paterson's dictum[4] ought always to be in our minds "Before starting the treatment of enuresis it is absolutely essential that organic disease should be ruled out" This is very difficult without too many complicated investigations, and a good rule is that of M F Campbell,[5] who says that if an intensive medical or psychological course of treatment is unsuccessful after, say, 2–4 months' trial, the child is entitled to a complete urological examination Anyway, admission to hospital for a fortnight's observation would be helpful because spontaneous remission is usually seen in the ward in cases of psychological ætiology (providing the intelligence quotient is not too low)[6]

(iv) We still have the special problem of adult enuresis, and whilst Thorne[7] and Cohen[8] consider this a symptom of a fundamental defect in the central nervous system most studies have concluded that in the non organic cases it is a symptom of a more generalised psychiatric disturbance

(v) Even if we discount the adult enuretic and separate the 5% or so of "organic" cases, we are left with the fact that "nocturnal enuresis is probably the commonest habit disorder"[9]

Despite these criticisms therefore, Dr Nichols's determined attack on the problem is to be applauded and his paper welcomed as a stimulus to general practitioners to take an interest in such a difficult and common disorder

Harold Hill Essex

R C **Greenberg**

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1 Mead M Sex and Temperament in Three Primitive Societies New York 1935

2 Gesell A Ilg F L Learned J Ames L B Infant and Child in the Culture of Today New York 1943 p 333

3 Stockwell L Smith C K *Amer J Dis Child* 1940 59 1013

4 Paterson D Sick Children London 1947 p 213

5 Campbell M F N Y St J Med 1934 34 190

6 Henderson D K Gillespie R D A Text book of Psychiatry London 1944 p 634

7 Thorne F C *Amer J Psychiat* 1944 100 686

8 Cohen D L *J Urol* 1947 57 331

9 Henderson D K Gillespie R D *Op cit* (footnote 6), p 633

SIR,—The method described by Dr Nichols is likely to prove useful But I want to point out an almost ubiquitous fallacy with regard to the management of enuresis Dr Nichols writes

> One cannot emphasise too strongly to the parents that the desire to be dry is much greater in the child than in the parents Being an enuretic is no bed of roses

This, however, neglects the existence, in many cases, of a need for self-punishment Also many children will confirm, and even explain at length, that both the wetting and the stay in a wet bed are to them a pleasurable sensation which they have no real wish to forgo The gaining of control over desires or functions is never pleasurable, and is always done in exchange for love —from parents or others

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D J **Salfield**

SIR,—You are to be congratulated on publishing the article by Dr Nichols not only because articles by general practitioners are all too rare in our overspecialised medical journals, but also because his article is full of excellent and practical advice His way of handling this common and distressing complaint is one which I, as a child psychiatrist, heartily endorse

Drugs are of limited use, and should only be considered as adjuvants It might be said that Dr Nichols has oversimplified the problem, and that in some cases enuresis is only a symptom of a deeper disturbance, but in the great majority of cases his approach, which is basically one of explanation and encouragement, is the best one—both to this and other problems in childhood His article also has a bearing on the whole question of psychotherapy in general practice, which is at last beginning to receive the attention it deserves

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C **Burns**

THE GREATER MEDICAL PROFESSION

SIR,—Recent comment in your journal concerning the almoner's future status within the "greater medical profession" appears to me to be based on a misapprehension of some importance both to the patients and to ourselves Implicit throughout what has been written is the assumption that the doctor has the power to stand with his patient in a place apart until he decides otherwise None should question the rightness of this while it concerns only the patient's body and sometimes his troubled mind It is, I suggest, a false assumption directly it is held to include the social emergencies consequent upon illness If the doctor fails to make this distinction events may move out of his control to the detriment of his patient

The social consequences of illness impinge with varying force on people other than the patient, and while they, and the patient, will wait with unquestioning thankfulness for the doctor's advice upon medical matters, they will frequently take the initiative themselves in an effort to relieve the anguish of his circumstances Appeals for help and advice are frequently made to the hospital almoner because she is known to stand close to the doctor on whom dependence is placed She has, I suggest, in consequence, not only the duty to obey the doctor's instructions with the greatest possible care but also the heavy responsibility of advising him on her own initiative upon matters about which her knowledge and experience may be wider than his own Only when the almoner accepts scrupulously that her final duty to the patient is confined within the doctor's instructions to herself and when the doctor recognises his almoner as a specialist with her own smaller but individual responsibilities can the patient's social difficulties adequately be relieved

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E **Sumpter**

CUSHING'S SYNDROME WITH CARCINOMA OF BRONCHUS

SIR,—In the article by Dr Harrison and others (Jan 5) I am quoted as having reported a similar case This is not so, and in fact my only reference to such a patient was during a discussion on the relationship of 17-keto genic steroids to surgery at a meeting of the Surgical Research Society in Birmingham last year The patient in question was in fact under the care of Dr H P Brody at the Sheffield Royal Infirmary, and the findings have been submitted for publication by members of his staff

When no actual contact has been made between an author and the person he is quoting, the words "personal communication" are not, I think, the most suitable form of reference

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R P JEPSON

PSYCHOTHERAPY IN GENERAL PRACTICE

SIR,—Your leading article of Dec 29 prompts me to describe my own voyage into this ill charted territory

I had for some time been distressed by the large amount of "neurosis" with which I had "to contend" in my practice Eventually I had to admit to myself that my understanding of these patients was deficient, and my management of their cases inadequate It was evident that if I were going to bring any relief to their suffering —and my own distress—my education and experience had to be supplemented in some way I knew of no postgraduate courses for this type of work, and was unfortunately unaware of Dr Balint's general practitioner discussion groups at the Tavistock Clinic I had already been practising untutored trial and error, and felt that it was fraught with danger

I had, however, been making use of the services of one of the Middlesex County Council's psychiatric social workers, Mr Eugene Heimler, and had been gratified by the progress which several of our patients had made We felt that it would be interesting to observe the effects of close collaboration between us, both on the patients and on myself I believed that my main disability was a lack of psychiatric orientation, and hoped that the psychiatric social worker (P S W) would help me achieve it

One afternoon each week was set apart for a joint "mental health session" with the P S W at my consulting room We decided to exclude children (for whom we both felt further experience would be necessary) and *to include the following groups of patients*

1 The overtly "anxious," in difficulties either at work or at home

2 Those presenting mainly with somatic symptoms where I had taken reasonable steps to exclude physical illness and where environmental stress was known or suspected

3 Those with a hysterical prolongation of an originally physical illness

4 Suspected psychotics

5 Psychiatric cases requiring supervision by a general practitioner

I found that I did not have to "sell" the idea of this joint approach to the patients in group 1, who were mostly only too pleased that someone was prepared to listen to their tale of woe In groups 2, 3, and 4, this was often not the case, for though I felt that a psychogenic ætiology existed, the patients often had other ideas The greatest difficulty at this point was to avoid being drawn into battle with the patients, but rather to offer them a reasonable alternative to repeated "reassurance" and unending medication I went to war less frequently as I gained experience, but it certainly took time

In the joint session, we attempted to consolidate the good rapport which I had tried earlier to establish A genuine interest in the patient's difficulties and a desire to help are the most desirable instruments At first I was little more than an onlooker, the P S W doing most of the work, and I realised more than ever how little I knew and how much there was to learn We started off by inviting the patient to discuss his symptoms, his difficulties, or anything about which he particularly wished to talk It was evident that the most important qualification was to be a good listener

I noticed that diagnosis presented little difficulty to me, but this had previously been exasperating, for it had not been a step towards active treatment These interviews, however, added another element to my clinical diagnosis a psychosocial diagnosis is a summary of the patient's potentialities in a given environment, taking into account his normal and abnormal psychological reactions

With the development of a good rapport, the patient became more receptive to any interpretations which we might give We tried to crystallise the problem, and to show him possible connections between his symptoms and any environmental factors to which he was responding, according to the pattern of behaviour which was peculiar to him We aimed to help him understand his reactions and the reasons for them, hoping to change his attitude, we also recommended alteration of the environment when this was both practicable and desirable Thus, when a harassed mother was receiving psychotherapy her child might be placed in a day nursery for part of the time, or a home help obtained Some patients improved with merely one interview, usually of about 45 minutes, while others needed several, those who failed to improve were referred to the psychiatric clinic, or were seen by a psychiatrist at home In cases of suspected psychosis a consultant's opinion was always sought We often saw the patient's relatives, giving them some explanation of the disability and advice on general management

The table shows the effect of treatment on the first 43 patients studied The numbers are small and several patients are still under treatment and may be regraded at a later stage The grading of the response is based on my subjective impressions

Group	No of cases	Response to treatment		
		No improvement	Partial adjustment	Satisfactory adjustment
1 (anxiety)	20 (*47 %*)	4	9	7
2 (psychosomatic)	13 (*30 %*)	5	3	5
3 (hysteria)	2 (*5 %*)			2
4 (? psychotic)	4 (*9 %*)	2	2	
5 (aftercare)	4 (*9 %*)	2	2	
Total	43 (*100 %*)	13 (*30 %*)	16 (*37 %*)	14 (*33 %*)

This experiment, which has been in progress for a year, has undoubtedly had its effects upon myself With the help of the P S W, I have gained some insight into normal and abnormal mental mechanisms This has helped me in the routine conduct of my practice, and has amply repaid the time spent on the afternoon sessions In many instances I can treat the less disturbed patients satisfactorily during my normal surgery hours I am also gaining insight into my own emotional responses to my patients, and some whom I previously would have felt as a source of irritation and frustration I now regard in true perspective as troubled men and women in dire need of help

Although the journey is just begun, I have at least gone some distance in the right direction, instead of wandering aimlessly in the wilderness There are some, working in general practice, who have already emerged as masters of this art, and it is to them that we must look for guidance and teaching

My thanks are due, above all, to Mr Eugene Heimler, for his capable navigation throughout the year, to Dr A C T Perkins, county medical officer for Middlesex, for his cooperation, to Dr G S Wigley, his deputy, for encouragement and advice, and to Dr Colman Kenton, the regional psychiatrist for helpful criticism The Middlesex County Council, naturally, accepts no responsibility for the views expressed in this letter

London N 13

NEVILLE DAVIS

SHORTAGE OF RADIOGRAPHERS

SIR,—I wish to comment on one or two important points in Mr Baxter's letter (Dec 22)

An Industrial Court award has recently been made granting radiographers an increase of salary of less than 10% This award raises the maximum salary of a superintendent in one of the largest X-ray departments to £850 per annum—a maximum no radiographer can hope to reach under the age of 45 It will be appreciated that the superintendent of a busy department requires certain medical knowledge, in addition to great technical and organising ability This is especially true in one of the many busy departments where there is no full time radiologist The superintendent radiographer's maximum salary of £850 is quite inadequate and compares most unfavourably with, for instance, the corresponding salary of £1025 of the chief laboratory technician

The salaries of the lower grades of radiographer are, of course, correspondingly more meagre, and considerably less than equivalent grades in other ancillary departments Here are some figures for comparison

	Junior	*Senior*
Physiotherapist Occupational therapist	£462 10s–£537 10s	£520 10s–£580 10s
Radiographer	£420–£485	£485–£570

The physiotherapists are at present negotiating an improved salary-scale

Unless a radiographer is lucky enough to have one of the very few tutor posts, she receives no payment for lectures given to radiography students There is likewise no reward for a radiographer attaining her fellowship In short, there is very little incentive for anyone to take up radiography, or even to stay in the profession

It seems incredible that the Industrial Court should see fit to make such a poor award in view of the grave shortage of radiographers, and the insistence in the recent M R C report on the hazards to Man of Nuclear and Allied Radiations [1] that repeat X-ray examinations must be avoided by careful work in the first place, by responsible technicians

The recent findings in Oxford, on leukæmia in children who were X-rayed in utero,[2] surely prove the necessity for maintaining a high standard in the radiography profession I feel that any person handling X-ray apparatus should be suitably rewarded for her skill as a technician and her responsibility to the public in using a potentially dangerous X radiation

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C J MYDDLETON

SIR,—May I comment on the views expressed by Dr G H Illingworth (Jan 5)?

The dissatisfaction with salaries is not by any means confined to a "few male radiographers"—attendance at any meeting of radiographers will prove conclusively otherwise

The statement in regard to educational requirements is again evidence of an ill informed opinion, the standard required is very reasonable, is accepted by radiological bodies and the Ministry of Health, and is consistent with the requirements of other similar medical auxiliary bodies A reasonable level of technical knowledge would seem desirable when one considers that a girl may have to operate and handle a rather complicated X ray machine, worth many thousands of pounds—apart from the fact that such a machine may be lethal to a patient in unskilled hands

Restriction to approved training schools can only *raise* the standard of radiography, and therefore lead to more efficient radiology Any radiologist worthy of the name would decry the 'hole and corner' training to which many student radiographers were formerly subjected

The Society of Radiographers has, if anything made entry and qualification easier in the past few years by (1) broadening the educational requirements, (2) increasing the scope in the examination papers, and (3) increasing the breadth of training and thus ensuring a better comprehension of the subjects

To say that there are only two essentials in the production of a radiograph is ludicrous, and the statement that physics, maths, and English are not essential strikes at the roots of the whole system of technological education, for its acceptance could lead to the production of a race of moronic button pushers

I believe that most radiologists and radiotherapists would agree that a superintendent radiographer is an essential member of the radiographic team, and only by having complete harmony between radiologist and superintendent (male or female) can an X-ray service or treatment be fully efficient

Furthermore, has Dr Illingworth considered how few X-ray departments have a full-time radiologist who can also function as a full time radiographic superintendent? It would seem evident that Dr Illingworth would prefer his department to be staffed by "unqualified X-ray assistants," whom we hear may infiltrate understaffed departments up and down the country

Many radiologists and the Society of Radiographers deplore this possible state of affairs, which could only lead to a lower standard of radiography and radiotherapy—at a time when many authorities, single and corporate, are demanding the intelligent use of radiation and are stressing the hazards of incompetency

To my knowledge over many years, the Society of Radiographers has striven to maintain the highest possible standards, consistent with radiological requirements, and only by the continuance of this endeavour can radiology be assured of the most efficient contribution of British radiography (possibly the best in the world) in the common cause of medicine

Cardiff

E R HUTCHINSON

AN ERROR TRACKED TO ITS SOURCE

SIR,—The silent intervals in this correspondence are a little reminiscent of my attempts to play chess by post with a Russian friend living in the Ukraine before the revolution of October, 1917

In my original letter,[1] I sought information as to the source of a phrase, in an instructive and interesting article by Dr Carstairs and his colleagues,[2] attributed by them to Galen I hate to throw any doubt on Dr Carstairs's claim,[3] but is it not possible—nay, probable—that the phrase in dispute is Burton's own and not Galen's?

In the *Anatomy of Melancholy* [4] we find the following passage

> "Besides, it [exercise] expells excrements by sweat, and other insensible vapours in so much that Galen prefers Exercise before all Physick, Rectification of diet, or any regiment in what kind so ever, 'tis Natures Physician"

As a marginal note alongside the passage, Burton quotes Galen's *De Sanitate Tuenda* liber I, in which work can be found passages which could justify his summing up

According to R M Green's translation of this work,[5] Galen says

> "And it is clear, even at this age, how much our nature is associated with exercise, for, not even if you shut them up somewhere, could you prevent children from running about and frolicking like colts and calves For in all animals nature is enough to incite the impulses appropriate for health and safety"

Later in liber II [6] Galen considers what is the distinction, or degree of distinction, between work, exercise, and movements, exercise to him connotes vigorous movement, and therefore, to him, the work of "those who dig, and those who reap and those who ride" is synonymous with exercise

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[1] H M Stationery Office 1956

[2] Stewart A Webb J Giles D Hewitt D *Lancet* 1956, ii 447

[1] Selwyn Clarke S *Lancet* 1955 ii 1138

[2] Carstairs G M Clark D H O Connor N *Ibid*, p 1025

[3] Carstairs G M *Ibid* 1956 ii 1268

[4] Burton R The Anatomy of Melancholy London 1676 p 168

[5] Galen, C De Sanitate Tuenda trans R M Green Springfield, Ill 1951 p 25

[6] *Ibid* p 53

Claudius Galenus (A D 129–199) is credited with having written over 500 treatises (all in Greek), and, although nearly four fifths of them were destroyed by fire in Rome, Dr Carstairs may know of one (other than *De Sanitate Tuenda*) which lends support to his contention

Society of
Medical Officers of Health
Tavistock House South,
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London, W C 1

SELWYN SELWYN CLARKE

ANTIBIOTICS AND IMMUNITY TO VIRUSES

SIR,—Immunity to many viruses has been considered to be a premunition resulting from persistence of the immunising virus in the cells of the host As some viruses appear to be sensitive to antibiotics, it would be of interest to know whether the present widespread and somewhat indiscriminate use of antibiotics does not destroy these persistent viruses, and, with them, the immunity they confer The implications are obvious

Amoebiasis Research Unit
Durban South Africa

R ELSDON-DEW

PUERPERAL TETANUS

SIR,—I was interested to read the article by Dr Ramsay and his colleagues[1] At the African Hospital, Zomba, Nyasaland, there have been two cases of puerperal tetanus in the past two months The first patient died, but the second recovered Case 1 I did not see, but case 2 I attended

CASE 1 —On July 30 the patient had a normal delivery in her village, but on the following day was admitted to hospital with a septic perineal tear By Aug 8 the patient's condition appeared to be satisfactory and she was discharged from hospital The following day (Aug 9) she began to have stiffness of the neck and jaw She did not return to hospital until Aug 14 when she had pronounced trismus and neck and back rigidity and generalised muscle spasms She was given 100,000 units of tetanus antitoxin intravenously and 10,000 units into the vulval wound At the same time she received 600,000 units of procaine penicillin intramuscularly and she was sedated with paraldehyde given rectally She died on Aug 16, two days after admission

CASE 2 —On Sept 26 the patient gave birth to a normal live baby The delivery was conducted by her mother in a small hut in a village, naturally enough with no aseptic precautions From the patient s description the delivery seems to have been uncomplicated with nothing to suggest a retained placenta On Oct 5 (i e, nine days after the birth of her child) she was admitted to hospital complaining of pain and stiffness of her jaw, back and neck On examination there was risus sardonicus and masseteric spasm the gap between the teeth being $^1/_2$ in when the mouth was open to its fullest In addition there was opisthotonos with severe neck and back rigidity At the time of admission there was only slight rigidity of the abdominal muscles, but by the following day these were extremely rigid Despite her condition she was fully conscious and cooperative, though any disturbance such as moving the patient or even tapping the bedclothes induced generalised muscle spasms Owing to the frequency of meningitis in these parts I performed a lumbar puncture and withdrew colourless fluid containing 2 lymphocytes per c mm and 30 mg protein per 100 ml and so excluded that possibility However, unlike Dr Ramsay and his associates, I have no pathological confirmation of my diagnosis

The following treatment was given (*a*) 200,000 units of tetanus antitoxin intravenously on admission, and then (on the supposition that *Clostridium tetani* organisms might still be forming toxin) 25 000 units intramuscularly every four days, (*b*) procaine penicillin 600,000 units daily, to avoid pulmonary infections, and for its specific effect, if any, on the organisms, (*c*) paraldehyde for the first three days given in the form of 10 ml intramuscularly six hourly and thereafter 30 ml in 300 ml of saline given rectally six hourly for the next seven days, (*d*) for the first five days all feeding was done through a Ryle's tube, giving 5% dextrose and saline milk, and eggs

After seven days there were no further muscle spasms By the tenth day the abdominal rigidity had disappeared and there remained only slight masseteric spasm and neck rigidity By the fourteenth day the patient could open her mouth fully and touch her chin on her sternum On Oct 29 (i e twenty four days after admission) the patient was discharged apparently fully fit, feeding her baby with a bottle

On clinical grounds I felt very certain of my diagnosis, but I must confess that I was rather surprised to see the patient recover Perhaps the incubation period was fairly long, but whatever the reason this recovery would indicate (*a*) that puerperal tetanus is not quite so rare among primitive peoples, and (*b*) that, although muscle relaxant drugs with assisted respiration may be the treatment of choice, in centres where this is not possible the older methods of treatment may still be effective

African Hospital
Zomba Nyasaland

J E P THOMAS

INTERMITTENT POSITIVE PRESSURE AND SPEAKING

SIR,—Intermittent positive-pressure artificial respiration is often used in conjunction with a tracheotomy tube fitted with an inflated cuff There is then no current of air through the larynx and the patient cannot attempt to speak Sometimes, the inflated cuff is allowed to leak so that the patient may be able to use the leaking air for speech, but there are disadvantages and even dangers in this arrangement

We have fixed a small tube, about 3 mm bore, to the convexity of the tracheotomy tube so that its open end lies in the trachea above the inflated cuff Through this tube a gentle stream of air or oxygen flows and passes up through the larynx so that the patient can modulate it and attempt speech, yet the lower trachea remains completely sealed off

Now, through the cooperation of a lady recovering from respiratory paralysis who is using intermittent positive pressure, we know that the arrangement can work About 15 cm of water pressure is needed, and 4 litres per minute permits an intelligible whisper though 6 litres per minute is needed for real speech The "air" can be taken from an oxygen cylinder, or an aquarium aerator pump will supply this order of flow There must be a simple safety blow off to prevent excessive pressure It may be necessary to seal the tracheostomy wound with 'Vaseline' gauze though we did not have to do this for the patient mentioned If the patient has the use of her hands it is quite easy to put the air flow under her own control

We recognise that the method has limitations and it may have some dangers If there be severe laryngeal involvement, speech would be impossible even with the provision of the artificial air stream Mucus always tends to accumulate in the glottis and trachea above the inflated cuff and the "speech air stream" at first blows this up into the mouth but this is not harmful We think it might be dangerous to introduce such an air stream in the early days of a tracheotomy before the planes of the neck had become sealed off, because of the risk of surgical emphysema if the tube became misplaced

However, even if the power of free communication can be returned only to a small proportion of these unfortunate patients, it would be worth while

Perhaps this simple idea has not yet occurred to other doctors and they may wish to work upon it We would, of course, be most interested to hear whether they find it practical

Department of Anæsthesia,
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Newcastle upon Tyne

E A PASK
JOHN S INKSTER

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[1] Ramsay, A M, France, F M, Dempsey, B M *Lancet* 1956, ii, 448

X RAYS AND LEUKÆMIA

SIR,—The fascinating arguments put forward last week by Dr Court Brown and Dr Doll seem to be based largely on the invalid "assumption of a simple proportional relationship between dose and effect"

No generalisation about dose effect relationships can be better than an approximation, but the relationship of simple proportion is not acceptable even as an approximation Pharmacologists assume as a first approximation that Fechner's law is obeyed Expressed in a form applicable to the present problem it is "The intensity of the effect is approximately proportional to the logarithm of the dose" Fechner died in 1887

Let us hope, Sir, that in these atomic times your correspondents have made a quantum jump from a wrong assumption to a right conclusion

London, W 1 G B LOXTON

UNIVERSAL-JOINT CATHETER CONNECTIONS

SIR,—Swivelling catheter mounts are not new but, so far as I know, are not at present obtainable in this country

Their need became apparent to me in the treatment of respiratory paralysis, where the conscious patient is turned, with resultant twisting of the cuffed tracheotomy tube

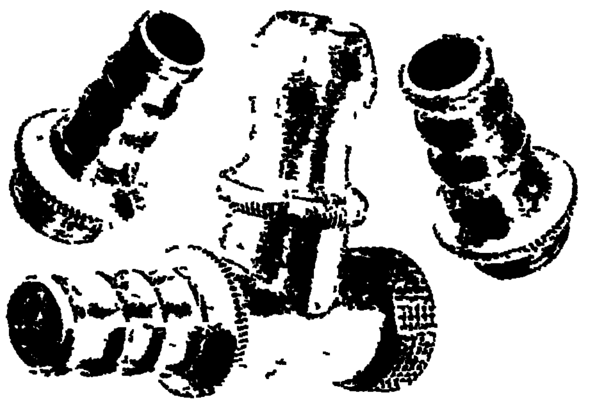

Fig 1

Connections like those shown in figs 1 and 2 have been used for about a year at the National Hospital and elsewhere and in every case have won the warm approval of the patients There has been no damage to trachea or to larynx

In anæsthesia there are many advantages in having an easily movable mount Interchangeable ends can be fitted for differing sizes of tube (fig 1)

The construction is so simple as to need no explanation The screwed portions are left loose and tapped with a fine thread, and are airtight even under the arduous conditions of pressure respiration

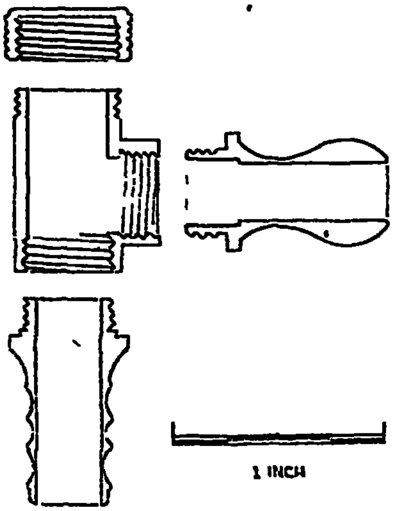

Fig 2

Theoretically a curved form gives a better flow, but this advantage is minimised by unavoidably increased size Therefore, for practical and structural reasons, the right angled shape was adopted

My thanks are due to Messrs A Charles King, 27, Devonshire Street, London, W 1, who coöperated so ably in the production of these mounts

National Hospital,
Queen Square London, W C 1 R ATWOOD BEAVER

MEAN VENOUS PRESSURES IN THE FIRST HOURS OF LIFE

SIR,—I was interested to read the paper by Dr Bonham Carter and his colleagues (Dec 29), because I hoped to find some useful information relating to hyaline membrane in the newborn

Like many others, I have believed for some time that the pulmonary syndrome of the newborn—or, as Edith Potter has called it, pulmonary congestive failure—results from a disturbance in the pulmonary hæmodynamics at the time of birth I have so far seen no reference to the brilliant experimental work of Born et al[1] in Oxford who have recorded pressure changes in the circulation of newborn lambs

From their work we learn that if the cord is ligated before respirations begin, profound asphyxia results and there is a great increase in blood pressure, partly because of asphyxia (operating through chemoreceptors) and partly because the systemic circulation of the lamb is cut off from the low peripheral resistance of the placenta Since the ductus arteriosus is open, this high pressure is communicated to the pulmonary artery The transitory pulmonary hypertension together with anoxia may perhaps be responsible for the changes in the lungs in pulmonary congestive failure, and the systemic hypertension and the anoxia may conceivably account for the occasional cerebral complications in these infants

Delay in pulmonary ventilation is common in premature infants and, though it is an increasingly common practice to wait for the cord to cease pulsating before ligating it (for quite other reasons), it must still be very common for the placental circulation to be excluded before breathing is established In cæsarean sections it is usual for the surgeon to sever the cord immediately so that he may have the baby out of the way often before the infant has started to breathe

I suggest that such an unphysiological state of affairs is likely to lead to a lesser circulation failure primarily, and systemic venous congestion may be delayed, if it occurs at all If this is so, it is not surprising that the venous pressures recorded by Bonham Carter et al in many of the babies with respiratory distress were low, since all except seven were taken within the first 6 hours after birth In none of the eight fatal cases were readings taken after 5 hours, though all survived for 18 hours or more Born et al found that the pressure in the inferior vena cava actually fell after the cord was tied despite a steady rise in pressure in the aorta, pulmonary artery and left atrium at this time (possibly because the large placental venous return was cut off)

I am putting these hypotheses to the test of clinical observation Meanwhile I suggest that it would be a good plan to delay ligation of the cord for as long as possible in premature deliveries and cæsarean sections, and, when breathing is delayed, to administer intragastric oxygen immediately in order to prevent too drastic a fall in the arterial oxygen content following loss of the placental circulation

Department of Child Health
Llandough Hospital Penarth Glam R J K BROWN

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[1] Born G V R Dawes G S Mott J C Widdicombe J G *Cold Spr Harb Symp quant Biol* 1951 19 10

TREATMENT OF SORE THROAT

SIR,—In their comprehensive trial of intramuscular penicillin in the treatment of acute sore throats, Captain Brumfitt and Captain Slater (Jan 5) set out to answer the question whether it is reasonable to exhibit penicillin routinely in all such cases Nevertheless they have not committed themselves to an answer

Because of our inexact understanding of the processes causing illness, it is often difficult to reconcile the scientific findings of one aspect of an illness with the clinical results as a whole The fact that no infecting organism could be demonstrated in 32% of the cases does not necessarily exclude streptococcal infection, for there are many examples in medicine where the infecting organism, although present, cannot always be isolated (Pyelonephritis is but one such example) Also, can "normal bacterial flora" always be dismissed as non-pathogenic? I have had cases of tonsillitis where culture has resulted in predominant growth of such an unlikely organism as *Escherichia coli*, and staphylococci of various types are not uncommonly found

Since acute sore throat is usually treated in general practice without bacteriological control, the differentiation of cases must be made on clinical grounds alone The decision to use penicillin then rests upon the latter My own routine is to treat all cases of tonsillitis, whether they exhibit follicular suppuration or not, with penicillin On the other hand the majority of cases of pharyngitis which I see are catarrhal in origin, although it is possible to distinguish a group with the stigmata of bacterial infection and these also I treat with penicillin

The régime of penicillin therapy described by Brumfitt and Slater was ineffective in eradicating the infecting organism in a proportion of cases I believe that in this particular condition oral penicillin in adequate doses is more effective than parenteral penicillin That penicillin has a more profound effect on the buccal flora when it is given by mouth than when it is given by injection, is evident from the fact that "black tongue" is a common complication of oral therapy but is rare with parenteral treatment The reason for this is not apparent but there may well be a similar difference in effect when treating throat infections with penicillin by the two routes The authors of this paper state that intramuscular penicillin is commonly used in practice for this complaint The vast majority of these cases are treated at home by general practitioners If the latter were asked, I am sure that it would be found that oral penicillin is far more commonly used in this condition than Brumfitt and Slater suppose Indeed the general practitioner is probably the only person who is in a position to give an authoritative opinion on this form of therapy, based upon personal experience

As Brumfitt and Slater say, the main object of antibacterial treatment in this condition is the prevention of those diseases believed to be due to streptococcal allergy Whether or not streptococci are being successfully eliminated from throats, there has been an enormous decline in the incidence of rheumatic fever since the dawning of the antibiotic era There would seem to be little reason to doubt that this is an example of cause and effect

Another very important object of antibacterial treatment of sore throats is the prevention of the more immediate complications due to spread of the infection Thus acute otitis media has been transformed in a decade from a surgical to a medical illness and mastoidectomy for acute mastoiditis has virtually disappeared These facts are surely again a tribute to the effectiveness of antibiotics in all these allied conditions

Therefore, Sir, I would conclude with a plea that no patient with a sore throat which might be expected on clinical grounds to respond to penicillin therapy should be denied the prophylactic and therapeutic benefits that such treatment confers Might I also suggest that information on this subject should be sought from those most intimately concerned with it—namely, the general practitioners

Twickenham, Middlesex DAVID WHEATLEY

SIR,—As a National Service medical officer spending his first year outside a hospital, I have been forcibly impressed by the problem confronting those who have to treat primary sore throat—an illness so common in everyday practice and so loudly proclaimed to be fraught with the possible sequelæ of rheumatic fever and acute nephritis, and yet so woefully neglected in the literature I was therefore greatly interested by certain points in the report by Captain Brumfitt and Captain Slater

1 As they remark, intramuscular penicillin, though less easily administered than the oral antibiotics and the cheap, but unfortunately "fading," sulphonamides, is the most effective drug in dealing with β hæmolytic streptococci

2 Sore throats due to streptococcal infection cannot be distinguished clinically from others, presumably due to viruses

3 In streptococcal sore throat penicillin neither shortens the clinical course of the disease appreciably, nor eradicates the organisms from the throat, unless given in adequate doses for 10 days The danger of rheumatic fever or acute nephritis is now really very small (Brumfitt and Slater suggest that it is probably less than 1% in endemic cases)

From all this it seems that, until some more effective chemotherapeutic agent is discovered, penicillin, sulphonamides, &c , can profitably be used only in severely toxic or septic cases of sore throat which have been shown bacteriologically to be streptococcal, and that, if penicillin is used, a full 10 day course should be given to reap the maximum benefit

Meanwhile nothing is to be gained by giving antibiotics or sulphonamides for any but these severe sore throats Such patients with less severe infections can be spared unnecessary and painful injections or tablet swallowing In fact we are back where we were 20 years ago, with formaldehyde lozenges, and, as my staff sergeant points out, iodine compound paint ("Mandl's paint"), as the mainstay of sore throat therapy

Royal Air Force,
Leconfield A R SMITH

PROLONGED PYREXIA IN CHILDREN POSSIBLY DUE TO INFLUENZA

SIR,—Pyrexia of unknown origin is common in children In some of them all investigations prove negative, no diagnosis is made and the pyrexia eventually subsides, as happened in 36% of the adult cases recorded by Reid[1]

Last January there was an epidemic of influenza in Northern Oxfordshire, and within two months, 32 of the 50 occupants of a home for physically handicapped children had bouts of pyrexia, many with pharyngitis and rhinitis and some with cervical adenitis In 24 the pyrexia lasted less than a week, but 3 had bouts of pyrexia lasting more than fourteen days without evidence of bacterial infection

CASE 1—A boy of 8 years complained of headache on Jan 20 His temperature was 101°F No abnormality was found in the chest, throat, nose, ears, or urine At the beginning of February he began to cough and had a slight cervical adenitis Nose and throat swabs grew only *Streptococcus viridans* He was given penicillin (500,000 units daily intramuscularly for five days) without any effect on the temperature He was allowed gradually to resume activity and on March 23, when he went home for Easter, his evening temperature was about 100°F Since his return he has been fit and well but with an occasional evening pyrexia, one night in three or four his temperature is 99–100°F

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[1] Reid, J V O *Brit med J* 1956, ii 23

CASE 2.—A boy aged 7 years complained of headache on Jan. 17. His temperature was 102° F., he had rhinitis and pharyngitis but no other abnormal signs. By Jan. 19 his temperature was normal and his rhinitis and pharyngitis much improved. On Jan. 23 his temperature began to rise again, though at that time he had no symptoms and no physical signs save some rhinitis. Small lymph glands were palpable in the posterior triangle of the neck on Feb. 15, when culture of the nasal swab grew *Staphylococcus aureus* (resistant to penicillin but sensitive to aureomycin) and of the throat swab *Strep. viridans*, pneumococci, and neisseria. Aureomycin 250 mg. six hourly, was given for five days but the temperature chart remained the same. Further cultures on March 16 grew *Strep. viridans* and neisseria but no *Staph. aureus*, but his temperature was 100–100.8°F on most evenings until the Easter vacation. After he returned he still had an occasional evening pyrexia of 99–99.6°F.

CASE 3.—A boy aged 6 years had headache and pyrexia on Feb. 4. No abnormality was found in the chest, throat, ears, nose, or urine. By Feb. 15 there was some nasal catarrh and cough. No cervical or other lymph glands were palpable. Culture of a throat swab of March 12 grew only *Strep. viridans*. Penicillin (500,000 units intramuscularly daily) was given for five days, but the temperature remained unchanged until he went home on March 23. He returned fit and well but has an occasional evening temperature of 99–99.8°F.

In all these children X-ray films of the chest and Mantoux tests were negative, the urine was normal on at least two examinations, and the erythrocyte-sedimentation rate was 10–15 mm. in one hour. Glandular fever was excluded by blood examinations. An ear, nose, and throat surgeon said that he could find no active infection in any of them.

When it was apparent that these 3 children had an abnormal temperature with no obvious clinical cause, the temperature of every child in the home was repeatedly checked and found to be normal save in one boy who was apparently behaving like the 3 under discussion. He was older (13 years) and appeared well.

All these children had severe paralysis due to poliomyelitis. Perhaps children with extensive paralysis are especially prone to this type of pyrexia, though I have seen it in a physically normal child.

CASE 4.—In February, 1953, when 6 years of age, this boy developed a cough, laryngitis with some laryngeal spasm, a bronchial wheeze, and a pyrexia of 102°F. He was treated with trisulphonamide ('Sulphatriad'), the bronchial wheeze disappeared but the cough and pyrexia remained. X-ray films: chest normal, sinuses, some mucosal thickening of the right antrum. Urine normal. Nasal swab, *Staph. aureus*. Throat swab *Strep. viridans*. Mantoux 1 in 100 negative. Erythrocyte sedimentation rate 15 mm. in one hour. White blood cells 7000 per c.mm. with normal differential count. Brucella agglutinations negative on two occasions. Penicillin and chloramphenicol had no effect on the temperature.

After six months he was allowed to follow an unrestricted routine though the evening temperature was 99–100°F. At the end of nine months it was observed that he did not tire so easily and appeared to have much more energy. His temperature at this time was 97.6–98.2°F.

In general practice one is often told about pyrexia which proves to be non-existent, due to erroneous readings for temperature of children.[2] In the cases reported here, however, these were made by competent observers. As Ellis[3] says, special tests need not be done in every case of undiagnosed pyrexia unless the fever lasts for more than seven days or recurs soon after the initial attack. In the 4 cases described above no investigations were made until the illness had lasted a fortnight, by which time they had then recovered from their initial symptoms. Intensive blood examinations (e.g., for brucellosis) were not made, because the nature of the outbreak seemed to exclude such a diagnosis.

If the pyrexia of influenza lasts more than a week, the possibility of such complications as otitis media and patches of pulmonary consolidation has to be considered, though uncomplicated cases may last up to a month.[4] In the above patients, pyrexia lasted from four to nine months.

This prolonged pyrexia followed a non-bacterial upper-respiratory infection, and was probably due to the continued activity of a virus in the upper respiratory tract. Though the virus was not typed, all the patients were ill during a known influenza epidemic. According to Burnet,[5] influenza virus invades and multiplies in the cells lining the respiratory passages, and, with the possible exception of the conjunctival epithelium, in no other type of accessible human cells. The process continues, "sweeping over the epithelial surface like a prairie fire." The speed of spread determines the acuteness of the illness. Perhaps in the above patients the "prairie fire" was a slowly crawling smoulder, with neither complete destruction of the invading virus nor a state of symbiosis.

Chipping Norton, Oxon. F. E. JAMES.

A SPECIAL CAR SEAT

SIR,—When the user of a folding chair previously described[6] came to designing, he had some experience behind him. He had had ankylosing spondylitis for some years, and the seizing-up of both hips and the spine made it impossible for him to use the normal seat in a car.

Getting such handicapped persons out and about is of tremendous help to their well-being, and a special car seat was designed and built. There are three basic requirements: a back-rest reclining at about forty-five degrees; some sort of pivot or turntable on which the seat is mounted; and long runners so that the seat can be slid back and the user's feet can clear the front of the door gap.

First a plywood box was made reinforced inside with a 2 × 2 in. wooden frame. To this were screwed two brackets of $^1/_{16}$ in. sheet steel to support the back-rest (see figure). The back-rest is an oak frame shaped like an inverted U and strung with camp chair canvas. The frame is bolted at its bottom ends into the 2 × 2 in. side-members, and some 12 in. above the bolts it is secured by a horizontal traverse rod passing through a length of hollow brass curtain-rail ($^1/_4$ in.). The rod is threaded at both ends and "clewed up" by wing nuts; it also provides the lower anchorage for the canvas.

The seat cushion is internally sprung and is comfortable even for long journeys. If the user wanted to replace it by one of foam rubber, the seat box would have to be altered to give the extra support to the flat area of rubber. The chair has been made so stout, however, that, though eight years old it shows no sign of falling to pieces and needing replacement. The head rest is a bit of three-ply wood some 6 × 10 in. which passes through a slot in the back of the frame, made of bent hoop iron. Padding for the back rest is provided by a normal sized pillow covered with chintz.

Before this chair was built a suitable car had to be found. It had to have a door gap at least 3 feet wide and unlimited height for easy access The height is needed when the disabled person has only one helper, otherwise a second helper, inside the car, has to take most of his weight and duck him under the roof beam Thus the choice fell on a coupé convertible When there is only one helper, the hood is opened to the halfway stage and the disabled person is lowered on to the seat This is then revolved on its turntable until it faces forward Getting him out is much simpler, for lifting a person towards one is easier than supporting his weight while moving him away from one

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[2] Moncrieff, A., Hussey, R. J. *Ibid*, 1948, ii, 972.

[3] Ellis, H. *Med. Pr.* 1955, 233, 562.

[4] French, H. Index of Differential Diagnosis. Bristol, 1945; p. 697.

[5] Burnet, F. M. Virus as Organism. Cambridge, Mass., 1946; p. 103.

[6] See *Lancet*, 1955, ii, 257.

Stocksfield,
Northumberland

E H TREWEEKS

Obituary

CHARLES-EDWARD AMORY WINSLOW

B S, A M, Dr P H

Dr Winslow, professor emeritus of public health at Yale University, died on Jan 8 at the age of 79

He was born at Boston and he took the degree of bachelor of science at the Massachusetts Institute of Technology in 1898 For some years he was assistant health officer at Montclair, New Jersey, and he worked during the summers in the engineer's office of the Massachusetts board of health In 1902 he was appointed instructor in sanitary bacteriology at the Massachusetts Institute of Technology and in 1905 he was promoted to assistant professor In 1910 he became associate professor of biology at the College of the City of New York and curator of public health in the American Museum of Natural History In 1915 he was appointed to the chair at Yale which he held until he retired in 1945 He was editor-in-chief of the *American Journal of Bacteriology* from 1916 to 1944 In 1942 he received the Sedgwick medal of the American Public Health Association After the late war he continued his earlier work for the health section of the League of Nations in the counsels of the World Health Organisation, and his monograph on W H O's immense task, *The Cost of Sickness and the Price of Health* (1951), was one of the last of his widely ranging publications on public health In 1953 he received the Lasker award

One of his medical colleagues in this country writes

Winslow was a commanding figure, yet he never seemed remote, in spite of his noble and somewhat aristocratic appearance In many ways one thinks of him as the ideal teacher—eloquent, scholarly, and humane He taught men and women of all ages and degrees of experience, at all levels from the World Health Assembly to the smallest classroom, without ever laying down the law He was one of us In his teaching there was none more infectiously enthusiastic there was none less rabid

He pursued his subject—the health of the people—with a devotion that was passionate in its intensity Yet he never lost touch with reality, and most of his public health ideals were severely practical Indeed, it is characteristic of him that, in contrast with an outward philosophic calm, his powerful mind was directed mainly to environmental hygiene The healthy housing of the people was his chief task, and he spent endless time and effort in working out the principles and demonstrating the practice In many respects he followed the lead of the English pioneers of public health and introduced the best of their work to the United States in the tradition of men like Shattuck and Hermann Biggs, but he went further, by instituting target standards in housing and environmental work, and he was tireless in showing how they could be achieved They are still a shining example to the world

The establishment of standards was one of his notable contributions to health and education, and their application to schools of public health has had a widespread influence on their teaching methods as well as on their range of subjects

Winslow was a beneficent influence on his time and generation, and his work and his gracious personality will be remembered in the annals of preventive medicine "Every noble life leaves the fibre of itself interwoven for ever in the work of the world"

Notes and News

INTRA-ARTERIAL PENICILLIN

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From these observations it was deduced that, in the treatment of infection of a limb, intra arterial injection is the method of choice 536 such injections were given to 110 patients using 20 ml of 0 5% procaine solution containing 100,000 units of penicillin The results were excellent in all acute infections, but in chronic osteomyelitis such injections did not prevent exacerbations In chronic trophic ulcers the results were good but not outstandingly better than with other methods of treatment The investigators conclude that injection into the main artery of the affected limb is the most effective means of ensuring high concentration of penicillin at the site of infection

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The awards will be made for one year in the first instance and will be renewable annually to a maximum of three years in all Stipend will be at the rate of £950–£75–£1100 per annum with superannuation Applications must be sponsored by the head of the appropriate department in the candidate's university or medical school and an undertaking will be required that a suitable academic post in a clinical department will be available to the candidate in that institution on satisfactory completion of the period of study under the fellowship Forms of application may be had from the secretary of the council 38 Old Queen Street London S W 1 to whom they must be returned not later than March 1 1957 and unlimited height for easy access The height is needed when the disabled person has only one helper, otherwise a second helper, inside the car, has to take most of his weight and duck him under the roof beam Thus the choice fell on a coupe convertible When there is only one helper, the hood is opened to the halfway stage and the disabled person is lowered on to the seat This is then revolved on its turntable until it faces forward Getting him out is much simpler, for lifting a person towards one is easier than supporting his weight while moving him away from one

Stocksfield,
Northumberland E H TREWEEKS

Obituary

CHARLES-EDWARD AMORY WINSLOW

B S , A M , Dr P H

Dr Winslow, professor emeritus of public health at Yale University, died on Jan 8 at the age of 79

He was born at Boston and he took the degree of bachelor of science at the Massachusetts Institute of Technology in 1898 For some years he was assistant health officer at Montclair, New Jersey, and he worked during the summers in the engineer's office of the Massachusetts board of health In 1902 he was appointed instructor in sanitary bacteriology at the Massachusetts Institute of Technology and in 1905 he was promoted to assistant professor In 1910 he became associate professor of biology at the College of the City of New York and curator of public health in the American Museum of Natural History In 1915 he was appointed to the chair at Yale which he held until he retired in 1945 He was editor-in-chief of the *American Journal of Bacteriology* from 1916 to 1944 In 1942 he received the Sedgwick medal of the American Public Health Association After the late war he continued his earlier work for the health section of the League of Nations in the counsels of the World Health Organisation, and his monograph on W H O 's immense task, *The Cost of Sickness and the Price of Health* (1951), was one of the last of his widely ranging publications on public health In 1953 he received the Lasker award

One of his medical colleagues in this country writes

Winslow was a commanding figure, yet he never seemed remote, in spite of his noble and somewhat aristocratic appearance In many ways one thinks of him as the ideal teacher—eloquent, scholarly, and humane He taught men and women of all ages and degrees of experience, at all levels from the World Health Assembly to the smallest classroom, without ever laying down the law He was one of us In his teaching there was none more infectiously enthusiastic there was none less rabid

He pursued his subject—the health of the people—with a devotion that was passionate in its intensity Yet he never lost touch with reality, and most of his public health ideals were severely practical Indeed, it is characteristic of him that, in contrast with an outward philosophic calm, his powerful mind was directed mainly to environmental hygiene The healthy housing of the people was his chief task, and he spent endless time and effort in working out the principles and demonstrating the practice In many respects he followed the lead of the English pioneers of public health and introduced the best of their work to the United States in the tradition of men like Shattuck and Hermann Biggs, but he went further, by instituting target standards in housing and environmental work, and he was tireless in showing how they could be achieved They are still a shining example to the world

The establishment of standards was one of his notable contributions to health and education, and their application to schools of public health has had a widespread influence on their teaching methods as well as on their range of subjects

Winslow was a beneficent influence on his time and generation, and his work and his gracious personality will be remembered in the annals of preventive medicine " Every noble life leaves the fibre of itself interwoven for ever in the work of the world "

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Hungarian Interpreter Telephone Service

In the coming weeks doctors who are asked to attend Hungarian refugees may find themselves in need of an interpreter's help The W V S (Women's Voluntary Services) ask us to say that one of their interpreters will be available by phone from 10 A M to 6 P M on weekdays and 10 A M to 12 30 P M on Saturdays at WHItehall 7383, ext 11, and from 10 A M to 6 P M on Sundays at WEStern 2053

Marlborough Day Hospital, London

On Monday, Feb 4 at 8 15 P M, at this hospital, 38, Marlborough Place, N W 8, Dr T F Main will speak on the Past and the Present in Neurosis

Chartered Society of "Queen Square"

This society will shortly hold an election for pensions (£20 p a each) for needy people with incurable nervous diseases Further particulars may be had from the society, Queen Square House, Queen Square, London, W C 1

Albania and Bulgaria Rejoin W H O

The People's Republics of Albania and Bulgaria have *informed Dr M G Candau, director-general of the World* Health Organisation, of the decision of their governments to resume active participation in the organisation

Cerebral Palsy in Mentally Retarded Children

A meeting on this subject will be held at the Fountain Hospital, Tooting Grove, London, S W 17, on Thursday, Jan 24 at 5 30 P M. Dr F A Elliott will be in the chair and Dr K Bobath and Dr John Foley will speak

Society for Applied Bacteriology

The programme for the conference which this society is holding in Leeds from July 2 to 5, will include an international symposium on the formation and germination of bacterial spores Further details of the meeting can be had from the secretary, G Sykes, Boots Pure Drug Co Ltd, Microbiology Division, Nottingham

Courses for General Practitioners at Liverpool

The following courses for general practitioners are to be held this year March 6–27 (obstetrics), March 31–April 28 (general), May 5–26 (general), May 20–24 (anæsthetics), June 2–23 (general), July 3–24 (eyes and E N T) Further particulars may be had from the dean of the faculty of medicine, The University, Liverpool, 3

Sir Gordon Gordon Taylor has been elected an honorary fellow of the Medical Society of London

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Births, Marriages, and Deaths

BIRTHS

ROWNTREE —On Jan 3, prematurely, at The Maternity Hospital, Fulford, York to Paul and Gwendoline—a son, Neil

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Appointments

FORREST, D M, M B N Z, F R C S senior surgical registrar The Hospital for Sick Children Great Ormond Street London

GALLOON, SAMUAL M B Cape Town F F A R C S D A consultant anæsthetist United Cardiff Hospitals and Welsh Regional Hospital Board

GILLIES, DEIRDRE M M M B Edin D A resident anæsthetist, The Hospital for Sick Children, Great Ormond Street, London

HUTCHINSON W J, M B Belf, D P H M O H, Hucknall

MACMILLAN, DONALD, M B Glasg deputy group medical superintendent, board of management for the Dundee General Hospitals

NAYMAN, J M B Witw'srand, F R C S surgical registrar Ipswich and East Suffolk Hospital

O'BEIRNE, KATHLEEN M B N U I school M O Hemsworth

WALSH L S M B Cape Town, F R C S consultant in neurosurgery Atkinson Morley Hospital, Wimbledon and neurosurgical department St George s Hospital, London

Colonial Appointments

CHIU, HO HUNG M R C P F F R senior specialist Hong Kong

COOK, J, F R C S E F A C S D P H senior specialist, Hong Kong

DEROLA T S, M B, D T M & H M O, Zanzibar

EDESON J F B M D Sheff specialist officer (grade B), malaria research division Federation of Malaya

ELLIS JONES D W M B Lpool D T M & H D O specialist ophthalmologist Uganda

JONES, T R M B Lond D P H health officer, British Guiana

MACKAY, D H M R C S A D M S, Kenya

WHELAN J P F M B Melb D T M & H DIP BACT specialist officer (grade B) bacteriological division, Federation of Malaya

Diary of the Week

JAN 20 TO 26

Monday, 21st

HUNTERIAN SOCIETY

8 30 P M (Mansion House, London, E C 4) Prof Luis de Pap (Lisbon) Ætiology of Spinal Osteo arthritis and Disc Degeneration

UNIVERSITY OF LIVERPOOL

5 15 P M (Liverpool Medical School) Prof Cornelius Tobias (California) Hypophyseal and Hypothalamic Irradiation with High Energy Protons

Tuesday, 22nd

ROYAL COLLEGE OF PHYSICIANS OF LONDON, Pall Mall East, S W 1

5 P M Dr Raymond Daley Autonomic Nervous System in its Relation to Some Forms of Heart and Lung Disease (Second of two Goulstonian lectures)

ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street W 1

8 P M *Medicine* Dr M D Milne, Dr A M Joekes, Dr E M Darmady Anuria in Medical Conditions

ST MARY'S HOSPITAL MEDICAL SCHOOL Paddington, W 2

5 P M Mr John Howkins Ovarian Tumours

BRITISH POSTGRADUATE MEDICAL FEDERATION

5 30 P M (London School of Hygiene and Tropical Medicine Keppel Street, W C 1) Prof H McIlwain, D SC Neurochemistry

INSTITUTE OF DERMATOLOGY, Lisle Street, W C 2

5 30 P M Mr A T Gray Ointment Bases

ROYAL ARMY MEDICAL COLLEGE, Millbank, S W 1

5 P M Dr K G Bergin Human Factors in Aircraft Design and Performance

UNIVERSITY OF LIVERPOOL

5 15 P M (Medical School Liverpool) Dr Rolf Luft (Stockholm) Hypophysectomy in the Treatment of Malignant Disease (James Arthur Smith lecture)

Wednesday, 23rd

HARVEIAN SOCIETY OF LONDON, 11, Chandos Street, W 1

8 15 P M Dr M C W Long Another Medicine! (Presidential address)

ROYAL SOCIETY OF MEDICINE

5 P M *Endocrinology* Dr J H Rey, Dr B T Donovan, Dr D G Ferriman, Dr P K Thomas, Dr P M F Bishop Mr R D de Vere Amenorrhœa and Hirsutism

POSTGRADUATE MEDICAL SCHOOL OF LONDON Ducane Road, W 12

2 P M Dr I Friedmann Malignant Granuloma and Other Granulomatous Diseases of the Nose

INSTITUTE OF DERMATOLOGY

5 30 P M Dr J O Oliver Blood Changes in Skin Diseases

INSTITUTE OF DISEASES OF THE CHEST, Brompton S W 3

5 P M Sir Clement Price Thomas Surgery of Bronchial Carcinoma

MEDICAL RESEARCH COUNCIL, National Institute for Medical Research, Mill Hill, N W 7

5 P M Dr Robley C Williams (University of California) Electron Microscopic Studies of Virus Structure

BIRMINGHAM MEDICAL INSTITUTE, 154, Great Charles Street, Birmingham, 3

8 P M *Psychiatry* Dr G W Hearn Borderland of Medicine and Psychiatry

MANCHESTER MEDICAL SOCIETY, Medical School, University of Manchester

4 30 P M *Sections of Pathology and Medicine* Dr J N Morris Social Pathology of Coronary Artery Disease

Thursday, 24th

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields W C 2

5 P M Mr F J Gillingham Management of Ruptured Intracranial Aneurysm

ROYAL SOCIETY OF MEDICINE

8 P M *Urology* Dr A C Thackray 10 Year Follow up of Cases of Adenocarcinoma of Kidney and the Relation of Survival to Pathology Mr F T Graves Aberrant Renal Arteries

BRITISH POSTGRADUATE MEDICAL FEDERATION

5 30 P M (London School of Hygiene and Tropical Medicine) Dr E J Zaimis Factors Influencing the Action of Neuromuscular Blocking Substances

INSTITUTE OF DERMATOLOGY

5 30 P M Mr A T Gray Cosmetic Preparations

RENAL ASSOCIATION

4 30 P M (Ciba Foundation, 41 Portland Place, W 1) Prof *C E Dent Dr S W Stanbury Renal Osteodystrophy*

LIVERPOOL MEDICAL INSTITUTION, 114 Mount Pleasant, Liverpool 3

8 P M Mr D W Bracey Inguinal Herniorrhaphy Using the Mobilised Inguinal Ligament, Mr Geoffrey Osborne Dupuytren s Contracture

UNIVERSITY OF ST ANDREWS, Queen's College, Small's Wynd Dundee

5 P M Dr J W Brown Congenital Heart disease

Friday, 25th

POSTGRADUATE MEDICAL SCHOOL OF LONDON

10 A M Mr C Naunton Morgan Carcinoma of the Rectum and Left Colon

4 P M Prof E J Wayne Clinical Surveys and Clinical Trials

INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330 Gray's Inn Road, W C 1

3 30 P M Mr N Asherson Ménière s Disease

ADDENDUM *Neurone Selection in the Relief of Pain* —Dr R M Maher asks us to say that for the pathological findings recorded in his article of Jan 5 he is indebted to Dr J A Shrigley, lately pathologist at the Christie Hospital, Manchester t least all which is obvious to the naked eye, is removed, nd that the remnants are secretory—to be stimulated, if ecessary, by the thyrotropic hormone of the pituitary

In operating on nodular goitres it is often found that he upper poles have escaped the nodular process and onsist of soft homogeneous secreting thyroid tissue In hese cases, particularly when toxicity is minimal or bsent, we never hesitate to leave behind the upper poles

This technique has been in use for some years, and it is urprising that patients in whom only very small remants of the selected tissue had been preserved continue o be perfectly euthyroid One can fairly assume that, rovided that a little normal or nearly normal tissue emains, the pituitary gland will stimulate it to produce sufficient amount of thyroid hormone for the patient Fig 5 schematically presents the essential steps in this technique)

Adequate Operation

Adequate operation is a sine qua non in preventing recurrence

In operating on a diffuse toxic goitre about 1–4 g of the posterolateral margin is left on either side In gauging the remnants account is taken of the size of the gland, the original degree of toxicity, the reaction of the gland to the anti thyroid drug, the patient's personality, and the presence of any cardiovascular involvement

In operations on the nodular variety the quality of the remnants—i e, removal of all nodular tissue—is the primary concern, the amount of gland to be left is determined by the patient's toxic state

In cases with lymphadenoid change it must be borne in mind that myxœdema is an almost inevitable sequel (Greene 1950, 1953) irrespective of the size of the remnants In such cases operation—e g, for the relief of pressure symptoms—has merely anticipated the natural course of the condition

Reconstitution

The operation is so designed that the remnants are reconstituted in such a manner as to resemble small lateral lobes With this in view, when the lobe has been delivered and the line of section decided on, the gland is sectioned in an oblique manner, so that the remnant can be folded over and medially and, with a few fixing or anchoring sutures, can be made to nestle snugly against the lateral aspect of the trachea (fig 6) Quite apart from the surgical neatness effected, this is also a hæmostatic procedure and ensures that the remnant is covered by its capsule, which cuts down oozing and the subsequent production of serum We believe also that this procedure does in a small but positive way prevent recurrences the growth of the remnant being limited by its capsule, and that in some cases, it does away with the necessity of draining the operation site

Summary

At the New End thyroid clinic and department of endocrinology cases of true recurrent goitre amounted to about two fifths of the number of cases referred as recurrent goitre

The commonest cause of recurrence is probably an inadequate initial operation Most "recurrences" therefore are in fact continued growths of pathological tissue which remained after the first operation Factors promoting recurrence are failure to ligate the inferior thyroid arteries and to remove the pyramidal lobe

We wish to thank Staff Nurse S M Torkington for figs 5 and 6 Miss E Mason for the photographs and figs 2 and 3 and Mrs M J Lange for help with statistics

REFERENCES

Greene R (1950) *J Endocrin* 7, 1
— (1953) *In* Memoirs of the Society for Endocrinology London vol 1 p 16
Lange M J (1953) *Brit J Surg* 40 ,44

THE TREATMENT OF TETRAETHYL LEAD POISONING

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Tetraethyl lead, $(C_2H_5)_4Pb$ (T E L), a highly toxic liquid, is manufactured on a large scale, distributed throughout the world, and blended with many types of petrol, yet poisoning is rare because of the stringent precautions taken in its manufacture and handling Recent cases have arisen sporadically in men cleaning tanks which have contained leaded petrol Such incidents have been reported in the United Kingdom by Cassells and Dodds (1946) and Walker and Boyd (1952), in the U S A by Kitzmiller et al (1954), and in Germany by Fischer (1950) and Muller (1953)

This organo-metal compound is absorbed through the skin and the respiratory and alimentary mucosæ, it is probably distributed in a non-ionic form and being lipoid-soluble, is concentrated in the brain, body fat and liver (Kehoe and Thamann 1931) Its toxicity is due to its lead content (Kehoe 1927) and because of selective uptake manifestations of poisoning are dominated by involvement of the central nervous system and differ from those of inorganic lead poisoning where the initial lead distribution is different Although the inhalation of T E L vapour for a brief period may be fatal the continued excretion of large amounts of lead in the urine for some time after the removal of symptomless workers from prolonged minor exposure, suggests that appreciable quantities of T E L may be absorbed and the lead stored in a relatively non-toxic form

The clinical picture has been described in detail by Machle (1935) and Kehoe (1925) Mild intoxication causes headache, irritability, restlessness, anxiety, fatigue, insomnia with bad dreams and minor gastrointestinal symptoms, including anorexia, vomiting and diarrhœa There is sometimes a persistent metallic taste These symptoms may easily be mistaken for those of an anxiety state In more severe intoxication there is a similar "prodromal" stage lasting a week or more, followed by a toxic psychosis, the pattern of which depends on the patient's underlying personality and is remarkably variable from individual to individual and sometimes from day to day Hallucinations, delusions and intense fear are usual and suicidal attempts not infrequent Coma and convulsions occur in the most severe cases Physical signs are few the most important being tremor, increased tendon reflexes, hypothermia bradycardia hypotension and loss of weight The classical signs of inorganic lead poisoning are not found Relapses are common, but chronic effects and permanent sequelæ have not been reported The diagnosis is confirmed by estimations of the urinary lead excretion but blood-lead levels are seldom much increased

Small hæmorrhages may be found in the meninges brain and the gastro intestinal tract, but there are no characteristic necropsy findings

Three moderately severe cases are described in this report and the effect on lead excretion of edathamil calcium disodium (edathamil $CaNa_2$, 'Versene'), given intravenously and orally, and of penicillamine given orally are compared A fourth case with a severe psychosis is mentioned, but the severity of the illness prevented detailed biochemical observation

The Outbreak

In March and April, 1956, a team of five men worked for 6 weeks cleaning underground tanks which had contained leaded petrol Four men (cases 1–4) who worked in the tanks were admitted to hospital suffering from tetraethyl lead poisoning The fifth man, who remained on the surface, showed neither clinical nor biochemical evidence of poisoning

The affected men scraped the deposit containing tetra ethyl lead from the floors and sides of the tank, and shovelled it into buckets, which were hauled to the surface and emptied into pits They were provided with protective clothing and equipment designed to protect against fluid and vapour, consisting of oilskin suits and hats, rubber boots and gloves, and a face mask with a positive pressure air-line For various reasons they neglected the strict precautions laid down for this type of work

The following investigations were performed in cases 1–3 on admission

Hæmoglobin and red cell count, examination of red cells for stippling, total and differential white count Liver function tests, including cephalin cholesterol and zinc sulphate flocculation, and thymol turbidity tests, estimation of serum albumin and globulin, electrophoresis of serum proteins, estimation of prothrombin content, and serum bilirubin Blood-urea Urine deposit and routine estimation for protein, reducing substances and excess urobilinogen Electro encephalogram Chest X rays and films of the upper abdomen for assessment of the density of the liver shadow In every case the results of these tests were normal

During the period in hospital urine was collected daily for estimation of lead, coproporphyrin and creatinine In addition lead analysis was performed on daily fæcal samples and on blood samples taken frequently

The urine and fæces were passed directly into lead free glass bottles and were collected over 24 hour periods Blood (20 ml clotted) was collected into special all glass syringes and when edathamil $CaNa_2$ was given intravenously the sample was taken immediately before the infusion The lead concentrations in urine, fæces and blood were estimated by modifications of the methods of Bambach and Burkey (1942) which give the following approximate values for non exposed men urine 50–100 µg daily, fæces 20–400 µg daily, and blood 10–60 µg per 100 g Coproporphyrin III was extracted from urine samples by a method based on that of Schwartz et al (1951) and then determined spectrophotometrically in a manner similar to that described by Rimington and Sveinsson (1950) (Normal = about 0–50 µg daily) Urinary creatinine was estimated by the Jaffe reaction

In cases 1–3 the men were treated in turn for 3 day periods with edathamil $CaNa_2$, 1 g per 30 lb body-weight per day by intravenous infusion, lasting 4–6 hours, with penicillamine 300 mg t d s by mouth and with edathamil $CaNa_2$ 1 g q i d by mouth In each case treatment was preceded by 2 control days during which urine, fæces and blood were collected for analysis and intervals of several days were allowed between the different forms of treatment

The men were confined to bed for the first few days and sedated as necessary with amylobarbitone in doses from gr $^3/_4$ t d s to gr 3 b d, with gr 3–6 at night A high fluid intake and full diet were encouraged throughout

After discharge from hospital the men were examined and further analyses were made weekly Edathamil $CaNa_2$ 1 g q i d was given by mouth for alternate weeks until their clinical condition was satisfactory and the basal lead excretion normal They then started work *of a different kind involving no exposure to toxic hazards*

Case-reports

Case 1 —A man aged 41 had cleaned tanks, including a few which had contained leaded petrol, regularly for 10 years and was foreman of the team He had never previously noted any ill effects

His first symptom, dryness of the throat, appeared 3 weeks after starting work and was followed by cramps in the legs, anorexia, occasional vomiting, *loss of a few pounds'* weight, difficulty in falling asleep, tremor of the hands and intense anxiety about his own condition and that of the other men for whom he was responsible On a sudden impulse he travelled 150 miles by taxi to see whether his workmates were also ill Before admission he had been treated with small doses of phenobarbitone without effect

On admission on May 1, 1956, he was intensely anxious, he appeared tired but required large doses of amylobarbitone to induce sleep Weight 165 lb (74 8 kg), temperature 98 4°F (36 9°C), pulse 70 per min, blood pressure (B P) 125/70 mm Hg There was a fine tremor of the outstretched hands, but no other physical signs of disease

Subjective improvement was apparent once he had been reassured about the condition of his workmates but he continued to show mood swings, apparently unrelated to treatment The B P stabilised at 110/60

He was discharged home after 20 days, weight 162 lb (73 5 kg), subjectively much improved but still complaining of a dry throat and occasional pains in the limbs Further improvement seemed to coincide with the oral administration *of edathamil $CaNa_2$ and he was symptom free and returned* to work 11 weeks after the onset of his illness

Case 2 —A man aged 28 had worked in tanks only on this one occasion After a month he complained of difficulty in falling asleep, nightmares, anorexia, a persistent metallic taste, intermittent diarrhœa and vomiting, *retro orbital* headaches and giddiness He had had occasional upper abdominal pain and vomiting for the previous 2 years but had otherwise been fit

When first seen on April 30, he claimed to have lost 20 lb (9 1 kg) *during the previous* 6 weeks He was anxious but not excited and he had no tremor His weight was 162 lb (73 5 kg), B P 110/75 As his symptoms persisted, he was admitted to hospital on May 9, when he weighed 161 lb (73 0 kg), temperature 98 2°F (36 8°C), pulse 60 B P 120/75 A barium meal examination showed nothing abnormal and the fæces were persistently negative for occult blood

Throughout his stay in hospital he was alternately elated and depressed and suffered from occasional attacks of upper abdominal discomfort, vomiting and diarrhœa, apparently unrelated to treatment His B P stabilised at 100/60 He was discharged home on June 2, but readmitted 2 days later because of further vomiting which rapidly subsided with antacids and a bland diet He was finally discharged on June 9, weighing 158 lb (71 7 kg)

Between June 9 and July 30 he was given two 7 day courses *of oral edathamil $CaNa_2$ He abandoned the first after 4 days* because of abdominal pain and diarrhœa The second course was uneventful At this time his B P was 115/70 and his weight had risen to 170 lb (77 1 kg) Apart from occasional headache he was symptom free on July 30 when he started work after 11 weeks' illness

Case 3 —A man aged 25 had also worked inside tanks for only 6 weeks When seen on April 30 he complained only of insomnia but by May 10 he looked pale and thinner and complained of irritability, impairment of concentration, loss of libido, headache, occasional auditory hallucinations, anorexia, nausea, abdominal discomfort, vomiting and loss of a few pounds' weight

On admission on May 17, he appeared anxious His weight was 146 lb (66 2 kg), temperature 97 8°F (36 5°C), pulse 64 B P 95/65 Improvement was gradual and initially seemed unrelated to treatment He was worried most *by his memory* defect Formal testing showed an average intelligence and suggested a good prognosis for recovery, which was subsequently justified He was discharged home on June 3, weighing 148 lb (67 1 kg), and was given three 7 day courses of oral *edathamil $CaNa_2$ during which* he said he felt particularly well He was symptom free and began work on July 10, when his B P was 110/55 and his weight had risen to 150 lb (68 0 kg)

Case 4 —A man aged 31 had worked intermittently in leaded petrol tanks for about a year When first seen on April 30 he *strongly denied any symptoms* but his blood pressure was 95/70 and he had a slight tremor of the hand He was known to have been a heavy drinker and to have suffered violent mood swings in the past

He was admitted to hospital on May 7 complaining of dizziness, confusion, and insomnia and was said to have lost consciousness for a few minutes some days previously He was restless and resisted examination His B P was 90/60 and weight 140 lb (63 5 kg) Amylobarbitone gr 3–6 seemed to aggravate his restlessness and within two days he was deluded, visually and aurally hallucinated and violent

He was transferred to a mental hospital on May 14 During the next few days he was frequently violent and appeared intermittently anxious, confused and paranoid Drug treatment was impossible and deterioration was progressive On May 25 he was given unmodified electroconvulsion treatment (E C T) and immediately became quiet and coöperative and for the first time had an adequate intake of food and fluids B P was 85/55 immediately after this treatment He slept well Edathamil CaNa$_2$ was given intravenously on the next 2 days but on the 3rd day he again became restless and was given a second treatment with E C T , after which he remained lucid and rational He was given infusions of edathamil CaNa$_2$ on the next 3 days with further improvement

He was discharged from hospital on June 5 and was given three courses of oral edathamil CaNa$_2$ on alternate weeks at the end of which his daily urine lead excretion was within normal limits At this time (July 23) his B.P had risen to 110/70 and his weight to 150 lb (68 0 kg) He was, however, still showing signs of a mild depression as well as certain paranoid traits and was therefore given six further treatments of E C T between Aug 15 and Sept 18 with the object of preventing these forming any ingrained pattern of conduct

After this he improved rapidly and he resumed light work on Oct 9 His illness lasted about 6 months

TABLE I—DAILY OUTPUT OF LEAD IN µG IN URINE AND FÆCES

Treatment	—	Case 1		Case 2		Case 3	
		Urine	Fæces	Urine	Fæces	Urine	Fæces
Before treatment		657	1440	227	560	310	1060
		718	560	314	520	133	360
	Mean	688	*1000*	270	540	222	*710*
Intravenous edathamil CaNa$_2$		4380	2280	2456	280	942	720
		2991	1220	1956	400	3304	300
		2212	1260	1906	48	1551	548
	Mean	3194	1587	2106	243	1932	523
Interval		1270	520	761	560	838	760
		794	1120	447	560	638	200
		905	940	416	280		
				412	1960		
	Mean	990	860	509	840	738	480
Penicillamine		2271	1720	511		609	420
		1119	620	463	170	774	400
		992	310	412	560	680	260
	Mean	1461	883	462	365	688	360
Interval				455			
		836	740	167		510	360
		669	370	428			
				394	660		
				536	310		
				468	320		
	Mean	753	555	408	430	510	360
Oral edathamil CaNa$_2$		275	1600	619	720	960	250
		1807	440	735	90	454	280
		973	800	744		664	280
	Mean	1018	947	699	405	693	270
Interval		1309	560	163	1320		
		1072	1080	1126	220		
		845	680	240	456		
				221		989	180
	Mean	1075	773	437	665	989	180
Intravenous edathamil CaNa$_2$		1291		925		1683	
		2228					
	Mean	1759		925		1683	

In each case the figures given are in daily chronological order

Effects of Treatment

Table I shows that, though the urinary and fæcal lead excretion before treatment was greater than normal, the ratio between the two was about the same as in non-exposed persons excreting normal amounts of lead The variation in lead excretion before treatment is to be expected, as many factors influence lead output Creatinine estimations confirmed the accuracy of the urine collection (Note In correlating urinary and fæcal lead excretion for a 24-hour period, the urine figures for that period were allied to the fæcal figures for the following period)

TABLE II—DAILY EXCRETION OF LEAD IN µG

Case	Urine	Fæces	Total
1	557	170	727
2	99	100	199
3	391	250	641
4	133	190	323

Of the three cases studied fully, the highest lead excretion was found in the man (case 1) who had been exposed to tetraethyl lead the longest, but had not previously suffered from symptoms of poisoning Before treatment his mean daily excretion was 1688 µg (urine 688 µg , fæces 1000 µg) compared with 810 µg (urine 270 µg , fæces 540 µg) in case 2, and 932 µg (urine 222 µg , fæces 710 µg) *in case 3, in both of which the symptoms* were no less severe Data on case 4 are scanty because of the nature and severity of the illness in this case but the mean daily excretion before treatment was 5123 µg. (urine 789 µg , fæces 4334 µg)

In case 1, lead excretion continued at a relatively greater rate than in the others, during and between the periods of treatment, and by July 9, about 2 months after treatment was first started and immediately following a week's course of oral edathamil CaNa$_2$, the excretion in each case had fallen as shown in table II

This suggests that in case 1 a large amount of tetraethyl lead had been absorbed over a long period (he had been exposed to it intermittently for 10 years) and that much of the lead had been stored in a relatively non-toxic form whereas in case 4 a smaller amount of tetraethyl lead had been absorbed over a short period (he was exposed to it for only 6 weeks), but he suffered severe poisoning because the rate of absorption much exceeded that of degradation and excretion

The greater excretion of lead on the first day compared with the subsequent days of the periods between treatments was presumably due to a residual effect of the drugs and this also explains why the lead excretion was greater in these periods than before treatment

Table III and figs 1 and 2 show that intravenous edathamil CaNa$_2$ (1 g per 30 lb body-weight) increased the urinary lead excretion sevenfold and the total excretion threefold, whilst oral edathamil CaNa$_2$ and

TABLE III—EXCRETION OF LEAD AFTER TREATMENT, EXPRESSED AS PERCENTAGE OF PRE TREATMENT FIGURE

Treatment	Case	Urine	Fæces	Total
Before treatment	Mean	100	100	100
Intravenous edathamil CaNa$_2$	1	464	159	283
	2	780	45	290
	3	870	74	263
	Mean	705	93	279
Interval	1	144	86	110
	2	189	156	167
	3	332	68	131
	Mean	222	103	136
Penicillamine	1	212	88	139
	2	171	68	102
	3	310	51	112
	Mean	231	69	118
Interval	1	109	55	77
	2	151	80	103
	3	230	51	93
	Mean	163	62	91
Oral edathamil CaNa$_2$	1	148	95	116
	2	259	75	136
	3	312	38	103
	Mean	240	69	118
Interval	1	156	77	109
	2	162	123	136
	3	445	25	125
	Mean	254	75	123
Intravenous edathamil CaNa	1	256		
	2	343		
	3	758		
	Mean	452		

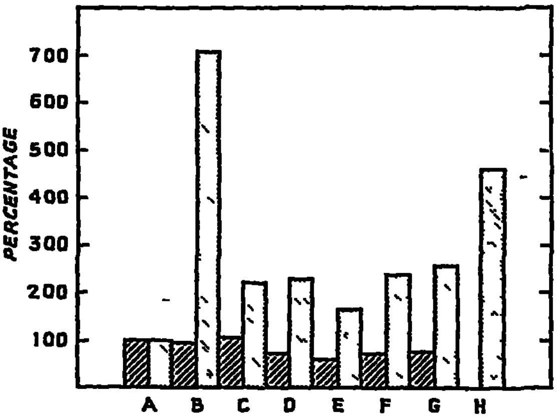

Fig 1—Total mean excretion of lead in cases 1, 2, and 3 after treatment, expressed as percentage of total mean excretion before treatment. Stippled in urine Hatched in fæces A, before treatment, B, intravenous edathamil, C, interval, D, penicillamine, E, interval, F, oral edathamil, G, interval, H, intravenous edathamil (1 day)

penicillamine had much less effect No drug affected the fæcal lead excretion, which fell progressively

There was no change in the blood-lead content as a result of treatment in cases 1, 2, and 3, where the mean blood-lead figures on admission were 51, 63, and 56 µg per 100 g respectively The highest values were found in case 4 (on admission 86, 89, and 89 µg per 100 g on consecutive days) and within a month the level had fallen to 50–60 µg per 100 g

The urinary coproporphyrin excretion was very variable from individual to individual and from day to day The mean pre treatment levels in cases 1, 2, and 3 were 12, 46, and 13 µg per day and there was no significant change during or as a result of treatment Before treatment there was a mean excretion of 142 µg per day in case 4, which fell to 30–60 µg per day within a month

Subjective improvement in cases 1, 2, and 3 was gradual but punctuated by mood swings and occasional emotional outbursts After discharge all but one of the men said that they felt better when taking edathamil $CaNa_2$ by mouth but there was no other correlation between treatment and the relief of symptoms The exception (case 2) complained that the abdominal discomfort and diarrhœa from which he had suffered periodically for 2 years was aggravated by oral edathamil $CaNa_2$ No other symptoms referable to treatment were noted No patient showed any desire to commit suicide

DISCUSSION

The treatment of tetraethyl lead poisoning should protect the patient against the ill effects of the substance and hasten his recovery by increasing the excretion of lead in a non-toxic form

All but the very mildest cases should be admitted to hospital Good nursing is essential to maintain hydration and nutrition and physical restraint may be necessary because of violence or suicidal attempts

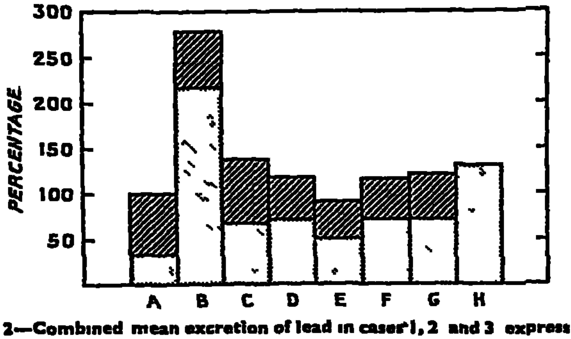

Fig 2—Combined mean excretion of lead in cases 1, 2 and 3 expressed as percentage of combined mean excretion before treatment Stippled proportion in urine Hatched proportion in fæces

Sedation with barbiturates is usually adequate in mild cases (cf cases 1 to 3), but in more severe cases it may aggravate the confusion and restlessness which become worse as the dose is increased in an attempt to control them In case 4 the patient was upset in this way by amylobarbitone in doses as small as gr 3 He tolerated paraldehyde by intramuscular injection much better

Means of Increasing Lead Excretion

Dimercaprol (B A L) and edathamil $CaNa_2$ are the only drugs available which effectively increase lead excretion and are suitable for clinical use They have been used extensively in inorganic lead poisoning and of the two, edathamil $CaNa_2$ is the less toxic and more effective Little is known of their value in tetraethyl lead poisoning

Though dimercaprol causes a transient increase in urinary lead excretion and a fall in blood lead level (the latter apparently by transfer to muscle and bone) which may relieve the symptoms of chronic inorganic lead poisoning, its frequent side effects—particularly nausea vasomotor symptoms and pain and necrosis at the site of injection—detract considerably from its value (Ryder et al 1947) Further, Graham and Hood (1948) have shown in animals and Vigliani and Zurlo (1951) in man, that it may aggravate acute poisoning Kehoe (personal communication 1951) and Kitzmiller et al (1954) do not regard it as valuable in the treatment of tetraethyl lead poisoning and we did not think its use was warranted

Edathamil calcium disodium is the monocalcium disodium complex of ethylene diamine tetracetic acid (edathamil, E D T A , versene), a chelating agent which combines with metallic ions forming non ionised, biologically inactive compounds Metals are displaced from the complexes by heavier metals In clinical practice the monocalcium disodium complex of edathamil is used to avoid reduction of the ionised serum calcium and it is the calcium atoms which are exchanged for those of heavier metals

Edathamil $CaNa_2$ has revolutionised the treatment of inorganic lead poisoning Most workers (Hardy et al 1954, Giles et al 1955, Wade and Burnum 1955) have given the drug intravenously in doses up to 1 g per 30 lb body-weight per day Symptomatic relief is rapid Colic disappears in a few hours (Marcus and Spencer 1955) The urinary lead excretion increases and is usually maximal on the first day of treatment, as in our cases of tetraethyl lead poisoning Side effects are uncommon but include malaise, joint pains and light headedness

Little work has been published on oral administration but Sidbury et al (1953) demonstrated a fivefold to tenfold increase in urinary excretion in inorganic lead poisoning and mentioned abdominal pain and diarrhœa as a side effect One of our patients, who had suffered from occasional abdominal pain and diarrhœa for 2 years, attributed an episode to oral edathamil $CaNa_2$

Nothing has been published in the British literature and the only report from America on the treatment of tetraethyl lead poisoning with edathamil $CaNa_2$ is that of Kitzmiller et al (1954), who treated three cases by intravenous infusion As in our experience and in contrast to that in inorganic lead poisoning, improvement was not dramatic and the increase in urinary lead excretion was relatively less than that found in inorganic lead poisoning Unfortunately detailed comparison between their results and ours is impossible because they collected only random urine and no fæcal samples

Penicillamine (ββ dimethyl cysteine), like dimercaprol contains 2 thiol (—SH) groups per molecule Walshe (1956) has shown that it increases the urinary excretion of copper in normal subjects and that in patients with hepatolenticular degeneration it does so as effectively as dimercaprol in doses containing equivalent amounts of sulphur The drug is given orally (300 mg t d s) and is apparently non-toxic It was given in these cases to see whether it would increase lead excretion without side effects There was little effect on lead excretion but no toxicity

The Psychiatric Side

The illnesses of our patients agreed closely with the descriptions of Machle (1935) and Kehoe (1925) and the manifestations were coloured by their underlying personalities In cases 1 and 3 the patients had stable personalities and a sense of responsibility They were worried by their illness, the first because he was responsible for the work and safety of the team and the third because he had to support a wife and young children The other two were unmarried and irresponsible The fourth patient in particular was known to drink heavily and to have been excitable He absorbed a considerable amount of tetraethyl lead over a short period and his intense excitement and violence were probably conditioned by his cyclothymic personality and aggravated by withdrawal of alcohol He was deliberately not given alcohol because this may further aggravate the toxic effects of tetraethyl lead It is probably significant that his " black out " before admission occurred in a public house although he had been warned not to take alcohol

E C T—Although Roth and Rosie (1953) have reported that E C T may produce striking improvement in toxic psychoses when the underlying cause has been treated, we know of no previous work on the effects of E C T in tetraethyl lead poisoning The response of case 4 was dramatic If other severely ill patients benefit in the same way, the problems of management and treatment would be simplified and mortality would probably be reduced

Summary

Four non fatal cases of tetraethyl lead poisoning are described The urinary lead excretion of the three studied in detail was increased sevenfold by edathamil $CaNa_2$ given intravenously, but little affected by edathamil $CaNa_2$ or by penicillamine by mouth One patient who was maniacal, hallucinated and deluded responded dramatically to electroconvulsion therapy

We wish to thank Dr J D N Nabarro for permission to study the patients, who were admitted under his care, Dr E L Udwin, who undertook the care of case 4 at Horton Hospital, Dr M Chapman, who gave the intravenous infusions and assisted in the collection of samples, Dr J M Walshe, who provided the penicillamine, Dr G Harrison, under whose direction the lead and coproporphyrin estimations were performed in the laboratory of the Associated Ethyl Company Limited, and the staffs of the clinical laboratories of the Courtauld Institute of Biochemistry and the Bland Sutton Institute of Pathology of the Middlesex Hospital Medical School who undertook other investigations and estimations

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HYPOTHERMIA BY INTERNAL COOLING*

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ARTIFICIAL hypothermia was first produced in mammals by Andjus (1951), who showed that albino rats so cooled could survive prolonged respiratory and cardiac arrest It has since been successfully used in man both as an aid to surgery (Lewis and Taufic 1953) and as an aid to anæsthesia Any method that is used for producing hypothermia can also be used for combating hyperpyrexia

There are at present two recognised methods of producing hypothermia surface cooling and extracorporeal blood cooling

Surface cooling is the more widely adopted method at present The patient's skin is cooled by putting him in cold water, a refrigerated blanket, or a box through which cold air is pumped Although surface-cooling is easy and generally applicable, particularly to small children, it takes a lot of time, and the body-temperature is difficult to control because it continues to fall after the surface cooling has been stopped Delorme (1953) and Brock (1956) have criticised this method because of undesirable effects

Extracorporeal blood-cooling was introduced by Boerema et al (1951) and Delorme (1952) Originally blood was taken from a large artery—e g, the femoral artery—cooled as it flowed through siliconed tubing immersed in cold water, and returned into a big vein Later vein-to-vein blood-cooling, using the venæ cavæ, was introduced by Ross (1954) Extracorporeal blood-cooling induces hypothermia more quickly than does surface cooling For cardiac surgery it has the advantage that it need not be started until the heart has been examined at operation Conversely, because it involves thoracotomy and cannulation of the venæ cavæ, it is clearly unsuitable for the other applications of hypothermia Even in cardiac surgery it adds further trauma to the heart and chest walls, and it is known to be associated with a high incidence of arrhythmias and ventricular fibrillation during cooling and operation Œdema of the brain has also been reported to follow the use of this technique

The difficulties and limitations in the above-mentioned two methods of producing hypothermia suggest that a simpler and safer method would be welcomed

Internal Cooling

Theoretical

The idea of producing hypothermia by filling the stomach with cold water in a balloon was suggested because of the rich vascularity of the gastric mucosa and the close relation of the stomach to the great blood-vessels of the abdomen and to important viscera, such as the liver All the major vessels of the abdomen lie in the stomach bed for a considerable length of their course, and so blood passing through them may be cooled in situ without having to be pumped outside the body and then back to the patient's circulation With each heart beat about half the arterial circulation of the body passes through the arteries lying behind the stomach, and the same volume is subsequently returned to the heart through the neighbouring veins A temperature gradient of a fraction of a degree between the large volume of blood flowing through these great vessels and the rest of the body tissues would affect the body-temperature considerably The large volume of blood cooled in this way at a small temperature gradient between it and the

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* Adapted from a paper read at the 2nd European Congress of Cardiology at Stockholm Sept 11, 1956

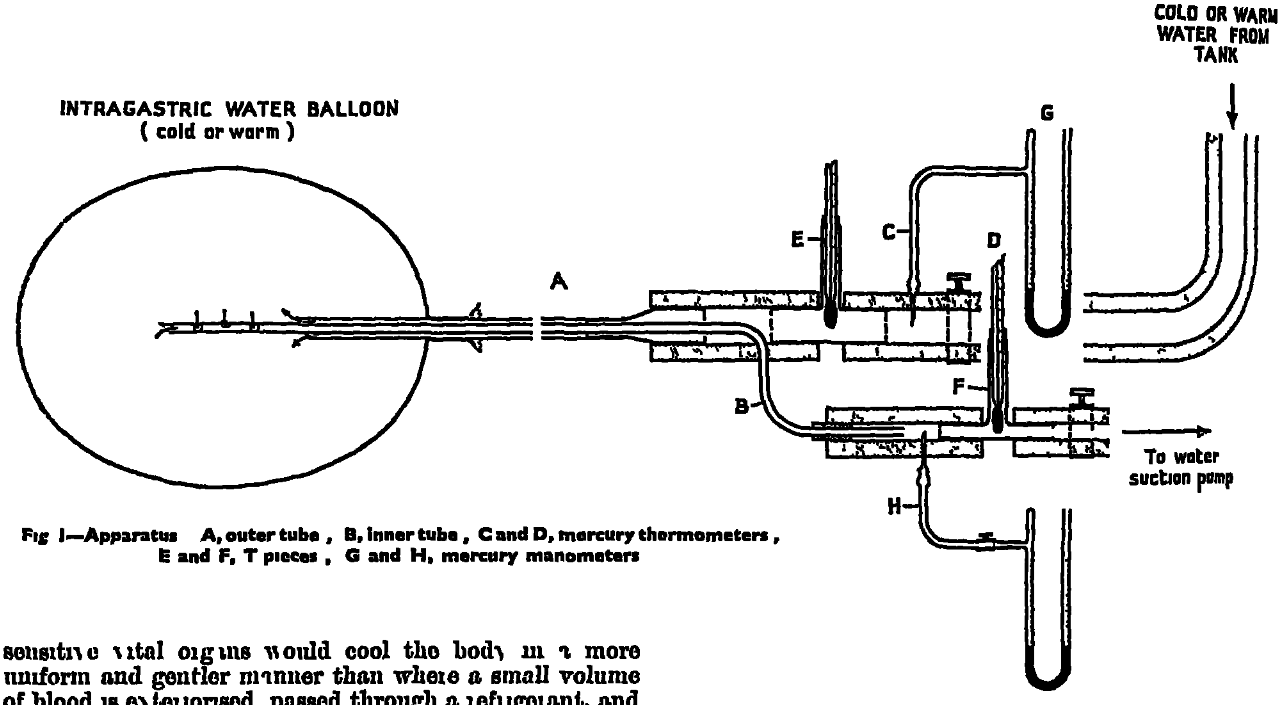
COLD OR WARM WATER FROM TANK
INTRAGASTRIC WATER BALLOON (cold or warm)
G
E
C
D
A
F
B
H
To water suction pump

Fig. 1—Apparatus. A, outer tube; B, inner tube; C and D, mercury thermometers; E and F, T pieces; G and H, mercury manometers.

sensitive vital organs would cool the body in a more uniform and gentler manner than where a small volume of blood is exteriorised, passed through a refrigerant, and then put back into the circulation at a wide temperature difference. Further, direct cooling of the abdominal viscera around the stomach will be an additional factor in cooling the body. This may also act by lessening the production of heat.

Experimental

In 1954 my preliminary experiments at Guy's Hospital on twenty rabbits showed that, by letting ice-cold water flow inside an intragastric balloon, the rabbits' body-temperature could be lowered from 39°C to 20°C and their heart-rate slowed from 250 to 60 beats a minute. They survived the experiment with no residual ill effects and were subsequently kept under observation for several months. Electrocardiograms during cooling showed bradycardia, prolonged conduction (P–R and QRS) and delayed repolarisation (S–T). Arrhythmias were rare, and ventricular fibrillation was never observed. There was no obvious change in the rabbits' behaviour after these experiments, and they did not lose weight.

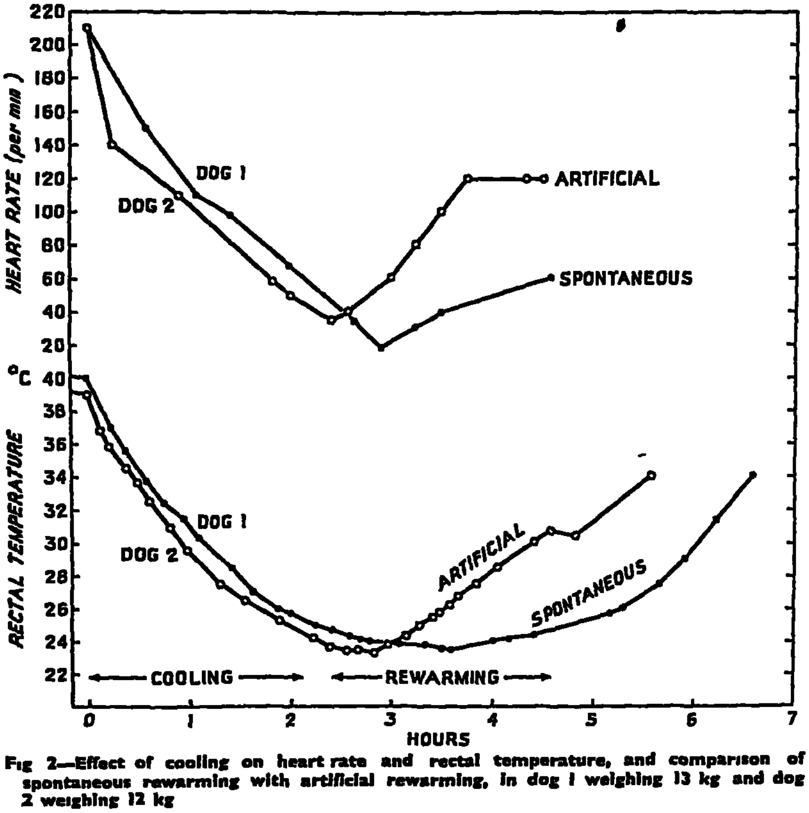

Fig. 2—Effect of cooling on heart rate and rectal temperature, and comparison of spontaneous rewarming with artificial rewarming, in dog 1 weighing 13 kg and dog 2 weighing 12 kg.

Clinical Trial

This technique of cooling by intragastric balloon was then tried with success on a hyperpyrexial baby (Khalil and MacKeith 1954). This case is of particular interest because surface-cooling with ice and fans had previously been tried for six hours without success, whereas internal cooling by the intragastric cold-water balloon improved the child's condition within a few minutes. The efficiency of this technique for cooling in man was evident. It was then decided to develop a practical apparatus for changing the body temperature by continuous infusion of cold or warm water through an intragastric balloon.

Materials and Methods

All the experiments were made in an air-conditioned room at 23°C. The subjects of the experiments were fourteen mongrel dogs weighing 12–20 kg and unselected as regards age and sex. Water was stored in two 160 litre tanks 1·5 m above the operating table. The water in one tank was cooled by mixing it with broken ice. Cold water passed down by gravity from the tank through rubber tubing to the balloon through the outer part of a double tube made of Porges 'Neoplex' (fig. 1, A) and left the balloon through the inner tube (fig. 1, B). The balloon used in each of these experiments was an ordinary rubber condom applied to the outer tube and with its end surrounded by a wide rubber band to make the balloon waterproof. To ensure that the size of the balloon remained constant inside the stomach, the outlet tube was attached through rubber tubing to a water suction-pump, and the rate of water flowing to the balloon was controlled at 2 litres a minute by regulating the gravity flow from the tank and the speed of the water suction-pump. This was indirectly tested by weighing the balloon. Two sensitive thermometers (fig 1, C and D), which had been compared beforehand, were inserted into the T-pieces (fig 1, E and F) fixed in the rubber tubing carrying water into and out of the balloon. Two mercury manometers (fig 1, G and H) were also connected to the two rubber tubes. The manometer H, connected to the outlet tube, was only used at intervals when the inflow of water and the suction were stopped. In the last eight experiments the electric suction-pump was out of order, and its place was taken by a tap-water suction-pump, which proved very practical and noiseless but did not return the cold water from the balloon to the tank.

Procedure

The dogs were first weighed. They were then given a fluid diet for twenty-four hours. On the day of the experiment they were only given water. Under open ether anæsthesia the dogs' tracheas were intubated. As the dogs' body-temperatures dropped, less ether was required to keep them well anæsthetised. The dogs were left to breathe ordinary air during the experiment. Since less oxygen is required in hypothermia, no artificial respiration was used, to avoid disturbing the acid-base balance by washing out carbon dioxide from the circulation. Body-temperatures were read from a mercury thermometer inserted about 10 cm into the rectum. After a sample of gastric juice had been collected, the empty balloon was easily introduced into the stomach and filled with cold water, till it weighed about a twelfth of the dog's body-weight, with a 50 ml two-way syringe, as used in direct transfusion. The filling of the balloon was indicated by the circumference of the abdomen, a double pneumograph (Palmer) being placed on the abdomen and connected by a Y-piece to a mercury manometer, on which the respiratory movements produced excursions of about 1 cm. Filling the intragastric balloon with water raised the level of mercury in the manometer about 5 cm and lessened the respiratory excursions to 0·2 cm. The manometer was then disconnected and adjusted to read 0 on both sides, and this reading was maintained throughout the experiment by controlling the rate of flow of the water. In this way the size of the balloon was kept constant. The pressure in the balloon was also recorded at short intervals during the experiment by temporarily closing both inflow and outflow tubes and connecting the outflow tube to the mercury manometer (fig 1, H). During cooling a continuous flow of cold water at 4–5°C at a rate of 2 litres a minute was maintained.

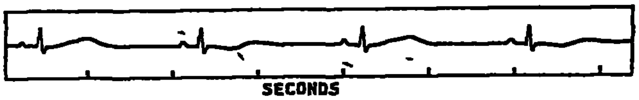

Fig 4—Electrocardiogram showing alternation in S–T segment in lead III at 23°C.

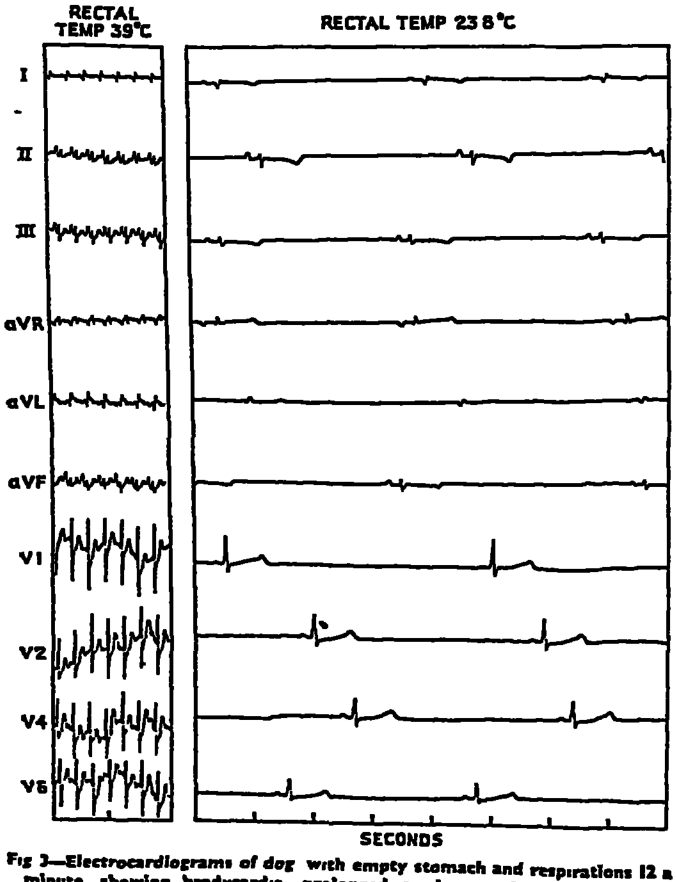

Fig 3—Electrocardiograms of dog with empty stomach and respirations 12 a minute showing bradycardia, prolonged conduction (P R and Q R S) and delayed repolarisation (S–T) at 23·8°C

Results

Although the intragastric balloon was filled till it weighed about a twelfth of the dog's body-weight, the epigastric region did not feel tense, and it seemed that there was room for more water. Possibly part of the balloon may have passed through the pylorus to the duodenum. The continuous flow of cold water inside the balloon lowered the body temperature and slowed the heart (fig 2) and respiration rates considerably. The fourteen unselected dogs were cooled from their normal rectal temperature of 39–40°C to one of 23·2–26°C, most of them to 23·2–24°C, and their heart rate slowed from 210 to 40 or thereabouts (fig 2). During cooling shivering was prevented by ether anæsthesia, which abolished the relevant reflexes. The dogs were left to themselves to rewarm, except that in the case of the last two warm water was circulated through the balloon. Without active rewarming, the rectal temperature went on falling and the heart-rate slowing (fig 2), and dogs cooled to 25°C warmed up much more quickly than those cooled to 23·2°C. With the onset of shivering the rectal temperature and heart and respiration rates rose, at first gradually and later rapidly. The dogs became semiconscious when their rectal temperature reached 27–28°C, they could sit and move at 30°C. Once started, the return of body-temperature to normal and the recovery of consciousness were remarkably rapid, even in the dogs which were not artificially rewarmed. On the morning following the experiment, the dogs looked well and took bread and milk readily. On the next day they ate a normal diet including meat and bones. Their subsequent steady increase in weight showed that their digestive function was not impaired by the procedure.

Electrocardiograms (fig 3) show most of the changes previously reported in hypothermia in dogs: bradycardia, prolonged conduction (P–R and Q R S), and delayed repolarisation (S–T), but arrhythmias were rare. A few ventricular extrasystoles developed at 24·5°C on two occasions but disappeared 5 minutes after warm water (35°C) had been passed through the balloon. No ventricular fibrillation developed The injury potential described by Osborne (1953) as the precursor of ventricular fibrillation appeared at about 29°C in four experiments but *did not lead to ventricular fibrillation, though some of the* dogs were cooled to below 25°C for a considerable time (fig 2) In one instance an alternation in the S–T segment appeared at 23°C (fig 4) The same thing happened in an experiment on a rabbit at the same temperature two years ago No adequate explanation has yet been put forward by numerous authorities who have seen the electrocardiogram

Discussion and Conclusions

This method is best named internal cooling It probably acts by cooling the blood in the large abdominal vessels and cooling the viscera

The low injury potential in the electrocardiograms, the rarity of arrhythmias, and the absence of spontaneous ventricular fibrillation were striking, this may be due to a gentler and more uniform cooling With extra-*corporeal cooling of the blood the heart receives cooled blood at many degrees below the body-temperature* Such cold blood does not readily give up its oxygen (Barcroft and King 1910), and this may affect the excitability and conductivity of the heart

The absence of trauma to the heart or great vessels is another attraction to this method of internal cooling

The organ most likely to suffer by this technique is the stomach The gastric functions have not yet been thoroughly investigated after internal cooling, but the early return of appetite and the absence of any gross evidence of permanent gastric dysfunction are good evidence that the stomach wall tolerates the procedure In the few dogs in which hydrochloric acid and pepsin were estimated there was no significant change a week after cooling Certainly in man the stomach is accustomed to wide variation in the temperature of the food it receives

Internal cooling may overcome some of the difficulties met with in current methods of producing hypothermia It is simple, practical, and easy to manage, and has given good results in one human case of hyperpyrexia, in which surface cooling had failed It does not interfere with the field of operation and so can be started at any time before or during the operation Internal cooling is almost as quick as extracorporeal cooling, and internal rewarming can be started during the operation as soon as hypothermia is no longer required Internal cooling combines the main advantages of the two other methods, and if it proves as successful in man as it has been in dogs it may even widen the field of application of hypothermia Intragastric cooling might be combined with intrarectal cooling or with surface cooling Such combinations might render the process of cooling quicker and more uniform and achieve lower hypothermia with safety Work is in progress to apply this method in man

Summary

A new method of inducing hypothermia in dogs by circulating cold water through an intragastric rubber balloon is described

This method was used on 14 animals and proved quite simple and practicable The rectal temperature was brought down to 25–23°C, and the heart rate from about 200 to about 40 per minute All the animals recovered quickly and apparently completely E C G tracings showed a striking absence of injury potential when the rectal temperature was above 29°C Injury potential appeared below this temperature in 4 out of 16 experiments, but it did not develop or lead to ventricular fibrillation

I thank Prof M L Dwidar for permission and facilities to conduct this work in the department of surgery, Alexandria University, Dr R C Mac Keith for his encouragement guidance, Dr P A Fleming for his help in interpretin electrocardiograms, Dr A S Soliman for his help in experiments, and Mr M S Mikhail for valuable tech assistance

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THE B C G LESION IN SARCOIDOSI

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IT is widely believed that most cases of sarcoid represent a peculiar form of reaction to the tube bacillus This supposition rests on an impressive b of circumstantial evidence, but attempts to prove it demonstrating tubercle bacilli in the sarcoid lesion ha with a few exceptions, met with failure One suggest put forward to explain their absence is that the bac having initiated the aggregation of histiocytes, rapidly destroyed by them in the sarcoid follicle (Ky 1921, Pinner 1938)

The primary purpose of the work reported here to test this hypothesis by observing whether attenua tubercle bacilli of the strain B C G survive, when ino lated into the skin of patients affected by sarcoido This experiment also provided an opportunity re-examine the claim made by Lemming (1940, 19 that the histological pattern at the site of such injection is peculiar to the disease and may therefo lend support to the diagnosis

10 patients suffering from sarcoidosis volunteered cooperate in the investigation They were given intracutaneous injection (0 1 ml) of a suspension B C G vaccine prepared by the *Danish Serum Institu* containing 0 5 mg of bacilli per ml The rate of develo ment of the local reaction was recorded Six weeks la the skin at the site of vaccination was excised a subjected to bacteriological and histological examinati

Clinical Features

The clinical and radiological manifestations of sa coidosis, uncommon in themselves, are unlikely to met in combination in any other disease *The diagno* in the 10 cases reported here was based on the *concurren* of two or more of these features The prevalence uveitis and of the intrathoracic manifestations of sa coidosis amongst them is to be attributed to the fa that most of the patients were under the joint care of eye hospital and a chest clinic

There were 8 women and 2 men, and they we between 24 and 55 years of age Uveitis was the cause the presenting complaint in 5 cases, in all of which it w

CLINICAL FEATURES AND RESULTS OF INOCULATION

Case no	Sex	Age	Clinical features	Mantoux test		Speed of reaction	*M tuberculosis* grown from skin lesion	*M tuberculosis* seen in skin lesion
				Before B C G	After B C G			
1	F	24	Erythema nodosum, enlarged hilar nodes	Neg to 10 mg O T	Pos to 0 1 mg O T	Delayed	+	+
2	F	37	Uveitis Enlarged hilar nodes Bilateral parotid enlargement	Neg to 1 mg O T	Neg to 1 mg O T	Delayed	No culture	+
3	F	52	Uveitis Enlarged hilar nodes	Pos to 0 1 mg O T	Pos to 0 1 mg O T	Immediate	No culture	—
4	F	24	Uveitis Enlarged hilar nodes	Neg to 1 mg O T	Neg to 1 mg O T	Delayed	+	—
5	F	31	Enlarged hilar and supraclavicular nodes	Neg to 1 mg O T	Neg to 1 mg O T	Delayed	+	—
6	F	30	Enlarged hilar and axillary nodes Lung reticulation	Pos to 1 mg O T	Pos to 1 mg O T	Delayed	—	—
7	M	55	Uveitis, enlarged hilar nodes reticulation of lungs Raised plasma globulins	Pos to 1 mg O T	Pos to 1 mg O T	Immediate	—	—
8	F	39	Enlarged hilar nodes Lung reticulation Raised plasma globulins	Neg to 1 mg O T	Neg to 1 mg O T	Not recorded	—	—
9	F	50	Enlarged hilar and axillary nodes skin lesions, lung reticulation	Pos to 0 1 mg O T	Neg to 1 mg O T	Delayed	—	—
10	M	28	Uveitis Reticulation of lungs	Neg to 1 mg O T	Pos to 1 mg O T	Delayed	—	—

associated with symmetrical enlargement of the hilar lymph-nodes, reticulation of the lungs, or both In addition to these findings in this group, chronic enlargement of the parotid glands was found in 1 patient and raised plasma globulins in another In 2 of the 5 cases of uveitis the jelly-like nodules in the iris and the large "mutton-fat" corneal precipitates were in themselves suggestive of sarcoidosis

*Amongst the other 5 patients, 3 showed the charac*teristic radiological pattern of symmetrical reticulation of the lungs, associated with bilateral enlargement of the hilar lymph-nodes Of these 1 had cutaneous sarcoid lesions, confirmed by biopsy, in another the lymph-nodes in both axillae were considerably enlarged, and in another the plasma globulins were raised Of the other 2 patients, one presented with erythema nodosum and symmetrical enlargement of the hilar lymph-nodes, and the other showed similar hilar appearances with a group of enlarged lymph-nodes above the left clavicle Primary tuberculosis was excluded in both by a series of negative tuberculin tests The salient clinical features of each case are set out in the accompanying table

Activity of the disease was assessed by progressive change in the radiological pattern of the lungs, variation in the size of the lymph-nodes, fluctuation in the severity of the uveitis, pyrexia, or a raised sedimentation-rate Some evidence of activity was found in each of the 10 patients at the time, or during the weeks immediately after the inoculation with B C G vaccine

Tuberculin Tests

The tuberculin sensitivity of each patient was tested with intracutaneous old tuberculin (O T) in doses of 0 01–1 mg, just before, and again six weeks after inoculation with B C G vaccine One patient was given an additional test with 10 mg of O T

The results of the tuberculin tests are shown in the table 6 patients were initially tuberculin negative, and 2 of the remaining 4 gave a positive reaction only to 1 mg of O T Conversion of tuberculin sensitivity six weeks after inoculation with B C G vaccine occurred in only 2 of the negative reactors and no rise of sensitivity was observed amongst the initially positive reactors

1 patient lost his tuberculin sensitivity after B C G inoculation

Development of the B C G Lesion

In healthy subjects the *inflammatory changes at the* site of inoculation may set in within a few hours or may be delayed for several days The delayed reaction, commonly seen in tuberculin-negative subjects, begins after an interval of five to seven days with a small area of erythema which slowly grows into a papule and ulcerates three to six weeks after inoculation The immediate reaction on the other hand starts within twenty-four hours and progresses to an ulcerated papule in a few days It represents the Koch phenomenon and is usual in tuberculin-positive subjects In either event the inflammatory reaction is generally confined to the site of inoculation, though the regional lymph nodes occasionally *become enlarged*

In our series the delayed reaction was observed in 7 patients, the immediate reaction in 2, while in 1 tuberculin-negative patient the rate of development of the B C G lesion was not recorded Correlation with tuberculin sensitivity was not complete, since the reaction was delayed not only in the tuberculin negative patients but also in 2 of the 4 initially positive reactors The appearance of the B C G lesion was identical with that seen in healthy subjects The regional lymph nodes were examined in 4 patients (cases 3, 7, 9, and 10) six weeks after inoculation, and were not palpable

Histological Findings

Despite the variety of its clinical forms, the microscopic lesions in the affected tissues in sarcoidosis are essentially similar This is the basis of the concept that the disease is a unity The histological appearance of the sarcoid lesion is that of a sharply defined follicular structure composed of epithelioid cells These follicles occur singly or in groups, and may show an occasional multinucleated cell of Langhans type They do not caseate and do not appear to provoke any inflammatory reaction in the tissue in which they are found Classically there is practically no leucocytic infiltration of a follicle other than an occasional *lymphocyte*

In this investigation we found that B C G vaccine produced a granulomatous lesion with an occasional follicle and Langhans giant cell, with a considerable infiltration of polymorphs and histiocytes, as well as lymphocytes The appearances in no instance were typical of sarcoid lesions In 2 cases acid fast bacilli were seen in the granulomata

Bacteriological Investigations

In an attempt to recover the strains of organisms used for vaccination, the cutaneous nodules were excised at the end of six weeks in all cases Part of the tissue was used for histological examination, while in 8 cases the remainder was ground up in sterile saline, treated by Jungmann's concentration method, and the deposit cultured on Lowenstein Jensen medium In 1 of the 2 specimens not cultured, acid-fast bacilli were seen in stained histological sections

From 6 of these cultures a growth of *Mycobacterium tuberculosis* was obtained, morphologically and colonially identical with the original B C G strains From each of three growths a suspension of the bacilli was made in sterile saline and injected intramuscularly into a guineapig, one month later, in all 3 cases the animals showed a positive Mantoux reaction to 1 mg O T, having been previously negative

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The absence of enlargement of the regional lymph nodes draining the site of vaccination deserves comment Adenopathy is a common feature of sarcoidosis, and if the disease is in fact due to an infection, enlargement of the lymph-nodes could reasonably be attributed to invasion by the infecting organisms 3 of the 4 cases in which the state of the lymph nodes draining the site of vaccination was recorded had enlarged mediastinal glands, yet none of them developed palpable regional glands after vaccination If the tubercle bacillus was responsible for the mediastinal lymphadenopathy, one might have expected the lymph-nodes on the direct path of invasion from the site of vaccination to be similarly affected

The histological appearance of the B C G lesion in sarcoidosis is not distinctive enough to be used as a diagnostic test The pattern is that of a chronic inflammation with histiocytes and lymphocytes predominating As might be expected in an ulcerated lesion exposed to secondary infection, polymorphonuclear cells were also common Giant cells were not always present and never contained the inclusion bodies described in sarcoidosis No section showed the characteristic cell arrangement of the sarcoid follicle

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Summary

Tubercle bacilli of the strain B C G inoculated into the skin of patients affected by sarcoidosis can be recovered six weeks later and are unaffected by passage

The rate of development and naked eye and histological appearance of the B C G lesion are not sufficiently distinctive to be relied on as a diagnostic test

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PLASMA-ŒSTROGEN LEVELS
IN LATE PREGNANCY, IN THE NORMAL MENSTRUATING FEMALE, AND IN THE MALE

J R K. Preedy
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RESEARCH FELLOW IN MEDICINE

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The chemical determination of œstrogens in the blood presents serious difficulties not only because of the minute amounts present but also because of the presence of material which interferes with the known methods for œstrogen detection

During the elaboration of a technique for the chemical determination of the three main œstrogens (œstrone, œstradiol-17β, and œstriol) in urine (Aitken and Preedy 1956), it appeared that the same technique could be applied to the estimation of œstrogens in the plasma of pregnancy

Since the chemical estimation of the three œstrogens in plasma using adequate separation techniques, has not been reported before, it may be valuable to present our findings in a small series of subjects in late pregnancy, in normal females, and in males

Material and Methods

Six patients in normal late pregnancy were studied, together with six normal females in the luteal phase of the menstrual cycle, and five normal males

Blood was collected heparinised, centrifuged immediately, and the supernatant plasma separated About 8 ml plasma was used in the pregnancy cases, and about 18 ml in the menstruating females and in the males The plasma was made up to 100 ml with water and refluxed in 1 8-N HCl for 45 minutes The procedure of Aitken and Preedy (1956), which involves gradient elution partition chromatography and fluorimetry, was then employed

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6	36	42	M	6 50	1 82	7 65

Results

Plasma œstrogen levels in the late pregnancy cases are given in table I The ranges are as follows œstrone, 2 65–10 3 µg per 100 ml , œstradiol 17β, 1 25–2 93 µg per 100 ml , œstriol, 4 28–17 5 µg per 100 ml A typical chromatogram from one of the pregnancy cases is shown in the figure The peaks due to the three œstrogens are labelled , the remaining peaks are due to interfering material.

Œstrogen levels in normal menstruating females are given in table II The levels are much lower than those in pregnancy, and in many instances are below the range that can be conveniently detected by this method, especially in respect of œstradiol 17β

Results in the five normal males are also given in table II In only one (case 1) was any œstrogen measurable

Discussion

As the accompanying figure shows, the separation technique elaborated for urine (Aitken and Preedy 1956) is quite satisfactory when applied to the plasma of late pregnancy The three œstrogens are not only widely separated from one another, but also from the relatively large peaks of fluorescent interfering material It is clear from this figure that, unless good separation is obtained, estimates of the amount of œstrogen present must be inaccurate

As part of an investigation into placental œstrogens Diczfalusy (1953) determined the œstrogen content of whole blood obtained from six pregnant women at parturition A fluorimetric technique similar to our own was used, but preliminary separation by 24-stage counter-current distribution, although adequate for pure œstrogen solutions, failed to give good separation of œstrogens from the interfering material in blood, especially in the first stages

TABLE II*—PLASMA-ŒSTROGEN LEVELS IN NORMAL MENSTRUATING FEMALES DURING THE LUTEAL PHASE AND IN NORMAL MALES

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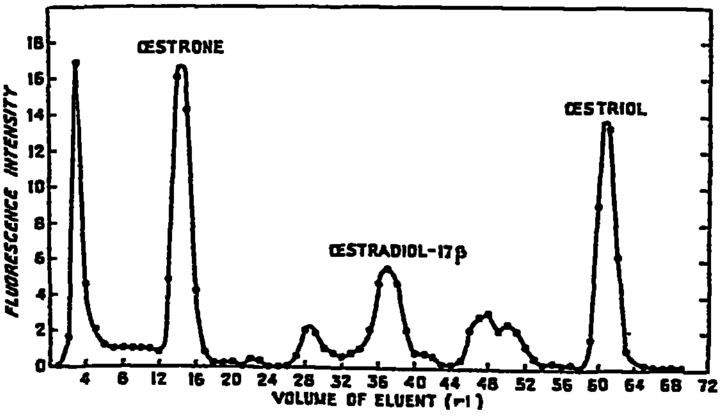
Œstrogen levels found in pregnancy plasma lie well within the sensitivity range of the present method As little as 8 ml plasma, or even less, is required for one estimation Serial determinations can therefore be performed in the same case

We decided to obtain plasma from the menstruating females during the luteal phase of the cycle, since Brown (1955) has shown that the urinary excretion of œstrone, œstradiol-17β and œstriol is highest during this phase Plasma œstrogen levels might then also be at their highest, although there is no evidence that urinary œstrogen levels accurately reflect those in the blood



A typical chromatogram of pregnancy plasma extract, showing the separation of œstrone œstradiol-17β, and œstriol obtained by gradient elution partition chromatography The unlabelled peaks are due to fluorescent interfering material typical of sarcoid lesions In 2 cases acid fast bacilli were seen in the granulomata

Bacteriological Investigations

In an attempt to recover the strains of organisms used for vaccination, the cutaneous nodules were excised at the end of six weeks in all cases Part of the tissue was used for histological examination, while in 8 cases the remainder was ground up in sterile saline, treated by Jungmann's concentration method, and the deposit cultured on Lowenstein Jensen medium In 1 of the 2 specimens not cultured, acid fast bacilli were seen in stained histological sections

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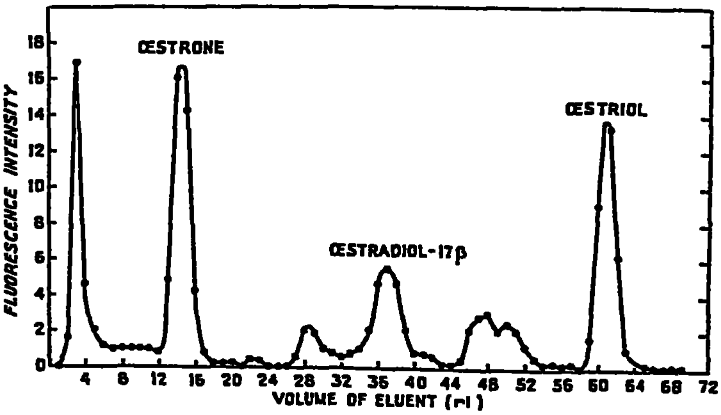

A typical chromatogram of pregnancy plasma extract, showing the separation of œstrone œstradiol 17β and œstriol obtained by gradient elution partition chromatography The unlabelled peaks are due to fluorescent interfering material

In spite of the use of much larger samples, however, only very small amounts of œstrogen could be detected in the plasma of the menstruating females Œstrone was measurable in three of the six cases only, and œstriol in two of the six cases No œstradiol-17β could be detected in any case The measured values can therefore be only approximate Furthermore, identification of the three œstrogens in these cases depends only on the finding of fluorescent peaks in the expected positions This is not entirely satisfactory

In the plasma of pregnancy, on the other hand, the œstrogen peaks in the chromatogram can be identified with reasonable confidence, because of the larger amounts of œstrogen present and the absence of any other immediately adjacent peaks Furthermore, the addition of pure crystalline œstrone, œstradiol 17β, and œstriol to pregnancy-plasma extracts resulted in a symmetrical increase in size of the three existing œstrogen peaks

The lowest amounts of œstrogen that can conveniently be detected in plasma by this method, using 18 ml, are œstrone, 0 06 μg per 100 ml, œstradiol-17β, 0 07 μg per 100 ml, œstriol, 0 15 μg per 100 ml

The state in which œstrogens exist in the blood is uncertain (Lieberman and Teich 1953) The distribution between plasma and cells is unknown, and the extent to which œstrogens are bound to plasma proteins is difficult to determine Œstrogens may occur in free form, or as glycoronides or sulphates In order to minimise the difficulties so created, it was decided to use plasma only, and to obtain figures for total œstrogen content by preliminary refluxing of the plasma for 45 minutes in 1 8 N acid This procedure denatures the plasma protein, and might be expected to release all œstrogen bound to the protein, although this would be difficult to prove At the same time œstrogen conjugates would be hydrolysed

It is known that uncombined œstrogens are resistant to refluxing in acid under these conditions (Marrian and Bauld 1951, Katzman et al 1954), and it therefore appeared unlikely that significant amounts of œstrogen would be destroyed by our procedure In addition, recoveries of pure crystalline œstrogens added to plasma before hydrolysis, extraction, and chromatography, were within the range of recoveries of œstrogen from urine reported by Aitken and Preedy (1956)

These results may provide a basis for the further study of plasma œstrogens, especially in normal and abnormal pregnancies Preliminary observations suggest that the method will also be of value in the study of plasma-œstrogen levels in hepatic disease

Summary

Plasma levels of œstrone, œstradiol 17β, and œstriol have been determined in pregnancy and in normal females and males by a chemical method, involving gradient-elution partition chromatography and fluorimetry

In pregnancy, the œstrogen concentrations were found to lie well within the sensitivity range of the method

In normal females and males, the concentrations were very low, and in several cases, no œstrogen could be detected

We should like to acknowledge our indebtedness to Prof C J O R Morris for constant help and advice We are most grateful to those colleagues and medical students who kindly gave blood for œstrogen determinations in the normal, and to the staff of the obstetric department, The London Hospital, for their cooperation in obtaining blood from the pregnant women

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PULLED ELBOW

M R Salkind
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Subluxation of the head of the radius distally under the annular ligament, or "pulled elbow," is a distinct clinical entity seen in children, which deserves to be better known

It was first described by Fournier (1671), and later by Lindeman (1885) In the United States Magill and Aitken (1954) give as high an incidence as 3% of all children aged 8 years or less, attending a Boston fracture clinic over a period of two years In children under 5 years of age it is twice as common as supracondylar fractures of the lower end of the humerus (Plewes 1956) Its frequency in general practice must therefore be far from negligible

No case has been reported in anyone over the age of 8 This is accounted for by the change in size of the head of the radius relative to the size of its neck Up to 5 years of age the head is smaller than the neck (Piersol 1930), and can thus slip easily under the retaining band of the annular ligament The head increases in size relative to the neck until at 8 years it is actually larger and so is retained in position by the annular ligament

The diagnosis should be simple The history is usually that the child's extended arm was pulled when he was lifted to a higher position There is sometimes a snap, and the child is unable or unwilling to use the affected arm In some cases the child comes to the parent, crying and fretful, with his arm limp, and no history of a pull is obtainable, though there has certainly been one Often the child cannot refer complaints to any particular site, but at times he complains of pain in the shoulder, clavicle, or wrist This accounts for the multiplicity of diagnose which have been made Now that poliomyelitis is more common, sudden limpness of an arm is an important symptom

Physical signs are few—namely, limitation of supination, and occasional tenderness over the head of the radius Presence of a rubbery resistance to passive supination and extension beyond 160° has been described (Magill and Aitken 1954) Radiographs are always normal

Reduction is immediately effective and can dramatically relieve the symptoms The doctor's thumb is placed just behind the radial head and the child's forearm is supinated and extended Sudden supination has also been recommended (Plewes 1956) In most cases, the child can at once move the arm, crying and fretting cease forthwith

Where the diagnosis is not made, a sprain is usually suspected The unfortunate child then wends his way from doctor to clinic and back again until such time as the manœuvre is carried out, often accidentally in the course of a physical examination, or even whilst radiographs are being taken Recurrence is common—perhaps the initial dislocation in some way leads to this

Case-reports

Case 1 —This girl had three subluxations

First —At 10 months She was crawling along a balcony when her father, in alarm, pulled her back by the arm It became limp, and she was taken to the nearest doctor The dislocation reduced itself during the examination

Second —At 2 years She was pulled upright from a sitting position She cried out, and her arm became limp Her shoulder seemed tender, but was not dislocated Radiographs showed nothing abnormal and the mother was told that nothing was wrong and that the trouble would right itself She was seen that evening in surgery and was asked to attend next morning if no improvement had taken place She did so, and was sent to the local children's hospital There the correct diagnosis was made and treatment gave immediate relief

Third—At 3 years She came running into the house crying with the same arm limp She was taken to the surgery and treated by extension and supination She left holding her toys in her arms No history of pull was obtainable on this occasion

Case 2—A girl who suffered two subluxations

First—At 5 months She was sitting on her father's knee and fell backwards. Her left arm was caught as she fell, it became limp and she was very fretful She was visiting relatives at the time, and was taken to the nearest teaching hospital The casualty officer was unable to make a diagnosis, but the elbow clicked back into position while radiographs were being taken

Second—At 10 months There was an exact repetition of the first episode When she was brought to the surgery she had limitation of supination and tenderness over the head of the radius Extension and supination resulted in immediate freeing of the elbow-joint

Summary

In young children the head of the radius is smaller than the neck, and subluxation under the annular ligament is not rare After a pull, the arm becomes limp Reduction, by supination and extension with a thumb behind the radial head, gives immediate relief

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AFFERENT-LOOP STRANGULATION FOLLOWING PARTIAL GASTRECTOMY

A CASE-REPORT

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A DESCRIPTION of 15 collected cases of small gut strangulation following partial gastrectomy has been given by Stammers (1954) and a further case is reported here It is unusual because it followed a short-loop antecolic anastomosis and was accompanied by a volvulus of the stomach Record is also made of the successful use of intra arterial transfusion in the resuscitation of the patient who was suffering from advanced non hæmorrhagic shock (Horton et al 1953)

Case-report

A man aged 47 came to the orthopædic outpatient department with pain in the back for two months He was found to have had melæna for five days and his hæmoglobin level was estimated to be 33% of normal Conservative treatment including blood transfusion was begun but after three days the pain grew worse and he vomited more than a pint of blood Immediate laparotomy was advised and although he had not complained of dyspepsia a giant benign ulcer was found on the lesser curve of the stomach for which partial gastrectomy was performed An ante colic Polya type of anastomosis was made with the afferent loop attached to the lesser curve and care was taken to ensure that the jejunal loop used was short

Postoperatively the abdominal wound ruptured and was resutured but despite this setback he made a good recovery and was discharged to a convalescence home

There on the 23rd day after the gastrectomy, he had severe pain in the back and left side of the abdomen it came on suddenly and gradually grew worse it was colicky and radiated to the left testis He vomited three times without relief Thirty hours later he was readmitted to hospital and signs of generalised peritoneal irritation, greatest on the left side, were noted His general condition was poor and it was apparent that he was suffering from advanced peripheral circulatory failure, the pulse rate was 110 per minute and the blood pressure 75/55 mm Hg (his normal was 120/80) It seemed that he had had a perforation of the gastro intestinal tract or possibly a delayed hæmorrhage from the spleen damaged during the gastrectomy Immediate operation was advised and, because of the possibility of hæmorrhage, he was taken to the theatre where resuscitation began Intravenous saline was used until compatible blood could be obtained His condition rapidly deteriorated and the systolic blood-pressure fell to 30 mm Hg, the respirations were gasping, and he appeared to be about to die When blood was available intra-arterial transfusion was performed using the right radial artery and two pints were given in seven minutes followed by a third more slowly There was an immediate improvement in his condition and respiration became more normal, at the end of twenty minutes the systolic pressure had risen to 75 mm and, as he was now better able to withstand operation anæsthesia was induced

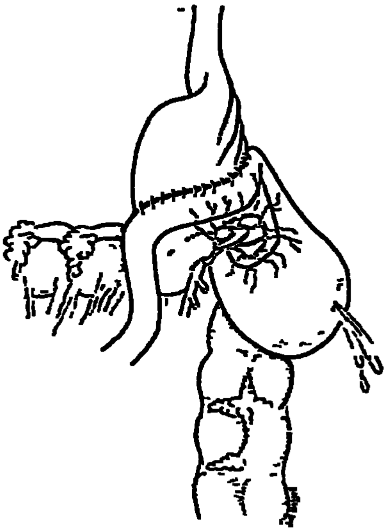

Diagram of operation findings

When the abdomen was opened through a left upper paramedian incision a loop of small gut was found in the left paracolic gutter It was distended to a diameter of 3 in and was discoloured green brown with a gangrenous patch in the centre of which was a perforation. Intestinal contents poured through the hole (see figure) Further search eventually showed that the stomach had undergone a volvulus through 180° about its long axis so that its posterior wall now faced anteriorly, the direction of the twist was such that the greater curve and efferent loop had passed in front and to the right, while the lesser curve and afferent loop had passed behind and to the left The distended gut first seen proved to be the afferent loop strangulated by the gap between the anastomotic jejunal loop and the transverse mesocolon, and it was hanging over the first jejunal branches of the superior mesenteric artery down into the left paracolic gutter The afferent and efferent loops were therefore replaced in their normal positions and the volvulus of the stomach untwisted The perforation which was not far from the duodenojejunal flexure, was closed and the gangrenous patch buried In order to prevent a recurrence the loops were fixed to the parietal peritoneum with a few interrupted catgut sutures During the operation further intra arterial blood was given, half a pint at a time, as indicated by the blood pressure, a total of four and a half pints was given and at the end of the operation the blood pressure had stabilised at 110/75 and a slow intravenous transfusion was now running He made a good recovery and when last seen in the outpatient department was well

Discussion

Strangulation of the small bowel as a complication of partial gastrectomy has been reported several times and may involve either the afferent or efferent loop We found in the literature 10 cases involving the afferent loop of an antecolic anastomosis, but in each one mention was made that a long loop was used, and in none of these cases was volvulus of the stomach noted (Quinn and Gifford 1950, West 1953, Stammers 1954)

It seems reasonable that the use of a short loop should avoid the complication of strangulation and has been advocated for that purpose That it does usually avoid it is probably borne out by the fact that, so far as we know, this is the first case recorded in which a short loop was used and it is hard to explain the mechanism of its occurrence It may be that this loop used was too short and formed a straight line with the œsophagus and lesser curve This could have acted as a firm pivot or bowstring about which the adjacent and more mobile portions of the gastro intestinal tract were able to rotate

In the early stages of shock intravenous transfusion increases the venous return to the heart, which responds with an improved output, and the distribution of the blood-volume begins to return to normal But in the later, or "irreversible," stage the cardiac output and blood-pressure are so low that the coronary circulation is inadequate and progressive myocardial depression ensues, it is this that prevents the usual response to intravenous transfusion and explains its failure to improve a shocked patient under these conditions At the same time there is anoxic damage to the liver, and this has been implicated in the development of shock, this damage, however, is reversed when the oxygen supply to the liver is improved

Because the arterial tree is a relatively closed system the pressure within it will be directly raised by pumping blood into it, in this way not only is the effective circulating blood volume rapidly restored but the blood pressure is raised so that increased coronary flow results and myocardial depression is reversed The progress of shock is arrested and the whole of the circulation now tends to return to normal and the oxygenation of the brain, liver, and kidneys is improved

The indications for intra-arterial transfusion in this case were the low blood-pressure and slowing pulse rate which suggested clinically that myocardial depression had set in (Wiggers 1949) We believe that the sequence of events following intra arterial transfusion in this patient was, in essence, as we have described, and that this accounts for the recovery of a man who had had an intraperitoneal perforation for more than thirty hours and had to undergo a major operation

Our thanks are due to Mr F d Abreu for permission to publish this report and to Dr R Wise who gave the anæsthetic on each occasion

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MANAGEMENT OF RESPIRATORY INSUFFICIENCY AFTER POLIOMYELITIS

AN ILLUSTRATIVE CASE

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AFTER the acute stage of poliomyelitis ventilatory capacity may be greatly reduced yet allow the patient to return home without artificial respiratory aid Such a patient is vulnerable to even a small further reduction of his respiratory reserve, which may lead to his admission to hospital as a respiratory emergency The following case illustrates the insidious onset of respiratory insufficiency 9 years after the attack of poliomyelitis, and is remarkable for the ease with which short periods of artificial respiration could profoundly disturb acid base balance

Case-report

A man aged 30 had had an attack of acute poliomyelitis 9 years before The respiratory muscles and limbs were extensively involved He was treated in a cabinet respirator for 14 months, and on discharge from hospital, 2 years after the onset, his vital capacity was about 1250 c cm At home he led mainly a bedridden existence, though he could walk a few steps His respirations seemed adequate until the beginning of June, 1956, when his breathing became noticeably shallower There was nothing to point to any specific illness though he was listless and unusually dry and thirsty

First Emergency

During the night of June 13, he lapsed into stupor and muttering delirium and next day he was admitted to another hospital where he was intubated and put into a cabinet respirator Despite this he became comatose He was then transferred to the National Hospital, Queen Square, on a Beaver positive pressure respirator His condition gradually improved and within 3 hours, though still drowsy, he could be roused sufficiently to answer questions The same evening, however, he again became comatose He was then being ventilated at 10 litres a minute Blood pressure was 85/50 mm Hg, pulse was regular at 100 a minute, blood sugar, blood urea, and serum potassium levels were normal

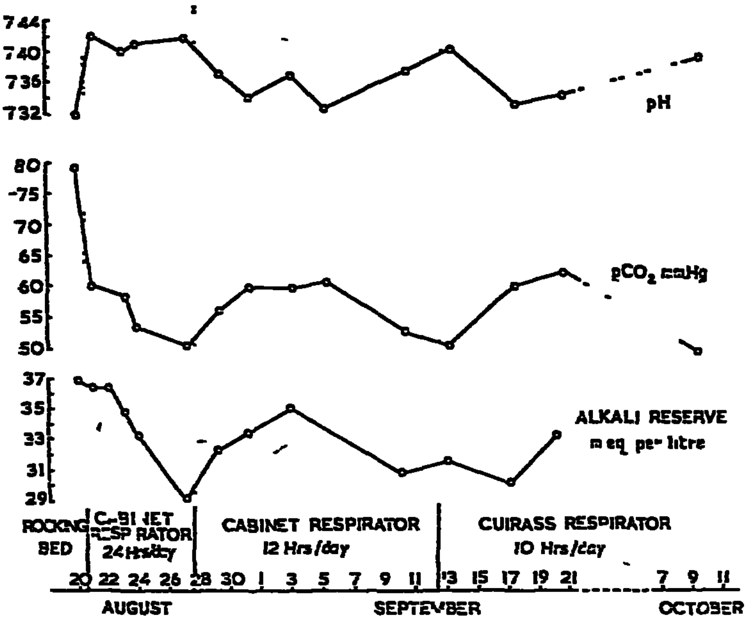
3 hours after the onset of this further relapse spontaneous muscle fasciculations were noticed in the upper limbs and a strongly positive Chvostek sign could be elicited These signs indicated that the patient had passed into a state of hypocapnic coma This conclusion was justified by an immediate and dramatic improvement in the conscious level when 3 litres a minute of a mixture of 5% CO_2 and 95% O_2 were added to the inspired air The muscle fasciculations ceased and the Chvostek sign disappeared after a few minutes The blood pressure rose slightly to 100/60 and the pulse rate remained constant

At midday on June 15, when he was being ventilated at 9 litres a minute including $1^1/_2$ litres of 5% CO_2 and 95% O_2 arterial puncture was performed The arterial O_2 saturation was 95%, the pH 7 57, and the pCO_2 (calculated by the Henderson Hasselbalch equation from the pH and plasma CO_2) was 30 mm Hg The alkali reserve was 30 2 m eq per litre This combination of a raised alkali reserve and lowered arterial pCO_2 indicated that respiratory and metabolic alkalosis were simultaneously present The metabolic alkalosis represented an attempted compensation for the previous respiratory acidosis resulting from his long standing chronic underventilation The respiratory alkalosis was due to the washing out of CO_2 by the artificial ventilation, and was still considerable even after several hours during which 5% CO_2 had been added to the inspired air There must have been, therefore, an even greater alkalosis when he was clinically in alkalotic coma

The patient was transferred to a cabinet respirator and the endotracheal tube removed His condition continued to improve so that by the 5th day weaning from the respirator could be begun On the 7th day, when his vital capacity had risen to 800 c cm, he was breathing unaided for an hour morning and afternoon At the end of one of these hour long periods the arterial O_2 saturation was 92%, with pH 7 36, pCO_2 51 mm Hg, and alkali reserve 31 7 m eq per litre Despite the mild degree of hypoventilation indicated by these results, his clinical condition appeared to justify his being left out of the respirator for increasing lengths of time, and on July 2 he was discharged

Second Emergency

On July 12 he was readmitted He had been well until that *morning, when he awoke* feeling listless, apathetic, and anorexic On admission he was rational but drowsy and cyanosed His respirations were shallow and the vital capacity was only 450 c cm The arterial O_2 saturation was 70%, the pH 7 37, the pCO_2 69 mm Hg, and the alkali reserve 35 m eq per litre He was put in a cabinet respirator at 7 30 P M and his cyanosis rapidly improved An hour later he became unresponsive, but when the rate of the machine was reduced from 20 to 16 cycles a minute he awoke and talked normally within 30 seconds At 9 15 P M he again became unresponsive



Effects of different forms of artificial respiration on pH, pCO₂ and alkali reserve. Determinations made on arterial or arterialised venous blood.

and exhibited a marked bilateral Chvostek sign. The pupils were constricted and did not respond to light, the corneal reflexes were absent, and there was marked muscle fasciculation. He was flushed and pink. The rate was reduced to 13 a minute, and within 20 seconds the pupils dilated widely and reacted to light through a small range. Within 50 seconds he became sufficiently conscious to answer simple questions and the Chvostek sign disappeared. During this episode the blood-pressure ranged between 105/70 and 110/90 and the pulse between 96 and 126 a minute. The loss of consciousness was therefore not due to circulatory collapse but to a lowering of the CO_2 tension in the blood by the artificial ventilation. Subsequent progress was satisfactory apart from a collapse of the left lower lobe, which re-expanded following bronchoscopic suction.

Preventive Measures

These repeated episodes of respiratory insufficiency clearly showed that this patient would continue to need some form of assistance to maintain adequate ventilation. An attempt was made over the next 4 weeks to wean him from the cabinet respirator to a rocking bed, since this would present few problems for home management and would be free from the danger of hyperventilation. Unfortunately, despite rocking for at least 12 hours each day, he gradually became so dyspnœic and lethargic that the rocking bed at this stage hindered rather than helped his breathing, since he was unable to synchronise his respirations with its movements. We therefore conducted a more detailed study of the blood gas and acid-base changes to decide on the most suitable form of respiratory aid.

These findings are illustrated in the figure. At the end of the period on the rocking bed the pCO_2 was 79 mm. Hg, the blood pH 7.32, and the alkali reserve 37 m.eq. per litre. The patient was again placed in the cabinet respirator and ventilated at 7–8 litres a minute. Within 24 hours the pCO_2 had fallen to 60 mm. Hg and the pH had risen to 7.42. At the end of a week, during which the pH remained at about 7.4, the pCO_2 had fallen steadily to 50 mm. Hg. The period in the respirator was then reduced to 12 hours each day, and though at first the alkali reserve and pCO_2 rose slightly, after about a week they again began to fall and the pH to rise.

Since CO_2 was thus not retained when the cabinet respirator was used for 12 hours a day, we decided to replace it with a cuirass respirator, and the figure shows that, after a similar initial few days for acclimatisation, 10 hours each night in the cuirass was sufficient to maintain ventilatory equilibrium. After 4 weeks of using the cuirass the vital capacity was 800 c.cm., the arterial oxygen saturation 91%, the pH 7.40, and the pCO_2 50 mm. Hg.

The patient was accordingly discharged home with his cuirass and has continued to make satisfactory progress.

Discussion

In patients with a grossly reduced vital capacity, a minor respiratory infection is known to be the commonest cause of respiratory failure, but it is not so widely realised that such a failure can take place without any obvious precipitating cause. Ferris et al. (1952) have demonstrated decreased compliance in convalescent poliomyelitis patients. This may be due to emphysematous changes in the lungs, produced by the artificial respiration, or to increase in the rigidity of the chest wall itself because its expansion is small. Such changes probably progress for several years after the original illness, the final stages of respiratory failure being precipitated by the increasing anoxia and rising CO_2 tension resulting from the impaired ventilation. Closer questioning of our patient's family revealed that there had been progressive reduction in his ventilation for the past 2 years, culminating in the respiratory failure of June, 1956.

The high alkali-reserve indicates a measure of compensation for such prolonged respiratory insufficiency. This metabolic alkalosis was responsible for the extraordinary rapid swing from hypercapnic to hypocapnic coma when effective artificial respiration was begun. We have never seen such a change in cases of acute respiratory failure, in which the onset is presumably too acute for any considerable compensatory metabolic alkalosis to arise. This seems to be borne out by Astrup et al. (1954) who, in a case of acute poliomyelitis, reduced the pCO_2 from 150 to 14 mm. Hg without untoward effects.

Even more startling than the ease with which our patient swung from hypercapnic to hypocapnic coma was his recovery of consciousness within a minute of reducing the rate of the cabinet respirator. The rapidity of this recovery was puzzling, since the reduction in ventilation could not have appreciably altered the arterial blood gas tensions in such a short period.

Although in this patient the fasciculation and the positive Chvostek sign helped to distinguish between hypocapnic and hypercapnic coma, these signs may be absent in hypocapnia, and Westlake et al. (1955) have described similar muscular irritability in hypercapnia following oxygen therapy in emphysema. Determination of the arterial pCO_2 is therefore a most valuable guide to the ventilatory state in these circumstances. Its value was further emphasised during the assessment of the most suitable type of respiratory aid for this patient.

Summary

A case of acute respiratory failure, 9 years after an attack of poliomyelitis, is described.

This patient showed an unusually rapid swing from hypercapnic to hypocapnic coma with only moderate artificial respiration.

The value of blood-gas analysis in assessing such disturbances of acid-base equilibrium and in selecting the most suitable type of respiratory assistance is illustrated.

We are grateful to the medical committee of the National Hospital, Queen Square, and to Dr. Michael Kremer, under whose care the patient was, for permission to publish this case; and to Dr. Kremer and Dr. R. Atwood Beaver for their advice.

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Preliminary Communication

REAGIN CONTENT OF CHROMATOGRAPHIC FRACTIONS OF HUMAN GAMMA-GLOBULIN

SEVERAL attempts have been made to decide which of the electrophoretic fractions of human serum proteins contain the skin sensitising antibodies—the reagins Electrophoresis convection [1–3] suggested that reagins may be present *in any or all of the globulin fractions* However, zone electrophoresis on starch [4] and continuous electrophoresis [5] showed definite localisation of reagin activity in the γ-globulin and particularly in the faster moving γ^1-globulin fraction

We observed that slight modification of the Peterson and Sober [6] technique of chromatography of serum-proteins on diethyl amino ethyl cellulose gave, with human serum, one main γ globulin fraction together with several smaller fractions of γ-globulin When examined by paper electrophoresis, the main fraction was found to move distinctly more slowly at pH 8 6 than the small fractions (which were indistinguishable from each other) It appeared that a simple fractionation of the slower and faster moving γ-globulin had been obtained and that the γ^1-globulin was further subdivided into several reproducible fractions In view of the previous evidence that reagins are largely in the γ^1 fractions, it was decided to fractionate sera from allergic subjects and to test whether the reagins were localised in one or more fractions It was found that with sera from six people allergic to a variety of substances, reagin activity was always highest in one γ^1 fraction, and in most cases was almost confined to that fraction

EXPERIMENTAL

Chromatography

Diethyl amino ethyl cellulose was prepared as described by Peterson and Sober [6]

The buffers used for development were 0 01 M sodium phosphate pH 7 5, 0 02 M sodium phosphate pH 6 2, and 0 05 M NaH$_2$PO$_4$ All were saturated with toluene before use Gradient elution was not used Each buffer was run through until no further protein was eluted, and the next buffer was then added The column was equilibrated with the weakest buffer at 2°C and the serum sample dialysed against this buffer before running on the column at 2°C 3 ml serum were fractionated on a 3 g column (1 1 × 12 cm) with a rate of flow of about 5 ml per hour Estimation of protein concentration in the eluate was by measurement of the absorption at 280 mμ in 1 cm cell in a spectrophotometer

Assay of Reagins

The chromatographic fractions were concentrated by pressure dialysis against 0 14 M NaCl and the volume of each adjusted to equal the volume of serum put on the column (3 ml) The fractions were sterilised by filtration through 'Oxoid' membrane filters (Oxo Ltd, London, E C 4)

Assay was by the Prausnitz-Küstner [7] passive sensitisation test

0 1 ml of three dilutions of the serum fractions were injected intracutaneously into the skin of the forearm, thigh, or back, of volunteers who, by previous tests, had been shown to be insensitive to the antigen used The sites of injection were marked, and 48 hours later were challenged by pricking through drops of antigen solution A positive reaction consisted in the appearance of a weal and erythema which was maximal in about 15 minutes and disappeared in 1–2 hours The area of the weal at its maximum was estimated by measuring the diameter in two directions at right angles

Serum was obtained from members of the staff of this institute who had a history of hay fever and/or asthma and who were shown by skin tests to be sensitive to mixed pollens ('Pollaccine'), horse serum, or extracts of cat or dog scurf Only one of the subjects examined had had a course of desensitising injections of antigen

The blood was drawn aseptically from the arm, and was allowed to clot, and the serum was stored at −10 C

RESULTS

Fig 1 shows the elution diagram when 3 ml serum (J M) was run on a 3 g column

The fast peak has come through the column at the solvent front without adsorption and is certainly a mixture of several components, peak 2 is adsorbed and retarded to some extent in 0 01 M phosphate buffer 0 02 M buffer was then run through and two more peaks emerged, the shape of the first suggesting that it might contain two partially resolved components Finally with 0 05 M buffer a large complex peak appeared Peaks 1, 2, 3, and 4, when tested by paper electrophoresis at pH 8 6, proved to be all γ globulin

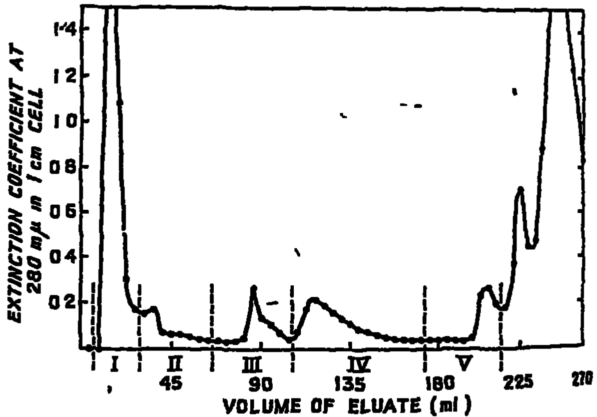

Fig 1—Chromatography of 3 ml human serum on 3 g diethyl amino ethyl cellulose (Column 12 × 1 1 cm)

0–45 ml eluting with 0 01 M sodium phosphate pH 7 5
45–180 ml eluting with 0 02 M sodium phosphate pH 6 2
180–270 ml eluting with 0 05 M sodium dihydrogen phosphate

In fig 2 the results with peaks 1 and 3 are shown

Electroendosmosis has moved both fractions towards the cathode, but it is clear that there is a distinct difference in their mobility Fractions 2, 3, and 4 were indistinguishable by paper electrophoresis Fraction 5 contained material moving between the γ and β bands, and later fractions were complex but contained no γ globulin

Of eight sera examined, all showed similar patterns with the same components present Some quantitative differences were seen in the relative proportions of each

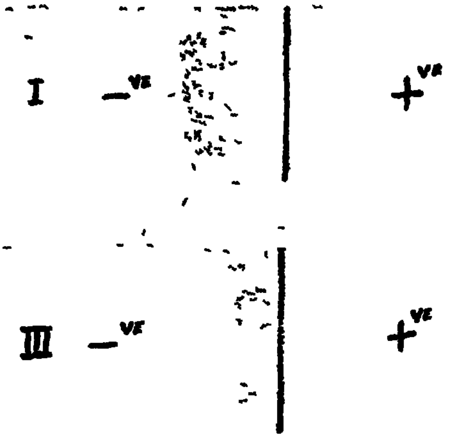

Fig 2—Electrophoresis on paper at pH 8 6 of fractions 1 and 3

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TABLE I—REAGIN ACTIVITY OF γ-GLOBULIN FRACTIONS
(Weal area in sq mm with J M serum)

Concentration	Fraction					Whole serum
	1	2	3	4	Euglobulin	
1/1	0	70	100	60	0	90
1/10	0	10	60	trace	0	80
1/100	0	0	trace	0	0	50

fraction but no attempt was made to evaluate these variations

Each fraction was concentrated to the volume of the serum used and then assayed for reagin activity This method of comparison gave the relative total amount of reagin in each fraction but it did not give the activity per milligramme of protein, for the weight of protein in fraction 1 was about two-thirds of the total γ-globulin and hence there was a much higher protein concentration in the test solution

The results of the reagin test with J M serum are given in table I The most striking feature is that fraction 1 is devoid of activity, some is present in fractions 2 and 4, but fraction 3 was by far the most active No activity was detected in the other fractions, nor was any present in the small euglobulin precipitate which formed when the serum was dialysed against 0 01 M buffer before chromatography With four other sera very similar results were obtained, and in some cases activity was found only in fraction 3

TABLE II—REAGIN ACTIVITY OF γ-GLOBULIN FRACTIONS
(Weal area in sq mm, with D A serum)

Concentration	Fraction					Whole serum
	1	2	3	4	5	
1/5	40	36	90	80	40	130
1/25	20	0	40	10	0	60
1/125	0	0	10	0	0	10

The sixth serum (D A), from a person who was very sensitive to horse-serum, gave a somewhat different result The reagin content appeared to be much higher, and the results obtained with the different fractions are shown in table II Activity is more widely distributed and some is present in fraction 1 Fraction 3 has most of the activity and, if judged by activity per milligramme of protein is much the highest, fraction 1 being clearly the lowest. It is possible that the relative distribution of activity here is similar to that in the other sera, but, as the total content is higher, it has now become more apparent in the least active fractions

Serum D A was tested for precipitins against horse-serum by the ring test and by diffusion in agar, but none were detectable

DISCUSSION

This work has confirmed the observations of Kuhns[4] and Brattsen et al[5] that reagins against several antigens are found chiefly in the γ^{1} globulins It has further shown that the reagins are principally in one fraction of the γ^{1} globulins, and this technique would appear to offer a simple method of purifying reagins The significance of restriction of the reagin activity to only about 10% of the total γ globulin fraction is not clear When sera from two "normal" people were chromatographed there was no apparent difference in the elution pattern Neither of these subjects had ever had any known allergic symptoms and they gave negative skin tests to the antigens tested It seems, therefore that fraction 3 is a normal constituent and that only a small part of it is reagin

No human serum with a satisfactory content of precipitins could be obtained, but when a rabbit anti-bovine serum-albumin serum was fractionated by the same technique, there were found to be three principal γ-globulin components and the proportion of antibody in each was the same (within the error of the method) This serum was taken from a hyperimmune rabbit (16 mg precipitating antibody per ml serum) and it is uncertain whether this result has much significance in relation to the results to be expected with a human serum containing precipitin It may perhaps be taken to suggest that human precipitin will be present in most fractions and not sharply localised as are the reagins Using the purified reagins of fraction 3, we were able to confirm that unlike that of precipitins, their activity was destroyed by heating at 56°C for 4 hours as has been reported using whole serum[8] Attempts were made to test for inhibiting or potentiating factors in the other serum fractions by comparing the weal size produced by fraction 3 alone and by fraction 3 mixed with other fractions, but no evidence of any such effect was observed

One possible explanation of these results is that suggested to explain the complexity of rabbit γ globulin[9] Different types of cells perhaps localised in certain tissues produced distinct kinds of γ-globulin Perhaps only a small number are capable of producing reagins; or perhaps the route of entry of the antigen is such that only a small number receive the stimulus Test of this suggestion could perhaps best be made by finding whether certain tissues were able to synthesise only some of the γ-globulin fractions

SUMMARY

When human serum is fractionated by chromatography on diethyl amino ethyl cellulose, the γ-globulin can be resolved into four components The reagin content of serum from allergic subjects is almost confined to one of these components which contains about 10% of the total γ-globulin

We are grateful to the members of the institute staff who gave blood or allowed us to test fractions in their skin The test antigens were kindly given by Dr John Freeman, Inoculation Department, St Mary's Hospital London, and by Major Milner of Bencard Ltd.

We wish to thank Miss J Morgan for her excellent technical assistance

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Medical Societies

ROYAL SOCIETY OF MEDICINE

The Nephrotic Syndrome

ADDRESSING the section of pædiatrics of the Royal Society of Medicine on Jan 18, Prof C A JANEWAY, professor of pediatrics at Harvard University, dealt chiefly with his clinic's experience of the nephrotic syndrome in children, in whom it was less variable in its ætiology than it was in adults Before the introduction of antibiotics, they had thought that there were two separate conditions "pure lipoid nephrosis" and "chronic glomerulonephritis with œdema" The lipoid nephrosis most commonly began at the age of 2 or 3 years and 83% of deaths were due to infection, pneumococcal septicæmia being the most frequent Chronic glomerulonephritis with œdema showed a similar age-incidence but only 27% of deaths were due to intercurrent infection; renal failure was responsible for 63% The introduction of antibiotics had completely altered the natural history of the disease Death from infection was now uncommon in most hospitals and clinics Early treatment of infection was very important With the knowledge and consent of the family doctor the parents of nephrotic children were given tetracycline drugs and instructed to begin treatment at the first evidence of infection, and to give prophylactic therapy at half dosage if a respiratory infection appeared in other members of the family Antibiotics had greatly prolonged life but had had little, if any, effect on final recovery About two-thirds of all nephrotic children still died of the disease, but now renal failure was by far the most common cause of death The classical "large white kidney" of the nephrotic syndrome was now a pathological rarity Such kidneys were previously found in children dying early in the disease from pneumococcal infection, but now the kidney at death showed periglomerular scarring with obliteration of nephrons

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[9] Askonas B A Humphrey J H Porter R R Biochem J 1956 63 412

Professor Janeway and his associates now thought that almost all examples of the nephrotic syndrome in children were due to a membranous type of glomerulonephritis, and it was impossible to predict the eventual outcome early in the disease Modern clearance techniques had given valuable information about the disordered physiology of the condition During the first month the glomerular filtration-rate was invariably low but the renal plasma flow was often normal, and therefore the filtration fraction was reduced Thereafter, during the early reversible phase of the disease, clearances were variable and the glomerular filtration-rate sometimes increased above the normal levels, but it often remained low During this stage full recovery was possible even in cases complicated by azotæmia, hypertension, or hæmaturia In the later irreversible phase the low glomerular filtration-rate became progressively reduced until death resulted from uræmia

The work of Professor Janeway's colleague, Dr Gitlin, had shown no evidence of abnormality in the chemical composition of plasma-protein in the nephrotic syndrome Albumin from plasma, urine, œdema fluid, and ascitic fluid was identical with normal plasma albumin when tested by delicate immuno chemical methods The albumin deficiency was partially attributable to increased urinary loss but also to increased metabolic breakdown In contrast, β-lipoprotein, consisting of macromolecules containing 90% lipid, did not pass through the glomerulus and was metabolised at a diminished rate This globulin therefore accumulated in the plasma and accounted for the lipæmia of the nephrotic syndrome Changes in electrolyte metabolism, demonstrated by Metcoff, and consisting of abnormal sodium retention and urinary potassium loss, were thought to be secondary to increased production of aldosterone by the adrenal cortex, which had been detected in the urine by Luetscher This was probably a physiological response to reduction of blood-volume due to lowered colloid osmotic pressure in the plasma Increase of circulating blood volume by salt retention, however, inevitably increased the extracellular fluid volume and thus caused œdema

Diet could not be so strict in the management of the nephrotic syndrome in children as it was in adults Children did not tolerate rigid salt deprivation, and often refused high-protein diets Cortisone and corticotrophin (A C T H) usually caused a satisfactory diuresis unless the patient was in the later irreversible phase of the disease There was inadequate evidence to determine whether the natural history of the nephrotic syndrome was modified by hormone therapy It had still not been finally decided whether treatment with hormones should be intermittent or continuous, but Professor Janeway thought that the balance of evidence was probably in favour of continued treatment until proteinuria had completely disappeared or had become very slight

Little progress had been made in elucidating the cause of the nephrotic syndrome The disease produced in rats by injection of anti rat kidney rabbit serum, as shown by Heymann, was very similar to the condition in man All cases of the nephrotic syndrome, as well as disseminated lupus erythematosus and acute glomerular nephritis, were associated with reduction of serum complement These facts suggested, but did not prove, that the condition might be due to an immuno chemical factor which was as yet completely undefined

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Reviews of Books

Diagnosis and Treatment of Peripheral Vascular Disorders

DAVID I ABRAMSON, M D , F A C P , professor and head of the department of physical medicine and rehabilitation, and professor of medicine, University of Illinois, College of Medicine London Cassell 1956 Pp 537 5 guineas

THIS book is not designed for the specialist in peripheral vascular disease, but it does offer in a very palatable form basic anatomical and physiological data concerning the peripheral vessels, the signs and symptoms associated with their disease, and some of the problems in differential diagnosis The text, written by a physician with physiological leanings, is concise, lucid, and well illustrated In the text medical therapy prevails to the virtual exclusion of surgical measures Many readers will regret that the scope and indications for surgery are not indicated more fully, as doubtless some physicians find difficulty in selecting patients to refer to a vascular centre With this reservation the work can be warmly recommended for the general physician or practitioner

The Complete Cookery Book for Diabetics

IRIS HOLLAND ROGERS London H K Lewis 1956 Pp 110 5s

THIS little book will be an eye-opener to many diabetics and those that cook for them, for there is enough variety in the numerous recipes given to destroy the monotony of the unnecessarily rigid diets followed by many diabetics

The carbohydrate, protein, and fat content of each dish is given so that it is still possible (invoking, it must be admitted, a modicum of intelligence) to keep the food value of the diet constant But achievement of this desirable goal is somewhat impeded by a slight defect in the book a number of 10 g carbohydrate exchange dishes are described under the heading of savouries but no attention is drawn to their content of fat and protein There is a good section on invalid meals designed to provide carbohydrate in easily assimilated form during intercurrent illnesses, and a useful table giving the weights and equivalent household measures of common foods Sorbitol is widely employed, especially for sweets, cakes, and preserves In some of these it could not be replaced by saccharin, but it has the disadvantage of being too expensive for some diabetics and of having some carbohydrate value, although it is assumed to have none in these recipes Many diabetics would prefer to use weighed amounts of cane sugar instead, even if they were allowed smaller portions of the foods thus prepared

Nevertheless this book is undoubtedly valuable

Clinical Hematology (4th ed London Henry Kimpton 1956 Pp 1185 £5 12s 6d)—The latest edition of Prof Maxwell M Wintrobe's work fully maintains its place as the premier hæmatological textbook Professor Wintrobe takes pains to emphasise that history taking, clinical examination, and study of the patient are essential, hæmatology cannot be effectively practised in the laboratory alone The changes in the five years since the last edition have made necessary new chapters on blood groups, blood transfusions, and syndromes associated with abnormal hæmoglobins The chapters on hæmorrhagic diseases, hæmolytic anæmias, and the production and destruction of red blood cells have been almost entirely rewritten Extensive revision is evident everywhere, and in the bibliography—a valuable asset—1600 references have been added and 887 deleted Therapy has been brought fully up to date This book is a sane appreciation of the present state of hæmatology, and the new edition will be needed by all who practise the specialty

THE LANCET

LONDON SATURDAY, JAN 26, 1957

Nurse and Doctor

No-one who has followed the brisk exchange in our correspondence columns during the past few weeks can doubt that sharp differences have developed between the medical and nursing sides of hospital staffs concerning the recruitment and training of nurses and the proper relation of nurse to doctor Nor can it be doubted that these differences must be resolved if our hospitals are to go on giving good service

The Royal College of Nursing plans to rely eventually on assistant nurses to do the bulk of the practical work, and on a group selected at the start (some of whom would take a degree course) to provide leadership[1] This plan has merits In the first place, the training of the ordinary nurses would be more realistic than that of the S R N at present Secondly, these "assistant ' nurses would be a relatively stable element, and accordingly students would be relieved of some of the routine work that now may overshadow their training (The chief medical officer of the Ministry of Health has lately declared "Too many hospitals still rely on student nurses for too high a proportion of their nursing services "[2]) The scheme would also bring to an end the damaging anomaly that in hospitals where nurses are trained for the State register the patients may be in danger of getting too little nursing attention owing to the trainees preoccupation with their studies and the rule that assistant nurses in training may not be employed in the same wards But the whole plan would founder without recruitment of "assistant" nurses in large numbers and this the arrangements so far proposed do not ensure

The college may hope to increase recruitment of "assistant ' nurses by its proposal to increase the number of training-schools for them. But this measure alone will not convince ' assistant " nurses that they are not pursuing a second-best course The very word ' assistant implies that they will be taking second place to nurses proper If they are to do most of the practical work this title will be even more misleading than it is now, and it will continue to damage recruitment The G.N C should overcome its hesitations and give these people the title they deserve—namely nurse—finding other names for other groups Furthermore, these nurses should be assured that if they show merit they can make the leap into the leaders group Such a provision is essential not only because many are reluctant to start on a career in which there is no hope of progress, but because thereby the stock of leaders may be usefully enriched the good practical nurse of 18 may emerge as an able administrator at 21 Indeed, can leaders be confidently selected at 18? Experience with candidates for other callings has encouraged no great confidence in selection methods, and such methods (as Dr **Fourman**[3] remarks) must be especially hard to apply in a vocational profession We still believe—as we believed twelve years ago[4]—that the choice of most of the leaders would best be deferred until basic training is completed. Besides encouraging recruitment of ' assistant ' nurses and easing the choice of leaders this might help to preserve the unity of the profession The offer of a different kind of training from the outset may attract to nursing some people with lively minds who otherwise would turn to other work but any such gain may be offset by the isolation of the selected group from the practical nurses who from the start follow a different course The unhappy effects of such isolation are evident in the United States, where university training has been carried much further than in this country At present nobody knows whether leaders are best chosen before or after basic training or by other methods including recruitment among older people, some of whom may have already graduated in arts or sciences at a university[4a] and therefore meanwhile no one method should be followed to the exclusion of others

Now some nurses, vigilant for their professional independence question the doctor s right to be heard on these questions 'It is surprising,' writes one correspondent[5] that doctors should consider themselves in a position to criticise nurse-education Many nurses could make pertinent criticisms of medical education, except that they do not consider they have any right to do so' This overlooks the fact that the quality of hospital medical care depends largely on nursing skill doctors cannot possibly remain indifferent to the way in which nurses are recruited and trained The same correspondent writes ' Nursing in the sense of caring for the sick, can be quite independent of medical care it can be good, bad or indifferent, so that the patient can be well treated medically but inadequately nursed Similarly, the patient can be well nursed but inadequately treated ' True, but where such division is manifest the patient is badly cared for In the best hospital practice the nurse is the agent of the doctor in much of her work Who shall say that the nurse keeping a fluid-balance chart, or recording a blood-pressure, or tending a patient recovering from anæsthesia is practising a nursing rather than a medical technique ' And it is these very tasks—so often difficult and requiring much skill—that largely justify the recruitment of gifted people to nursing and the continuing growth of the profession s prestige Dr **Anderson**[6] doubtless with such tasks in mind, wrote that nursing should develop along the lines of the needs of the doctor and of the public "whom we both serve This drew from a senior nurse[7] the retort that "the nurse renders her service to the patient, not to the doctor"—a thought which, if carried far enough, would deny the nurse much of her most interesting and most rewarding work and would bring the routine of acute wards to a halt More than one medical correspondent[8] [9] has pointed out that a dangerous alternative to continued integration of medical and nursing work is the establishment of parallel services in which the nurses would communicate with the doctors (in Dr **Ritchie Russell**'s words[8]) "only through carefully delineated channels" In the ward, parallel services should have no place, because one person must take final responsibility the care of patients cannot be conducted by committee Such responsibility should, as hitherto, be vested in the clinician, and this arrangement, dictated by necessity, subordinates the nurse to the doctor no more than the hospital biochemist or physicist is subordinated to the doctor Both doctor and nurse must wish to work towards easing tensions in their old and unbreakable alliance The doctor's relation to the nurse differs from his relation to any other of the medical team To the physiotherapist and the almoner, for instance, he turns intermittently, but to the nurse (as Miss **Edwards** remarks in her letter on p 217) he looks for continuous and intimate help Her eyes and ears, and many of her techniques, are extensions of his own In hospital the doctor cannot work properly without the nurse's close support, nor can the nurse without the doctor's It would be folly for either to pretend otherwise

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[1] Observations and Objectives Published by the Royal College of Nursing Henrietta Place London W 1 See *Lancet*, 1956 ii 1090

[2] Report of the Ministry of Health 1955 Part 2 On the State of the Public Health H M Stationery Office 1956

[3] Fourman J *Lancet*, Jan. 19 1957 p 156

[4] *Ibid* 1945, i 664

[4a] See *Ibid* 1956 i 395

[5] Budge U V *Ibid*, Jan. 19 1957 p 156

[6] Anderson T *Ibid* Jan 5 1957, p 45

[7] Lamb M *Ibid* Jan. 19, 1957 p 155

Ménière's Disease

It is nearly a hundred years since **Prosper Ménière** described the condition which bears his name and related the symptoms to disturbed labyrinthine function As far as clinical description is concerned, little has been added since Classically, attacks of rotatory vertigo, often accompanied by vomiting, are heralded by increasing tinnitus and deafness As the attack subsides, the tinnitus tends to become less prominent, but the hearing gradually or quickly deteriorates with each successive attack Distortion of sound, which is a special feature of Ménière's disease, reduces still further the patient's ability to use his residual hearing Psychological disturbances are common, and this is not surprising in patients who are ever expecting further attacks of disabling giddiness It has therefore been said, with some justification, that any treatment applied with sympathetic interest is likely to be helpful[10] This fact, and the natural tendency to remissions of up to several years, combine to make the assessment of any treatment a long and difficult task

Elucidation of the pathological basis of Ménière's disease has lagged a long way behind its clinical recognition, because opportunities for post-mortem studies were few, and even those examinations that were possible were made technically difficult by the ivory-hard bone surrounding the internal ear It was not until 1938 that **Hallpike** and **Cairns**[11] demonstrated that the essential lesion is a dilatation of the endolymphatic system, accompanied by a degeneration of the sensitive cochlear and vestibular end-organs They suggested that the sudden attacks of vertigo began when the endolymphatic pressure rose to the critical point at which the blood-vessels were obliterated, and the resultant ischæmia paralysed the end-organ Since then, hydrops of the labyrinth has often been confirmed as the lesion of Ménière's disease, but the mechanism of this accumulation of endolymphatic fluid has not yet been satisfactorily explained Among the many hypotheses put forward, vasomotor disturbances in the internal ear have commanded most interest in recent years an allergic vascular spasm,[12] a Raynaud-like mechanism,[13] and autonomic imbalance[14] are among the most acceptable The autonomic nervous system has no direct influence on the organs of hearing and balance, but stimulation of the sympathetic trunk in cats can reduce the blood-flow through the spiral ligament[15] The endolymph is produced more slowly after sympathetic stimulation and it is altered in character, so that later the endolymphatic pressure rises as a result of osmotic exchanges **Lewis**[16] believes that there is some primary fault within the labyrinth, which produces its effects by way of the vascular supply to the internal ear Sympathectomy, by its action on the blood vessels, modifies the course of the disease without affecting the primary cause

Medical treatment is often successful The use of sedatives or anti-histamine preparations aims at reducing the immediate symptoms until the organism has had a chance to readjust the endolymphatic balance Fairly large doses of vasodilator drugs, such as nicotinic acid, may help the patient to achieve this balance more quickly and to maintain it, and they have enabled up to 90% of patients to return to and remain at work[17] But for those patients who do not promptly respond to conservative treatment, and who have only a distorted and useless remnant of hearing, surgical destruction of the diseased labyrinth offers the surest escape from the demoralising attacks of vertigo, with their dangers to life, limb, and livelihood[10]

There remains a small, difficult, but interesting group in which surgery is required because medical treatment has failed, but in which it is important not to destroy the hearing in one ear The indications for such conservative surgery have recently been set out by **Harrison**[18] in patients with unilateral disease, a conservative operation may be considered for those with good hearing in the affected ear and those whose hearing on the opposite side is reduced by some other cause, and when the disease is bilateral, it is always desirable to halt the loss of hearing as well as the vertigo But the chief defect of all the conservative operations is the uncertainty of preserving the hearing while abolishing the vertigo **Portmann**'s operation[19] of draining the saccus endolymphaticus has been used intermittently since 1927 Logical though the method seems, the results have seldom been satisfactory **Flett**[20] says the operation offers a 25% chance of retaining the hearing and relieving the vertigo and tinnitus, and a 60% chance of relieving vertigo but with a gradual loss of hearing. Limited operations on the vestibular labyrinth[18] seldom succeed, since any sort of intralabyrinthine instrumentation in Menière's disease usually leads to complete loss of both cochlear and vestibular function. If some function is retained, both the cochlear and vestibular elements may well continue their disordered action as they did before the operation. The intracranial division of the vestibular portion of the 8th nerve is a major operation, but in most cases reported in this country[10] and elsewhere the patient has retained his hearing. It is undertaken in bilateral disease to salvage the better-hearing ear, and in some unilateral cases with good hearing. Destruction of vestibular function without operation has been achieved with streptomycin. Unfortunately both sides are affected, making the treatment most suitable for the younger patient with bilateral disease—an unusual combination. To offset the total loss of vestibular function calls for considerable adaptation which the elderly find very hard to achieve and the resulting incapacity may be greater than before.[21] The drug may also damage further the already declining hearing, and a very careful check must therefore be kept on the state of the hearing. Any further deterioration means that the streptomycin must be stopped at once. The vestibule has also been successfully destroyed on one side by ultrasonic rays,[22] but in this country the efficacy of this method has not yet been assessed.

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[8] Russell, W R *Ibid* 1956 ii, 1201
[9] Macbeth R *Ibid*, Jan 12 1957 p 96
[10] Cawthorne T *J Laryng* 1956, 70 695
[11] Hallpike C S Cairns H *Ibid* 1938 53 625
[12] Williams H L Ménière's Disease Springfield Ill 195[illegible]
[13] Atkinson M *Proc R Soc Med* 1946 39, 807
[14] Passe E R G *Arch Otolaryng Chicago* 1953, 57, 257
[15] Seymour J C, Tappin J W *Acta oto laryng Stockh* 1953 43, 618
[16] Lewis R S *J Laryng* 1956 70 673
[17] Kodicek J Taylor, L R S, Bateman G H *Ibid* 1950 64 647
[18] Harrison M S *Ibid* 1956 70 680
[19] Portmann G *Ibid* 1927 42 809
[20] Flett R L *Proc R Soc Med* 1954, 47 672

Cervico dorsal sympathectomy is a method of treatment of which more has been heard lately. LEWIS[16] and HARRISON[18] found that injection of the stellate ganglion was not a success either in treating the attacks of giddiness or in selecting cases for operation. On the whole, patients with unilateral disease did better after sympathectomy than those with both ears involved, probably because the disease is usually more severe when both ears are affected. It is interesting that the improvement or disappearance of the vertigo was sometimes delayed for up to a month after the operation. Many of their patients have had no further loss of hearing over the course of several years, and the operation is probably effective in preventing or retarding the progression of the deafness. The place of sympathectomy in the treatment of Menière's disease, however, seems to be limited to those few patients in whom the disease is bilateral and the deafness progressing in spite of medical treatment. Early operation may preserve the hearing but improvement of hearing after late operation is rare.

Pressure and Flow in Arteries

THE formula devised by FRANK[23] expressed the relationship between arterial pressure and flow as resistance, and measured it in the specific terms of dynes per cm^{-5} per second. This is a convenient single expression connecting pressure and flow but it is almost certainly not a valid measure of the peripheral resistance of the cardiovascular system. FRANK's formula is based on Poiseuille's law which was intended to define the relationship between pressure and flow of an ideal liquid passing steadily through a rigid tube of uniform calibre. But in the mammalian circulation a pulsating stream of a complex suspension flows through elastic tubes, with changes of velocity and cross-sectional area at each subdivision of the network. The relation of pressure to flow must therefore be clarified before FRANK's formula can be applied to the circulation in anything but a casual way. The ultimate aim of many inquiries into pressure and flow has been to measure cardiac output from an aortic or arterial pressure tracing, and with this object in view the arterial system as a whole has been investigated. Eventually HAMILTON and REMINGTON[24] put forward an empirical formula which related various parts of the aortic pulse contour to the volume of the blood ejected from the heart. The formula gave a reasonable prediction of the cardiac output of the dog under specified conditions but it failed to do so when the conditions were altered.[25] This and other careful investigations have made it clear that our present views on hæmodynamics cannot fully explain the pressure and flow changes observed in the animal circulation as a whole.

It seems that progress will be faster if the complex problem can be broken down into its constituent parts. COULTER and PAPPENHEIMER[26] studied the seemingly straightforward matter of the physical properties of blood flowing along a tube, and, as might have been feared, these turned out to be far from simple. Though the "viscosity" of blood may be measured, the measurement has meaning only if it is made under conditions which are closely and clearly defined. When blood flows along a tube, the corpuscles flow in an axial stream and the viscosity of the blood varies with the velocity of the stream and the area of cross section of the tube. When the velocity is great, as in the aorta during systole, turbulence develops[27] and the effective viscosity of the blood is much increased. These findings upset the simpler ideas of blood viscosity: for example, it is usually held that viscosity must be increased when the red-cell count rises, but this is true in only a limited sense, for PAPPENHEIMER has shown that at high velocities of flow the effective viscosity of polycythæmic blood may be less than that of normal blood, because the increased mass of the corpuscles tends to stabilise the stream and make turbulence less likely. The problem has also been simplified by investigating only a part of the circulation. LANDIS[28] measured pressure, diameter, length, and rate of flow in the arterioles and capillaries of the frog's mesentery, and GREEN et al.[29] studied the connection between mean pressure and flow in the perfused hind leg of the dog. Both inquiries made it plain that many adjustments were needed before the observations could be combined in a relationship based on Poiseuille's law. PETERSON[30] injected a known volume of blood into the aorta of a dog at selected instants during the pulse cycle, and showed that equal injections did not cause identical or even predictable superimpositions on the pressure pulse curve In his view, the systolic force needed to impart linear acceleration to the blood-mass in the arterial tree is an important consideration in pressure flow changes within the aorta McDonald[27] and Womersley[31] have re-examined pressure and flow in the dog's femoral artery under standard conditions They measured the changes of pressure gradient between two points along the artery, and the coincident changes in blood-flow velocity were recorded by means of high-speed photographs of an oxygen bubble in the artery They found that the oscillating pressure-gradient was related to the volume-flow which it generated after a time lag, in rather the same way that an alternating voltage is related to the corresponding current In fact, Womersley has devised an "alternating-current" theory of flow, to be distinguished from the relationship based on Poiseuille's law (which can be considered as the "direct-current" theory) According to the "direct" theory, it may be permissible to think and speak of the sum of the resistances of the branches of a network of vessels, but when there is an oscillating pressure in a branching system it would be more correct to consider the effect of branching as analogous to a sum of impedances Using the "alternating' theory of flow and the standard principles of hydrodynamics, the flow to be expected over a known pressure-gradient in the femoral artery was calculated, and the agreement between the observed and calculated volume of flow was within the limits of observation error Thus, the theory seems to have been justified

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[21] Cawthorne, T., Hewlett, A. B. *Ibid*, p. 663.
[22] Arslan, M. *Minerva otorinolaring.* 1953, 3, 141.
[23] Frank, O. *Z. Biol.* 1928, 88, 215.
[24] Hamilton, W. F., Remington, J. W. *Amer. J. Physiol.* 1947, 148, 14.
[25] Remington, J. W. *Fed. Proc.* 1952, 11, 750.
[26] Coulter, N. A., jun., Pappenheimer, J. *Amer. J. Physiol.* 1949, 159, 401.
[27] McDonald, D. A. *J. Physiol.* 1955, 127, 533.
[28] Landis, E. M. *Amer. J. Physiol.* 1933, 103, 432.
[29] Green, H. D., Lewis, R. N., Nickerson, N. D., Heller, A. L. *Ibid*, 1944, 141, 518.
[30] Peterson, L. H. *Circulation Res.* 1954, 2, 127.

Observations by Burch[32] encourage the hope that similar fundamental work may be possible in man, using relatively simple methods Burch used venous-occlusion plethysmography to measure the phasic changes of blood-flow in the finger The finger-tip is enclosed in an airtight rigid container which does not obstruct the circulation When the venous outflow is briefly occluded by a pressure cuff on the finger, the volume distal to the cuff increases by the amount of blood flowing into it during the period of occlusion, and equal volumes of air are displaced to and from the plethysmograph into a continuous recording system Until now it has been customary to measure the mean rate of blood-flow over a brief period, though the original description of the plethysmographic method by Hewlett and Van Zwaluwenburg[33] was much concerned with observations of the phasic changes in the rate of flow Burch has adapted the finger plethysmograph to record the rapid changes of flow into the finger during the phases of the pulse cycle To this technique he has given the cumbersome name of electro-rheoplethysmography, but perhaps the title is justified since he observes the time-course of the volume changes, the rate and acceleration of inflow and outflow, and the difference between inflow and outflow of a single pulse cycle Tracings are taken from two fingers simultaneously, and the venous outflow of one is intermittently occluded, the other serving as a control for spontaneous changes in the finger-volume The rate of volume-change can then be measured over any portion of the pulse cycle The first derivative of the volume-time chart gives the time-course of the inflow and outflow rate, and the second derivative the acceleration-rate of the blood inflow The form of such curves has yet to be related to the form of the arterial and venous pressure pulses They vary considerably in different physiological and clinical states, and the study of these changes is likely to further our knowledge of the function of the central and peripheral circulation in health and disease

But it is doubtful whether the finger-tip is the most suitable part in which to study the circulation The smaller vessels of the digits are specialised to take part in the control of body-temperature, and they are particularly rich in arteriovenous anastomoses,[34] which are readily opened and shut by thermal and nervous stimuli For this reason blood-flow fluctuates widely in the finger-tips, and it might also be expected that there would be an unusual range of pressure gradient between the arterial and venous ends of the capillaries Observations on these vessels, therefore, cannot be interpreted as typical of the circulation as a whole Furthermore, plethysmographic records from the finger-tips may be unsatisfactory for technical reasons The part of the inflow curve from which reliable readings may be made is limited by the artefacts caused by the inflation of the cuff at the beginning of the curve and by venous congestion at the end When the vessels are dilated and the arteriovenous anastomoses widely open, the artefacts may so approach each other that no reliable estimation of the blood flow can be made Burch considers possible methods of dealing with these limitations, but his suggestions are not entirely convincing, and the forearm or calf might be a better part of the anatomy to investigate

These important and interesting investigations bristle with technical difficulties Electromanometers are not hard to find, so that the recording of phasic pressure changes in the cardiovascular system is relatively simple, but the simultaneous recording of phasic flow changes is a different matter Improved methods, however, will probably simplify the present abstruse picture of pressure and flow Meanwhile, there should be no serious objection to expressing the relationship between mean pressures and mean flow in terms of "peripheral resistance," so long as it is clear that the term is no more than an arithmetical arrangement of pressure and flow measurements, and that a change of "peripheral resistance" does not necessarily denote a change of calibre of arterioles or "resistance vessels"

The New Minister of Health

Mr Dennis Vosper has been appointed Minister of Health in Mr Macmillan's Government

Mr Vosper, who is 41, was educated at Marlborough College and Pembroke College, Cambridge During the late war he served with the Cheshire Regiment and held the rank of major He was returned to Parliament as member for the Runcorn division of Cheshire in 1950, and the following year he became a Lord Commissioner of the Treasury From 1950 to 1954 he was a whip As parliamentary secretary to the Ministry of Education since 1954 he has taken a special interest in the welfare of handicapped children

Mr J K Vaughan-Morgan, who has represented Reigate since 1950, has been appointed parliamentary secretary to the ministry He has been chairman of the Conservative health committee

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[31] Womersley J R *J Physiol* 1955, 127 553
[32] Burch, G E *Circulation*, 1956 13, 641
[33] Hewlett A W, Van Zwaluwenburg J G *Arch intern Med* 1913, 12, 1
[34] Grant, R T, Bland, E *Heart*, 1931 15, 385

Annotations

SAVING THE POTENTIAL SUICIDE

"O Britain infamous for suicide!" wrote the Rev Edward Young[1] in 1742, and he might still thus apostrophise our nation As Dr Parnell and Dr Skottowe observe in their article on p 206, the Registrar-General recorded, in 1954, in England and Wales, 5043 suicides—which represented an increase of nearly 50% in ten years In Britain today, more people commit suicide than are killed on the roads Of the 100 suicides about which they gathered information, Parnell and Skottowe found that in 53 the victim had not recently been under medical care But in the majority there had been warning signs, of which a change of mood, with noticeable depression, was the commonest As Parnell and Skottowe see it, the best chance of saving the man or woman with thoughts of suicide is admission to a mental hospital for supervision and treatment but they acknowledge the difficulties of convincing not only the patients but their families and the general public of the importance of this precautionary measure

From the general practitioner's viewpoint depression is so common a symptom that it is often hard to pick out the patient who is heading for disaster In ten years Watts[2] saw 387 patients with endogenous depressions, including 6 who committed and 8 who attempted suicide, 3 of those who killed themselves were not under medical care at the time As Craddock[3] has pointed out, it is all too easy to overlook endogenous depression, for, like cancer and tuberculosis, it usually comes on insidiously Oliven,[4] among others, has offered useful advice to the family doctor who must decide whether or not a patient is in danger of suicide In his view, even vague or minor signs of depression, and its concomitants, such as insomnia, loss of appetite, and libido, and abnormal fatigability, should be taken as danger signals, though the greatest care will never save the occasional patient who commits suicide without warning More could perhaps be done by reminding the public that depression is a reason for seeking medical advice And certainly, as Parnell and Skottowe emphasise, doctors must be less chary of asking frank questions about how depressed the patient is and whether he has any suicidal intentions The depressed patient more often escapes notice than the psychopath, the schizophrenic, or the alcoholic, and "that a patient does not threaten suicide, or again that he speaks logically, is no excuse for inaction"

But the best answer may lie further back—in a livelier awareness, among public and profession, of what can be done by the preventive measures of social psychiatry and psychotherapy[5] A world of unstable international and national conditions and loss of faith may favour despair in people who are not so stuffed with bread and circuses that they doze through their waking hours The man who says "I couldn't care less" may be closer than he knows to taking an action which will relieve him of the need to care any more about anything Another even more depressing view is that the importance of the individual and his welfare has been so overplayed in some countries that the will to struggle for life and livelihood has been lessened, and will not be restored until the cushion of the Welfare State is made a bit harder However that may be, it is, in the first place, to preventive psychiatry that we must turn for real help in reducing the number of suicides and in enabling those that are saved to find stability, even in an unstable world

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[1] Young Rev E The Complaint or Night Thoughts on Life Death and Immortality London 1742

[2] Watts, C A H *Brit med J* 1956 i, 1392

[3] Craddock D Introduction to General Practice London 1953

[4] Oliven J F *New Engl J Med* 1951 245 488 see *Lancet* 1951 ii 1026

[5] See *Lancet* 1956 ii 1087

FAILURE OF ARTERIAL GRAFTS

THE commonest site for advanced degenerative disease of peripheral arteries is at the junction of the femoral and popliteal arteries, and from here the clot spreads upwards or downwards It is unfortunately quite clear that the results of direct vascular surgery have been very unsatisfactory in these limb vessels, and the causes of early and late failures in grafting are therefore of the greatest interest Several possible causes demand attention First, the surgeon may be technically at fault by creating a stricture at the anastomosis between the graft and host artery, so that thrombosis inevitably follows That this is of great importance is suggested by the superior results of grafting when big vessels such as the aorta or iliacs are involved It is equally certain that the use of small vessels, such as the posterior tibial, for the distal anastomosis is followed by a 100% thrombosis rate Other technical faults are the lifting and loosening of athero matous plaques by the needle point or the leaving of too much free silk within the lumen in contact with the bloodstream Because of the larger lumen which can be fashioned, the end-to side type of anastomosis is less likely to thrombose than the end-to-end type The kind of graft which is most suitable for peripheral arteries is still a matter for debate Free vein grafts, homologous arteries, and tubes of synthetic fibres all have their supporters of the man-made fibres, polyvinyl alcohol seems most promising The benefits of crimping the graft to make it flexible without kinking have been shown in vivo to be short lived because the invading connective tissue rapidly converts it into a smooth semi rigid structure

Szilagyi et al.[1] have confirmed some of the earlier reports of degeneration, thrombosis, calcification, and aneurysm formation following the use of homologous arterial implants The problem of homograft degeneration is a difficult one, and data regarding the source of the grafts and their processing or storage do not help The way in which host tissues vary in their acceptance of homografts of grossly similar characteristics suggests that the host-graft reaction may be an immunological one[1]

The factor which has most to do with success or failure may be the selection of the patients There is no doubt that results of grafting for traumatic or congenital lesions of arteries are much more satisfactory than those of operations undertaken for arteriosclerosis, and, in the arteriosclerosis group, vessels with relatively localised segmental thromboses do much better than those in which the narrowing involves the whole tree Furthermore, the degeneration is progressive and the relief of a localised thrombosis is often followed by further lesions elsewhere in the leg

Szilagyi et al[1] reviewed their experience with 120 homograft operations for aorto iliac or femoro popliteal occlusions In 23 there was clotting immediately after the operation During the next thirty three months, 21 more grafts failed to transmit blood 7 of these were re explored and studied clinically or histologically Szilagyi et al concluded that the most common cause of late graft failure was the extent and severity of the preexisting arterial disease Occlusions due to defects in the homografts which developed after their implantation were uncommon, but there was often progressive narrowing or unevenness in the follow-up angiograms and this might lead to eventual obstruction Szilagyi et al's paper was read before the American Surgical Association, and from the discussion which followed it was clear that many surgeons were uneasy about the results of small-vessel grafting The proportion of late closures in the region of the femoral artery was as high as 70% The variation in failure-rate reflects differences in the original selection of patients and indeed illustrates the outstanding clinical problem for the vascular surgeon Should he select only those patients with early disease and moderately severe symptoms in whom the results of grafting are fair or should he reserve direct surgery for very advanced disease, in which the results are in general poor but occasionally dramatic[9]

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[1] Szilagyi D E, Whitcomb J G Smith, R F *Ann Surg* 1956, 144 611

AUSTERITY DIETS

THE National Food Survey has been in being since July, 1940 Year by year it has recorded the food consumed in many thousands of households, and analyses of these data enable some assessment to be made of how the food consumption of the people measures up to accepted standards of physiological needs The Survey's findings were of great value to the Ministry of Food in planning and coordinating its policy during the late war and immediately afterwards, when food was scarce During those years the staff of the Ministry had not the time to analyse fully the mass of data available and to present the results in a scientific report When the pressure of the times became less heavy, the Ministry concentrated very wisely, on the preparation of up-to-date annual reports, of which the first to be published was for 1950, but a report was also prepared which gave some account of the trends in the earlier years A second report[1] now issued presents a large selection of the information available for the years 1944–49 It was not possible to fulfil the original programme which included the earlier years—for one thing, old punched cards get worn and unusable—but the new report does cover the period when food was most scarce and the rationing system most strict, it is an important historical document describing household diets when the war-time system of controls was in full operation The pre-war free economy, with much unemployment and social inequality, had been replaced by a controlled economy, with strict rationing of basic food, and by full employment

It is at once apparent from the report that this change had profoundly altered food consumption Boyd Orr demonstrated that in the pre-war years about 10% of the population (that is some 4 million people) were living on diets which were deficient in both quantity and quality, and this estimate has never been seriously challenged Yet, in the years 1944–49, no section of the community was eating a diet which fell significantly short of the standards set by the British Medical Association Higher wages enabled the working man to buy for his family a better diet, but for the middle classes there was a real reduction in the variety and palatability of their food The country's food, though wholesome and nutritionally adequate, was dull

The report tries to determine how the diet was affected by various circumstances One chapter records details from families who were badly housed, but it turns out that their diets differed surprisingly little from those consumed in other working-class homes Another chapter shows that family size determines the quality of the diet far more than the occupation of the parent The amount of milk, meat, vegetables, and fruit consumed was significantly less in families with four or more children and in this group the protein intake was below the B M A recommendation in all groups of working-class families

Separate analyses are given for the households of agricultural workers, miners, builders, metal workers, and ship builders, but the differences are remarkably small Of more interest is the analysis of the regional differences Less fruit, vegetables, fish, rationed meat, and eggs were eaten in Scotland than in any other part of the country, but the Scottish consumption of cakes, buns, and scones was 12% above the national average The Scots spent only $^1/_{10}d$ a head per week on coffee, whereas the English spent a $^1/_2d$ In England, most cheese was eaten in the Midlands, most fruit in London, most potatoes in the South-West, and most cereals in the North East It might be interesting to try to relate these variations to the incidence of degenerative disease For those concerned with atheroma, it is perhaps unfortunate that fat consumption in the home seems to have been remarkably uniform and almost independent of social class, occupation of wage earner, number of children, or region

The committee responsible for this report have presented skilfully, clearly, and concisely a large amount of information, to which many research workers, among others, will turn with interest

CONSTRICTIVE PERICARDITIS

THE diagnosis of constrictive pericarditis is seldom difficult, if the possibility of the condition is borne in mind and if special investigations are carried out to confirm the diagnosis in atypical cases No age is immune and, though many patients are under 40, older patients may have constrictive pericarditis which may be misdiagnosed as ischæmic heart disease The cardinal symptoms are shortness of breath on exertion, swelling of the ankles, and distension of the abdomen, the cardinal signs, found in almost every patient, are a raised jugular venous pressure and an enlarged liver Often there are a pleural effusion, ascites, a paradoxical pulse, a loud third heart sound, and a reduced pulse pressure but these are not essential to the diagnosis In half the patients the heart size is normal on fluoroscopy, and the remainder have only slight or moderate cardiac enlargement Usually the cardiac pulsation is diminished, but in a quarter of the cases the radiologist reports that movement is not restricted, even though he knows the diagnosis and it has been confirmed by other means[1] Calcification of the pericardium is a helpful finding but it is seen in only about half the cases, even when tomography is used The electrocardiogram is always abnormal but never characteristic. There is usually flattening or inversion of the T waves, and three quarters of the tracings show wide or notched P waves, which closely resemble the P mitrale of mitral stenosis[1]

Cardiac catheterisation is invaluable in confirming the diagnosis and also in assessing the degree of cardiac embarrassment in the rare symptom free patient who is found by chance to have a calcified pericardium The characteristic findings are a raised end diastolic right ventricular pressure, an early diastolic dip and plateau pattern in the right ventricular pressure tracing, and (depending on the degree of left ventricular involvement) a raised pulmonary capillary pressure[1]

The disease is progressive, and once there are symptoms operation is indicated The operative mortality is 10–15%, but better results may be expected as surgical techniques improve and patients are operated on at an earlier stage, before the onset of auricular fibrillation and severe liver damage Recurrences are common (of 78 patients, 11 required more than one operation[1]) but the need for second or third operations will cease when wider incisions are used, to allow of a more extensive pericardectomy, and when anti-tuberculous drugs an

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1 Studies in Urban Household Diets 1944–49 Second Report of the National Food Survey Committee H M Stationery Office 1956 Pp 143 5s 6d

1 Dalton J C, Pearson, R J Jun White, P D *Ann intern Med* 1956 45, 415

given in adequate amounts for an adequate period[2] Bigelow[3] and his associates recommend a trans-sternal approach with both sides of the chest open All the pericardium over the left and right ventricles is removed, including that over the apex and diaphragmatic surface The phrenic nerves are dissected out and the pericardium posterior to them removed Such a wide exposure allows the venæ cavæ to be cleared and permits speedy repair of the myocardium if the heart is inadvertently opened Bigelow keeps his patients on digitalis in the belief that this prevents postoperative myocardial dilatation Further improvement can be expected for several months after pericardectomy, and the Canadian workers report that venous filling pressures have continued to drop for up to a year after operation

RICHARD PFEIFFER

Koch, Ehrlich, Behring, Gaffky, Loeffler, Carl Fraenkel, Wassermann, Frosch, Wernicke, Kolle, and Richard Pfeiffer—those were some of the staff of the Institute of Hygiene of the University of Berlin in 1887 It is unlikely that so many men of ability have ever pursued the same end with so much vigour under the same roof The games in Valhalla are traditionally hearty, and, knowing German habits in scientific debate, one can be pretty certain that discussion sometimes passed the limits of ordinary politeness It was the golden age of Germany and of bacteriology, and it is characteristic of the purposeful vigour of the times that a thesis on the bacteriology of water was considered grounds for seconding Pfeiffer, an army surgeon of 29, to the institute The choice was wise and from it stem two lines of inquiry which are still productive Pfeiffer's bacillus (which we now call *Hæmophilus influenzæ*) has been dethroned from its place as the "cause" of influenza, but, as Sir Paul Fildes points out in an account[4] of Pfeiffer's life, his observations on the fractions of whole blood necessary for the growth of this organism were the first steps in the path which Fildes has himself trodden—with much distinction Pfeiffer was, in fact, the father of the study of bacterial nutrition, but in those years at the Institute of Hygiene in Berlin his most famous work was probably the demonstration of the "Pfeiffer phenomenon"—the lysis of cholera vibrios injected into the peritoneal cavity of an immunised guineapig Like most of the fundamental observations at that time, this was made in the course of experiments designed to solve a problem of practical hygiene The administrative measures recommended by Koch to combat an epidemic of cholera in Hamburg in 1892 were founded on the assumption that the disease was due to *Vibrio choleræ* The discovery of saprophytic vibrios in many places gave an urgent need for a method by which these might be distinguished from *V choleræ* Pfeiffer showed this could be done by cross immunity experiments in guineapigs *V choleræ* injected into the normal animal multiplied freely in an animal immunised with the same organism the vibrios swelled and vanished In the presence of immune serum the same thing happened in vitro—as readily with the typhoid bacillus as with the cholera vibrio It was indeed the "crowning mercy" in the long debate on the relative parts played by cellular and humoral defences in overcoming infection Pfeiffer followed several lines of inquiry from this original observation and most of them have been fruitful in his hands or in those of others Immunology had arrived

Pfeiffer assisted Koch in his investigations into plague in India and malaria in Italy He obtained the chair of hygiene and bacteriology at Konigsberg and later at Breslau, where he remained until his retirement in 1926 Shortly before the late war he moved to a small watering-place in the neighbourhood He was still co-editor of the *Zentralblatt fur Bakteriologie*, he read avidly, he played the piano and tended his garden He was surrounded by devoted friends and the war was far away In 1945 Silesia was occupied by the Russians Pfeiffer could not or would not leave, and he died in September, 1945, cared for by an old maidservant It was only recently, however, that this was known for certain by his friends in the West So passed almost the last survivor of the heroic age of bacteriology, a man whose contributions to knowledge have benefited the whole world of learning

SEPSIS IN THE NEWBORN

SEPSIS neonatorum can be troublesome in most maternity hospitals and departments and anything that reduces its incidence is worth considering Commonly the primary infection is in the skin and Bruce[1] has carefully investigated the incidence of soreness and sepsis in the skin in a group of newborn children bathed in the usual way, and compared it with the findings in a group in which a semi-dry technique was used (only the face and napkin area were cleaned, with dilute (1 in 500) cetrimide) She found that the differences between the two groups were not significant, but, because it saved labour, lessened handling by the nurses, and allowed the baby to spend more time by its mother, the non-bathing technique was introduced into the hospital as a routine

Though the investigation was very carefully controlled, it was not conclusive as far as sepsis is concerned, since two important features in the natural history of the disease were not considered Firstly, the incidence is irregular There are periods of many months when infection is quiescent few babies are affected and the lesions are mild, then quite suddenly an outbreak flares up with widespread infection and severe lesions, reaching a peak and subsiding within a month or so Secondly, the clinical manifestations are not confined to the period spent in the maternity department A relatively small skin lesion appearing in the first week may heal rapidly and all is thought to be well, but there may be a smouldering focus of infection or perhaps a bacteræmia which bursts out again with septicæmia and a "fixation" abscess in bone or lung as much as sixteen weeks later These cases, by far the most important, appear in the pædiatric wards, and on inquiry it is common to find that almost all the children were born in hospital even in an area where half the babies are delivered at home

Bruce conducted her investigation in a hospital where there are some 2000 deliveries a year, and it covered a period of four months, with 160 and 129 infants in the two groups An investigation lasting two years and including about 1000 infants in each group would have been more conclusive because there would probably have been at least one flare up in that time The observations were limited to the lying-in period, presumably fourteen days or less, a follow up of four months might have revealed some sepsis later

MEDICAL EDUCATION

WE have already mentioned[2] a conference called by the Royal College of Physicians of London on Nov 23 to consider the formation of some permanent organisation for discussing problems of medical education, for exchanging information, and for further research The college's initiative was welcomed by the conference, most of whose 69 members came from teaching schools and licensing bodies, and a steering committee was appointed to report on the possible form and scope of such an organisation This is to meet shortly

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[2] See leading Article *Lancet* 1952 i 1055

[3] Bigelow, W G Dolan F G Wilson D R Gunton R W *Canad med Ass J* 1956, 75 514

[4] Fildes P *In* Biographical Memoirs of Fellows of the Royal Society Vol 2 November 1956

[1] Bruce L *J Obstet Gynæc, Brit Emp* 1956, 63, 735

[2] *Lancet* 1956 ii 897

Special Articles

TOWARDS PREVENTING SUICIDE

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Deaths by suicide in England and Wales have been increasing, especially in the past few years In 1954 there were, according to the Registrar General (1954), 5043 suicides compared with 3447 in 1944—an increase of 1596 (46%) In recent years, moreover, their number has exceeded that of fatal road accidents, yet they attract much less public attention, and their prevention is seldom publicly discussed

Suicide is commonly committed in a mood of depression Since this state of mind is usually amenable to treatment, it should be possible, by earlier and more effective recognition of it, to reduce the number of suicides The fact that suicides have increased with more widespread use of physical treatments has led some workers—e g, Frost (1956)—to question whether physical treatments are being adequately supported by other measures, or even, it seems, to question the value of electroconvulsion therapy, although Maclay (1953) has called attention to evidence (Huston and Locher 1948, Fetterman et al 1951, Slater 1951) of the preventive value of electro convulsions

Four Questions

The general attitude to suicide varies in different cultures, but, if it is accepted that suicide should be prevented, all possible steps, both medical and social, towards this end need examining The prospect for more effective prevention depends on the answers to the following questions

(1) Is there a sufficiently large proportion of actual suicides who have not received full medical and social help ?

(2) If so, what warning signs can be discerned ?

(3) Is there evidence that admission to mental hospital is preventive not only in the sense of immediate prevention by constant observation but also in the sense of reducing the prospect of future attempts ?

(4) What evidence is there of the frequency of particular diagnoses among those attempting or committing suicide, and that those showing warning signs could be persuaded to enter mental hospitals, if most of them were not so manifestly ill as to warrant the making of an order under the Lunacy and Mental Treatment Acts (1890–1930) ?

EXTENT OF MEDICAL HELP

That a large proportion of suicides have not received help is shown by a series of 100 consecutive suicides from inquest registers of 1949–56 together with the information kindly provided by two coroners who noted whether the suicide had been under medical care

Not under medical care (including 4 where it was refused)	53
Under medical care	
Under general practitioner	17
Under general practitioner and consultant psychiatrist	10
History of having been in a mental hospital during the past year or so *	13
Not known	7
	100

* Among the remainder there were 7 who had been admitted to a mental hospital more than a year before committing suicide

The majority had not received medical care and, so far as is known, only 13% had been lodged at some time during the year or so before their deaths in a mental hospital, and 27% had recently attended their medical practitioner but had not been admitted to hospital This analysis suggests that there is plenty of scope for prevention, provided that warning signs are recognised

WARNING SIGNS

A previous attempt at suicide had been made in 11 cases Sainsbury (1955) reported 9% Statements such as that death came as a surprise were recorded in only 6 cases altogether, and even here not always as a surprise to all the suicide's associates, although it was to either family, doctor, or employer It seems that warning signs were present in the majority Their recognition comes next and supports this first impression of their frequency One coroner had recorded statements to the effect that the deceased had been noticeably depressed or worried in 42 of 74 (57%) of his cases, and in 8 others comments concerning insomnia, violent temper, or nervous breakdown suggested the relevance of psychiatry The next largest group, 21 of 74 (28%), was associated with recent surgical operations (8 cases), recent childbirth (2 cases), long lasting pain or severe illness (9 cases), and fear of this or fear of mental illness or mental hospital (2 cases) In the third group social causes related to marriage or remarriage (5 cases) and to fear of or impending legal action (4 cases)

In summary, so far it may be said that a change of mood with the appearance of depression, worry, or hopelessness appears as much the commonest warning sign

PREVENTIVE EFFECT OF ADMISSION

The number of suicides during residence in a mental hospital is small, for example, in 1954 there were only 51 suicides in mental hospitals out of the total of 5043 among the general population The suicide rate in mental hospitals was slightly higher than in the general population, but the mental-hospital population is much more highly disposed, as can be inferred from the frequency of attempted suicide among patients before admission to mental hospitals In our psychiatric and somatometric survey of newly admitted patients at four mental hospitals in the Oxford region we found that an attempt at suicide was a prominent reason for admission in 9% of 445 men and 10% of 521 women Furthermore, there was a history of a previous attempt in another 3% of men and 6% of women In so far as these proportions are representative, the figures enable an estimate to be made of the number of attempted suicides leading to admission to mental hospitals throughout the country This may be compared with the actual number of suicides

	Men	*Women*
Admission to mental hospitals in England and Wales (1954)	29,751	41 918
Estimated proportion attempting suicide	9 %	10%
Estimated number attempting suicide	2678	419
Actual number of suicides	3178	1865

It is evident that a much greater proportion of men commit suicide than of women On the other hand more than twice as many women attempt suicide unsuccessfully and gain admission to hospital as kill themselves These figures, of course, exclude many suicidal attempts not leading to admission to mental hospitals and cases of suicide where an open verdict is returned for lack of evidence They do, however, confirm earlier reports—e g, Stengel (1952)

In view of these three findings—the small number of suicides in mental hospitals, the very large number of unsuccessful suicide attempts arising from illnesses that are subsequently treated successfully in mental hospitals, and the small proportion (13%), among actual suicides, of persons previously treated in a mental hospital—it seems safe to conclude that admission does exercise the important preventive effect expected of it

PATIENTS COOPERATION

The prospect for further prevention would be dim indeed if potential suicides were all of temperament so independent that all refused outside help There are three main forms of evidence—personal, medical, and social—with which to answer this question

Personality Evidence from Physique

As mentioned above, somatometric data are available about patients attempting suicide There is already evidence that men of lean and muscular build are more disposed to suicide These findings we hope to report in greater detail when samples become large enough to permit further analysis by age It already seems clear however, that much overlap exists between the distribution of physical types found among healthy men men who only contemplate suicide, men who attempt it, and those who succeed, further the correlations between physique and temperament are unlikely to be so high as to exclude all hope of persuading potential suicides to enter hospital when the need arises

Stengel (1952) suggested that the two groups of people attempting and committing suicide formed two different populations These views derived partly from the assumption that suicidal intent was greater when single minded than when characterised as it is in so many unsuccessful attempts by a special appeal to individuals or to society for attention But Stengel also recognised the strong tendency for the two groups to overlap

Clinical Evidence

This has been collected from clinical examination by one of us (I S) and from an analysis of notes of patients who have attempted suicide to show the frequency of depression and other diagnoses (see table I) As is well known patients with affective disorders, such as anxiety and depression, are more likely to cooperate than those with thought disorder or psychopathic behaviour.

TABLE I—FREQUENCY OF DEPRESSION AND OTHER DIAGNOSES AMONG PATIENTS ATTEMPTING SUICIDE

—	Number	Dominant mood change		Disorder of thinking—e g schizophrenia	Other disorders (psychopathy hysteria &c)
		Depression	Anxiety		
Men					
Suicide attempt (reason for admission)	39	28	1	3	7
Previous attempt (not recent)	12	9	0	2	1
Total	51	37	1	5	8
Women					
Suicide attempt (reason for admission)	47	37	4	1	
Previous attempt (not recent)	33	22	1	3	7
Total	80	59		4	12

Depression was diagnosed in 72 5% of men and 73 8% of women attempting suicide It will be remembered that 57% of the coroners series were stated to have been noticeably depressed or worried Although psychiatric diagnoses and the statements of witnesses in court are not equivalent it seems that those who attempt suicide and those who succeed at least share the description of being depressed Dominant changes of mood, especially if anxiety states are included with depression account for or are at least associated with, the great majority of suicidal attempts Abnormal, antisocial, and other psychopathic behaviour, without prominent change of mood or thought, was seen in 12 (14%) of 86 patients who had recently attempted suicide Batchelor (1954) has suggested that such a diagnosis is appropriate in up to 25% of patients admitted to the observation wards of a general hospital after attempted suicide Such cases, because of their frequent impulsiveness may be harder to prevent but even in general hospital experience they are not very common From the preventive point of view the most significant fact in the present findings is the small number of patients showing disorders of thinking, the change so often regarded by the general public as a sine qua non for admission to a mental hospital.

TABLE II—FIRST ATTENDANCES FOR CONSULTANT PSYCHIATRIC ADVICE FIRST ADMISSIONS TO HOSPITAL AND ATTEMPTED AND ACTUAL SUICIDES AMONG OXFORD STUDENTS IN 1953–56

—	1953	1954	1955	1956
First attendances as outpatients at Park Hospital				
Hilary term	11	26	22	24
Trinity term	17	18	18	21
Michaelmas term	10	29	19	22
Total	38	73	59	67
First admissions to Warneford Hospital	10	20	12	19
Attempted suicide	[illegible]	[illegible]	0	2
Suicide	4	2	0	1*

* Oct 15 1956

Social Evidence

Parnell (1951) drew attention to the number of suicides among Oxford University students By the end of 1953 there had been 15 suicides in seven years, an average of more than 2 a year In the three years from July 1953, to July 1956, there were only 2 suicides—in men aged more than 33 working largely on their own for postgraduate degrees Though no claim could be fully justified that comparative freedom from suicide among undergraduates in the past three years is due to social action it is appropriate to recall that, from 1951 onwards successive vice chancellors took steps to awaken wider interest in this problem The results are certainly not discouraging It is reasonable to suppose that greater willingness by tutors and others in frequent contact with students to recognise the implications of an alteration in mood or behaviour and to seek early advice from a college doctor may be partly responsible for whatever improvement has taken place It must be admitted however that the continuance of suicides of students elsewhere raises some doubts The incidence of mental ill health in general among students remains little changed and is summarised for the past four years in table II Because undergraduates are free to seek advice wherever they choose, and may do so in London or elsewhere during the vacation as well as at other hospitals in Oxford, the figures should be regarded as minimal.

With an average of 5951 male students in residence in 1952–56 the minimal annual first-admission rate to mental hospital is roughly 25 per 10,000 For the general population of similar age the figure was 11 per 10 000 in 1951 but this included a small proportion of readmissions For students, therefore, not only is the admission rate high but also the total rate may be higher, and the figures provided for comparison with other young men underestimate the difference

The following extracts from statements of witnesses at inquests emphasise both warning signs and social attitudes

Change of mood

"He was very depressed, which was something quite new"

"He was a cheerful man until the last fortnight but became very depressed He had had a previous breakdown"

"He had been unwell for years, but for a few months before his death had been very depressed"

Possible delay in obtaining advice

"He had been in abnormally good spirits six months ago but since then depressed and unable to concentrate On the night before he died we were discussing him and agreed it was desirable he should see his family doctor or a psychologist"

Moral attitude of witnesses

"He told me about his previous attempt at suicide, and I said he must snap out of that frame of mind, the best he could do was to stick it"

"He said he had been very depressed and that it had taken the form of a very strong temptation to commit suicide He had been quite *normal* in conversation"

The last quotation illustrates the emphasis placed on so called normal or logical thought as a reason for not seeking medical advice Our evidence points to the primary importance of a change of mood, illnesses in which disordered thinking is prominent are comparatively seldom associated with suicide Even here depression is likely to form part of the picture, as in the report "He thought he had cancer (although the doctor told him he had not) and he had been ever so depressed" If the occasional patient is illogical, the logical one may be even more difficult to manage

"Dr X said that the patient was a logical man whom he would have been unwilling to certify as insane in order to obtain shock treatment" This particular patient had been adamant in refusing hospital care, but his wife thought she could have persuaded him Persuasion, therefore, by all concerned is indicated

Lastly, a common report "He had never threatened to commit suicide" Direct questioning will often reveal otherwise concealed intentions Sometimes direct questioning is avoided for fear of putting suicidal thoughts into a person's mind This is a mistake Once a patient has admitted that he feels depressed, frightened, or hopeless, leading questions about the depth of his depression can and should be asked There is no evidence that such questions, put in a proper way, have any aggravating effect on the depression—rather the reverse, for confession often brings relief—or ever drive to suicide a patient who would not otherwise contemplate it A rough guide is needed to the depth of depression Does it cause the patient to weep without knowing why, or to feel that he wishes he could cry although unable to? Does he feel that life is not worth living? Has he thought of doing anything about it? If so, what? This is no time for hesitation in using all means of persuasion To prevent suicide people should forget about logic as a sign of health and remember that many more lives are saved by getting depressed patients to hospital than by applying tourniquets for hæmorrhage or artificial respiration for drowning Skottowe (1955) reported that nearly a third of his patients with depression had been ill for more than a year at the time of their admission to hospital The frequency of depression in general practice has been well described by Watts (1956), who emphasises how often it is overlooked

Choice of Method

Brooke (1956) has drawn attention to the increasing use of coal-gas poisoning and barbiturates during recent years In the coroners' series of suicides here cited, 48% died from coal-gas, 9% from barbiturates, 6% from aspirin There was evidence that barbiturates and aspirin were chosen more often by city dwellers, whereas more violent methods of shooting, hanging, and drowning were commoner in the rural area concerned Obviously it is desirable to stop the public from obtaining lethal doses of dangerous medicines too easily, but the number of 391 suicides by barbiturates in England and Wales in 1954 is only a small proportion of the total Since the choice of method is partly dictated by the means available, it is clear that effective prevention is more likely to depend on correct management of depressed people during the severe phase of their depression

Conclusions

In a consecutive series of 100 suicides a majority (53%) had not received medical advice Only 13 had *been in a mental hospital in the year preceding death*

Warning signs were present in the majority A change of mood, with depression prominent, was commonest Previous attempts had been made by 11 suicides

Evidence is presented that admission to a mental hospital has the preventive effect expected of it

(1) The number of suicides in hospital is small

(2) Large numbers of patients who have made unsuccessful attempts at suicide are subsequently treated successfully in mental hospitals

(3) Only 20% of actual suicides had ever been *treated in a* mental hospital

Analysis of hospital notes of patients attemptin suicide shows the paramount importance of mood change and depression Disorders of thinking are comparativel uncommon

The high incidence of mental ill health among Unive sity students, judged by mental-hospital admissio rates, remains unchanged, but the number of suicides Oxford University has dropped since widespread publ and private discussions brought better *recognition* this problem

Newspaper reports indicate the need for a change the attitude of the public The dangers inherent depression must be grasped more realistically, as well the favourable outlook with treatment That a patie does not threaten suicide, or again that he spea logically, is no excuse for inaction When depression recognised, leading questions about suicidal thoughts a necessary to gauge the risk

Choice of method for committing suicide is influence by the means available Control of drugs is importan but less important than control of patients' depression

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Before Our Time

OLD MOORE AND HIS ALMANACK

A Tercentenary

In his FitzPatrick lectures of 1913 Charles Mercier gave a remarkably lucid account of the science and art of medical astrology. He traced its written history from about 4000 B.C. and emphasised its paramount importance to medical men down to at least the period of the Renaissance. He then referred to its decline and wrote: "Astrology is now utterly extinct. It has been dead so long that it no longer stinks; perhaps because it is embalmed in the writings of so many men that were eminent in their day." If astrology was dead in 1913 it has certainly come to life again, witness the innumerable columns in the popular press devoted to "planning with the planets" or "what the stars foretell" and the enormous trade in "horoscopes". Quite recently, too, a London surgeon revealed that patients frequently ask him to operate on a day which they regard as propitious; and he very properly grasps this opportunity of sharing his responsibility with the stars. If any further evidence is required of the vitality of the ancient art of astrology it is provided by the number of Almanacks and Prognostications which continue to pour from the press. The most remarkable of these from the point of age is *Foulsham's Original Old Moore's Almanack*, which is the lineal descendant of an almanac compiled by Francis Moore in 1699 and which has apparently been issued without a break since 1701. The certified net sale of *Old Moore* at the present time exceeds one and a half million copies annually.

* * *

Francis Moore was born at Bridgnorth, Shropshire, on Jan. 29, 1657. He is said to have acted for some time as assistant to the notorious astrologer John Partridge (1644–1715). Having obtained a licence to practise physic—presumably one of the Bishop's Licences which constituted one of the few legal qualifications open to general practitioners at that time—he established himself in 1698 at the sign of "Dr Lilly's Head" in Crown Court, near Cupid's Bridge, Lambeth, in the capacity of physician, astrologer, and schoolmaster. In 1702 he was living near the Old Barge House in the parish of Christchurch, Southwark, where he probably died between July, 1714, and July, 1715.

In 1699 appeared an almanac entitled *Kalendarium Ecclesiasticum*, by Francis Moore, Licensed Physician and Student in Astrology. This duodecimo of 48 pages contains a table of the Kings of England, the Law Terms, tide tables, astronomical data, and a list of fasts and feasts, in addition of course to the calendar. The prophecies are confined to the weather. The only sections of direct medical interest are the list of the Signs of the Zodiac with the parts of the body which they are said to influence, and short notes placed at the head of the calendar for each month. That for January reads:

> "Let not blood this month unless necessity require it. Be careful of taking cold, for thereby Rheum and Flegm is much increased. Fast not long in the Morning, for it is hurtful. Use Meats moderately hot. Warm Cloaths, warm Diet, a good Fire and a Glass of Sack with a Toast is very seasonable, if you can get it."

The heading for March says:

> "In this month advise with the Astrological Physician, for now Purging and Blooding is good. Blood and Humours increase, therefore now be sure use Meats of good Digestion, forbear salt Meats as much as possible, now good Drink is necessary; but above all, a good Breakfast, if you can get it, will do no harm."

The phrase "if you can get it" is often repeated, and it suggests that Moore, like most of his kind, rarely looked on the bright side of things. In his later almanacs, which give much greater space to prophecies, he illustrates one of the most constant characteristics of the early prognosticators—their almost entirely unrelieved gloom. Perhaps it was that plague, pestilence, famine, and sudden death were fairly safe things to foretell.

Moore's literary style, like that of many of his medical contemporaries, is by no means lacking in grace and vigour. His note for the month of May begins quite poetically:

> "Now both Garden and Field afford Physick as well as Diet. Rise early, and walk abroad by the running Streams. Sage and sweet Butter is a cheap and wholesome Breakfast. Clarified Whey, with Sage, is also good, and so is Scurvy-grass Ale and Wormwood-Beer. Forget not to eat and drink betimes, you that have it."

With the last page of this little book we come to what was probably the main reason for its publication—an advertisement for Moore's wonderful pills:

> ADVERTISEMENT
>
> From Crown-Court, near Cupid's Bridge, in Lambeth Parish, in Surry, Aug. 15, 1698.
>
> Where is sold, by the Author, his Famous, Familiar, Family, Cathartick and Diuretick Purging Pill, very excellent for the Scurvy, Dropsie, French Pox, and most other Distempers incident to the Body of Mankind. They work so gently, that you may take them at any time of the year; they hinder no Business. A Note of Direction will be given with each Box, which contains 40 Pills, for 2*s.* and the Half box, containing 20 Pills, for 1*s.*

* * *

In July 1700 Moore completed a new almanac: *Vox Stellarum; being an Almanack for the Year of Human Redemption 1701*. This was dedicated to Sir Edward Acton, recorder and M.P. for Bridgnorth, Moore's native town. The general make up is similar to that of its predecessor, but *Vox Stellarum* contains much more of medical interest. The twelve Signs and their dominion over man's body are now set out in verse, and each page of the calendar has a column of medical notes. Thus for January—

> "Full Moon the 13th day at 1 afternoon will undoubtedly be made sensible of its Effects. They both cast an anxious Square to Venus, which threatens Females in general with stubborn Diseases, especially such as do proceed from Cold, which may turn to violent Fevers even at this time of the Year, and send some to the Shades, whilst others are swallow'd up in the Grave of despair; and an eminent Lady afflicted with much Sorrow, if not Death."

The last page again contains an advertisement:

> "By the Author hereof (only) is sold his famous familiar Family Cathartick and Diuretick purging Pills.
>
> The Author also thro' the Blessing of God, cures all sorts of Agues at once, whether Quotidian, Tertian or Quartan, tho' of long standing, and left off by others, as many now living can testifie, who have by God's Blessing, been cured by him at last. This Distemper often comes by supernatural means, which is the reason it will not yield to natural means, nor be subject to the will of every Pretender; nor indeed many other Distempers besides. The Author also has an excellent Method and Medicine for the Epilepsia or Falling Sickness, and Convulsions in Children. He gives his Judgment *gratis* to all that come to him, and allows his Medicines at reasonable Rates. *Vivat Rex.*"

* * *

Francis Moore was not of course the first maker of almanacs. Almanacs, Kalendars, and Prognostications were among the earliest productions of the printing press and they have been issued in enormous numbers at all periods. The first Englishman to produce a printed Almanack and Prognostication was the famous Andrew Boorde in 1545. Moore himself had a host of rivals. The copy of the 1701 issue of his *Vox Stellarum* in the British Museum is bound up with 26 other almanacs for the same year. Among the more famous of Moore's immediate predecessors and contemporaries were his teacher John Partridge, William Lilly, William Andrews, John Gadbury, William Salmon, and George Parker. Almost all the early printed almanacs were the work of medical men. Some of the compilers were regular doctors of physic, but the majority were, like Moore, "licensed physicians," or "students in astrology and physic"—the general practitioners of the day These little books represent a prime source—as yet virtually untapped—for the study of the connection between astrology and medicine, for the history of certain aspects of medical practice and its regulation in this country, for the biography of many practitioners of great repute in their day, and for the history of medical advertising Many of the early almanacs are exceedingly rare, only one or two copies, and these imperfect, having survived Very few of the compilations that have appeared over a number of years exist in complete sets In continuity, *Old Moore* is unrivalled, and its successive issues would provide a fascinating picture of the changes in popular medical beliefs and fashions over a period of more than two and a half centuries

It may be noted that the present day Old Moore does not offer any medical advice at first hand His Almanack contains a great many advertisements for hair restorers, depilatories, rupture cures, slimming tablets, and oriental herbs of great potency It also includes portraits of the Misses Marilyn Monroe and Dawn Addams, and a Pools Forecast for 1957 One is glad to see that the anniversaries recorded for January include the birthday of a former secretary of the British Medical Association, but oddly enough the nativity of the genuine, original Old Moore himself, on Jan 29, 1657, is not mentioned

W J BISHOP

Public Health

B C G Vaccination

IN his annual report for *1955*, *Dr W A Horne*, medical officer of health for Glasgow, refers to further extension of B C G vaccination in the city The total number of vaccinations performed again increased, and immunisation was extended to include further groups, notably Glasgow Police Force During a period of seven weeks 118 schools were visited and some 12,000 children were tested, of whom over 8000 received vaccine Two features of the campaign were notable—the striking increase (10%) in public response and the rise of almost 7% in the number of negative reactors, compared with 1954

Almost 1300 members of the police force accepted the offer of B C G vaccination, and the results of Mantoux testing showed an unexpectedly high number of negative reactors, the over all average being 13 4% It was also surprising to find that negative reactors were distributed among all the ages tested, which ranged from 20 to 57 As a result of these findings, Mantoux testing, followed by vaccination if indicated, has been made a requirement for entry to the Glasgow Police Force

The London County Council has had made a three-minute coloured film entitled *B C G Vaccination*, to be shown at local cinemas throughout the county during 1957 It encourages parents to allow their children to be tuberculin-tested, and vaccinated if the test is negative

Births and Deaths in 1956

Provisional figures for England and Wales in *1956* have been issued by the Registrar-General [1]

Live Births —The birth rate was 15 7 per 1000 population—the highest rate since 1950

Infant Mortality —The infant mortality rate—23 8 per 1000 related live births—was the lowest annual rate ever recorded in this country The rate was 24 9 in 1955, 25 4 in 1954, 26 8 in 1953, and 52 8 in 1938

Deaths —The death rate was 11 7 per 1000 population The rates for 1955 and 1954 were 11 7 and 11 3

Stillbirths —The stillbirth rate was 23 0 per 1000 total live and still births In 1955 the rate was 23 2 and in 1954 23 5

In England Now

A Running Commentary by Peripatetic Correspondents

WE have geologists the way some folks, as Thurber would say, have mice Into a biological department they introduce large piles of crazy paving (the floor has had to be reinforced) and enormous wooden boxes Not content with this, they telegraph us from remote areas "Have found dinosaur stop send *packing case* eight by six by four stop" We found one, by a fluke, but on that day the van was wanted for the agronomists' annual wayzgooze, and we had to despatch the thing to Waterloo on a handcart pushed by two junior technicians All went well as far as Fleet Street There a wheel came off Fresh from an initiative test, the two juniors ditched the cart, removed the lid of the case, laid it on the inverted body, and finished the journey inside, like a panto horse, navigating blind and led by a policeman

Only a few days later, another of the geological boxes produced a surprise Its owner came in to see me with a vague expression on his studious face and a dirty block of apricot table jelly in his hand, divided up into squares as such things are "I want you to look at this" he said "Do you think the same about it as I do?" It was wrapped in oiled brown paper I smelt it, tasted it, put a piece in water, agreed with him that it was a half pound chunk of blasting gelatin, and offered to take it up on the roof and destroy it When he refused this unselfish offer (I suppose he thought it would go off and damage some of his lumps of rock) I told him to take it down the road and hand it in at the police-station

Half an hour later he was back "I gave it to the duty sergeant" he said "the chap agreed that it wasn't a table jelly He said he was going to put it down the toilet and pull the string, and he went and did"

So if a member of the Force becomes the first artificial satellite vehicle, *I expect they'll blame that lot on Archbishop Makarios too*

* * *

An enforced rest in a small ward of one of our great hospitals has lately given me an opportunity denied to surgeons and their anæsthetists of observing preoperative treatment

The operations on two young men aged about 11 were set for 4 30 P M When lunch passed them by they seemed sad One confided to a passing porter that he would be glad when it was half past four

"Why, are you going home then?"
"No, that's when I have my operation"
"Oh, you'll know nothing about that"
"I know, but it's the injection I don't like I say, tell the staff nurse we're hungry"

This, of course, had no effect But one of them soon found the remedy in the jar of sugar in his locker and consumed a fair quantity This gave him the energy for preoperative physical exercise such as lifting the bed table up and down with his feet and playing ball with his neighbour All this makes me, a mere physician, wonder how much anæsthetists really know about the preoperative stomach contents and blood-sugars of their patients

* * *

Last week, in Boston, I gave four set talks, and also three little speeches on ward rounds I am hoarse without *emotion But this is a great country* for the medical *visitor, for there is something he can be doing* all the time in the way of meetings, panels, discussions, seminars, or even just drinking good coffee They also manage to keep their students keen and interested throughout the course instead of falling into exam-ridden apathy in the final year Most of this is, I think, due to their large staff *in proportion to patients and students*—but it's not all logistics, there is also an attitude of mind (which I admire) which makes for uninhibited discussion by folk of all levels of seniority (and intellect) I'm not entirely enchanted, however I keep in mind that I've only seen the best places, and also that the large staff and the *attitude that it's all great fun may* sometimes bear hardly on the patient, especially if he is coloured and perhaps a bit simple I may be wrong about this—it may be that the Americans are getting the medicine they deserve, they certainly pay enough for it I'm amazed by the popular interest in health, and I guess that office doctors here have to read advance copies of *Time* and the *Reader's Digest*

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[1] Registrar General s weekly return no 2 1957 H M Stationery Office Pp 20 1s 3d

* * *

Luke is a dales farmer A good one, but with a reputation for meanness and a capacity for getting anything that is going from the Government or Anybody Else Recently he became a grandfather for the first time and was more than delighted with the arrival of twin grandsons When I saw him on market day last week, I ventured to congratulate him on his new status and especially on the twins "Aye," he said, "ain't it a grand thing Straight into t' subsidy first time"

* * *

This week John came out in spots Too much porridge, perhaps, his mother thought "I am quite worn out with porridge," said John wearily

* * *

Lord Osis disliked the Health Scheme because he could no longer annoy his doctor by owing him money He had his blazonry inscribed upon his N H S card and dispensed specimens of his urine in Veuve Cliquot bottles of a particularly brilliant year He was a small sunburnt man with tufted hair, like an indignant coconut, and, as his message was late (as usual) and urgent (as always), I called on my way to the night train by which my chief was returning, and I, his locum Ananias, departing

Lady Osis, large, rufous, and wrinkled like a Californian sequoia tree—which she further resembled by adding a ring for every year of her age, thus making her look as though she had been pebble-dashed with diamonds—broke trail along the landing to His Lordship's bedroom through the Osis fan-club of retainers, valets, grooms, secretaries, and dogs, which she trampled underfoot or ground unconcernedly against the wall

"He's swelled up like a poisoned pup!" she bellowed, cheerfully unveiling her groaning and tympanitic spouse and suggesting almost unlikely cause for his distension "Now if he was a cow," she added, presumably following the train of thought inspired by his dismal noises, "do you know what I should do?"

I didn't know, and still wish I still didn't know, but I adopted my best manger-side manner and examined the patient's abdomen by proceeding over it upon a Great Circle course It was, I concluded, a case for masterly inactivity plus a good old-fashioned turpentine stupe

"Turpentine?" shouted Lady Osis at my request, "Good God!" Are you going to paint pictures on it?" and made suggestions about selling advertising space, before issuing commands at the bedroom door Long minutes passed, during which Lord O retired under his bedclothes like Achilles sulking in his tent, his wife rent strips off a moth-infested horse-blanket, and I beat frenziedly with my dressing-case upon the hordes of dogs which were now surging about the room A timid voice then informed us that there was no *turpentine*, and Her Ladyship erupted on to the crowded landing with the impact of a violently propelled cue-ball upon a snooker "pyramid" Bodies shot off in all directions into every orifice, and the noises of ill-usage of drawers and cupboards reverberated like the cannonading at Austerlitz

When the barrage lifted I received a grimy cobwebby bottle with no label and an impacted cork This, with several spiders, was removed by Lady Osis with a corkscrew she happened to be wearing I sniffed the bottle, the smell was aromatic, but I couldn't identify it Her Ladyship, however, brandishing her strips of horse-blanket in a blizzard of moths, cried, "Get to it, boy! I know turpentine when I see it!" and the stupe was lashed into place

My nose twitched thoughtfully as I drove to the station but not until I entered the newly decorated waiting-room was my olfactory problem solved I told my chief through my carriage window, "You'll find all the case records in the car, and when you visit old Lord Osis, take along a blow lamp I've made his turpentine stupe with coach varnish"

Letters to the Editor

TREATMENT OF SORE THROAT

SIR,—The paper by Captain Brumfitt and Captain Slater (Jan 5) and the letter last week by Dr Wheatley raise important principles on the use of antibiotics in general and in sore throats in particular

My own interpretation of the two divergent points of view expressed is as follows Brumfitt and Slater have shown that the place of antibiotics in the treatment of acute sore throat is still doubtful, both as regards which cases should be treated with these powerful drugs and as to whether the results are really very much different from those treated with non specific measures Wheatley on the other hand advocates that *all* cases of sore throat should be treated with *oral* penicillin in order to prevent complications related to strepto coccal infections He also states that it is the general practitioners whose views on the matter should be listened to (But what, if not general practitioners, are the National Service medical officers?)

I feel that certain relevant points should be appreciated

Ætiology—What is the cause of the hundred odd cases of acute sore throat that the average family doctor sees each year? The usual finding from throat swabs is that only about half will grow any organisms that are usually recognised as pathogenic In my own practice in the past 400 cases of sore throat in adults hæmolytic streptococci were grown from only 45% What is the cause of the other 55% of cases? If these are not caused by specific organisms, then what is the rationale of using specific antibiotics?

Course—Acute sore throat tends to clear up spontaneously and uneventfully after four or five days If oral penicillin is to be advocated, then we should be shown that beyond doubt this shortens the illness

Complications—It is because of complications that the wholesale use of antibiotics is usually advocated It is stated that their universal use has brought about the dramatic decline in the numbers of new cases of rheumatic fever and acute nephritis But very probably the hæmolytic strepto coccus was beginning to lose its virulence even before these specific drugs were being widely used In my own practice I find that I am using penicillin in only 20–25% of cases of acute sore throat, the proportions being equal in streptococcal and non streptococcal cases In spite of these low proportions, in the past ten years I have had no cases of rheumatic fever and only 4 cases of acute nephritis, 2 of these were treated with parenteral penicillin, and the other 2 were so mild that they did not feel it necessary to consult me Acute otitis media, mentioned in Dr Wheatley's letter, is also a much milder disease, and in spite of using antibiotics in only 20% of cases I have had no acute mastoids or chronic running ears or permanent deafness in these ten years

The advocation of the wholesale use of oral penicillin causes me considerable disquiet on two scores First, its very ease of administration leads to possible abuse Secondly, its absorption is doubtful in some cases, and we often find that our instructions are not followed by some patients who omit to take the preparation and still recover uneventfully My own routine is to use only the intramuscular route and to give all the injections myself—the extra trouble to doctor and patient acts as a brake on facile use and abuse

The time has surely come for us to reflect and review our habits in the use of antibiotics and to take into account the natural changes that have occurred in the common diseases for which they are so often given

Beckenham, Kent JOHN FRY

SIR,—To me there seem to be three important points in Dr Wheatley's letter

(1) The treatment of sore throat is *primarily the task of the general practitioner* This is indisputable, but medicine depends for its advancement, *not* merely on intelligent observation but on painstaking and controlled investigation which the average practitioner, because he lacks either facilities, or—that more important commodity—time, is not in a position to undertake Brumfitt and Slater are to be

commended for their perspicacity and initiative in seizing the golden opportunity of studying scientifically this common malady

(2) *Penicillin lozenges*, not intramuscular penicillin, is the means of administration which the overworked practitioner must adopt But if blood borne penicillin cannot eradicate the streptococci lurking in the depths of the tonsillar crypts, what chance has the superficially acting penicillin lozenge ?

(3) Dr Wheatley attributes to antibiotic therapy the decreased incidence of local septic complications and toxic allergic sequelæ of sore throat Yet I have treated 73 sore throats—some of them quite severe—without antibiotics and I have not had a single case of septic involvement of the middle ear cleft, and has the reputedly high incidence of rheumatic fever and acute nephritis ever been conclusively proved to be higher than it is today ?

Dr Wheatley says nothing about the risk of inducing resistant strains of bacteria by indiscriminate use and inadequate dosage of the antibiotics Nor does he mention the risk of sensitising the patient He has, I think, been fortunate not to have met the nasty stomatitis which can develop during penicillin lozenge therapy

I wish that Brumfitt and Slater had not been so hesitant in interpreting the obvious lesson of their inquiry, which has exposed the uselessness of routine penicillin for sore throat and which should lead to a further saving of this big gun for big occasions

Royal Air Force,
Leconfield
A R SMITH

SIR,—Dr Wheatley suggests that information on the treatment of sore throat be sought from general practitioners May I draw his attention to a recent report on the treatment of acute sore throat in general practice? [1] If Flying-Officer A R Smith (Jan 19) reads this paper he may change his view that "nothing is to be gained by giving antibiotics or sulphonamides" in acute sore throat

St Mary Cray, Kent
E TUCKMAN

SIR,—In my opinion there is far too much tendency to prescribe sulphonamides, penicillin, or the broad-spectrum antibiotics for the ordinary follicular tonsillitis seen in general practice

Tonsillitis being a simple infection of the upper respiratory tract, it follows that simple measures will suffice I find that rest in bed for 3–4 days, combined with mist acid acetylsalicyl *N F* and an abundance of bland fluids, will in the vast majority of cases be all that is required It is important that a child should not return to school for at least another 4 days, and an adult for at least a week

Of course, where there is any underlying condition, such as congenital or acquired heart-disease, or a past history of rheumatic fever, it is imperative that either a sulphonamide or parenteral penicillin be given

Putney
BERNARD SWEETMAN

THE Rh BLOOD-GROUPS

SIR,—Dr Wiener's letter of Jan 12 is full of confusion which suggests that he does not understand the CDE notation

Dr Nicholas last week showed how misleading Wiener's two tables are as presented Had this been the only inconsistency it would not have been so bad, but there are other statements which may lead the unwary astray Thus, Wiener says that anti-C and anti-D are less rational names than anti rh′ and anti Rh_0, and gives the following example "corresponding to the gene symbol r'^w, Fisher and Race use the 'chromosome' symbol C^wdeF, which includes the letters d and F for antigens for which no testing sera exist " But *d* and *F* do not here stand for antigens but for genes, and should therefore have been in italics The example is, therefore, irrelevant to the argument One cannot maintain that a gene may not have a symbol simply because no testing sera are known Therefore, one can only conclude that, in his mind, Wiener has confused symbols for genes with those of their products

If Wiener really wants a logical nomenclature he should follow that given by Ford [1], the most logical yet formulated

Department of Zoology,
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P M SHEPPARD

BLOOD-GROUPS AND DISEASE

SIR,—Dr Wiener's letter of Dec 22 seems to call for some comment, although his bias against any idea of an association between blood groups and disease (other than hæmolytic disease of the newborn) is well known Far from being a waste of space, the publication of data, however fragmentary, concerning the genotypes of groups of patients, compared with those of satisfactory controls is essential if progress is to be made in understanding the inherited basis of disease

Instead of denigrating new work, most of which has been much more carefully controlled than that of thirty years ago, *it would be more profitable for so eminent an* authority on immunology (he is, after all, one of the discoverers of the Rh blood-groups) to try to integrate the following *facts*, which suggest that there may be immunological processes operative in peptic ulceration

(1) That in six countries, the U S A included, many authors have demonstrated a marked association between blood group O and peptic ulcer This is the most striking of several apparent associations between blood groups and disease It can hardly be due to chance that, of the many disorders studied, all the positive results concern diseases of the gastro-intestinal tract, carcinoma of the stomach, pernicious anæmia, and duodenal and gastric ulcer

(2) That there is a strikingly higher proportion of non secretors of the ABO blood group antigens in duodenal ulcer patients compared with general population controls This association has also been shown to hold within families The data also suggest, though they do not yet prove, that the association is greatest in those sibships which do not segregate for blood group O

(3) That within sibships the association between blood group O and duodenal ulcer is not apparent though not disproved [2]

(4) That drugs such as corticotrophin, cortisone, aspirin, and phenylbutazone, all of which cause or exacerbate peptic ulceration in man, also have an effect on antigen antibody reactions and are frequently used in the treatment of hyper sensitivity states

(5) That many leguminous plants which form an important constituent of human diet contain ABO blood group agglutinins many of these will be neutralised in secretors but not in non secretors (see accompanying letter by Cain)

The initial cause of mucosal damage in patients with peptic ulcer is quite unknown, and it seems to us that there is a good prima facie case for investigating the possibility that immunological reactions play a part in the genesis of ulceration

C A CLARKE
R B McCONNELL
P M SHEPPARD

Heredity Clinic
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Liverpool

POSSIBLE SIGNIFICANCE OF SECRETOR

SIR,—The widespread occurrence of the secretor/*non secretor* polymorphism is now well established [3] It is a stable polymorphism as defined by Ford [4] This means

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[1] Chapple P A L, Franklin, L M Paulett, J D Tuckman E, Woodall J T, Tomlinson A J H, McDonald J C *Brit med J* 1956, i, 705

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[1] Ford E B A uniform notation for the human blood groups *Heredity* 1955 9 135

[2] References relating to paragraphs 1, 2, and 3 are Fraser Roberts, J A Aird, I Bentall, H H, Mehigan J A Wynn Edwards J *Brit med J* 1954 ii, 315 Clarke C A Wynn Edwards J W, McConnell R B Sheppard, P M *Ibid* 1956, ii, 725, Anonymous Haddock D R W, Howel Evans A W, *Ibid* p 723

[3] Mourant, A E Distribution of the Human Blood Groups Oxford, 1954

[4] Ford E B *In* The New Systematics (edited by J S Huxley) Oxford 1940

that (at least until extremely recently) it has been maintained by stabilising selection, which in turn implies that both secretors and non secretors have some definite selective values On the advantage of non secretors it is useless to speculate until we know something positive about the condition, but one possible selective advantage of secretor can be suggested

As Fisher [5] and others have shown, a selective advantage of as low as 0 5% can bring an allele to fixation in a population comparatively rapidly, and field studies [6-8] have shown that apparently very trivial characters, when properly investigated, may have startlingly high selection coefficients Moreover the different effects of alleles can be profoundly altered by selective accumulation of modifiers [9] Consequently, so well-marked a condition as secretor is exceedingly unlikely to be a mere by-product of some other important effect of the allele It is far more likely to be there for a definite purpose

The effect of secretor is to allow a considerable outpouring of antigens into the alimentary canal at its most anterior part This suggests immediately that something is being taken in, as part of the food, which it is advantageous on the whole to neutralise as quickly as possible This substance could be one that would damage the free cell surfaces of the epithelium actually lining the alimentary canal, especially those which are absorptive and therefore cannot be covered over with some impermeable protective substance

The discovery that large quantities of blood-group agglutinins which can be neutralised by secretors [10] occur in the seeds of leguminous plants widely used for food goes far to support this hypothesis, and further suggests that these antibodies have a definite, if mild, deleterious action on some parts of the absorptive epithelium of the alimentary canal Such an action, even if of little importance to civilised man, might of course be of considerable importance under the far more strenuous conditions under which man has lived for many thousands of years The considerably lowered incidence of duodenal ulcer in secretors, as compared with non-secretors of the ABO blood group antigens,[11] suggests very strongly the actual nature of this deleterious action

The hypothesis proposed, therefore, is that ABO agglutinins deleterious to the absorptive epithelium of the alimentary canal, which are taken in as part of the food, are wholly or partially neutralised by secretors This hypothesis has the advantage of being susceptible of experimental verification

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A J CAIN

A RAPID BLOOD-SUGAR SCREENING METHOD

SIR,—With the increasing interest in glucose enzyme tests and their application in urine examination, I should like to draw attention to a rapid blood-sugar screening test which is also based on the use of glucose enzyme test strips The method has been developed in this hospital The difficulties encountered in trying to apply the enzyme test to quantitative estimations in urine are not met with to the same extent in blood, which is far less subject to variations in chemical composition and pH In 500 experiments performed by independent observers in parallel with blood sugar determinations by conventional biochemical methods, it was found that, within certain ranges, there is a definite and constant correlation between the blood glucose level and the intensity of the colour developed on the strip

The technique consists in placing a drop of blood from a finger or ear prick on the tip of a glucose enzyme strip, leaving it there for about fifteen seconds, and then washing the blood off under running water The plasma soaks quickly into the filter-paper and the red blood-cells are washed off, permitting the reading of the result without interference from the colour of the blood The colour developed is compared with an arbitrarily chosen three tone colour scale The whole procedure takes less than a minute and no reagents are necessary

The test can indicate the following ranges of blood-sugar very low, low, normal and slightly elevated, moderately elevated, and high It does not require any particular experience and can easily be performed by any doctor A full report is in preparation

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J KOHN

ANALGESIC DRUGS IN CHILDBIRTH

SIR,—I was very interested in the paper by Dr Roberts and her colleagues last week and congratulate them on their investigation of an important and very difficult problem The use of levallorphan to diminish the respiratory depression caused by the narcotic analgesics in childbirth is one of the most valuable potentialities of this antagonist That its use did not result in a significantly improved minute volume in the infants may have been due to the fact that the dose of levallorphan was inadequate I believe that a 1 100 ratio of levallorphan and pethidine [1] might have given more satisfactory results

Manchester

MARK SWERDLOW

UNMARRIED PARENTHOOD

SIR,—It must have struck other readers of Mr Greenland's sensible paper last week on the ecology of unmarried mothers that it contained only one reference to the fact that pregnancy can be prevented by suitable measures If in fact the "unmarried mother" differs from her sisters chiefly in being more fertile, if efficient contraception may "tend to reduce the number of illegitimate maternities among the higher-income groups," if unmarried mothers sometimes die of abortifacients and unmarried babies often die of neglect, the point is surely relevant

I think that the trouble is that social agencies find themselves engaged in two distinct attempts—the prevention of unwanted pregnancy, and the attempted prevention of sexual behaviour in young people Their merits apart, experience suggests that the first offers better chances of success than the second "Moral welfare" has perhaps a real part to play in preventing married men from seducing unmarried women, and intelligent health and social education might inculcate a better idea of responsible sexual behaviour all round Unfortunately the devotion of moral agencies to the prevention of coition has often eclipsed their anxiety over the tangible suffering unwise coition may cause Some have regarded pregnancy as a desirable disincentive —few seem able to agree that, if they cannot prevent the initial step, it would be humane *to limit its* consequences

Obviously the venue and personnel of unmarital relations are not promising for fully reliable contraception, and it may be that no contraception is "fully reliable" But I imagine a halving—if we got no more—only of the death rate from abortion would gratify the devout as much as it would gratify me Unfortunately, while it took Parliament about seven days, all told, to legislate against contraceptives in slot machines, it has not implemented the recommendations of the Royal Commission on Population in seven years

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[5] Fisher, R A. Genetical Theory of Natural Selection Oxford 1930

[6] Cain A J Sheppard P M *Genetics* 1954, 39 89

[7] Dobzhansky Th Genetics and the Origin of Species New York 1951

[8] Fisher R A *Ann Eugen* 1939 9 109

[9] Ford E B *Advanc Genet* 1953 5 43

[10] Boyd W C Shapleigh E *Blood*, 1954 9 1195

[11] Clarke, C A, et al *Brit med J* 1956 ii 725

[1] Swerdlow, M *Anaesthesia* (in the press)

I certainly do not underrate either the value or the interest of the sociological approach to local differences It might be well worth sending anthropologists to study the patterns of life which produce high outputs of illegitimate babies A study of the economic causes which hinder marriage would also be interesting, and probably useful, especially in Peru But while proper and general contraceptive education is no more an answer to a social problem than B C G is an answer to tuberculosis, it seems an obvious first step without it, as Mr Greenland says, " children will continue to die needlessly, many of those who survive will be miserable, and the unmarried mother will suffer for our indulgences as well as her own "

Loughton, Essex **ALEX COMFORT**

SHORTAGE OF RADIOGRAPHERS

SIR,—As a radiographer, I would like to challenge several of the points raised by Dr G H Illingworth (Jan 5)

Firstly, he claims that only male radiographers are dissatisfied with their salaries This is not the case Both men and women feel strongly about the present low figures, and resent the Whitley Council's unrealistic attitude to our salary claim Girls are beginning to realise more and more that there are plenty of jobs open to them with better remuneration and less exacting duties even in hospitals, let alone outside the N H S Male radiographers are, of course, becoming extinct There is absolutely no incentive to take up the profession, and there are strong inducements for those already in it to leave In fact, they are leaving, in scores Radiography will indeed be " a job for a girl " and will suffer in consequence

Dr Illingworth suggests that superintendents can largely be dispensed with Yet the efficient administration of all but the smallest departments, with only 2 or 3 on the staff, would take far more time than the average radiologist would be *willing or able to devote to it* Administration would inevitably devolve on the most senior of the radiographers, and she would soon find herself a superintendent in all but name

In so far as educational standards are concerned, Dr Illingworth himself defines just the type most desirable for X ray work " An intelligent girl of 17 or 18 with an aptitude for the work " We are surely not aiming too high in asking for a General Certificate of Education with a bias towards science subjects, to ensure filling the prescription, as it were

As for the membership examination, which, incidentally, most students have no difficulty in passing in the two year period, it is necessary to maintain our standard of knowledge at a reasonably high level, otherwise the quality of work will gradually suffer There has been considerable exaggeration of the abstruse nature of the physics and apparatus construction taught Only the fundamental parts and principles are dealt with, and any complexity is due to the diverse units and functions of a modern set (Several hundred pounds worth of damage can be done to a tube through ignorance of its properties)

I would like to register a strong objection to the implication in Dr Illingworth's letter that the Society of Radiographers is deliberately making its membership examination too difficult, *in order to limit entries and thus strengthen its hand* Under the all powerful Whitley Council our own society seems to have very little to say, as the recent negotiations have proved

Finally, a word about the training of staff Surely the approved training school, with its facilities for all types of special work, organised groups of lecturers, and so on, is the most efficient way of training personnel Learning radiography started in a haphazard pick it up as-you-go along way, as with all new sciences, but a better system has been evolved over the years, and it would be retrogressive to return to learning in the department alone In any case, it is becoming increasingly difficult for radiographers in the busy short staffed departments of today to devote all the time they should to the practical training of their students sent down from the training-school

X Ray Department
Royal Infirmary Sheffield **N ROBINSON**

SYRINGE CARRIER

SIR,—We doubt that the syringe carrier referred to by Dr Lerman (Jan 12) solves the problems of the anæsthetist

In our view, the time consuming labour is largely spent in cleaning, sharpening, lubricating, and assembling, all of which have to be done in any case, while saving is represented only by the time taken to insert the syringe in the container Using the Nuffield type of aluminium container this would *not be substantially greater, and Dr Lerman is mistaken in* thinking that these are expensive—they cost merely a few pence and can be damaged only by direct violence

The multiple syringe carrier has three disadvantages Firstly, by any one arrangement it must contain a fixed set of syringes, which may or may not accord with the demands of varying circumstances Secondly, the contents are rendered potentially non sterile on first opening, and subsequent openings add to the opportunities for contamination of all remaining syringes by air, droplets, or hands Since the " life " of one boxful may be prolonged, this is no small risk Thirdly, a syringe could be accidentally replaced in the box without necessarily giving any indication (e g , by the presence of a broken seal) that it had been used

We would expect cultures included in the box to be sterile after treatment by hot air or steam, but are more concerned at the results which might be obtained by placing a small plate of medium inside the box and examining it when the last syringe has been used

Lewisham Hospital,
London, S E 13

C K McDONALD
J PIRNIE

ALLOXAN AND CARCINOMA OF THE LIVER

SIR,—In their stimulating preliminary communication (Jan 12) Professor Gillman and his colleagues report that alloxan, given intravenously, seems to retard tumour *growth without causing diabetes* If this finding is confirmed, it will be of great theoretical interest, for there may be a fundamental link between it and the important discovery made long ago by Warburg[1,2] that in cancer cells respiration is decreased and glycolysis increased

Glycolysis proceeds at a lower oxidation reduction potential (Eh) than aerobic carbohydrate metabolism (respiration) It would seem, therefore, that if a substance which raised the Eh of the tissues were introduced intravenously it might block the main pathway, glycolysis, from which cancer cells derive their free energy, and so cause retardation of growth or even necrosis Alloxan has the potential properties of just such a substance

Both ascorbic acid and glutathione, when injected intravenously, lower the Eh of the tissues[3,4] *This was* first demonstrated by measuring changes in the decolorisation-times of oxidation-reduction dyes injected into the skin, and was confirmed by measuring directly the fall in the Eh of the tissues with an inserted electrode In *1954 I suggested that the term " reductosis "* might be introduced to describe this condition

" A disturbance resulting in a *tendency* towards a decrease in pH is called an acidosis, and one *tending* to an increase in pH, an alkalosis It is possible that analogous tendencies towards changes in the Eh of the tissues may occur as the result of disease and the administration of drugs , *tendencies* towards increase or decrease in the Eh of the tissues might be labelled ' oxidosis ' and ' reductosis ' respectively, corresponding to a decrease or increase of available electrons "

Although ascorbic acid and glutathione undoubtedly, and cortisone and corticotrophin probably, cause a reductosis, no substance has yet been shown to cause an oxidosis But alloxan and dehydroascorbic acid, which are found in Nature, might be expected to do so in

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1 Warburg O *Pflüg ges Arch Physiol* 1913, 154, 599
2 Warburg O *Ibid* 1914, 158, 19, 189
3 Loxton G E , Le Vay D *Nature Lond* 1953 171, 524
4 Loxton G E , Le Vay, D *J Pharm Lond* 1954, 6 178

massive intravenous doses If in fact they do, they might also be expected to retard tumour growth, by direct action on cancer cells rather than through the intermediary of the endocrine system

There are three interesting questions

1 Does alloxan, in the doses given by Professor Gillman, cause a measurable oxidosis, and if so for how long ?

2 Does dehydroascorbic acid given in similar doses also retard tumour growth, and does it cause an oxidosis ?

3 If alloxan acts in the way I have suggested, then by analogy with the reductosis caused by the intravenous injection of ascorbic acid and glutathione one would expect the effect to last for only about an hour Is the retardation of tumour growth enhanced by repeated administration ?

London, W 1

G E LOXTON

HEAD INJURIES

SIR,—Mr Lowden (Jan 12) asks for guidance in the selection of cases requiring neurosurgical management May I suggest that he solicit advice from the nearest neurosurgical consultant by telephone ? Initially because of a paucity of neurosurgical beds in Bristol, we instituted a system of "vetting" by a consultant, or perhaps a senior registrar, of all cases referred for admission to the neurosurgical unit Judged by the results, the system has worked well in the interests of the patients

It may be asked, can a case of head injury be provisionally assessed on the telephone ? It certainly can, as experience shows This stems from the fact that diagnosis is based on signs which can reliably be described state of consciousness, pupils, reflexes, and so on, and particularly the chart readings, of which pulse and respiration rates are the most important We have encouraged the practice of fifteen-minute readings for the first two hours, then half-hourly, then hourly, so that the trend of the case may be the more quickly judged, especially if a verbal consultation may have to be sought Where possible the patient should be brought to the neurosurgical "base"—not so much for operation as for observation if diagnosis is in doubt, and so that he can be seen frequently, if need be, by the specialist surgeon in the tricky postoperative days The surgeon may have to see his ill patient several times a day Secondary operations are not uncommonly required and often with very short warning

The practice of obtaining expert advice should eliminate the risk of a death in the ambulance Concerning casualty departments and cases of head injury, a safe rule was in force in my former medical school—admit everyone with a history of unconsciousness, even if very brief The beds were found, despite very large waiting lists

Frenchay Hospital,
Bristol

G L ALEXANDER
Neurosurgeon

THE RELATION BETWEEN SMALLPOX VACCINATION AND POLIOMYELITIS

SIR,—Dr MacIver[1] found that of 35 cases of poliomyelitis in children aged $3\frac{1}{2}$ years or less, only 2 showed evidence of vaccination in infancy He emphasised that written records can be fallible and that all these children had been examined for an actual vaccination scar Our own survey,[2] which showed 29 vaccinated children among 34 under 5 years who had had paralytic poliomyelitis, was a "backward investigation" covering the years 1951–55 It was based on the records, because we could not get visual evidence in a number of the children who had left the area since their illness But in view of Dr MacIver's emphasis on the importance of evidence of a scar, those children in our survey who are still available in the area have been examined Of the original 29 vaccinated polio myelitis cases and 23 vaccinated controls, 19 cases and 17 controls were seen Vaccination scars were confirmed in 18 cases and in 17 controls In only 1 case was there no definite visible evidence of vaccination

While we did not claim that the results of our survey were statistically significant, the check against visible evidence supports the original findings It is also satisfactory that within this admittedly small field of inquiry the accuracy of the written records is sustained

During 1956 there have been few cases of paralytic poliomyelitis in this division Of the 8 cases among children below school-age, inspection of the arm shows that vaccination had been successful in 5 This additional evidence supports our previous view and does not confirm Dr. MacIver s findings , but we hope nevertheless that he will continue to keep records of the vaccinal state of children who contract poliomyelitis and will also compare them with suitably selected controls

Since we last wrote, we have seen the results of an investigation undertaken in Vienna by Dr F. Puntigam and Dr K Berger.[3] Examination of the records of 121 children aged 1–4 years who suffered from poliomyelitis between 1951 and 1955 showed that in Vienna (as in South-East London) there was no statistically significant difference in the incidence of the disease among vaccinated and unvaccinated children

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H D. CHALKE
F. L CLARK

CARDIAC ARREST

SIR,—By his Hunterian lecture in January, 1956, Mr B B Milstein has contributed greatly to the problem of the management of cardiac arrest, and his letter (Jan 5) shows that he considers that every physician and surgeon, and presumably, therefore, every registrar and houseman, should be prepared to undertake open cardiac massage when faced with such a catastrophe A few comments from one who, in the past, has had some considerable experience of this complication, in surgery other than thoracic, may not be out of place

In 1926 I became resident surgical officer of the General Hospital, Birmingham, and six months after my appointment a new Coroner's Act became law, one clause of which permitted the surgeon, in the event of an inquest into the cause of a death under anæsthesia, to be represented by the resident surgical officer, provided the latter was present at the operation, instead of, as hitherto, having himself to appear in court The result was that, as soon as there was an impending disaster in any operating theatre, I was hastily summoned in order that I should be present in case the worst should happen.

This was in the days when anæsthesia was very different from the skilful affair it is today—mainly ' rag and bottle no intratracheal tube methods, very primitive gas and oxygen apparatus and almost no understanding of modern methods of general preparation of patients for operation During my three years as resident surgical officer, I saw 30 cases of cardiac arrest At first, I used the methods of management current in the late '20s, when open cardiac massage was generally regarded as the most dramatic and very last thing to be done

At about this time, Dr W B Primrose, wrote a paper[4] stating that, unless the heart could be started within three minutes, irreversible changes would develop in the central nervous system, and this is just what my own short experience had shown So far as I am aware, this was the first paper to bring to the notice of surgeons and anæsthetists the significance of this absolutely fundamental time factor, and it had an immediate effect on those most likely to be involved on these occasions From then on, we set about direct heart massage as soon as the anæsthetic had been withdrawn and a clear air way assured

However, in those days there were no thoracic surgeons, and certainly no heart surgeons it was the general surgeon who faced these crises, most often in abdominal cases but by no means always so It was not unnatural, therefore, that the popular route for direct cardiac massage was through the under surface of the left diaphragm. If not already open the abdomen was rapidly entered through an upper left mid-rectus incision A further incision, through the left half of the central tendon of the diaphragm into the pericardial cavity, was then made with a knife held with the forefinger along the back of the point, and the thumb and middle finger protecting all but the terminal half inch of the cutting edge The first two fingers were then slipped into the pericardium and around the heart, which was massaged between them and the thumb (which remained below the diaphragm) at a rate of about 60 per minute In 6 of the above 30 cases the heart was re started by this technique and the patients made a complete recovery Of the remainder, in well over half the heart was re started but the patients did not survive, either because spontaneous respiration was not established, or because the heart stopped again and could not be re started, or because, although spontaneous respiration did start, changes in the central nervous system developed and the patient failed to recover consciousness and died within seventy two hours in spinal rigidity and hyperthermia I can vouch for the fact that the heart had indeed stopped in all 30 cases In those days we had not learned to differentiate between "cardiac arrest" and "ventricular fibrillation", but I can recall how on occasions, when I first put my fingers on the left ventricle, there was a sense of vibration, like touching the neck of a purring cat, presumably due to fibrillation, whilst on other occasions, I gained the impression of a completely inert bag After three or four firm compressions a spontaneous "kick" could be felt, and with a few more compressions regular beating would continue When the heart was slow in starting to beat, or failed altogether to start beating, firm regular massage by this route produced a palpable pulse at the wrist and in the carotids, and therefore an adequate cerebral circulation

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[1] MacIver, D *Lancet* 1956, ii 683
[2] Chalke H D Clark F L *Ibid*, p 545
[3] Puntigam F Berger K. *Wien klin Wschr* 1956, 106, 412
[4] *Brit med J* 1935 ii, 540

I had occasion to massage the heart twice during Army days in the late war, one patient recovered, but the other died as a "spinal animal" Since then I have had to apply massage in 2 further cases, neither patient recovered, though on both occasions spontaneous action of heart and respiration were restored

Nowadays, with modern ancillary services, and especially with good anæsthesia, the general surgeon encounters these occasions less commonly than does the thoracic surgeon, and the latter, having the chest open, will naturally apply massage directly Since surgery of the heart has been developed, it would seem that ventricular fibrillation has become much commoner The heart in arrest can be re started by massage, the heart in ventricular fibrillation is much more difficult to resuscitate, and often requires electrical defibrillation It is fibrillation, it seems to me, that makes the difference between the thoracic and abdominal approaches, since the defibrillator pads cannot be applied through the diaphragm Because "arrest" and "fibrillation" cannot be differentiated until the heart is exposed to sight or touch, I think general surgeons must persuade themselves that the thoracic approach is preferable—though admit that, were I faced with the need during an abdominal operation, I should proceed from below

One final remark although Mr Milstein's letter suggests that the technique of thoracotomy for cardiac massage can be mastered by all, the question does arise—how junior a resident might be expected to undertake this procedure if no more senior person happened to be available? I think it depends on his experience, should he be serving on a thoracic firm, or have seen cardiac massage performed previously, he would obviously be in a better position to try to rescue the situation Yet I do not consider that a man should be blamed for not making the attempt if by temperament or lack of experience he does not feel competent to do so The question is important from another point of view, occasions have happened when, in a coroner's court subsequently, a pathologist has expressed the opinion that such an attempt by a relatively young man should not have been made I regard this as a most unfair criticism for anyone to make who himself is never likely to be faced with such a crisis

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Birmingham, 15

F A R STAMMERS

FLUORIDATION A MISQUOTATION

SIR,—In a pamphlet from California entitled "Fluoridation Unmasked" the following statement about myself appears

> "Professor R A Peters, Biochemist of Oxford, England, says 'Fluoroacetic acid prevents the body from breaking down the citric acid created when sugar is burned into simpler compounds Retention of waste citric acid acts as a violent poison on heart and nervous system Fluoroacetic acid is used by African natives to murder their enemies What will happen to the person drinking fluoridated water when he uses vinegar?' (acetic acid)"

I do not know upon what writing of mine this is supposed to be based, but I think it as well to point out that it gives entirely the wrong impression Inorganic fluoride acts completely differently in the body from fluoroacetic acid, in which the carbon is linked firmly to the fluorine Fluoroacetic acid is a rat poison which is much more toxic than fluoride The suggestion in the last sentence that fluoride and acetic acid will combine easily to form fluoroacetic acid is very wide of the truth It is in fact quite difficult to synthesise fluoroacetic acid, and certainly there is no evidence that it can happen in the body, furthermore, acetic acid (vinegar), if given early enough, is an antidote to fluoroacetic acid poisoning in some animals

A R C Institute of Animal Physiology,
(Biochemistry Department)
Babraham, Cambridge

R A PETERS

PROLONGED PYREXIA IN CHILDREN

SIR,—The answer to Dr F E James's problem (Jan 19) is probably brucellosis, despite his careful investigation He has apparently ruled this diagnosis out because the outbreak appeared more like an upper respiratory infection, and because in one case the agglutinations were negative The first reason is not an adequate one Brucellosis often presents as prolonged "influenza," which does not respond to sulphonamides or penicillin A good example of a similar outbreak was given by Elkington et al,[1] and I have seen a minor epidemic near here

The negative agglutination has been the downfall of many a physician, and it cannot be too often or too strongly emphasised that a negative agglutination test does not rule out brucellosis Harris[2] goes so far as to say "In the chronic phase of brucellosis the finding of a positive blood agglutination reaction in a significant titer is the exception rather than the rule"

Apart from this, the histories are suggestive the continued low grade pyrexia, the lymph glands in the posterior triangle, and the reference to tiredness and lack of energy Without any prior knowledge, I venture to guess that the milk-supply at the time was raw (possibly from tuberculin tested herds, but not pasteurised), and that among the people who drank it there were several with prolonged fever, headaches, constipation, lassitude, irritability, and perhaps later rheumatic or neurological symptoms It may be too late to detect the organisms in the milk, but a diagnosis could be made in the patients even now The next step is a brucellin skin test, which is similar to the Mantoux test If it is positive, it shows that the patient has at some time been infected with brucella It has, however, a higher proportion of negative results than the Mantoux After that, the agglutinations should be repeated to see if there is a rise in titre or a change from negative to positive This rise may take place about the second week after the skin test, or it may be delayed for four or five weeks It is possible that a more reliable answer may be obtained if search is made for blocking antibodies and Coombs antibodies (Bürki and Fey[3]).

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[1] Elkington, G W, Wilson, G S, Taylor, J, Fulton F *Brit med J* 1910 1, 477

[2] Harris, H J, Stevenson, B L Brucellosis (Undulant Fever) Clinical and Subclinical New York, 1950, p 282

Bath HUGH WALLIS

REFLUX ŒSOPHAGITIS

SIR,—Your leader last week is full of interest. We note with regret, however, that of thirteen references to the literature all but one are American and that you have omitted articles which appeared in your own journal on this subject over our two names in 1955 and 1956.[4]

In these two communications we recognise a point to which your leader refers—namely, the importance of digestive juices other than gastric in the production of œsophagitis. We also suggested a method (Roux-en-Y) of avoiding this sequel to operation.

In the operation we described, the rapid emptying of gastric remnant is essential to success, and we should like to take this opportunity of drawing attention to the fact that we now make an antecolic gastrojejunal anastomosis. Previously we drew the jejunum through the mesocolon, but we have reason to believe that this may cause some obstruction. The more anterior arrangement lies comfortably. Passage of the jejunum through the mesocolon near the splenic flexure seems very liable to be followed by a certain amount of fat necrosis, which may prove very troublesome. We intend to make this the substance of a further communication.

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CHARLES WELLS
J. H. JOHNSTON

THE FUTURE OF NURSING

SIR,—May I as a nurse ask your readers not to regard either the tone of Miss Margaret Lamb's letter last week or certain statements in it as characteristic of the outlook of the nursing profession.*

The last paragraph, which suggests (if I follow its meaning) that the standards and code of ethics of nurses have nothing to do with and are not the concern of the medical profession, seems to me to call for a disclaimer on our part.

As I, and I hope many other nurses, see it, the trained nurse acts in a dual capacity. First, she assists the doctor by carrying out the treatment he requires for his patients (using the word "treatment" in the widest possible sense), and by giving him the results of her expert observation of his patients, since her contact with them is much less intermittent than his. Secondly, she uses in the service of the patients her own skills, which include much not normally the concern of the doctor—important details of basic nursing care, and the maintenance of a therapeutic environment (which should include such amenities as quiet, order, fresh air, and flowers or other pleasant things to look at), and if she acts in a senior capacity she should be the twenty-four-hourly coördinator of the now almost innumerable services provided for the patient—from catering to religious ministrations, from pathological-specimen taking to visitors, from physiotherapy to floor polishing, from voluntary helpers to social surveyors. In domiciliary nursing the nature of the duties may be different, but the need for coördination is no less great. Without this coördination the patient is liable to be exposed to chaos. The nurse cannot secure it unless she is wise enough and tolerant enough to realise that all have a common aim, to show that she respects the contribution of all who serve the patient, and to keep herself free from the professionalism run riot which so easily infects certain groups.

The nurses' high privilege of being the only ones on whom the patient depends for constant care all round the clock should make it easy for them to accept that it is ultimately the doctor who is in charge of the patient. Although the ward sister, for instance, has lines of responsibility directly to her medical staff and another to her matron as professional head of the nursing service, the fact that conflict between these responsibilities is so remarkably rare suggests a true partnership, in which the nursing profession willingly assists the medical profession, but both make also their individual contribution to the well-being of the patients.

This could not but suffer if nursing became an entirely independent profession with differing standards and ethics, and a training in which doctors take no part. One can only suppose that those who put forward such suggestions have not fully thought out the implications.

King Edward's Hospital
Fund for London,
Division of Nursing,
21, Cavendish Square, W.1

MURIEL M. EDWARDS

SIR,—As a nurse who has for the past thirty years been actively concerned with the training of nurses, may I try to sum up the situation which concerns many at the present time? As I see it, we require three groups in the nursing profession.

(1) A small group, highly trained and with great ability, to plan future progress, to negotiate with the appropriate Whitley Council, and to represent the profession at Ministerial level and on important bodies when nursing opinion should be expressed. It is for the benefit of members of this group that some advocate the institution of a university degree in nursing. While the value of this is debatable, none will deny that a trained mind is of great importance in those who aspire to lead their profession.

(2) A large body of nurses who are capable of fulfilling all the needs of the sick—a far wider requirement than bedside nursing care, important although this is—who can give intelligent assistance to their medical colleagues, who are wise in handling and capable of teaching student nurses, and who by word and example can guide the public on matters of health and hygiene.

We expect much of our nurses, and our methods of training in the past have met with some measure of success, if we may judge by the regard of patients, and by the esteem in which British-trained nurses are held in many countries overseas.

That the training needs constant consideration, and frequent modification to meet changing conditions, is fully realised by the General Nursing Council, which includes medical and educational representatives, but reorganisation must be undertaken with great care, lest a retrograde step causes the loss of much of the progress made during the past century.

(3) There is unquestionably need to give every opportunity to many who for various reasons are unable to meet the full demands of training for State registration, and yet have real gifts of nursing. Assistant-nurse training is still in its infancy, and both nurses and doctors can do much to overcome the ignorance which at present delays the full acceptance of this grade as an essential and invaluable part of the nursing service.

Strong representation has long since been made to the appropriate Whitley Council both to give equal consideration to those engaged in assistant nurse and in State registration training, and also to approve a grade of "senior" assistant nurse. Early recognition of these principles would help considerably to give the assistant nurse a full and honoured place in the health team.

With such varied requirements and faced with candidates of widely differing ability, it is hard to envisage one basic training likely to give equal opportunity and satisfaction to all, and although theoretically such a scheme has much to commend it, in practice we might well lose many of the very students whom we are most anxious to attract.

For the present I would choose rather to see a more careful selection of students with guidance of each individual into the type of training likely to give the fullest satisfaction and benefit to all concerned.

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[3] Bürki, F., Fey, H. *Schweiz. Z. allg. Path.* 1953, 16, 91.
[4] *Lancet*, 1955, i, 937; *Ibid*, 1956, ii, 479.

Finally may I reaffirm my view that 18 years is the minimum age at which the average student should be expected to face the physical, mental, and spiritual strain which training in a general hospital imposes, and which can perhaps only be fully understood by those who have taken such training, also that the State registered nurse, after three years' training, is still very young at 21 to accept the heavy responsibility which qualification brings

The conflicting requirements of the sick patient and of the student nurse present perhaps the greatest problem with which the nursing profession is faced at the present time, and this emphasises the need to encourage the appropriate training and full use of all who can participate in this essential service

Addenbrooke's Hospital,
Cambridge

L J Ottley

RECURRENT MOTOR PARALYSIS

Sir,—The following case appears to us to be unique

A girl, aged 6 years, was first seen by one of us (G E B) at St John's Hospital, Uxbridge, on March 23, 1956 She had been sent in as a case of poliomyelitis because she was "dropping things" and her arms and hands were weak There was an indefinite history of frontal headache and pains in the elbows during the previous weeks but no fever or meningism On admission she had hypotonia of both arms with bilateral weakness of the shoulder girdle, triceps, biceps, and extensors of the wrists No sensory changes were detectable Lumbar puncture yielded a normal fluid, a blood count was normal, as also was the serum potassium There was no porphyrinuria

The child made steady progress and on April 25 was discharged home, but, as there was some residual weakness of the right deltoid and the extensors of both wrists, she was to attend a nearby hospital for physiotherapy Eight days later, on May 3, she was admitted to this hospital as an acute respiratory emergency. This time she was moderately febrile There was complete diaphragmatic paralysis, with weakness of swallowing and of the voice and hemiparesis of the soft palate (left) and of the tongue (left) There was also right facial paralysis and generalised weakness of all four limbs On admission her vital capacity was only 400 c cm As this decreased to 300 c cm within an hour, tracheotomy was performed and a cuffed endotracheal tube was inserted as a preliminary to intermittent positive pressure ventilation The improvement which resulted from these procedures, however, was such that her intercostals supplied her needs and she was not in fact mechanically ventilated Intragastric feeding had of course to be instituted Subsequent progress was slow but steady On May 22 the tracheotomy tube was removed and by May 25 she was swallowing satisfactorily, her voice had become much stronger, and her vital capacity had increased to 800 c cm Power was also returning to her limbs and she was allowed up

On June 19, however, the right facial palsy, which had fully recovered, recurred, and fears were entertained that a further bout of paralysis might ensue Fortunately, these were not realised and by July 2 her vital capacity had increased to 1040 c cm although her cough was still poor

By July 17 she was walking well and the right facial palsy had, for the second time, almost recovered There was still, however, poor dorsiflexion of the wrists and a tendency to bilateral dropped foot Her tendon reflexes were just present and equal in all four limbs No sensory disturbance was demonstrable at this—or any other—time apart from some slight loss of vibration sense at the left external malleolus She was accordingly discharged home on July 17 and asked to return periodically for observation

She remained well at home until July 28 when she complained of pains in her legs and her walk became unsteady A week later the rash of chickenpox (to which she had been exposed by her cousin) appeared, and simultaneously a marked weakness of the left side of the face was seen Readmitted on Aug 4, she had no other cranial nerve palsy Chest movements were good and the diaphragm was acting normally, although her cough was still not very forcible Her limbs appeared to be much as they had been on discharge, although, while the upper arm tendon reflexes were just present, the knee and ankle jerks were absent on both sides The abdo reflexes were present, and there was again no se loss

The facial paralysis persisted for some days and recovered rapidly Repeated investigations at this showed normal fundi, a normal cerebrospinal fluid, n serum potassium, and absence of porphyrinuria The gamma globulin and pyruvate levels were also no Progress was rapid, and dorsiflexion of the wrists be strong at last though there was still slight bilateral dr foot She was discharged on Sept 8, since when she has seen several times She is in good health, intelligent, and cheerful with very slight residual weakness of th side of the face and of the limbs

Here then is a child who, within five months, sust four separate episodes of motor paralysis invo (1) both upper limbs, (2) the diaphragm, the pha the larynx, the left tongue, the left side of the palate the right face, (3) the right face, and (4) the left To what can these recurrent palsies have been due seems very unlikely to have been an infective a To begin with, fever was absent during the first ep and only slight at the onset of the second, was a during the third, and during the fourth was due prim to the chickenpox There was no meningism at time, the cerebrospinal fluid was normal throughou also was the blood count Again, in view of the no gamma globulin, it is hardly conceivable that, after a severe challenge to the defences as was sustained i second episode, antibodies would not have appear sufficient titre to ensure immunity for months, if no years

The alternative is an error of metabolism (analo perhaps, to migraine) producing some toxin or defic with a selective action on the lower motor neur Efforts were made to discover whether any parti drug or article of diet could have been respon When the right facial palsy recurred on June 19, she still in hospital under observation and close inquir all conceivably relevant factors was made The suggestive fact was that, a few days previously, she been given phenolphthalein as a purgative—at mother's suggestion, because she had been accusto to it at home The mother was advised that this better be avoided and she was not given it again A final episode of facial palsy coincided with the ons chickenpox, it is tempting to connect the two, but was no evidence of encephalitis or of geniculate herp the only ways, in our experience, in which the vari zoster virus affects the facial nerve

We should be interested to know if any of your re has encountered a similar case Moreover, as the pa returns for periodic observation, we would welc suggestions as to any further investigations that m in retrospect, usefully be made

South Middlesex Hospital,
Isleworth, Middlesex

G E Breen
R T D Emov

VIVA-VOCE EXAMINATIONS

Sir,—It is generally agreed by psychiatrists that unconscious transference of the emotions of love hate between patient and therapist is the most po factor in the psychotherapeutic interview It is not in psychiatric treatment, however, that this phenome plays an important part, and even statesmen w do well to recognise its importance in their dealings each other

There is one aspect of this matter which serio affects recruits to the medical profession in viva examinations The candidate is inevitably in a s of nervous tension, and under these conditions a powe transference situation arises between examiner examinee So often a candidate will pass in his pa and fail in his viva, not through lack of knowledge, by this unconscious factor which interferes lamentably with his self-confidence

Since failure may result, today, in his having to give up a medical career after having spent several years and much money on a medical training, it would seem very unjust that a possibly brilliant career should be jeopardised by such an irrational element Would it not be possible, in cases where this occurs, for the candidate, having passed his paper, to appeal against the decision of the viva voce examiner, and be given a second chance by another examiner ?

Bath E R **MATTHEWS**

VAGITUS UTERINUS

SIR,—I can add another case to those enumerated in Mr Russell's interesting article last week I did not report it at the time as I thought that the existence of the phenomenon was unquestioned

In this case, when I was resident obstetrician at Park Hospital, near Manchester, I was scrubbing up to do a forceps delivery on a woman who had had premature rupture of the membranes I am unable to recall the indications for forceps delivery, but the woman had only had vaginal examinations and no manipulations Suddenly the uterine cry of the baby was heard by myself, by the anæsthetist, by the sister in charge, and by the staff nurse It was repeated on a number of occasions, and when delivery was effected the baby continued to cry lustily during the extraction as well as immediately afterwards No ill effects were observed on the baby, whose cry in the uterus was quite strong and could be heard distinctly by me standing several yards away scrubbing up at the time

Manchester B **SANDLER**

SIR,—Mr Russell's article reminds me that several years ago, when I was in private practice, I was puzzled by the fact that in a primipara with an apparently normal left occipito anterior position the membranes ruptured two weeks before delivery

When she went into labour I found that one of the child s hands was at the side of its head, and causing obstruction Manual replacement having failed, and no progress being made, I decided to apply forceps as the cervix was well dilated Then it happened ! At 2 A M in a silence that could be felt, a distinct muffled cry occurred coming from the mother s abdomen I turned to the maternity nurse, and her normally rubicund face was ashen with shock

A perfectly normal forceps delivery followed, and the child cried at once, with no ill effects

Health Department
Shoreditch Town Hall
London E C 1

B **BROADBENT**

MEAN VENOUS PRESSURES IN THE FIRST HOURS OF LIFE

SIR,—We are indebted to Dr Brown (Jan 19) for at least two reasons His letter gives us a chance to acknowledge the work of the Oxford physiologists, G V R Born et al,[1] and it will bring this excellent work into greater prominence in medical circles We did know of it and perhaps should not have been so species specific Dr Brown's letter also gives us the chance to emphasise the oddity in our paper This is not that the venous pressures in the fatal cases were "low" (they fell in fact within the normal range) but that the survivors' pressures were "high"—i e, over 5 cm dextrose solution If we might amplify this a little further without too much speculation, we would like to do so by commenting on Potter's phrase "pulmonary congestive failure"

A circulation can fail because the propulsive power of the heart diminishes because the vascular resistance to this propulsive power becomes too great because there is not enough blood to pump round, or because of combinations of these The Oxford group have shown in lambs the great increase in vascular resistance in the pulmonary circuit caused by asphyxia, we do not yet know what the vascular resistance is in normal unexpanded human lung, but it is possibly high To overcome this and any increase due to asphyxia it is possible that a high cardiac output dependent upon a high venous pressure is necessary Many serial readings in both groups were done but were not included because of the possible effects of therapy They showed in general that in the survivors the pressure returned to normal levels with clinical improvement within 12 hours and in the fatal cases did not rise except in one as a terminal event after 30 hours

University College Hospital
London W C 1

R E **BONHAM CARTER**
JEAN M SMELLIE

A SIMPLE SELECTIVE TEST FOR NURSES

SIR,—I accept Dr Haward's explanation (Jan 5) that his test was offered as a supplement, and I agree that these are early days for nursing selection techniques Nevertheless, one cannot help being mildly suspicious of its apparent intention to measure "scholastic ability"—a supplement at that If it is ever to be put forward as a test "par excellence," then it should attempt, even at this early stage, to measure concentration as a separate factor

Dr Haward asks me what I mean "by requesting a correlation for *each* student ?" I will merely say here that on occasion I have found students who though they could not give suitable written answers to questions, could dictate "excellent" answers Such cases justify my previous criticism of Dr Haward's test, that it does not attempt to measure "writing fluency"—an important consideration An intelligence test is the better alternative in *such cases*

Runwell Hospital,
Wickford Essex

T **ROBERTS**

X RAYS AND LEUKÆMIA

SIR,—My letter of Dec 15 was prompted by a consideration of the practical steps which radiologists would have to take if they accepted Dr Stewart's findings Perhaps it may help to restate the problem Dr Stewart's results have, for the first time in the history of radiology, suggested that a very small dose, hitherto regarded as absolutely safe, may be harmful If, in fact, a dose of 1r (to a fœtus or adult) can cause leukæmia in later life then we must revise our view that a dose of 0 3r per week for every week of the working life of a radiographer or radiologist is harmless Radiation doses are cumulative, therefore a dose of 1r every three weeks or 16r every year has been permitted for an X-ray worker A whole-body dose of well over 200r during a working life has hitherto always been considered safe On Dr Stewart's figures, we are jeopardising the lives of all who work in diagnostic departments, because it is impossible to keep the radiation scatter dose below 1r in, say, ten years without rebuilding every diagnostic department and without stopping all screening

I therefore examined Dr Stewart's report in the hope of finding a simple explanation for her surprising results The figures are entirely based on statistical not on clinical considerations The word "routine" on an X-ray form has been interpreted as meaning that the patient is perfectly fit, but to a radiologist or obstetrician it indicates that there is suspicion of either a fœtal abnormality or some maternal disease

In my experience a pregnant mother is never referred for an X ray examination unless there is some definite suggestion of either maternal or fœtal abnormality, but this is seldom mentioned on the form because that is usually handed to the patient

Moreover Dr Stewart does not explain why 15 more of the leukæmia mothers had non abdominal X ray examinations than did the mothers in the control group before conception of the survey child The total excess of X-ray examinations on leukæmic babies over normal controls is only 18, and it is on this figure alone that the whole of Dr Stewart's argument is based Both sets of figures may be of equal importance, and the only way in which they can be explained is by stipulating a pre existing morbid factor, in either mother or fœtus, which predisposes to the later occurrence of leukæmia

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[1] Born G V R, Dawes G S, Mott J C, Widdicombe J G *Cold Spr Harb Symp quant Biol* 1954 19 102

Dr Court Brown and Dr Doll, in their very interesting reply (Jan 12) to the points I raised, state that 20,000,000 people will have to be exposed to a mean marrow dose of 1r in excess of that received by the general population and observed for ten years before it can be decided whether or not a dose of 1r can be responsible for leukæmia This may be the statistical ideal, but it does not seem feasible to apply such a method in practice

In the consideration of low-level radiation effects, however, the data which we possess on the general incidence of leukæmia are most helpful Natural atmospheric background radiation received by every human being amounts to 0 1r per year Therefore, after ten years, everybody has been subjected to 1r, and after a lifetime of seventy years, to 7r If small doses of radiation are a cause of leukæmia one would expect, on statistical grounds alone, that as dose increased with age so would the incidence of leukæmia, and, in fact, this is not so

Dr Court Brown and Dr Doll consider that the present evidence does not justify the belief in a threshold dose of between 100 and 200r, but they have not been able to adduce a single fact or experiment in which it has been proved that a low dose of radiation was leukæmogenic To their comments I should like to make the following points

(1) They attribute the absence of leukæmia in the offspring of pregnant mothers in Hiroshima to shielding by buildings I gave the figure of 1500r as a maximum dose to which some had been exposed The fact that so many of them developed severe radiation injuries indicates that they must have been exposed to many hundreds of r While these women had many abnormal children, especially micro cephalics, none of them developed leukæmia within nine years of observation [1]

(2) I suggested that among the survivors of Hiroshima and Nagasaki beyond a distance of 2000 metres, doses of 100 or even 200r must have been common because so many people had radiation sickness Dr Court Brown and Dr Doll think that this may be the malaise, with nausea, vomiting, and diarrhœa, induced by physical and emotional stress I am convinced that the very careful investigators of the Atomic Bomb Casualty Commission would not have classified these cases as due to radiation if they had been of psychological origin I cannot remember similar symptoms in people exposed for months on end to the stresses of air raids in this country But even if the total exposure dose received by the 155,000 people was only 8r at a distance beyond 2000 metres, that still confirms my original contention that such a dose was inadequate to increase the normal incidence of leukæmia If Dr Stewart's argument is correct, then even this low dose would have raised the amount of leukæmia considerably beyond the normal limits Yet the incidence among the very large number of exposed people remained roughly within normal limits [2]

(3) In quoting the figures collated by Dr Court Brown and Dr Doll on the radiation treatment of ankylosing spondylitis, I intended to give further support to my argument that all recorded cases of post radiation leukæmia were caused by large doses—in this case, doses of at least 400r

(4) I fully admit that the course of leukæmia in animals after irradiation [3] is not exactly comparable to that in human beings Nevertheless it seems unlikely that man is 100 to 200 times more susceptible than a rat, or that a dose of 1r produces leukæmia in man when 2500r is needed in dogs Experiments have proved that a small dose must be repeated many hundred times in every kind of animal before a tumour develops With a daily dose of 0 1r at 250 kV it was not possible to produce leukæmia in rats however many doses were given With 0 5r daily at 250 kV, 225 and 491 treatments had to be given before leukæmia occurred in 2 animals With 1r daily at 1000 kV, it was impossible to induce leukæmia in any of 42 rats Though animal experiments were not primarily designed to investigate low level radiation the fact that leukæmia could not be induced with these doses suggests that a fairly substantial dose is, in fact needed to produce it [4]

I am glad that radiologists, such as Dr Brailsford (Jan 5), with many decades of experience have confirmed that they have never seen a case of leukæmia which could be attributed to a diagnostic dose of radiation

For practical purposes the risk to the fœtus (even assuming there is one) seems so small as to make it desirable to counteract the erroneous impression created among the general public by the preliminary results of the investigation At present, when the recruitment of radiographers is becoming increasingly difficult an official statement by the Faculty of Radiologists on the lack of evidence that small doses of radiation are harmful might be appropriate

London, W 1 J RABINOWITCH

Medicine and the Law

The Duty of Care

IN a case at the Glamorgan Assizes before Mr Justice Sellers the duty of care owed by a hospital committee for the state of the hospital premises was under scrutiny

The widow of a patient claimed under the Fatal Accidents Act 1846 for herself and under the Law Reform Act 1934 for her husband's estate The husband, aged 59, a diabetic for many years, had returned home early from work feeling dazed and giddy He was admitted to hospital in the afternoon to a general male surgical ward and seen by the sister and doctor who made routine examinations Next morning, apparently very cheerful as usual, he went to wash and to the sluice room A few minutes later he was found dead in the yard beneath a corridor window The window was open and there was some scraping on the brickwork below It seemed clear that he had fallen, but there was no reliable evidence as to whether the window was open before he went along the corridor, or information as to who had opened it

According to the medical evidence called for the hospital it seemed that the possibility of a prediabetic coma producing uncontrolled swaying in this man was slight, and that the duty owed must be seen as that owed to a general ward patient In giving judgment for the hospital the judge based his conclusions on the foreseeability of the event happening If the reasonable man could have foreseen that this accident was "on the cards" and that to prevent it steps ought to have been taken to make the windows secure, and these steps were not taken, the hospital might have been liable in negligence But this was a corridor window, the sill 2 ft 3 in from the ground (its total depth 15 in) and the lower sash opened to 2 ft Nothing unusual had been observed in the conduct of the patient to make extra precautions necessary, and allowing the patient to move about was a feature of treatment, in that maximum freedom of movement was desirable For young children or mental patients extra precaution seemed clearly necessary, but it appeared to be unreasonable and even undesirable to restrict the amount of air and the sense of freedom available in the hospital The widow had admitted that, though she and her family tried not to leave the deceased alone in the house, he might well be upstairs on the first floor alone, and no blocks had been fitted to the windows The position there seemed to be parallel to the state of affairs in the hospital

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[1] Plummer G *Pediatrics* 1952 10 687

[2] Folley J H Borges W, Yamawaki T *Amer J Med* 1952, 13 311

[3] Medical Research Council Report Cmd 9780 H M Stationery Office, 1956 p 87

[4] Metcalf, R G, Inda F A *In* Biological Effects of External Radiation New York, 1954

There was one other feature In 1954 a patient had apparently committed suicide by jumping through a window at the hospital, and blocks had been fitted by order of the committee responsible so that the window opened to no more than 7 in On the painting of the frames the blocks were removed from this and other windows and there seemed no clear evidence as to why the blocks on this window had not been put back The question then arose—had the hospital set itself a standard of care in supplying blocks, the removal of which by some servant of the hospital and the failure to replace by a relevant authority, had provided the required incident of negligence? His Lordship did not accept this as a test, and applied clearly the test of reasonable foreseeability so that, to avoid the situation whereby the hospital authorities became insurers, the defendants were held not liable to the widow The floor was in a good condition and the height and width of the ledge made it improbable that the man could have fallen unless already part projected through the window frame It was difficult to see what blame—since fault and breach of duty must be seen in this tort—could be cast upon the hospital committee or its servants for an incident which could not reasonably have been foreseen as likely to happen

"Truth Drugs"

Narcoanalysis is a legitimate and valuable technique in psychotherapy, though it is true to say that the barrier to repressed material can often be raised by analytical methods alone If drugs are used their main advantage is to speed up the process But when the information that is sought is being held back by conscious suppression of guilty knowledge, drugs seldom release it Most of the evidence suggests that voluntarily suppressed matters are rarely revealed under narcosis, and that "truth drugs" are useless in police inquiries Indeed, a guilty person may, under narcosis, manufacture evidence to suit himself, or what is worse, devise fantasies involving himself in crimes he has not committed Moreover, the suggestible neurotic or psychopathic criminal can be made to say almost anything These and other objections to evidence obtained under the influence of drugs were well brought out at a meeting[1] of the Medico-Legal Society.

Even if there were a drug that could unlock the truth, statements made under its influence would clearly be inadmissible in a court of law First it is a fundamental legal principle that a statement must be made voluntarily without threat, duress, or other influence Secondly, the statement would have to be read by the doctor who administered the narcosis or someone other than the accused and that would make it hearsay and therefore inadmissible The principle at the root of the British exclusion of hearsay evidence is the absence of the oath It is clear that a man deprived of his senses cannot swear to speak the truth, and when he regains full consciousness he is at perfect liberty to say that his statement under the drug was nothing but a product of delirium and without a vestige of truth

Only a qualified doctor should induce narcosis—yet few would be prepared to do so for reasons other than medical treatment Indeed it is hard to imagine a more striking breach of the Hippocratic oath than the use of medical skill to obtain evidence that will lead to a prison sentence Moreover the doctor concerned would have to be called by either prosecution or defence, thus immediately seeming to show partiality and the doctor could quite fairly, be charged by the other side with the manufacture of evidence by suggestion—a charge which would be hard to refute

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[1] *Med leg J* 1956 24 59

Obituary

ERIC BARRINGTON BROOKE

M.A, M B Camb, F R C.P, D.P.H

GERIATRICS is one of the youngest of the specialties, and by the death of E B Brooke it has lost one of its pioneers His work at Carshalton and later at Southampton was a memorable demonstration of how much can be achieved by personality in administration

Dr Brooke was educated at Bradfield College, Cambridge University and St Bartholomew's Hospital After qualifying in 1923 he held house-appointments at Barts and later became assistant medical officer at St Giles Hospital Camberwell In 1925 he took the D P H and two years later the M.R C.P. The next years he spent at Redhill Hospital Surrey, at first as deputy medical superintendent and then as superintendent But the most important part of his work began with his appointment in 1941 as superintendent of St Helier Hospital Carshalton D D relates how he met the challenge of those war-time days when the buildings under his charge were new and empty and when man-power and materials were difficult to obtain

The patients at St Helier in the early years were a heterogeneous collection — evacuees from London hospitals, air raid casualties and soldiers as well as people from a large area of North Surrey Determined to make the best use of the beds, Dr Brooke kept a close personal watch on all the wards, but he never interfered with the clinical work of his colleagues in other departments Indeed no matter how remotely any new development or change of administrative policy might affect our work he invariably sought our opinions before taking action. With the general practitioners of the area also, he established a friendship and coöperation which they and the hospital staff continue to enjoy His geriatric work grew out of his personal interest in the patients and their doctors, for try as he would the aged sick could not always be admitted to hospital and often had to wait for a bed He worked out a scheme to help them to live more happily at home perhaps after a short stay in hospital for investigation and rehabilitation and his imaginative understanding of the needs of old people led him to bring hospital facilities, laundry services and meals on wheels to their homes so that hospital beds could be freed for more urgent cases

His determination was well exemplified by the way he managed somehow to extricate himself unaided in spite of severe facial injuries, from his house when it was reduced to ruins by one of the bombs that fell on the hospital Returning to work after treatment he would joke about our 'one eyed superintendent' and regale us with stories of the matey people whose company he had enjoyed in the large ward that he preferred to a private one during his short stay at a convalescent hospital The secret of his success seemed to lie in his intense interest in people and his almost boyish sense of humour In the early days he knew all his staff well, from maids to medical specialists and as the work of the hospital grew he still managed to retain this personal touch. His aim was to have a happy as well as an efficient hospital and visitors from many countries whom he conducted round it never failed to be impressed by the atmosphere that he had created

Another of the innovations he introduced to meet an administrative emergency was domiciliary visiting which quickly proved its clinical worth and is now an accepted technique in the care of the aged P McE, who visited St Helier in those early days, describes a domiciliary-visit round on which he accompanied Dr Brooke

With Dr Brooke was his registrar and his secretary First he had a short talk with the relatives, then he investigated the patient Then the relatives, the secretary, and Dr Brooke (or the registrar) went over the whole matter and gave advice and decisions, and the secretary made the necessary notes for the case record It was all simple, easy, free from fuss The procedure had a wonderful effect on waiting-lists, and Dr Brooke was, through his secretary, in constant friendly touch with doctors

Of a hospital ward round J N A writes

Dr Brooke was extremely gentle and considerate both to his patients and to those of us who went (as I did) to learn from him Yet he was an animated and tireless man Going round his wards with him I perhaps got the impression he was not first and foremost a clinician He loved the administrative aspect and the logistics of geriatric work But he was a humanist his patients loved him, and he knew them (450 at a time) almost all by name and background

In 1953 he was elected FRCP By then the empty building that he had taken over had been for several years a very busy general hospital of over 700 beds and had gained an international reputation for its geriatric work But Dr Brooke was not content to stay and watch the results of his work, for he still had the spirit of a pioneer He left St Helier to reorganise a geriatric service in the Southampton area There he followed, though on a wider scale, the principles of administration that had served him so well at Carshalton Broadly speaking, the acute geriatric beds at Southampton General Hospital were used for the clinical assessment and treatment of new patients Those who responded to treatment returned home or were admitted to welfare establishments, while those who failed to do so were transferred to long-stay beds in one of the three outlying hospitals He continued to be a firm believer in the domiciliary visit before the patient's admission to an acute bed and in "half-way houses" for "frail ambulants" before their admission to welfare homes Financial stringencies often frustrated his best intentions, but he lived to see much-needed reconstruction both at Moorgreen and Ashurst Hospitals

Though he was dogged by ill health he filled his professional life with more hours of work each day than most fit men can manage He was a founder member of the Medical Society for the Care of the Elderly and he hardly ever missed a meeting in whatever part of the country it was held He travelled abroad to many international conferences, and he was always willing to help, as counsellor or speaker, when any organisation for old people was being started He was a fluent speaker, a master of the happy phrase, and he delighted in appropriate quotations from the lyrics of W S Gilbert and the poems of A A Milne

Dr Brooke died at his home at Southampton on Jan 13 He leaves a widow and two adopted children

RUFUS CLIFFORD THOMAS

FRCSE, FRCOG

IN 1937 Croydon started a comprehensive obstetric service offering "antenatal, natal, and postnatal supervision under the same specialist obstetrician" and Mr Rufus Thomas, who was already on the staff of the council, was appointed to its charge as assistant medical officer for obstetrics and gynæcology In 1945 he reported in our columns that it covered three-quarters of the births of Croydon, and before he retired in 1948 the scheme had made civic and public-health history as an exercise in cooperation and coordination

He qualified from Westminster Medical School in 1915 and held house-appointments there After serving in the R A M C he became supervisor of anæsthetics in the gynæcological department of Edinburgh Royal Infirmary and later senior anæsthetist to the Royal Gwent Hospital, Newport, Monmouth In 1924 he took the FRCSE He next spent six years in India as chief medical officer to the Maharajah Jamsaheb of Nawanagar (better, if less formally, known to many s Ranji) For his work at Jamnagar Mr Thomas wa awarded the order of merit of the State of Nawanagar In India he continued to make a special study of obstetrics, and soon after his return to this country he joined the staff of the Croydon public-health department, as clinical head of its maternity and gynæcological servic

O M H, who worked with him as MOH of the borough writes

Under a quiet and retiring manner Thomas hid an alert incisive, and analytical mind, eager always to try new ide to formulate his own, and to put his whole personality into ensuring their success He made an ideal head of a compl clinical unit By his clinical skill and dexterity, and h understanding of their problems, he had the respect of t doctors, nurses, and midwives under his direction Nev demonstrative, always courteous and calm, he obtained t unquestioned confidence of those for whom and with who he worked To me, as his old chief, his memory will rema that of a completely reliable and loyal colleague, and a ve likeable and cultured Welsh gentleman

In 1947 he was elected FRCOG, and the followi year he retired from his Croydon appointment und the age-limit He continued to lecture and examine f the Central Midwives' Board and he was consulta obstetrician and gynæcologist to Kent County Council

R G S, one of his surgical colleagues, recalls fir meeting him in 1930 at Croydon

I soon learned to respect both his clinical acumen a manual dexterity He brought to his chosen specialt vast experience in general medicine and surgery, gai largely in India, and his flair for diagnosis evolved part from this and partly from his careful attention to detail a to routine observations He expected the same high standa from his subordinates and inspired them by his exampl In addition to his clinical work he took an active interest many other aspects of medicine, and his sagacity and for sight were of great help to his colleagues on the many com mittees on which he served, often as chairman His enforce retirement saddened him for a while, but, with typical ze he continued with his committee work and found time last to play his beloved golf, a game at which he excelle His other hobbies were fishing and story telling, for he h an apparently inexhaustible supply of anecdotes about t years he spent in India and had a remarkable memory f detail

Mr Thomas, who died on Jan 11, leaves a wido and a daughter

Appointments

BROGG, W G A, MB Glasg, DPM assistant psychiatrist bas at Glengall Mental Hospital, Ayr
CHAMFRETTE, N P PALMER, MB Hong Kong, DPM part ti psychiatrist, child guidance clinic Manchester
[illegible], C I, MB Adelaide, FRCS consultant orthoped surgeon, Mansfield Hospital area, Sheffield
GORDON, V D, LRCPI medical superintendent, Invern group of hospitals
GORDON RUSSELL, J B, MB Aberd, MRCP, DPM medic superintendent, Roundway Hospital, Devizes
GOULDING, ROY, MD Lond senior MO (pharmacologist), Minist of Health
NELSON, I D M, MB Belf, DIH MOH, Barrow in Furness
RIES, D L, MD Lond, MRCP consultant dermatolog Glantawe HMC
WOODS, GRACE E, MD Brist, DIH, DCH deputy medic superintendent, Hortham Hospital, Almondsbury, near Bri

Colonial Appointments

BONNER, FRIEDA B, MB Dubl assistant MO Bahamas
CRAWFORD, W S, MB MO, Kenya
JUPE, T P, DFC, MRCS assistant MO, Bahamas
MARKHAM, J W, MB Lond assistant health adviser Aden
MELVILLE, H A H, MB Wales, DOBST MO, General Hospit Barbados
POCOCK, RUTH L F, MB St And, DOBST MO Southe Cameroons Federation of Nigeria
STEWART, D, LRCPI, DPH MOH, Jamaica
STIGGELBOUT, J, MD Amsterdam MO Northern Nigeria
THOMSON, P B, MB MO, South Pacific health serv Fiji
YOUNG, J K, MB Sheff MO Kenya

Notes and News

WORLD HEALTH ORGANISATION

THE nineteenth session of the executive board of the orld Health Organisation is being held under the chairman up of Prof G A Canaperia from Jan 15 to Feb 5 in Geneva he proposed budget of $12,048,000 for 1958 represents an icrease of $1,348,000 over the 1957 budget, designed to estore the level of field activities originally proposed for 957 but cut by the World Health Assembly

QUACKS THROUGH THE AGES

In an entertaining lecture to the Royal Society of Arts ast November, Mr A Dickson Wright defined a quack as one who sells a secret remedy" He spoke of many of them, rom the *Apocrypha* to the present century, showing that hey were often favoured by notabilities and the public, lespite the indifferent success of their treatment Oberndorf, n 1602, described "quack-saluers" in language worthy of ir Thomas Urquhart Less harshly, Mr Dickson Wright oncluded that "essentially they are those who choose short uts to the curative art and avoid the trial and tribulation of he long and arduous training in medicine"

VIDIUS

AMID our present vicissitudes we may do worse than look o our past for guidance, and what more pleasant way of doing so than to read, for instance, Dr Brockbank's Thomas Vicary lecture,[1] which he called The Man who was Vidius? Vas medical life more satisfying in the 16th century, or were he frustrations to be met under the patronage of Kings and Princes as withering as any that bureaucracy can offer?

To most of us Vidius is no more than a name to be connected n a vague way with the Vidian nerve Born in Florence when he Renaissance was in full flower, a Greek and Latin scholar with an easy style in the latter language, and fortunate in having family connections with the arts, Guido Guidi (he ater latinised his name to Vidius) was a highly esteemed and uccessful *practitioner* of medicine in his home city before he vent to Paris on the invitation of Francis I in 1542 It was n Paris that he completed the translation from Greek to Latin, with commentaries and additions of his own, of a set of ancient manuscripts containing certain works of Hippocrates alen, and Oribasius *It is on this* book, entitled *Chirurgia* hat his fame rests, the more massive *Ars Medicinalis*, ompleted and published after his death by his nephew, at Guidi's request, contains more of his personal teaching on nedical matters, but only *the* section on anatomy can be egarded as important Even those who cannot read the text of the *Chirurgia* can understand and enjoy the magnificent voodcuts with which it is adorned—some of them being eproduced in Dr Brockbank's paper They are mostly llustrations of *methods* by which forcible traction could be pplied to dislocated or fractured limbs Force was the watch vord levers, screws, the windlass, block and tackle, and gravity were all brought into play, and no doubt force was necessary to overcome the spasm in muscular subjects fully onscious

Whether a doctor's life was better in those days than now nay be arguable but there is no doubt where the patient's preference would lie, for the surgical apparatus of the period despite its humane purpose, bore a striking resemblance o the instruments used for torture

MATERNITY FILM

Birth of a Baby is a re issue of a 17 year old film for cinema audiences which has been modified to incorporate advances U S A 62 minutes)

Mary Burgess visits her doctor, who confirms her pregnancy and hen explains, with the aid of diagrams the physiology of conception and implantation of the ovum He advises her to live normally voiding strenuous exercise and horse back riding On receiving a normal blood report the doctor comments on the rhesus factor which in Mary's case is positive and therefore not incompatible with her baby's blood, and he then tells his nurse that he wishes his patients could have their babies in hospital as do most American mothers now instead of at home Recounting a recent visit to a New York Lying in Hospital we see a group of expectant mothers with their husbands on an antenatal tour of the maternity department and labour wards At parents classes Mrs Burgess attends ectures and demonstrations which are shown in some detail and he doctor comments that those who attend the classes make better patients and happier people Fathers are also encouraged to attend The anatomy of the birth canal and the mechanics of parturition are described briefly with models and, at her final visit to her doctor before the delivery is due, Mrs Burgess listens to her baby's heart through a stethoscope Finally the delivery at her home is shown briefly, silver nitrate being dropped into the infant's eyes, and the film ends with an account of the advantages of breast feeding

Rhesus negative mothers might be unduly alarmed until they can discuss the film with their doctors, and references to "anæsthesia during labour, but you will be awake to see your baby born" give a muddled impression Technically the film is bad, the retained portions of the old film, showing the age and dress of the characters seventeen years ago, is mixed haphazardly with modern shots, the contrast in photographic quality and sound recording accentuating the differences The film is unlikely to cause the sensation it did when first shown publicly in this country

TRAINING OF THE DISTRICT NURSE

WHEN the working party on the training of district nurses presented its report, we expressed concern at the recommendation by the majority that the period of training should be cut[1] We hoped that the minority view would prevail, and that the period would remain that recommended by the Queen's Institute of District Nursing The report was discussed at a meeting of the Queen's Institute later that year,[2] when the proposal to shorten the course found no support The differences in technique and approach between home and hospital nursing, and the time needed to learn these, were emphasised

A revised syllabus[3] has now been published The lectures have been increased in number and changed in emphasis to accord better with modern needs, but the period of training is to be as long as it was before—i e, six months for State registered nurses without special qualifications, and four months for those who are also midwives, health visitors, or tutors, or have had at least eighteen months' experience in district nursing

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University of Bristol

On Jan. 18 the following degrees were conferred

M.D—D R Coles C H Gurd, Lisa E Hill Roy Hill
Ph D (in the faculty of medicine)—Syed Murtaza Ali Zaidi

University of St Andrews

At a recent final examination for the degrees of M B, CH B, the following were successful

L. M. Aitkenhead, L R Butler-Manuel D C Crawford, R A Haddow, Philip Hossen, M. J Illingworth, *D W Jervis, J L Maddison J P M. Penney D J Sutherland, *T T Thompson, H E G Thomson, Elinor M. Whyte

* In absentia

Welsh National School of Medicine

Dr J G Lawson, lecturer in obstetrics and gynæcology University of Aberdeen, has been appointed senior lecturer in obstetrics and gynæcology

Empire Rheumatism Council

This council is appealing for £250,000 to enable it to carry out a 10 year programme of concentrated research Contributions should be sent to the Council, Tavistock House (N) London, W C 1

Royal Society of Medicine

Section of Anæsthetics—This section offers a prize (£30) for the best paper submitted by a senior registrar or registrar holding a clinical appointment in an anæsthetic department of a hospital Papers for the 1958 award must be submitted by Jan. 1, 1958 Further details may be had from the hon secretary of the section, 1, Wimpole Street, London, W 1

Sheffield Regional Hospital Board

In this board's research prize competition for 1956 prizes of £50 each have been awarded to Dr A. H. Morris, senior registrar in diagnostic radiology at Leicester Royal Infirmary, for his entry on radiological features of Hodgkin's disease in the thorax, and to Dr N M Gibbs, senior registrar in clinical pathology at Derbyshire Royal Infirmary, for his entry thrombo embolism

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[1] Brockbank W *Ann R Coll Surg Engl* 1956 19 269

[1] *Lancet* 1955 ii 543

[2] See *Ibid* p 1331

[3] Syllabus of the Course and Regulations governing the training and examination in District Nursing given in Training Centres approved by the Queen's Institute of District Nursing, 57 Lower Belgrave Street London, S W 1 November 1956

Society for Biological Rhythm

This society is to hold a conference from Aug 26 to 28 at Semmering, Austria, on time in biology Further particulars may be had from the secretary, A Sollberger, anatomical department, Caroline Institute, Stockholm, 60, Sweden

Laboratory Animals Bureau

Prof J H Gaddum, F R S , will open the congress which this bureau is holding at the Royal (Dick) School of Veterinary Studies, Edinburgh, on April 4 and 5 Further particulars may be had from the bureau, M R C Laboratories, Holly Hill, Hampstead, London, N W 3

National Association for Mental Health

The annual conference of this association will be held at Church House, Westminster, on April 11 and 12 The subject chosen for discussion is the maladjusted child, and the speakers will include Dr Kenneth Soddy, Dr John Bowlby, and Dr Mildred Creak Further particulars may be had from the association, 38, Queen Anne Street, W 1

Seminar for Overseas Health Workers

This seminar will be held by the Central Council for Health Education at Passfield Hall, London, from April 15 to 19 The subject for study will be the principles, methods, and media of health education Further particulars may be had from the medical director of the council, Tavistock House, Tavistock Square, London, W C 1

Royal Society

Dr D W Kennard has been appointed Stothert research fellow He will carry out research at the Physiological Laboratory, Cambridge, on the reflex activity of the spinal cord

On Thursday, Jan 31, at 11 A M , at this society, at Burlington House, Piccadilly, London, W 1, Mr A S Parkes, SC D , F R S , will open a discussion on the viability of mammalian cells and tissue after freezing Other speakers will include Dr P L Mollison and Dr Audrey Smith.

Liverpool University Medical Students' Society

The annual dinner, for past and present members of this society, will be held at the Adelphi Hotel, Liverpool, on Feb 7 Lord Cohen of Birkenhead will be in the chair and the guest of honour will be Prof Stanley Alstead, president of the Royal Faculty of Physicians and Surgeons of Glasgow Tickets (25s) may be had from the Medical Dinner Secretary, Medical School, University, Liverpool, 3

Mundesley Sanatorium

The East Anglian Regional Hospital Board is acquiring this privately owned sanatorium for use as a post acute hospital which will serve the hospitals in the Norfolk and Norwich, Cromer, King's Lynn, Yarmouth and Lowestoft, and Bury St Edmunds hospital groups (*Eastern Daily Press*, Jan 9) The transition will be gradual, but it is expected that Mundesley Hospital will be in full use in about three months

Société Française de Médecine Psychosomatique

This society, which was founded last year, would like to get in touch with other societies, groups, and individuals interested in the exchange of information on psychosomatic medicine The president of the society is Dr F Moutier and the secretary is Dr L Chertok, Centre de Médecine Psychosomatique, 54, Avenue de la Republique, Villejuif (Seine), France

Training in Hospital Administration

Applications for a further 16 training posts for hospital administrators are invited by the Minister of Health and the Secretary of State for Scotland under a scheme which began last year The posts are open to young officers of promise already employed in the National Health Service and to university graduates and professionally qualified people who wish to make hospital administration their career

The normal age limit will be 30 but candidates up to the age of 35 will be considered During their training which will normally last for three years the student administrators will be given practical experience with different hospital authorities and instruction at the Hospital Administrative Staff College of the King Edward s Hospital Fund for London or at the University of Manchester

x fees will be paid and they will also receive a salary beginning

500 applications were received last year, 143 of

ates were already in the hospital service 14

of whom already held hospital posts) and 2 women

lected

Institute of Dermatology, London

A semi permanent exhibition by Dr G Weddell on the neurohistology of the integument and changes in leprosy will be held at the institute, Lisle Street, W C 2, from Feb 5 to 2

British Hospitals Contributory Schemes Association, 1948 —This association has published its directory of contributory schemes for 1956 Copies may be had (10s post free) from the honorary secretary, Royal London Buildings, Baldwin Street, Bristol, 1

Diary of the Week

JAN 27 TO FEB 2

Monday, 28th

MANCHESTER MEDICAL SOCIETY, Medical School, University of Manchester
9 P M *General Practice* Dr J H Cyriax Manipulative Medicine

Tuesday, 29th

BRITISH POSTGRADUATE MEDICAL FEDERATION
5 30 P M (London School of Hygiene and Tropical Medicine Keppel Street, W C 1) Prof C A Keele Causes of Pain.
ST MARY'S HOSPITAL MEDICAL SCHOOL, W 2
5 P M Mr T L T Lewis Use of Drugs in Modern Obstetrics
INSTITUTE OF DERMATOLOGY Lisle Street London W C 2
5 30 P M Mr A K Monro Gravitational Ulcers
ROYAL ARMY MEDICAL COLLEGE, Millbank London, S W 1
5 P M Sir Geoffrey Todd Operative Treatment of Pulmonary Tuberculosis and its Prognosis
ROYAL STATISTICAL SOCIETY
5 30 P M *Medical Section* (Westminster Medical School, Horseferry Road, S W 1) Mr F D K Liddell Statistical Problems of the National Coal Board Medical Service
UNIVERSITY OF LIVERPOOL
5 15 P M (Arts Theatre) Prof Wilder Penfield, O M , F R S. Cerebral Cortex of Man—an Interpretation of Responses to Electrical Stimulation (Sherrington lecture)

Wednesday, 30th

POSTGRADUATE MEDICAL SCHOOL OF LONDON, Ducane Road W 1
2 P M Dr Norman Ashton Pathology and Ætiology of Retrolental Fibroplasia
INSTITUTE OF DERMATOLOGY
5 30 P M Dr Henry Haber Nodular Lesions of the Legs
INSTITUTE OF DISEASES OF THE CHEST Brompton, London, S W 3
5 P M Dr J L Livingstone Asthma
MANCHESTER MEDICAL SOCIETY
4 30 P M *Medicine* Dr H T Howat Cancer of the Pancreas
ROYAL FACULTY OF PHYSICIANS AND SURGEONS OF GLASGOW 242 St Vincent Street Glasgow
5 P M Dr Douglas V Hubble Homœostasis (Burns lecture)

Thursday, 31st

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Field London, W C 2
5 30 P M Prof E W Walls Critical Anatomical Assessment of Certain Signs and Symptoms in Otorhinolaryngology
UNIVERSITY COLLEGE LONDON, Gower Street, W C 1
5 15 P M Prof Franz Bergel, D SC Recent Advances in Cancer Research
INSTITUTE OF DERMATOLOGY
5 30 P M Mr Monro Skin Tumours
UNIVERSITY OF ST ANDREWS, Queen's College, Small s Wynd Dundee
5 P M Dr W W Payne Renal Tubular Dysfunction Childhood

Friday, 1st

ROYAL SOCIETY OF MEDICINE, 1 Wimpole Street W 1
10 30 A M *Otology* Dr G Aschan Mr W Stirk Adams, M J Angell James Irradiation of the Nasopharynx
2 30 P M *Laryngology* Mr W A Mill Mr R J Y Batt Mr J H Hovell Facial and Palatal Repair in th Treatment of Malignant Disease
5 30 P M *Anæsthetics* Dr D W Shannon Resuscitation the Burnt Child Dr H G Middleton Anæsthesia f Burnt Children
8 15 P M *Otology* and *General Practice* Mr L R S Taylor Dr I Friedmann, Dr G F Abercrombie Recurren Otitis Media in Children
POSTGRADUATE MEDICAL SCHOOL OF LONDON
10 A M Mr H Hamilton Stewart Renal Calculi
4 P M Sir John Parkinson Syncope
ROYAL MEDICO CHIRURGICAL SOCIETY OF GLASGOW
8 30 P M (Royal Faculty of Physicians and Surgeons of Glasgow Mr Donald Lawson, M R C V S Intervertebral Discs i Dogs

Saturday, 2nd

INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330, Gray's Inn Road London W C 1
NOON Dr J E Laage Hellman (Goteborg) Surgery of th Parotid Salivary Gland
NORTH EAST METROPOLITAN THORACIC SOCIETY
10 30 A M (London School of Hygiene and Tropical Medicine *Joint meeting with the South East Metropolitan Regional Tuberculosis Society and the North West Metropolitan Thoracic Society* Mr Donald Barlow, Dr A W Frankland Dr Denis Leigh Dr F J Prime, Dr Joseph Smart Bronchial Asthma
MIDLAND THORACIC SOCIETY
3 P M (Birmingham Chest Clinic, 151, Great Charles Street Birmingham, 3) Dr L E Houghton Cortisone and Chemotherapy in Pulmonary Tuberculosis

INDIVIDUAL VARIATIONS IN EXPENDITURE OF ENERGY

J BOOYENS *
M Sc Potchefstroom

R A McCANCE
C.B.E M D, Ph D Camb F.R C P, F R S
PROFESSOR OF EXPERIMENTAL MEDICINE IN THE UNIVERSITY OF CAMBRIDGE

IT has generally been accepted that variations in individual calorie intakes are due to differences in age size, and muscular activity at work and recreation tempered to some extent by the degree of efficiency and training (Orr and Leitch 1938, Passmore and Durnin 1955, Mayer 1956a and b) It has also been shown, however, by Widdowson (1936), Widdowson and McCance (1936), and Widdowson (1947) that in any homogeneous group of adults or children, there are always some individuals who have calorie intakes greatly in excess of those of others and that the differences cannot necessarily be explained by size or obvious muscular activity. Edholm et al. (1955) took these observations a stage further when they found that cadets who appeared very similar outwardly sometimes expended surprisingly different amounts of energy in lying sitting, and standing The records for the first of these occupations were made after the cadets had been recumbent for ten minutes The men were not, therefore, in a strictly basal state, and some of the individual differences may have been due to this Similar differences were found during sitting and standing, but this is much easier to explain, for these occupations allow much more latitude, and some people are always more "restless" than others whether they sit or stand

It has been shown by Wiehl (1944) that schoolboys spend most of the twenty-four hours lying or sitting This has also been found to be true for factory workers (Bransby 1954), cadets (Widdowson et al 1954 Edholm et al 1955), and mine workers and clerks (Garry et al 1955)

In the light of these findings Edholm et al (1955) suggested that differences in the energy expended during lying and sitting might be responsible for large individual variations in calorie intake It has subsequently been felt that similar differences might underlie the facility with which some people appear to put on weight, whereas others find it difficult to do so We therefore decided on the following programme

(1) To check over the findings of Edholm et al (1955) and to demonstrate again if possible that in a group of healthy and outwardly homogeneous people, there are usually some who expend considerably less energy in lying sitting, and standing than do others

(2) To study in detail the calorie expenditure of some people who utilise large or small amounts of energy when they are lying, sitting, and standing and to find out to what extent their calorie intake and body build may be influenced by this.

(3) To single out other matters which influence individual energy requirements and if possible to find out the cause

Experimental Arrangements

General plan —A trial investigation was first made in which the expenditure of energy by healthy people was measured while they were lying, sitting and standing under comparable experimental conditions A few people whose expenditure of energy fell at the extremes of the normal range were then selected to determine and compare their total turnover of energy

Material —Fourteen females and twenty-two males volunteered for the trial investigation Information about their age, height, weight, and surface area is given in table I Apart from a few science students, all the people were attached to the Department of Experimental Medicine and were accustomed to the idea of experimental work hence psychological influences on that score were eliminated as far as possible

Standardised Procedure

All metabolic measurements were made towards the latter part of the morning or of the afternoon about four hours after the previous meal The people first lay down for thirty minutes and their pulse rate was used to indicate when their metabolism had reached a steady state (Collett and Liljestrand 1924 Karrasch and Müller 1951)

All measurements were made in the same room, in which the temperature was about 20°C A comfortable bed and an upright chair were available on which the subject lay and sat, and while measurements were being made, only the subject and the observer were in the room

In the preliminary survey the sequence of events was always the same -

During the first thirty minutes of recumbency three ten-minute samples of expired air were collected and the pulse

TABLE I—ENERGY EXPENDED IN LYING, SITTING, AND STANDING

					Expenditure of calories (per sq m per hr)					
					Lying		Sitting		Standing	
Subject no	Age (yr)	Height (cm)	Weight (kg)	Surface area (sq m) (Du Bois 1916)	Expenditure	% of average for group	Expenditure	% of average for group	Expenditure	% of average for group
Males										
1	23	180.0	81.0	2.01	37.1	98.7	42.7	101.6	44.8	96.8
2	41	180.0	69.5	1.88	37.3	99.2	40.9	[illegible]	47.5	10[illegible].6
3	25	178.0	67.2	1.84	37.5	99.9	38.5	91.8	42.[illegible]	[illegible]
4	23	183.0	78.0	2.00	48.0	127.6	53.7	126.8	58.5	126.2
5	26	185.5	78.6	2.02	44.5	118.3	47.2	112.4	62.0	133.6
6	26	180.0	77.3	1.96	39.7	105.5	41.3	98.4	46.8	101.0
7	31	172.0	52.7	1.62	26.7	71.0	28.9	69.4	31.0	67.4
T B	24	185.0	86.8	2.11	32.2	85.6	42.6	101.4	54.0	116.6
8	29	171.5	63.2	1.74	43.1	114.6	46.8	111.6	43.8	94.6
9	26	175.0	72.3	1.87	37.[illegible]	9[illegible].8	52.9	126.0	55.1	118.[illegible]
10	23	185.0	73.1	1.95	44.6	118.4	52.6	125.2	5[illegible]	12[illegible]
11	21	180.0	70.9	1.78	39.7	105.6	40.1	[illegible]	4[illegible].5	95.3
12	32	171.0	54.5	1.63	41.9	111.0	41.9	99.8	43.4	93.[illegible]
13	23	180.5	73.3	1.90	32.2	86.1	39.[illegible]	95.0	45.7	98.[illegible]
14	22	1[illegible].0	7[illegible].9	2.03	44.9	119.2	44.3	105.4	54.9	11[illegible].4
15	41	177.[illegible]	70.0	1.87	32.1	85.6	32.[illegible]	77.0		
16	21	190.0	78.6	2.04	35.3	94.6	38.[illegible]	91.0	39.1	[illegible]
17	21	18[illegible].0	69.5	1.91	3[illegible].0	101.0	47.4	112.9	[illegible]	97.6
18	21	1[illegible].0	61.[illegible]	1.70	36.3	97.2	39.[illegible]	94.2	43.4	[illegible]
19	20	177.0	73.1	1.89	36.2	96.8	40.3	96.0	40.4	[illegible]
20	21	176.5	70.9	1.87	39.2	104.1	46.5	110.[illegible]	42.7	92.2
P M	57	179.0	52.3	1.66	24.3	64.6	27.5	65.5	29.0	62.5
Average	27.3	179.3	69.9	1.88	37.6		42.0		46.4	
S D					[illegible].92		[illegible].93		7.2[illegible]	
Females										
21	26	160.0	6[illegible].6	1.72	32.[illegible]	91.[illegible]	38.7	92.4	[illegible]	9[illegible]
22	1[illegible]	172.0	61.3	1.7[illegible]	3[illegible].3	106.[illegible]	4[illegible].3	105.1	[illegible].9	10[illegible]
23	27	16[illegible]	[illegible].8	1.[illegible]	40.6	113.4	4[illegible].9	101.[illegible]	46.1	9[illegible].1
24	29	161.0	50.9	1.[illegible]	[illegible]	8[illegible]	4[illegible].1	10[illegible]	[illegible]	10[illegible]
25	31	160.5	60.[illegible]	1.[illegible]	33.9	9[illegible]	[illegible].9	90.5	41.2	[illegible].6
26	20	16[illegible].0	51.5	1.[illegible]	[illegible].4	9[illegible].1	37.[illegible]	90.[illegible]	[illegible].9	[illegible]
27	22	1[illegible].0	[illegible]	1.[illegible]	[illegible].9	103.1	[illegible].1	[illegible]	41.7	[illegible]
28	17	1[illegible]	4[illegible]	1.43	40.[illegible]	113.[illegible]	4[illegible]	118.1	4[illegible].9	10[illegible].3
29	37	160.0	54.3	1.56	39.8	111.1	47.3	112.9	51.9	111.6
30	24	16[illegible].0	[illegible].7	1.[illegible]	34.1	9[illegible].2	42.[illegible]	102.2	40.5	8[illegible].1
31	41	1[illegible]	60.4	1.[illegible]	3[illegible].7	102.[illegible]	[illegible]	10[illegible]	[illegible]	110.[illegible]
32	22	1[illegible]	[illegible]	1.[illegible]	3[illegible]	103.[illegible]	44.[illegible]	10[illegible]	[illegible]	111.[illegible]
33	21	16[illegible]	[illegible]	1.[illegible]	39.2	109.[illegible]	4[illegible]	109.[illegible]	44.[illegible]	9[illegible].1
34	37	164.0	61.8	1.69	24.7	69.0	27.5	67.2	31.8	68.4
Average	2[illegible].0	161.[illegible]	[illegible].2	1.6[illegible]	[illegible]		41.[illegible]		46.[illegible]	
S D					4.61		[illegible]		[illegible]	

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[*] Supported by financial grants from the Transvaal and Orange Free State Chamber of Mines and the South African Council for Scientific and Industrial Research

rate was measured at five-minute intervals After this thirty-minute period a fourth ten minute sample of expired air was collected The subject then sat up on the chair for five minutes, after which a ten minute sample of expired air was collected The subject next stood for five minutes, and again a ten minute sample of expired air was collected The subjects were asked to stand as they would normally stand, that is at ease

Expired air was collected with Douglas bags and a conventional mouth-piece and valve holder (Douglas and Priestley 1948) Volumes of expired air were measured with a standard calibrated dry gas meter, and samples of expired air were kept in rubber containers for analysis but never for more than an hour, to minimise the loss of carbon dioxide from the samples (Orsini and Passmore 1951)

Expired air was analysed with the automatic Hartmann and Braun (1956) analyser, and the accuracy of the analysis made with this apparatus was checked against duplicate analysis of the same samples of expired air on the Haldane apparatus (Haldane and Graham 1935) during the early stages of this investigation Differences in carbon dioxide content and oxygen deficit in samples of expired air given by the two methods never exceeded 0 09% and were mostly within a 0 05% range of agreement Calorie output was calculated from the non-protein respiratory quotient and the calorie-liberation tables of Cathcart and Cuthbertson (1931)

Six people were selected from the preliminary survey for detailed individual studies These were made as follows

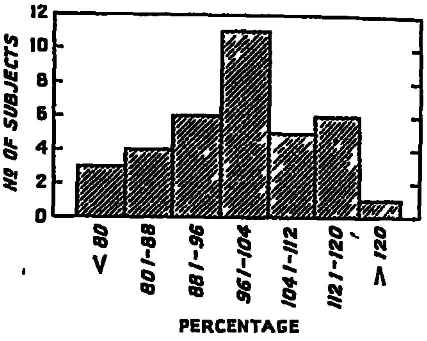
(1) All foods and liquids consumed by each person were weighed separately, and the weights were recorded daily for a week by four of the subjects and for two weeks by two of them The calorie intakes of each person for each day were calculated from the food tables of McCance and Widdowson (1946)

(2) The subjects kept an exact record of the time spent at each task or occupation on a form similar to that used by Garry et al (1955), except that the printed sheet used in this investigation covered all the twenty four hours of the day and not only eighteen of them By means of the diary sheets the times spent at the various occupations were calculated daily for each person

(3) Individual expenditures of energy at all, or nearly all, the recorded tasks were measured Douglas bags were used to collect the expired air at the lighter occupations, and the Kofranyi Michaelis portable respirometer (Kofranyi and Michaelis 1940, Orsini and Passmore 1951, Muller and Franz 1952) fitted with a standard Siebe Gorman mask during the heavier tasks The volume recordings of the Kofranyi Michaelis respirometer were calibrated by passing air through a calibrated dry gas meter into the Kofranyi Michaelis respirometer at various flow-rates At least two estimates of the energy expended at each task were made on all the subjects, and more if it was possible The energy expended on the quiet occupations—lying, sitting, and standing—was measured in each of these special subjects after fasting for fourteen hours or more and at varying intervals after meals until the post absorption metabolic level was reached Figures used in the final computation of the expenditure of energy by the six selected subjects while lying, sitting, and standing are the averages of measurements made from four to fourteen hours after the previous meal By combining the time spent (minutes) on each occupation with its cost in calories per minute the calories expended at the various occupations daily were calculated, and hence the total daily expenditures

Results

Table I gives the ages, heights, and weights of the thirty-six people Those selected for further study are shown in heavy type The figures for basal metabolic rates (B M R) shown in the table were taken to be the lowest of the measurements of oxygen consumption made in the recumbent position Usually there was little difference between the last two figures obtained, hence, for all practical purposes, the subjects were down to basal levels at the end of twenty minutes In many of the subjects there was no fall after the first ten minutes, so the gross adjustments to basal levels evidently took place during this time The frequency distribution of the basal expenditure of the men and the women is given in the accompanying figure The men's average weight for height (not given in the table) was 102 5% of the Odier and Mach (1949) standard, and the women's 101 0% The subjects were, therefore, a fair sample of a European population Their average B M R was 105 1% (females) and 101 2% (males) of the Robertson and Reid (1952) average As previously described (Kirk and Kvorning 1946), a few people even in this perfectly normal group had very low B M R Table I also gives the energy expenditure of these subjects sitting and standing and the averages for each of these activities



Distribution of basal expenditure

In confirmation of the results of Edholm et al (1955) some of the subjects differed widely from the group average when they were lying, sitting, and standing In Edholm et al 's small series one man had a relativel low metabolic rate while recumbent and a high one while standing, but most men had a consistently low or high metabolic rate at the three occupations This was true of some of the people who had high B M R in the present study (e g , subjects 4, 5, 10, 14, 22, 28, and 29), and a similar consistency was found in some of those who had low B M R (e g , subjects 7, 13, 15, 34, and R M) but others who had a normal or a low B M R had a hi metabolic rate while sitting or standing, and vice ve (e g , J B and subjects 8, 9, 12, and 24)

Among the men subject 7 and R M had exceptiona low expenditures of calories while lying, sitting, an standing, whereas subject 4 had an exceptionally high expenditure J B had a low B M R , but his sitting and standing rates were normal and high respectively, and he was selected for further study, not so much because of his exceptional expenditure of calories as because he was of very similar physique to subject 4

Of the two women selected for further study subject 34 had exceptionally low, and subject 29 exceptionally high, expenditures of calories at the three standard tasks The B M R of five of these subjects lay well outside the 10% or, at most, 15% limits usually reckoned to be "normal" (Du Bois 1927, Robertson and Reid 1952), and, if the B M R was exceptionally low or high, the expenditure of energy in sitting and standing was of the same type These variations were not consistently related to age, height, or weight/height ratio of the subjects This again confirms the findings of Edholm et al (1955) in some of their subjects (e g , numbers 5 and 6)

Table II gives the average daily intake and expenditure of calories, with their measures of variability, by each of the six persons selected for detailed study Most of the diets conformed to the conventional pattern, even to the occasional "old-fashioned" cocktail before supper but R M was eating a diet somewhat peculiar to himse in that it consisted largely of potatoes, legumes, and othe vegetables, and had no bread in it, not much meat o animal protein, and very little fat He ate nearly 1 5 kg of potatoes a day during the fortnight The diet provided 95 g of protein, 45 g of fat, and 450 g o carbohydrate daily

TABLE II—ANALYSIS OF INTAKE AND EXPENDITURE OF ENERGY BY SIX SELECTED PERSONS

Subject no	Sex	Length of study (days)	Total intake and expenditure of calories (daily average and range)		Percentage of time and energy spent on									
					Lying		Sitting		Standing		Indoor activities		Outdoor activities	
			Intake	Expenditure	Time	Cals	Time	Cals	Time	Cals	Time	Cals	Time	Cals
4	M	7	3602 (2294–4142)	3405 (2890–3897)	38 5	25	35 7	29 1	5 1	4 6	5 1	4 8	15 6	36 3
7	M	7	2417 (2144–2544)	2212 (1933–2328)	39 0	18 3	22 4	11 4			25 6	30 7	13 0	39 6
J B	M	7	3022 (2740–3289)	2900 (2751–3102)	45 7	26 2	35 5	26 4			8 9	13 9	9 8	33 5
R M	M	14	2432 (2133–3712)	2674 (2183–3183)	31 9	12 4	31 0	13 3			18 5	19 4	18 6	53 9
29	F	7	2419 (2313–2471)	2458 (2399–2593)	34 8	21 9	23 7	17 1			34 6	40 6	6 9	20 4
34	F	14	1595 (1063–1883)	1660 (1438–1952)	32 3	20 4	41 0	28 2	7 5	7 0	6 8	19 8	11 5	24 6

The subjects' work did not call for great changes in their expenditure of energy or in their intake from day to day, and there was no clear relationship between them, either immediate or delayed (Edholm et al 1955) There were, however, considerable differences between the calories expended daily by the individual subjects No 7 (male), for example, utilised only 2212 calories a day, and no 34 (female) 1660, whereas no 4 (male) required 3405 calories a day, and these average figures for expenditure were always closely matched by the intakes No 4 (male) and R M weighed themselves carefully before, during, and after their experimental periods, and their weights may be said to have remained the same throughout

The hours occupied by lying in bed or sitting down were of the now familiar order (Widdowson et al 1954, Passmore and Durnin 1955) J B spent more time than any of the others in bed, and R M less, and lying and sitting together account for from 26 7% (R M) to 54 6% (no 4) of the subjects' total expenditure of calories The time spent lying and sitting ranged from 58 5 to 81 2% of the subjects' total time No 4 and no 34 spent some time standing at outdoor lectures and ward rounds respectively, without other movements, but the others did not

Indoor activities consisted of shaving, washing and dressing, working in the laboratory, and domestic chores (table III) The outdoor activities consisted of walking, cycling, and recreational pursuits, which varied from digging holes for fence posts to cleaning a car, playing cricket, and cycling The pattern of these indoor and outdoor activities depended on the subjects' work and interests

No 4 was a male student who had no responsibilities in the house and spent much of his time sitting indoors studying Consequently his activities were mostly outside, getting to and from his work and playing cricket, but together they took up 15 6% of his time and accounted for 1226 calories a day—36% of his total expenditure

Nos 29 and 7 both worked in the laboratory but moved actively about it and sat very little Both of them also had responsibilities at home No 29 looked after her cottage and acted as gardener and carpenter It was she who dug the holes for the fence posts Consequently her indoor activities occupied 34 6% of her time and utilised about 1000 calories—40 6% of her calorie intake Her outdoor activities took up less than 7% of her time but required 500 calories—more than 20% of her total

J B's indoor activities were slight both in time and in the proportion of his calories spent on them His outdoor activities consisted of cycling about the town They did not take up much time, but they accounted for 970 of his 2900 calories

No 34 spent nearly 50% of her time sitting or standing indoors Both of these she did with very little expenditure of energy (table I) Her housework did not take much time although it used up nearly 20% of her calories Her walking and car cleaning were considerably less strenuous than J B's cycling took up little more time, and required only 400 calories a day Her total turnover of calories was therefore much lower than that of any of the others

R M's indoor activities occupied a very usual amount of time at a cost of less than those of no 29 and no 7, who expended about the same total calories He took advantage of this experiment, however, to put in as much time as possible on his usual outdoor hobbies and activities, which were cycling and walking, and in the fortnight for which he weighed his food he cycled 692 miles and on the Sunday walked 39 miles over well made roads in undulating country These activities took up 18 6% of his time and nearly 54% of his calories—about 1400 a day Apart from this exercise R M's expenditure of energy would have been little more than 1000 calories a day

Table III gives the calories utilised by the six select subjects on various tasks and occupations The energ expended at each of the recreations was only measured,

TABLE III—ENERGY EXPENDED BY SELECTED PERSONS ON VARIOUS TASKS AND OCCUPATIONS

Nature of activity	Energy expended (calories per sq m per hr)					
	Subject 4	Subject 7	J B	R M	Subject 29	Subject 34
having washing dressing &c	81	100	81	62	67	100
alking	159 (own pace)	196 (3 7 m p h) 225 (4 3 m p h)	195 (3 3 m p h) 239 (4 1 m p h)	138 (3 11 m p h) 168 (3 93 m p h)	135 (3 25 m p h) 205 (4 1 m p h)	1 1 (1 21 m p h)
ycling		171 (in town 8 6 m p h)	232 (in town 10 5 m p h)	144 (in town 8 7 m p h) 221 (in country 12 m p h)		
ousehold chores washing up making tea making beds sweeping					126	107
ving about the house standing alking occasional stairs odd obs	79			95		
rking in the laboratory (see text)		116	91		76	
creation and type (see text)	201 (cricket)				[illegible] (digging)	101 (cleaning a car)

once The energy expended on all the other occupations was measured at least twice, and any unexpected finding was confirmed several times These expenditures were measured to arrive at an over all figure for the subjects' total utilisation of calories, and some of the occupations were composite ones The figures for lying, sitting, and standing have already been shown in table I Figures for the expenditure of energy at various exercises are often given in terms of calories a minute, regardless of the person's height and weight (Edholm et al 1955, Passmore and Durnin 1955) Here, however, the results have been given as calories per square metre of body-surface per hour because the B M R is usually expressed on this basis, and this was the one used in the construction of table I They can be converted to calories a minute from the information given there

Shaving, washing, and dressing—The expenditure of calories by these subjects in these activities averaged 82 calories per square metre per hour, which is on the low side according to Passmore and Durnin (1955), and one of the figures now presented included having a cold bath and drying afterwards (R M)

Walking—The expenditures in walking ranged from 138 to 239 calories per square metre of body surface per hour according to the rate and the subject They are of the order of those given by Passmore and Durnin (1955) in their first figure, but only those for no 7 and possibly no 29 lay within the range of scatter shown by the subjects selected for their nomogram Since both the present subjects weighed considerably less than those used for the construction of Passmore and Durnin's figure they both seem to walk with more than the average expenditure of energy J B's expenditure for his given speed was considerably higher than would have been predicted from the figure R M's was lower, and those of no 34 were lower still There is evidently more individual scatter than the figures given by Passmore and Durnin suggest Moreover these workers do not mention whether women tend to expend more or less energy than do men on walking

Cycling—No 7's cycling was really a composite activity It was the journey he made four times daily between his house and the laboratory and included a little walk along a passage about one hundred yards long J B's expenditure on cycling agrees with the figure given by Edholm et al (1955) for their fifth subject, but both are on the high side for their speeds when compared with Edholm et al's other subjects J B's expenditure on cycling at 9 4 m p h would probably have agreed quite well with the figure of 7 0 calories a minute given for one of the subjects cited by Passmore and Durnin (1955) R M's expenditure on cycling was much lower than any of the comparable figures cited by Edholm et al or by Passmore and Durnin—see below

Working in the laboratory—For no 7 this meant standing, using pipettes, attending to a centrifuge, crushing ice, &c J B was emptying Douglas bags and taking pulse rates, and no 29 was standing manipulating apparatus on her bench

Other activities—No 4's cricket was net practice and consisted of bowling for a third of the time and fielding for two thirds No 29's recreation was digging holes, and no 34's [illegible]ning and polishing her car

DISCUSSION

Basal and Static Occupations

Evidently the present results confirm and extend the conclusions of Edholm et al (1955) that some people have metabolic rates for basal and relatively motionless occupations which depart much more widely from the average for the group than is usually considered to be the case In this study some people maintained these unusual rates for months on end, and they must be accepted as part of their permanent, or at any rate, semipermanent characteristics Since, moreover, adults and indeed children also spend such a large part of the twenty-four hours lying, sitting, and standing, a person with a consistently low rate at all three occupations will require less food to meet these expenditures than does one of similar build with a consistently high rate The calories expended on these occupations, therefore, are an important reason for variations in the total energy expenditure of individuals They may be the onl important cause in persons who lead outwardly simil lives and must be taken into account no less than th obvious and visible differences in active physical work

Walking and Active Exercise

These activities were only investigated in the su subjects selected for more detailed investigation, and th individual results have been compared with publishe ones rather than with the average for their own sma group Except for cadets and soldiers, walking is n a standardised exercise, and no two people use th arms and auxiliary muscles in the same way when th are on the move Nevertheless the chart given b Passmore and Durnin (1955) indicates only a minor deg of scatter at any given rate In terms of calories a minu the present subjects had a much wider one

J B, for example, walking at 3 9 m p h expended near 8 calories a minute, and R M only 4 5 This was partly d to large differences in body weight (Mahadeva et al 19 but there is more in it than that The same differences ca out in cycling R M did this exercise with very little expe diture of energy His sixteen mile run in the country was tak in three stages on a circular course involving a long hill a a rise of 100–150 feet and a descent against the wind on exposed road His expenditure on this run was lower than th of subject 7 or of J B cycling more slowly on the level is only fair to say that R M was riding a light bicycle wh had been built to his own specification, but he is both a cycl and a long distance walker of great experience and has a hig developed sense of rhythm, and all unnecessary movemen were probably eliminated from both occupations twenty fi years ago

Cause of Variations in Lying, Sitting, and Standing

If we apply these ideas about walking to the expe diture of energy while lying, sitting, and standing can see why one person may depart so widely fr the average The basal rates probably depend more the metabolism of the internal organs than do any of other rates, but there must be a muscular element them, and the small increases in the expenditure minute when people sit up and then stand up may attributed to the small additional amounts of musc energy needed for these tasks It is suggested th R M and subject 7 can achieve a high degree muscular relaxation at all three occupations keeping with this is the fact that R M's pulse ra is only 42–45 under basal conditions Subjects 4 a 29 never achieved even the average degree of relaxati and were always far above it, and J B, who had a ba rate well below the average when he was lying do and was evidently able to relax more than the avera person in that position, expended just the avera amount of energy while sitting, and his expenditu while standing, walking, and cycling were prolific Th was due to tension, minor "unnecessary" movement and lack of "rhythm"

Expenditure of Energy and Body weight

Fat men and, still more, fat women have often long for some excuse for their obesity, and physicians ha supported them in their search for some minor departu from the metabolic norm which would explain th tendency to put on weight It was thought at the out of this study that if persons were found with exceptiona low metabolic rates lying, sitting, and standing they mi all tend to be fat and have trouble in keeping their wei within normal bounds Subject 34 and J B have t trouble, but R M and subject 7 are both exceptiona thin and do not have to worry about the food they in spite of their low metabolic rates Subject 4, has a very high metabolic rate while lying, sitting, standing, is a big man and maintains his weight q easily, and subject 29 is a woman of normal proporti

These masked variations in expenditure of ene explain well enough why some people require few calo maintain their weight and others twice as many, but re is nothing to suggest that they play any part in fundamental control of appetite This is a problem ch remains to be solved, although some of the recent k on the peripheral and central mechanisms have n most illuminating (Kennedy 1951, Janowitz and llander 1955, Brobeck 1955, 1956, Mayer 1955 1956 a b) In modern life, however, the food served for the ociety" in which we live and the food eaten by nt and convention in it are adjusted unconsciously out the person who is average in all respects Persons h low expenditures of energy, whether obvious masked, can only maintain or retain a strictly average ght if they stop eating the strictly conventional ounts of food provided for their "society"

nical Relationships

The intensive search for new syndromes and for ortunities to apply new remedies has led Freedberg al (1955), Kurland et al (1955), and Tittle (1956) to cribe a condition characterised by a low basal meta ic rate with one or more of the following symptoms no other signs of myxœdema or subnormal function the thyroid gland "lethargy, easy fatigability vousness, irritability, emotional instability sensi- ty to cold, headache, ill defined skeletal pain, inished sexual potency in the male and menstrual gularity in the female" It is claimed that these sons will respond to triiodothyronine but not to roid extracts or to thyroxine If this becomes public owledge, there is a risk (*Lancet* 1956) that many o come to general practitioners with a vague story ered by these equally vague symptoms will be given odothyronine *The Lancet* goes on to say that the use triiodothyronine for this purpose is unjustifiable and uld be discouraged With this statement we agree l add that very low B M R in apparently normal and lthy persons have been well described in the past ompson and Thompson 1928, Lee 1935 Kirk and orning 1946) It has still to be proved that a B M.R -35% below the average for the group is necessarily normal Our experience and that of others (Means d Lerman 1935, Means 1937) suggest that it is not

Summary

The metabolic rates of thirty six healthy men and men were estimated while they were (1) in the basal ite, (2) sitting on a comfortable upright chair, and standing Three had rates more than 30% below, d one a rate of more than 24% above, the average for e group for all three occupations

The energy balance sheets of these four and of two other rsons were investigated for seven or fourteen days The ake was measured by weighing the food, and the output a time and motion study combined with measurements the important occupations

It was concluded that (1) the limits usually accepted the normal basal rates are too narrow, and (2) an usual rate for lying, sitting, and standing may make a eat difference to the total daily expenditure, but although a small expenditure at these three occupa- ns may lead to a small energy requirement it does not cessarily lead to obesity or even to a tendency to put weight

Our acknowledgments go to the subjects for their willing operation, and to Dr E M Widdowson for suggesting the estigation

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NEONATAL COLD INJURY

DUE TO ACCIDENTAL EXPOSURE TO COLD

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EVERY winter brings in its train a number of infant deaths due to accidental exposure to cold In the past three years 14 babies thus exposed have been treated in Brighton and no less than 8 of them have died If these figures are typical of the country as a whole the yearly number of deaths from this cause may exceed a hundred

The disorder finds no place in the Registrar-General's Statistical Review, because it goes unrecognised and is hidden under various other diagnoses, of which the two commonest are hæmorrhagic pneumonia and sclerema neonatorum

When this disorder was previously described (Mann 1955) it was thought that no earlier description of it had appeared However, as Everley Jones (1953) pointed out, the account of "œdema of the newborn" given by Henoch in 1889 corresponds fairly closely to the condition that we have observed, and cold, along with bad air and wretched nourishment, was then recognised as an ætiological factor Three further accounts of the disorder, each emphasising the part played by chilling, have since been found in Dutch medical literature (Munk 1937, Campagne 1941, Veldkamp 1946), and a fourth, from Palestine, entitled Cold Injury in a Sub-tropical Climate (Nassau 1948), suggests a suitable name for the condition We make a plea for its adoption in the hope that it will encourage recognition of the disorder in this country and elsewhere

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Clinical and Pathological Picture

Presenting Features

A composite picture of the disturbance may be sketched roughly as follows The baby makes satisfactory initial progress after a normal birth in the home, the pregnancy having been uneventful Although the birth-weight is often below the average full-term figure, prematurity is certainly not a constant feature

In the first week or two of life, sometimes later, increasing apathy appears, and causes concern when the infant first takes insufficient milk and shortly afterwards refuses its feeds completely As part of the general sluggishness, the cry becomes feeble and may be described as a whimper or a whine Coldness of the body to touch and swelling of the extremities or other parts, such as the eyelids, may be observed, but surprisingly both are often overlooked by the parents, and even by the attending doctor or nurse Other less constant presenting features may be related to a hæmorrhagic tendency or to impaired kidney function, thus blood may be vomited or passed per rectum, or decreasing amounts of urine may be voided until micturition ceases altogether

On detailed examination the body temperature, recorded in the rectum with a low-reading thermometer, is nearly always well below 90°F Although apparently conscious, the child lies motionless The facial expression is serene and does not suggest ill health There is an aura of coldness about the body, immediately apparent when the examining hand is placed under the clothes or cot coverings The skin, especially over peripheral parts, feels remarkably cold and corpse-like The face, hands, and feet are often strikingly red, with a particularly high colour of the eyebrows, cheeks, nose-tip, and chin At times the erythematous areas have a cyanotic tinge, often shared by the lips In contra distinction, generalised skin pallor may occasionally be found, but despite this the infant may still not appear ill Pitting œdema of at least the extremities is usual, and on careful scrutiny may be found to be more extensive than is at first apparent Local hardening of the superficial tissues over frankly œdematous parts, most usually the legs, is common at some stage of the illness and may not appear until rewarming is in progress, generally speaking this sign indicates a poor prognosis The illness is commonly complicated by some infection, characteristically rhinitis with profuse nasal discharge Although most physiological processes appear depressed by the hypothermia, the heart rate is often comparatively rapid when the patient is first seen

Clinical Course

In the majority of cases (13 out of 14) rewarming was passive, or " slow " as it is more commonly called This involves mitigating heat-loss, the baby warming up largely by its own metabolic efforts The time taken for the temperature to return to normal levels under these conditions varies widely, and we could find little or no correlation between the rate of increase in temperature and subsequent survival or death In 1 case active (" rapid ") rewarming was tried, but although the temperature was raised satisfactorily, and at first without apparent ill effect, the child died 32 hours later

The scope of investigation of recent cases is indicated in the account of case 2 (see below) The only important biochemical abnormality we have found is lowering of the blood sugar level, which may at times be profound Determinations before treatment were made in 6 cases only, in 2 the level was 10 mg per 100 ml or less, the remaining levels were 37 mg, 46 mg, 55 mg, and 94 mg per 100 ml The baby showing the highest of these levels subsequently gave values of 65 mg (second day) and 57 mg per 100 ml (fourth day)

The hæmatocrit was studied in 3 infants Although the figures tended to be high, only in case 2 were they above the normal range for the healthy newborn

The complications have chiefly been infective, ranging from rhinitis and ophthalmia, which were fairly common, to pneumonia (2 cases) and otitis media (3 cases, found at necropsy) Hæmorrhagic manifestations included petechiæ, vomiting of altered blood, *melæna*, and, perhaps in a separate category, pre-agonal bleeding from the mouth and nose

In 3 cases generalised epileptiform fits occurred which in 1 baby at least, were related to hypoglycæmia Fits are not necessarily a sign of serious import, 2 of the affected infants survived, while the 3rd died from a fulminating infection due to *Hæmophilus influenzæ*

The duration of survival of fatal cases ranged from 7 to 100 hours with a mean of about 40 hours The manner of deterioration was similar in all The baby began to look ill, erythematous areas became dusky, in several infants facial pallor was a notable terminal feature Death in all cases appeared to be due to respiratory failure In 3, terminal straining occurred during which the face flushed and shortly afterwards sanguineous frothy material poured out of the upper respiratory passages

Necropsy Findings

Necropsies were performed on all fatal cases In 5 of the 8 examined, the dominant finding was massive pulmonary hæmorrhage At first this was called " hæmorrhagic pneumonia," but the consistent absence of pathogenic bacteria on culture (and of influenza virus in the 1 case in which tissue was sent to the Virus Reference Laboratory), together with the lack of any histological evidence of inflammatory reaction in the lungs, compelled revision of this diagnosis True hæmorrhagic pneumonia was present in one case, already mentioned, which showed massive *H influenzæ* infection, but the abundant pus in bronchioles and bronchi gave a picture which even in the gross could be recognised as quite different

Hæmorrhage *in other tissues* was *not a conspicuous* feature In 2 cases there were skin petechiæ, but these were scanty and slight 3 cases showed acute gastric erosions with a small amount of bloodstained mucus in the stomach, and in 2 cases hæmorrhages were found beneath the serosal surface of the colon The findings did not suggest, in any of the cases, that the pulmonary hæmorrhage was an expression of a generalised hæmorrhagic tendency

Œdema of the extremities and deep coloration of the skin has already been mentioned A small amount of ascites (5–15 ml) was constantly present These changes, with occasional evidence of rhinitis or otitis, constituted the only other abnormal necropsy findings Clearly infection does not play a dominant rôle Massive pulmonary hæmorrhage, since it occurs in several other conditions and was not always present in our series, can hardly be regarded as pathognomonic, but if it is found *in association with mild ascites and œdema and cyanosis of the extremities, cold injury should be suspected*

Illustrative Case-records

Mild Case with Recovery

Case 1 —A baby, *aged 6 days*, birth weight 7 lb 8 oz, was admitted to the Royal Alexandra Hospital on Jan 30, 1954, with swelling of the hands and feet which had developed over the previous two days He had been born on a cold, snowy day (minimum air temperature 31°F) a few hours after his parents had moved into a new prefabricated house The only heating in the bedroom was by a small electric fire, but when bathed after birth (and daily thereafter) he was taken into the warmer front room

On examination temperature 86°F (see fig 1), heart rate 142, respirations 36 per min The face and extremities were bright pink and there was pitting œdema of the hands, legs, and feet There was no cyanosis and no hardening of the skin or subcutaneous tissues The chest was clinically clear

Treatment and progress —The child was nursed in a cot at room temperature (about 70°F) Expressed breast milk was

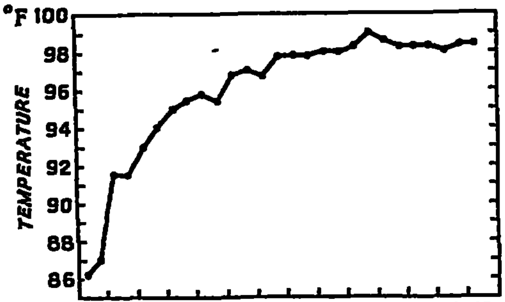

Fig 1—Body temperature in case 1

given by bottle, and aureomycin 25 mg orally every four hours for ten days The body temperature was 91°F on the day after admission and gradually rose to normal in nine days, the œdema slowly subsided over the same period No oliguria was recorded A slight eye discharge was noted on the second day in hospital but lasted less than twenty four hours After fourteen days the infant was discharged well, being fully breast fed When seen sixteen months later he was a normal, healthy child

Severe Case with Recovery

Case 2 —This baby, aged 12 hours, birth weight 6 lb 1 oz, was admitted to the Royal Alexandra Hospital on Feb 8, 1956 The birth took place in a new council house, not yet fully dried out, in a bedroom heated by one electric fire, on a cold day (minimum air temperature 34°F) Delivery, at term, was complicated by a knot in the cord and meconium stained liquor, breathing was established with some difficulty The infant was bathed in front of the fire, at 10 30 P M, and placed in a carry cot with one hot water bottle, which was not changed At 1 A M (contrary to instructions) the fire was switched off, the baby cried all night The cot-temperature on the afternoon of admission, after the fire had been on all day, was only 53°F

On examination he was a normal looking infant with an active lusty cry, there was cyanosis of the skin and a marked aura of coldness rectal temperature 81°F, heart rate 120 No œdema was present, the chest was clear Slight stickiness of one eye was noted *Investigations* (before rewarming)—Hæmatocrit 59%, hæmoglobin 16 4 g per 100 ml, blood sugar less than 10 mg per 100 ml, serum proteins 4 5 g per 100 ml, blood urea 30 mg per 100 ml, serum potassium 4 36 m eq per litre, serum chloride 96 4 m eq per litre, serum bicarbonate 27 7 m eq per litre Blood culture was sterile, and there was no albuminuria, and an electrocardiogram showed only diphasic T waves in the standard leads

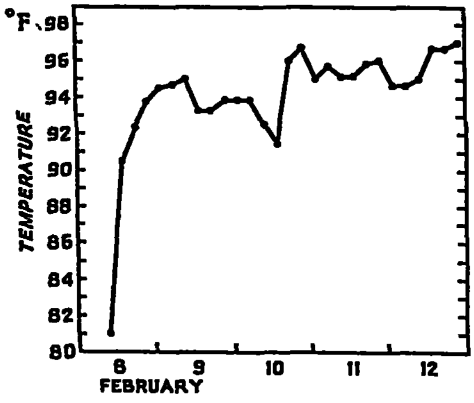

Fig 2—Body temperature in case 2.

Treatment and progress (see accompanying table)—The baby was nursed initially in an incubator, fed by compressed air at a temperature of 84°F 70 ml of fresh frozen plasma and 85 ml of 5% glucose were infused intravenously during the first twenty hours Simultaneously 15 ml of 5% glucose was given hourly by intragastric drip

Fifteen minutes after the start of rewarming, skin erythema developed over the entire body except the feet Later violent coarse limb tremors, preceded by crying, began, these continued intermittently for eight days On the third day he had three generalised convulsions and appeared moribund Both tremors and fits were probably due to hypoglycæmia The blood sugar level remained extremely low till the fourth day, when it reached a normal level following increased glucose dosage (30 g daily) The glucose intake was then relaxed to 9–12 g daily, and the hypoglycæmia promptly recurred (blood sugar under 10 mg on day 6) The temperature rose within twenty four hours to 95°F on the third day it fell transiently to 91°F, but thereafter it was never low again

On the fourth day, because of oliguria and a rising hæmatocrit (73%), a further 50 ml of fresh frozen plasma was given On the sixth day the rectal temperature reached 97°F, pulse rate 100–120, the child was bubbly at the mouth and showed generalised œdema, now congestion and pulsation of the neck and scalp veins became obvious, he vomited altered blood In view of this evidence of cardiac failure digoxin was given, with remarkably good results, the signs of failure were relieved, and there was a brisk diuresis Investigations at this stage (sixth day) showed serum-protein 4 8 g per 100 ml, blood urea 36 mg per 100 ml, serum potassium 6 05 m eq per litre, and serum chloride 94 m eq per litre

DATA ON CASE 2

—	Day								
	1	2	3	4	5	6	7	8	9
Blood sugar (mg per 100 ml)	<10	<10	<10	100		<10	73	53	60
Glucose intake (g.)	6	12	36	30	9	12	23	25	20
Lactose intake (from breast milk) (g)					4	10	15	12	24
Hæmatocrit (%)	59	75	75	73		61			57
Fluid intake (intra venous and oral) (ml)	180	350	325	280	230	240	260	430	400
Urine output (ml)	26	32	35	4	28	180 +	70 +	43 +	25 +

Recovery after the successful treatment with digoxin was uneventful, and the child was discharged home when a month old At the age of eight months he appeared quite normal

Diagnosis

The facial erythema and misleading appearance of well-being exhibited by the majority of these infants when first seen have been emphasised in both the Palestinian and the Dutch reports Nassau (1948) tellingly quotes the comment of a nurse "The child is as florid as if it had just been for a winter's walk!" Much of the delay in recognition of the fact that the child is ill is undoubtedly due to this paradoxical erythema

In 4 of our cases no one had noticed before admission to hospital that the baby had become chilled, and in none of the 14 had the severity of the hypothermia been appreciated by the midwife or the family doctor It cannot be too strongly stressed that in home confinements the baby's body-temperature should be recorded once daily at least, and that for this purpose a low-reading thermometer (range 85–110°F) should be used With the conventional thermometer it is all too easy to assume that the reading shown is the baby's temperature, when in fact it represents merely the point to which the mercury was shaken down before use

In most of the series no definite diagnosis had been reached by the doctor referring the case to hospital In some an infective process was suspected, in others hæmatemesis or melæna led to a suspicion of hæmorrhagic disease of the newborn We find that in hospital there is a strong tendency to attribute the infant's condition to an underlying infection or, if hardening of the panniculus becomes noticeable, to term the condition sclerema These two diagnoses obscure the important fact that the disturbance is primarily due to exposure to cold

It is true that a septic process in the newborn sometimes leads to slight depression of the temperature instead of the more customary rise, and doubtless when this happens the infant will be more susceptible to chilling While admitting that an infection may in this way predispose to hypothermia, we are convinced that in none of our series did sepsis play a major causal rôle

Misinterpretation of the lung changes resulting from hæmorrhage has often contributed to the assumption that the cause was infective, especially when the final diagnosis was based solely on gross necropsy findings Of course pneumonia may complicate cold injury, indeed prolonged hypothermia seems to predispose to infective complications To quote Debré and Lelong (1952) "Le refroidissement sensibilise le nourisson a l'action des germes pathogenes Ce sont des infections rhinopharyngées, otiques, pulmonaires"

There has always been great confusion over the use of the term sclerema Yet as long ago as 1811 Underwood gave a masterly clinical description of that condition Comparing his account with the syndrome described here it should be apparent that the two conditions have little in common and that their differentiation should be possible at first sight Thus Underwood, describing sclerema, correctly refers to the yellowish-white discoloration of the skin and the appearance of dying, and also remarks (which we regard as a crucial point) that "The feel of the skin and flesh is hard and resisting but not œdematous" In contrast, in cases of neonatal cold injury the skin is often erythematous, the child does not look ill initially, and, when hardening of the skin and subjacent tissue has been present, œdema has always preceded and accompanied it

Ætiology and Predisposing Factors

The majority of our infants with cold injury were first seen during spells of cold weather when minimum air-temperatures were below freezing-point It was noticeable that cases tended to be admitted to hospital immediately after a sudden fall in outside temperature Study of home circumstances, with special reference to the thermal environment to which the baby had been exposed, showed that in many instances the conditions were quite unsuitable for a confinement in winter time We have found, as Munk (1937) did, that cold injury may occur in well to-do surroundings, a comfortable and well-provided home may yet be cold

Special hazards arise when delivery occurs in very cold weather after a move to fresh accommodation, as happened in two of our cases Another source of trouble is the use of an open coal fire for heating the room where the child is born and nursed, the room-temperature may fall precipitately in the early hours of the morning when the fire goes out The same may happen with gas or electric heating if it is switched off at night as an economy measure, and this point needs special emphasis because fatal damage has occurred to infants at room-temperatures (59°F) which would be regarded as quite tolerable by adults in this country

Cold injury does not develop in every infant exposed to a low temperature, certain other factors must help to precipitate it As in adults (Pugh and Edholm 1955), the rate of cooling may be related to the thickness of the subcutaneous fat, which probably varies considerably from baby to baby, even in those of full gestational age Other predisposing factors may be asphyxia at birth (McClure and Caton 1956), birth injury, and an infection of some kind (Yllpo 1935) Chilling is of course more likely if clothing and cot coverings are lacking, and then there is the risk of unnecessary cold exposure resulting from the routine cleansing bath—a ritual practice which we find may not be waived by the midwife even in the most frigid conditions (Talbot 1925)

A further aggravating factor, to which Campagne (1941) referred, may be inanition, thus, if not operative

Treatment

The three essentials in the management of this di are to rewarm, to feed, and to prevent inf Hitherto our approach has been empirical The r mendations we make are based on the experien gained and have not been fully proved in pra nevertheless we feel that they may have some va only by marking the pitfalls we have encountere

Rewarming

The best method of treating patients subject prolonged cooling is still disputed There is g agreement that half-hearted rewarming is to be av (Burton and Edholm 1955), so the choice lies be active (rapid) rewarming (Grosse Brockhoff 19 passive (slow) rewarming (Talbott and Burton Burton and Edholm 1955) Our experience of the method has been limited to 1 case Here, althou rewarming was quite successful, the child died two hours afterwards for no very clear reason, in spect, the most probable cause was overloading intravenous fluid and there is no real justificati blaming the rewarming technique In all other slow rewarming was used either by nursing incubator with the circulating air maintained a or so above the infant's rectal temperature, or, simply, by keeping the baby normally clothed ordinary cot at a room-temperature of 70-80 method which seems to be equally effective

Feeding

One of the first effects of rewarming is accelerat the metabolic processes of the tissues, giving r increased demand for glucose Since glycogen re may already have been severely depleted durin period of exposure to cold (Grosse-Brockhoff Burton and Edholm 1955) profound hypoglycæn liable to follow, this was present in at least 2 ca our series It seems to us extremely importa recognise and correct this hypoglycæmia, but, where the pre-treatment blood sugar is normal, gl therapy is no less vital, as a considerable glycogen may still exist Administration of glucose reduce proportion of "rewarming deaths" both in dogs 1954) and man (Grosse-Brockhoff 1950)

In these infants glucose, if it is to be effective, be given in high dosage Our experience in case which the infant was profoundly hypoglycæmic for days and responded only to a glucose dosage of the of 30 g daily, seems to show that this amount was adequate, while theoretical considerations, taking account not only the infant's basal energy requiren (Smith 1951) but the needs for rewarming an replenishing the glycogen deficit, suggest that the of 30 g might even be doubled for an infant of av size The administration of so much glucose daily newborn infant is, however, a problem in itself usual 5% intravenous glucose is quite useless, if se fluid overloading is to be avoided, a more concent solution must be given Such a solution is liable to thrombosis when given intravenously, and we p therefore, to give 15-20% glucose by continuous gastric drip

Although we found no liability to electrolyte imba in the few cases where biochemical studies were u taken, it seems prudent not to continue glucose the alone for more than forty eight hours As soon a infant's temperature rises above 90°F—which, passive rewarming, it usually does within twenty hours—glucose may be given in milk, rather th aqueous solution There may indeed be no objection to the use of such a milk mixture from

The risk of fluid overloading must be guarded against The hæmatocrit may be high when the infant is first seen and may continue to rise, even reaching a level of 75% as in case 2 When this trend occurs there may be a temptation to reverse it by giving intravenous plasma, but this should be resisted The rising hæmatocrit value is the result of a fluid shift from one body compartment to another (Horvath 1951), and when, with rewarming, a contrary shift occurs, acute heart-failure may follow if plasma has been given Our experience with case 2 and other cases last winter suggests that there is a need for extreme caution in giving intravenous fluids, plasma or others, in cases of cold injury

Prevention of Infection

As infective processes are very difficult to detect in these babies, and as they seem unusually prone to septic complications, antibiotic therapy should be given from the outset Because of uncertainty of absorption of drugs from the alimentary tract in hypothermia, parenteral treatment seems advisable until rewarming is well under way Tetracycline is a useful antibiotic for prophylaxis, especially as it can be given intramuscularly or intravenously

Other Treatment

Cortisone, because of its reported value in sclerema, might seem to be indicated in cases of cold injury But, because of the susceptibility to infection, this treatment is hazardous, even with antibiotic cover, and we know of one case where an unsuspected suppurative appendicitis was found at necropsy in a hypothermic infant treated with cortisone and oxytetracycline (R W Brookfield and B W Neal, personal communication)

Hypothermia prolongs the action of certain drugs (Herrmann 1941) Because of this, barbiturates, and especially phenobarbitone, must be administered very cautiously If fits occur the possibility of hypoglycæmia must be seriously considered, and increased glucose administration, possibly coupled with subcutaneous adrenaline, may be more effective and less dangerous than anticonvulsant therapy

Both Grosse Brockhoff (1950) and Burton and Edholm (1955) concluded that oxygen administration is without value in hypothermia, and this has certainly been our impression in one or two cases where it has been used from the beginning of treatment We have considered the possibility that pulmonary hæmorrhage might have been due to over-use of oxygen, but this seems unlikely because in at least one of the cases lung hæmorrhage began before any oxygen had been given

Prevention

There can be no question that neonatal cold injury is preventable, and that, with wider recognition of the cause, its incidence will be greatly reduced Smallpeice (1955) has rightly observed that it is a reproach to us all that newly born infants should become chilled in icy bedrooms in cold weather Young infants need constant warmth by day and night No less dangerous than the coal fire going out in the early morning are lukewarm baths in cold surroundings, electric or gas fires switched off for economy's sake, or exercise of the popular British belief that some mystic quality of health resides in a stream of cold air coming through an open window

In many homes it is simply not practicable to maintain in really cold weather a steady air temperature of 65°F or more in the room in which a baby is born and nursed There are two possible solutions Firstly, the home conditions for a confinement which is expected in winter should be rigorously assessed, if the heating appliances are obviously inadequate, delivery should take place in hospital Alternatively, some form of safe portable heating equipment should be provided for use during and after the delivery

The main task, in prevention, is to ensure that those concerned in domiciliary midwifery are alert to the danger of exposing the baby to cold The simple rules for midwives set out in the appendix may help to encourage such watchfulness

Summary

Neonatal cold injury is a not uncommon disorder with a high mortality Cases generally arise after home confinements, especially in severely cold weather

Commonly the disorder is misdiagnosed as hæmorrhagic pneumonia or sclerema, the predominant rôle of exposure to cold being overlooked

Presenting features may include increasing apathy, food refusal, coldness to touch, and oliguria, but the infant does not look ill

The most constant clinical findings are hypothermia, œdema of the extremities, purulent nasal discharge, and striking skin erythema which contributes to the misleading appearance of well-being

The treatment advised is slow rewarming, liberal glucose administration by intragastric drip, and antibiotic cover

Prevention, which is of paramount importance because of the high mortality, can be achieved only by safeguarding against a fall in room-temperature This requires watchfulness by professional personnel, who should warn parents of the risk

Our thanks are due to Dr W Mestitz and Mrs Keith Powell for their kind help with the translation of German and Dutch papers, Dr Margaret Hunter and Dr Monica Barrett for their valuable clinical assistance, Sister M Janes and her staff for all their painstaking work with these babies; the many midwives in Sussex who have collaborated with us, Dr R Morrison, of the Brighton Health Department, for her guidance with preventive measures, Dr F O MacCullum for the virus investigation of one case, and Mr F Needham Green and Mr G G Morgan for providing us with details of weather

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Appendix

1 In assessing for a home confinement bear in mind the season when the delivery is expected Ensure in advance that the lying in room can be properly heated, if there is any doubt about this seek medical advice

2 Make sure, in good time, that the baby is adequately provided for, especially as regards garments and cot coverings

3 The temperature of the room where the baby will be born and subsequently nursed should not be allowed to drop below 65°F in the first fourteen days of life Wall thermometers on which the 65°F low limit is clearly marked should be fixed in full view in or near the baby's cot The parents should be told how to read the thermometer and what action to take if the room temperature falls below the critical level

4 Premature infants are especially prone to chilling and may require a warm environment for some weeks At times this applies equally to newborns whose birth weights exceed $5^1/_2$ lb

5 In winter newborn babies *should not* be bathed except in thoroughly warm surroundings (70°F)

6 The baby's clothing should not restrict free bodily movement which, within loose but adequate wrappings, aids the maintenance of body warmth

7 The baby's rectal temperature should be read and recorded at least once daily for fourteen days In cases showing temperature instability readings should be continued even longer

8 Mothers should be told to feel the baby's face and extremities periodically and to report if the skin feels cold

9 If the *rectal temperature falls to 96°F or below*, medical aid should be sought In providing extra warmth in such instances, avoid increased wrappings which will insulate the baby from surrounding warmth

10 Birth injury and asphyxia (blue or white) both predispose to chilling in the newborn Babies so affected, regardless of birth weight, require careful scrutiny and may need additional warmth

11 A coal fire in the delivery room should not be used as an incinerator for damp and soiled maternity dressings after the birth

SYPHILITIC AORTIC INCOMPETENCE
WITH SPECIAL REFERENCE TO PROGNOSIS AND EFFECT OF TREATMENT

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MORE than ten years have elapsed since penicillin was first used in cardiovascular syphilis No study of its long-term results has yet been published Moreover the prognosis of the various forms of cardiovascular syphilis remains uncertain Since uncomplicated aortitis, aneurysm, and aortic incompetence have an inherently different prognosis, it is obviously necessary to consider each form of cardiovascular syphilis separately The present investigation was therefore limited to cases of aortic incompetence It was undertaken to establish the prognosis of syphilitic aortic incompetence, to estimate the influence of various factors on the prognosis, and to assess the value of the different forms of treatment, including penicillin

Many workers have held that the average survival of patients with syphilitic aortic incompetence is only 2 years from the onset of symptoms Most estimates have been based on American series containing a high proportion of Negroes, in whom the prognosis is admitted to be poorer than in white people The largest series of cases of syphilitic aortic incompetence confined to white people in the English literature are those of Cotton (1926), Grant (1933), and Grimble (1955), their findings are discussed below

Material and Methods

The present series consists of 374 patients in whom syphilitic aortic incompetence had been diagnosed at the National Heart Hospital (183 cases), the cardiac department of the London Hospital (93 cases), the department of cardiology of the Middlesex Hospital (73 cases), the Norfolk and Norwich Hospital (19 cases), and St Bartholomew's Hospital (6 cases) The study covers 30 years (1926–55) and is based on the careful examination of the very full clinical records of these patients and on personal examination of 32 of the 102 survivors

TABLE I—AGE AND SEX DISTRIBUTION

Age	20–29	30–39	40–49	50–59	60–69	70–79	80 or more	Total
Male	—	25	51	102	79	11	1	269
Female	2	13	37	32	17	4	—	105
Total	2	38	88	134	96	15	1	374

Every patient had aortic incompetence without any other valvular lesion In 360 patients (96%) either the Wassermann or the Kahn reaction was positive In the remainder necropsy findings (5), calcification and dilatation of the ascending aorta (4), a positive treponemal immobilisation test (3), and tabes dorsalis (2) provided evidence of syphilis All patients with saccular aneurysm of the aorta and general paresis were excluded 15 patients with tabes dorsalis and 1 with syphilitic meningomyelitis were retained because the outcome was unaffected by the neurological condition In addition 28 patients had minor neurological abnormalities on clinical examination, and a further 7 patients had an abnormal cerebrospinal fluid without neurological signs Other conditions present included carcinoma (3), diabetes mellitus (3), rheumatoid arthritis (3), ankylosing spondylitis (2), Reiter's syndrome (1), and pulmonary tuberculosis (1)

The age and sex of the patients are shown in table I The sex ratio was about 2 5 males to 1 female The mean age was 54 The maximal incidence was in the fifth and sixth decades in females and in the sixth and seventh decades in males All the patients were of European origin except 2 Negroes and 1 Chinese Of the 374 patients 224 were followed either to death or to the present time by examination of the hospital records or by writing to the patients or to their general practitioners Of the 150 patients who were not discovered by these means 100 were later traced from the deaths recorded in Somerset House Eventually only 50 patients (13%) remained untraced

Clinical Features

Previous History

111 patients (30%) gave a past history of either primary syphilis or gonorrhœa The mean interval from the primary infection to the diagnosis of aortic incompetence was 31 years (range 8–52 years) Information on the type and quantity of antisyphilitic treatment given in the early stages of the disease was scanty

Symptoms

49 patients (13%) were symptom-free at the time of diagnosis, this group is analysed separately later The symptoms described by the remaining 325 patients were breathlessness on exertion, 234 (72%), cardiac pain, 180 (55%), paroxysmal nocturnal dyspnœa, 71 (22%), atypical chest pain, 33 (10%), palpitation, 25 (8%), loss of weight, 18 (6%), and Adams Stokes attacks, 2 (0 7%) The mean duration of symptoms before diagnosis was 17 months

Palpitation was mentioned by 25 patients In a few instances it was due to uncontrolled auricular fibrillation, 2 patients had attacks of paroxysmal auricular tachycardia

Loss of weight was a prominent symptom in at least 18 patients (14 males, 4 females, mean age 52) and may have been overlooked in others This symptom appears to carry a bad prognosis the mean survival of the 15 patients who died was only 27 months (The mean survival of all the patients who died in the whole series was 48 months)

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Adams-Stokes attacks occurred in 2 patients with complete heart-block

Physical Signs

The characteristics of the aortic second sound and diastolic murmur are too well known to need further consideration here Attention is, however, drawn to a few of the lesser-known physical signs which may be present

Systolic murmurs—A systolic murmur was heard in 315 cases (84%), it was present in 30 of 32 patients personally examined

Thrills—42 patients (11%) had a systolic thrill at the aortic area, 21 patients (6%) had a diastolic thrill, in 11 patients both systolic and diastolic thrills were present A *systolic* thrill may result from aortic valvular stenosis, which rarely supervenes in syphilitic aortitis as a result of atherosclerotic degeneration Most workers agree that an aneurysm may cause a systolic thrill, but it is usually denied that a systolic thrill can occur in syphilitic aortic incompetence without aneurysm (Friedberg 1949, Wood 1956) Of 7 of these 42 patients examined post mortem none had aortic stenosis or aneurysm A *diastolic* thrill in aortic incompetence is commoner in syphilis than in rheumatism, it usually results from gross retroversion of the valve cusps, as in the 2 patients in this series examined at necropsy

Austin Flint murmur—A delayed diastolic murmur at the apex, with or without presystolic accentuation, was noted in 29 patients (8%) The mitral and tricuspid valves were normal in 6 of these patients at necropsy Left ventricular failure was present in 15 of the 29 patients, and in some the murmur disappeared as the failure improved Laubry and Pezzi (1926) observed that the murmur was usually heard in the presence of left ventricular failure

Arrhythmias—26 patients (7%) had auricular fibrillation at some stage of their illness, as expected, it was commoner in the older patients The mean age at the onset of auricular fibrillation was 60 Complete heart-block was present in 3 patients, in 1 of these a fibrous plaque in the region of the bundle of His was found at necropsy Paroxysmal auricular tachycardia occurred twice, and partial heart-block once

Hypertension—43 patients (12%) had a systolic pressure higher than 200 mm Hg, and 8 of these had a diastolic pressure higher than 95 mm Hg In several others moderate hypertension developed terminally in association with congestive failure

Investigations

Wassermann Reaction

As already stated, the Wassermann reaction was initially positive in 360 patients (96%) The effect of treatment on the Wassermann reaction was studied in 116 patients In 29 (25%) the test became negative after treatment, in 87 patients (75%) it remained positive It was impossible to compare the effect of different forms of treatment on the reaction

Treponemal Immobilisation Test

This test was positive in 5 patients in whom the Wassermann reaction was originally negative or became so all had received previous treatment with either penicillin or arsenic and bismuth

Erythrocyte-sedimentation Rate

The erythrocyte sedimentation rate (E S R) is raised in most untreated cases of cardiovascular syphilis (Danzer 1931 Wood 1936) Results of this investigation were available in 143 patients (38%) at some stage of the disease The standard Westergren method was used in nearly every case The mean initial reading in these 143 patients was 27 mm after 1 hour

In 73 patients the E S R was estimated before any antisyphilitic treatment had been given, the mean E S R in this group was 32 mm The effect of congestive heart-failure in retarding the E S R was less than had been expected 25 of the 73 patients had congestive heart-failure and a mean E S R of 27 mm, the mean E S R of the 48 patients without congestive heart-failure was 35 mm However, 36% of the patients with heart-failure had a normal E S R (0–10 mm), whereas only 20% of the patients without heart-failure had a normal E S R.

The effect of treatment on the E S R was studied in a small group of cases In 26 patients the E S R was estimated before and immediately after a course of penicillin, the mean reading before treatment was 33 mm and after treatment 34 mm However, a year or more after treatment with penicillin the mean E S R in 31 cases was only 13 mm These findings suggest that effective treatment lowers the E S R slowly over many months

Wood (1936) noted that 4 of his patients with a very high E S R died quickly In the present series 24 patients had an initial reading higher than 50 mm, 11 had heart-failure 15 of the 24 are dead, and their mean survival was only 14 months, compared with a mean survival of 48 months for all the patients who died in this series Of the remaining 9 patients 5 are untraced, of the 4 survivors all have received penicillin, and the E S R in 3 of them has fallen to 17 mm, 8 mm, and 8 mm, it was not estimated in the 4th patient

Radiography

Radiographs of 64 patients were personally examined Calcification of the ascending aorta was present in 22 (35%) and was confined to the ascending aorta in 7 There was calcification of the arch in 21, the descending aorta in 6, and the aortic valve in 4 The aorta was normal in 6 patients and enlarged to various degrees in 58 The left ventricle was normal in 5 and enlarged in the remainder

Either radiological reports or orthodiagrams were available for 282 patients calcification of the ascending aorta was noted in 16 of these, the aorta was specifically described as normal in 37, and the left ventricle was said to be normal in 18

If carefully sought, the true incidence of calcification of the ascending aorta in syphilitic aortitis is likely to be about 40% (Thorner and Carter 1948), in the present series this is close to the proportion found in the films personally examined It is often necessary to take oblique and postero-anterior films with highly penetrating X rays to show the calcium, which is sometimes more easily detected by fluoroscopy

Calcification probably results from atherosclerotic degeneration superimposed on syphilitic aortitis, it would therefore be expected to occur more commonly in older patients The mean age of the patients in this series with calcification of the ascending aorta was 63 Calcification of the ascending aorta is rare in atheroma alone (Jackman and Lubert 1945) and is therefore important in differential diagnosis

Electrocardiography

We examined 342 electrocardiograms, but most of the earlier tracings were confined to the standard limb leads Twelve lead electrocardiograms were available for 74 patients and these were separately analysed Table II shows the findings.

The term "left ventricular strain" has been used where definite ST depression and/or T-wave inversion has occurred in left sided precordial leads and in other leads depending on the electrical position of the heart "Left ventricular hypertrophy" describes voltage changes in the standard and unipolar limb leads and precordial leads in excess of the various criteria of

TABLE II—ELECTROCARDIOGRAPHIC FINDINGS

—	12 lead E C G	Standard leads	Total
Number of patients	74	268	342 (*100%*)
Normal E C G	6	47	53 (*15%*)
Left ventricular strain only	23	189	251 (*73%*)
Left ventricular hypertrophy only	3		
Left ventricular hypertrophy and strain	36		
Cardiac infarction and ischæmia	11	10	21 (*6%*)
Auricular fibrillation	6	20	26 (*7%*)
Left bundle branch block	4	12	16 (*5%*)
Right bundle branch block	2	10	12 (*4%*)
Complete heart block	1	2	3 (*1%*)

Goldberger (1953), Sokolow and Lyon (1949), and Gubner and Ungerleider (1943) It was impossible to differentiate left ventricular hypertrophy and strain in the standard leads only It is often very difficult to decide whether ST segment and T-wave changes are due to left ventricular strain or to myocardial ischæmia

We found only a rough correlation between the electrocardiograms and the diastolic blood-pressure, cardiac pain, and heart-failure Many of the patients for whom a twelve lead electrocardiogram is available are still alive; and it was impossible to correlate the electrocardiogram with survival

Causes of Death

222 patients died, and the cause of death was ascribed to the cardiovascular system in 207 The other causes of death were cerebral thrombosis or hæmorrhage, 4, carcinoma, 3, pulmonary tuberculosis, 1, appendicitis, 1, pancreatitis, 1, uræmia, 1, hæmatemesis from gastric ulcer, 1, coal gas poisoning, 1, barbiturate poisoning, 1, and war injuries, 1

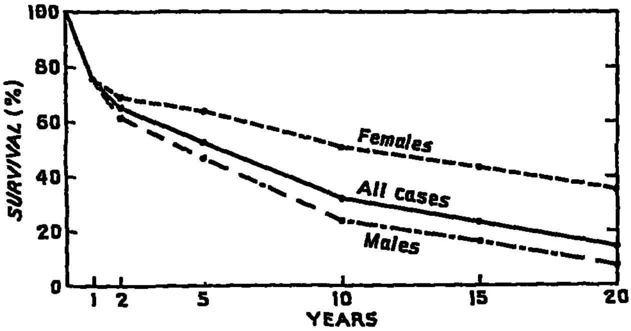

Fig 1—Survival-rate of whole series and of males and females

Of 60 patients who came to necropsy all had syphilitic aortitis Detailed information about the aortic valve was available in 36 patients, the incompetence was considered by the pathologist concerned to be due mainly to cusp damage in 31 and to stretching of the aortic ring in 5

The coronary ostia were specifically described in 35 cases the right ostium was normal in 8, narrowed in 21, and occluded in 6, the left ostium was normal in 12, narrowed in 20, and occluded in 3 Of the patients with normal ostia 3 had complained of cardiac pain, in 1 of these the left coronary artery was occluded 1 3 cm beyond the ostium by a mass of syphilitic arteritis, a rare finding in this disease, 1 other patient had moderate atheroma of the coronary arteries In 11 of the patients with ostial stenosis or occlusion there had been no history of cardiac pain

The coronary arteries were described in 19 patients, and only 4 had a moderate degree of atheroma

Bacterial endocarditis of the aortic valve was found in 1 patient, *it had been suspected clinically in 2 others* but not proved

Factors Influencing Survival

Of the 374 patients 222 are dead, 102 are alive, and 50 are untraced The survival of the whole series was determined, and an attempt was made to assess the effect of various factors on survival It is usual to calculate survival from the date of onset of symptoms Because of the difficulty in determining accurately the onset of breathlessness, we have calculated survival *from the date of diagnosis* unless otherwise stated

Merrell and Shulman (1955) have pointed out the fallacy of relying on the mean length of survival of patients who subsequently died when a considerable proportion of the original patients are alive or untraced We have therefore calculated the percentage survival according to the life-table method (see Merrell and Shulman 1955) In certain instances, however, we have also calculated the mean length of survival of patients who subsequently died, it is important to remember that these figures will be an underestimate This error will proportionately increase with larger numbers of untraced and surviving patients

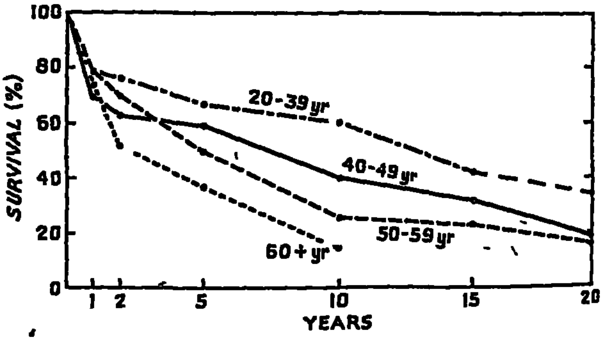

Fig 2—Survival rate of patients in different age-groups

Age and Sex

Fig 1 shows the survival-rate of the entire series *and of males and females separately* It will be noted that 75% survived 1 year, 54% survived 5 years, 32% survived 10 years, and 14% survived 20 years Females had a better prognosis than had males after the first year

The effect of age at diagnosis on survival is shown in fig 2, which shows the better prognosis of the younger patients after the second year Thus, after 10 years, 60% of those aged less than 40 are still alive, compared with only 15% of those aged more than 60 Table III shows that heart failure was much commoner in the older age groups This was probably the main cause of the poor prognosis of the older patients, but the older age-groups contained a higher proportion of males (table I) It is therefore difficult to separate the effects of age and sex on survival

TABLE III—EFFECT OF AGE, SEX, CARDIAC PAIN AND HEART FAILURE ON SURVIVAL

—	All cases	Males	Females	Age (yr)				Angina	Heart-failure
				20–39	40–49	50–59	60 or more		
Total	374	269	105	40	88	134	112	180	111
No of patients who died	222	168	54	19	57	77	69	121	89
Mean survival of patients who died (mos)	48	42	66	71	69	45	26	56	18

Table III shows the mean survival of patients who died and of the different sex and age groups These figures also show the better prognosis of the female and younger patients

Occupation

Inadequate data prevented an assessment of the effect of occupational factors on survival

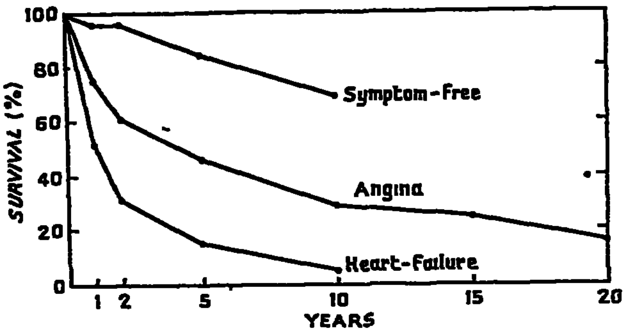

Fig 3—Survival-rate of symptom-free patients and of patients presenting with angina and with heart failure

Lack of Symptoms

49 patients (35 males, 14 females, mean age 52 years) who were free from symptoms at the time of diagnosis were analysed separately McDermott et al (1942) emphasised the good prognosis in such patients, and the present series confirms this Fig 3 shows that 96% were alive 2 years after diagnosis, 84% 5 years, and 69% 10 years Most of them had been intensively treated with penicillin and bismuth The good prognosis of aortic incompetence before the development of symptoms emphasises the importance of diagnosis and treatment at this stage of the disease

Cardiac Pain

This occurred in 180 patients, of these, 153 had angina of effort and 77 angina at rest, especially at night Table IV shows the age and sex of patients presenting with cardiac pain Angina was particularly common as a presenting symptom in women aged less than 50 The sex ratio was 2 4 males to 1 female Jones and Bedford (1943) fully described the pain of cardiovascular syphilis and concluded that the pain did not differ from that in coronary artery or in aortic-valve disease Our personal observations accord with their conclusion

TABLE IV—AGE AND SEX OF PATIENTS PRESENTING WITH CARDIAC PAIN

Sex	Age (yr)			
	20–49	50–59	60 or more	Total
Male	34 (*45%*)	54 (*53%*)	38 (*42%*)	126 (*47%*)
Female	32 (*62%*)	15 (*47%*)	7 (*33%*)	54 (*51%*)

Angina in syphilitic aortic incompetence is usually considered to carry a bad prognosis (Friedberg 1949, Levy 1951 Evans 1956, Wood 1956) Jones and Bedford (1943) found that the average survival of their patients who died with syphilitic angina was 29 months (67% of their series had aortic incompetence) In our series 180 patients presented with angina, the mean survival of 121 patients who died was 73 months from the time of onset of angina and 56 months from the time of diagnosis of aortic incompetence (range 0–324 months, see table III) 29 patients are alive, and the mean survival of this group so far is 115 months from the onset of angina and 100 months from the date of diagnosis These figures may be compared with those of Reader et al (1947), who found the mean survival of patients with cardiac pain in syphilitic aortic incompetence to be 9 4 years Fig 3 shows that 39% of patients presenting with angina lived for 10 years and 16% for 20 years Three-quarters of this small group of long survivors are women, more than half have continued to have angina throughout the course of their disease, some have had long remissions

TABLE V—AGE AND SEX OF PATIENTS PRESENTING WITH HEART FAILURE

Sex	Age (yr)			Total
	20–49	50–59	60 or more	
Male	16 ([illegible])	32 (*31%*)	39 (*43%*)	87 ([illegible])
Female	8 (*15%*)	7 (*22%*)	9 (*43%*)	24 (*23%*)

One woman presented in 1930, at the age of 34, with 5 months' history of typical angina of effort and with, more recently, nocturnal attacks On examination by Sir Thomas Lewis she had mild aortic incompetence, the Wassermann reaction was positive She was seen by us 26 years later at the age of 60, she was still having typical attacks of angina The physical signs were unchanged except that she had developed auricular fibrillation the Wassermann reaction was still positive

It is apparent from this series that the prognosis of angina in syphilitic aortic incompetence is not nearly so serious as has been previously held Long survival, particularly in women, is not rare This symptom is especially common in young women in this disease (table IV), unlike heart-failure, angina as a presenting symptom does not become more common with increasing age An average survival of 7–9 years is very like the average survival of patients with angina pectoris in ischæmic heart-disease (White et al 1943)

TABLE VI—RELATION OF DIASTOLIC BLOOD PRESSURE TO SURVIVAL

Diastolic B P (mm Hg)	0–30	35–50	55–70	75 or above
Total no of patients	28	104	144	98
No of dead patients	17	72	82	51
Mean survival of dead patients (mos)	33	40	51	59

Heart-failure

A clear history of paroxysmal nocturnal dyspnœa or definite signs of congestive heart-failure was present in 111 patients (30%) at the time of diagnosis The age and sex of these patients are shown in table V The sex ratio was 3 6 males to 1 female, a higher male preponderance than in the series as a whole Heart-failure became increasingly common in the older age groups

The grave prognosis of heart-failure is clearly shown in fig 3 52% survived 1 year, 31% survived 2 years and only 15% survived 5 years Table III shows that the mean survival of the 89 patients who died was only 18 months (range 0–100 months)

TABLE VII—TREATMENT GROUPS

Group	Males	Females	Total
1 Inadequately treated	51	11	62
2, Arsenic and or bismuth	43	20	63
3 Penicillin alone	28	14	42
4 Penicillin plus arsenic or bismuth	49	28	77

Diastolic Blood pressure

In the absence of associated hypertension or of heart failure the diastolic blood-pressure is accepted as a good guide to the severity of aortic incompetence Table VI shows the relation of the diastolic blood pressure to survival It confirms the impression that patients with the lowest diastolic pressure have the poorest prognosis

Effect of Treatment on Survival

Information on the treatment given was available in 367 patients Barnett (1933) pointed out that patients dying within a year would tend to be included in the inadequately treated group This group would thus be unfairly weighted with seriously ill patients We therefore eliminated 84 patients who died within a year of diagnosis and 39 patients who had been followed for

TABLE VIII—MEAN SURVIVAL OF PATIENTS WHO DIED

—	Group 1	Group 2
Total no of patients	62	63
No of dead patients	53	46
Mean age of dead patients (yr)	55	49
Mean survival of patients who died (mos)	63	115 (group 2a 88 group 2b 135)

less than a year, 244 patients remained for analysis These were divided into four groups according to the treatment given (table VII)

The criteria for inclusion in each group were as follows

Group 1 patients who received only potassium iodide and mercury by mouth and less than 6 injections of arsenic or bismuth

Group 2 patients who received at least 6 injections (about 3 0 g) of arsenic or 6 injections (1 2 g) of bismuth This group was later subdivided into

Group 2a a "partly treated" group who received 6–11 injections (about 3 0–5 5 g) of arsenic or 6–17 injections (1 2–3 4 g) of bismuth

Group 2b a "fully treated" group who received at least 12 injections (6 0 g) of arsenic or 18 injections (3 6 g) of bismuth or 6 *injections (3 0 g) of arsenic* plus 9 *injections* (1 8 g) of bismuth.

Group 3 patients who received at least 4 0 mega units of penicillin in 8 days (most patients had received a considerably larger dose)

Group 4 patients who received the above mentioned course of penicillin and at least 6 injections of either arsenic or bismuth

As will be seen, considerable difficulty was found in ensuring that the different groups of cases were truly comparable It was necessary to eliminate many patients, and the final size of each group is relatively small Even then it is impossible, because of the natural history *of the disease, to be certain that the results are of definite* significance

Comparison of Arsenic and Bismuth with "Inadequate Treatment"

Table VIII shows the mean survival of the patients who died in groups 1, 2a, and 2b If group 1 is compared with group 2, it appears that the survival period was nearly doubled by treatment with either arsenic or bismuth Further examination of these figures, however, revealed three important fallacies (1) 44% of group 1 were aged more than 60, compared with only 13% of group 2, (2) 34% of group 1 had heart failure at diagnosis, compared with only 16% of group 2, and (3) group 1 contained 80% males and group 2 only 67% males All these factors combined to load the "inadequately treated" group with patients having a poorer prognosis for other reasons Accordingly, all patients aged more than 60 and all patients with heart failure were eliminated The amended results are shown in table IX These selected groups, though small, were more comparable for sex and age, the balance slightly favouring the "inadequately treated" group

TABLE IX—MEAN SURVIVAL OF PATIENTS WHO DIED AGED LESS THAN 60 WITHOUT HEART FAILURE

—	Group 1	Group 2a	Group 2b
Total no of patients	27	17	28
No of dead patients	22	13	20
Sex ratio of dead patients	M 11/F 8	M 9/F 4	M 14/F6
Mean age of dead patients (yr)	48	50	49
Mean survival of patients who died (mos)	100	110	151

Similar results were obtained by calculating the survival of these selected patients from groups 1 and 2b according to the life table method (see fig 4 and table X) This method, of course, utilises the living and untraced patients as well as the dead and therefore gives a truer estimate of survival The difference in the percentage survival at 10 and 20 years is statistically significant (P approximately 0 03 and 0 005 respectively)

From the results of both methods of calculation it seems justifiable to conclude that intensive treatment with arsenic and/or bismuth substantially increased the period of survival

Comparison of Penicillin with Arsenic and Bismuth

The difficulties of assessing the effects of treatment are even greater as regards penicillin than as regards arsenic and bismuth 119 patients had been treated with penicillin 42 alone and 77 with either arsenic or bismuth Analysis of the patients who received penicillin alone (group 3) shows that, as in group 1, there was a high proportion of elderly and ill patients Thus 46% of group 3 were aged more than 60, compared with only 22% of group 4 26% of group 3 had heart failure, compared with only 10% of group 4

It therefore appears that the elderly and ill patients who, in pre-penicillin days, would have been "inadequately" treated are now given a course of penicillin alone The younger and fitter patients in this series have usually received at least one course of arsenic or of bismuth in addition to penicillin Moreover 35 patients in group 4 were symptom free at the time of diagnosis, this would favourably influence the prognosis of this group, since hardly any patients in the other groups were asymptomatic

TABLE X—EFFECT OF TREATMENT ON PERCENTAGE SURVIVAL RATES (EXCLUDING PATIENTS AGED MORE THAN 60, ASYMPTOMATIC PATIENTS, AND PATIENTS WITH HEART FAILURE)

—	Group 1	Group 2b	Group 3	Group 4
Males	19	17	10	15
Females	8	11	8	13
Total	27	28	18	28
Mean age (yr)	48	48	49	49
Percentage survival				
At 1 yr	100	100	100	100
" 2 yr	92	100	83	93
" 5 yr	76	88	83	85
" 10 yr	31	60	50	63
" 15 yr	10	52		
" 20 yr	5	35		

Another difficulty is that in groups 3 and 4 more than half the patients are still alive, it is thus impossible to calculate reliable figures for the mean survival of patients who died in these groups

We therefore calculated the survival-rates of groups 1, 2b, 3, and 4 by the life table method after eliminating asymptomatic patients, and patients aged more than 60, and patients with heart failure The results are shown in fig 4 and table X

It appears that the combination of penicillin with arsenic or with bismuth is not better than a full course of arsenic or of bismuth alone Patients treated with

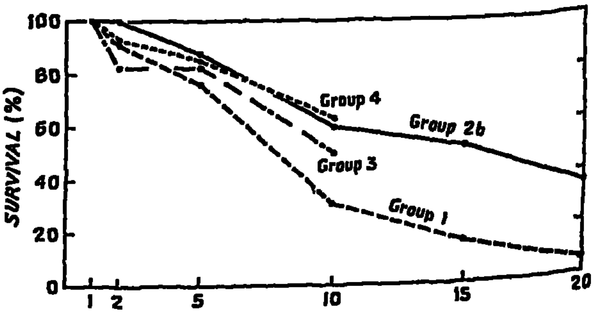

Fig 4—Effect of treatment on survival group 1, "inadequately treated", group 2b, arsenic and/or bismuth, group 3, penicillin alone group 4, penicillin plus either arsenic or bismuth

enicillin alone, however, had a rather lower survival-ate than patients in groups 2b and 4 The 'inadeuately" treated group fared worst of all.

Discussion

The previous literature on the prognosis of syphilitic heart-disease is confused and difficult to interpret Uncomplicated aortitis, aneurysm, and aortic incompetence have often been grouped together Many of the series are too small for reliable statistical assessment

One of the earliest reports in this field was that of Bruce (1911), who estimated that the mean survival of 24 patients who had died with cardiovascular syphilis was 5·3 years from the onset of symptoms Not all these patients had aortic incompetence

Cotton (1926) reported a controlled series of 114 patients with aortic incompetence, half of whom received annually a 6 week course of arsenical injections The treated and control patients "closely resembled each other in age, symptoms and signs" During 5 years observation he found a mortality rate of 24% among the treated patients and 34% among the controls

Moore and Danglade (1930) and Moore et al (1932) found a mortality rate of 90% in untreated patients with all varieties of cardiovascular syphilis during 5 years' observation; the comparable mortality among the treated patients was only 40% The mean survival of untreated patients with aortic incompetence alone was 32 months from the onset of symptoms, the mean survival of the treated patients was 65 months

Barnett (1933) criticised these results, he pointed out that the inadequately treated group was heavily weighted with patients with heart-failure and with patients dying within a year He presented a series of 99 patients which showed the fallacy of drawing conclusions from groups of patients that were not initially comparable

In reply to these criticisms Padget and Moore (1935) re-examined 165 patients previously described by Moore et al (1932) They excluded all the patients who had died within a year of diagnosis They found that, in patients who had died with aortic incompetence, intensive treatment with arsenic and heavy metals improved the prognosis only 1·37 times This figure was said to be not of certain statistical significance

Meanwhile Grant (1933) in the United Kingdom, had published his review of 1000 patients with valvular heart-disease, of whom 189 had syphilitic aortic incompetence 20 also had aortic aneurysm. He found that the average duration of life was more than 5 years, and that more than a third of the patients survived 10 years His good results have been partly attributed to the fact that his patients were ex Service pensioners leading a sheltered life He discussed the influence of treatment on prognosis and concluded that intensive treatment with arsenic reduced the mortality-rate over a 10 year period from 57 to 41%, when cases of aneurysm great cardiac enlargement, and congestive failure were excluded

Stratton's (1935) series is too small to be of much value in assessing prognosis, and his inadequately treated patients include a very high proportion with heart-failure

Cole (1937) eliminated all patients observed for less than a year and found that intensive treatment in cases of aortic incompetence increased the mean survival from 40 to 55 months

Kampmeier and Combs (1940) reported 163 patients with aortic incompetence of whom 128 were Negroes They found that 54·6% of the patients died within 3 years. After excluding patients who died within a year from the onset of symptoms they concluded that treatment with arsenic and bismuth improved the mean survival of their patients who had died from 41 to 89·5 months in white males and from 30·8 to 43·7 months in Negro males

In recent years several papers have been published on 1020 cases of aortic incompetence from the Johns Hopkins and New York Hospitals (Padget et al 1950 Densen et al 1952 Webster et al 1953) In spite of the exceptionally large number of cases no conclusions were reached on the effects of treatment on survival 119 of their patients had received penicillin but no further information was given To give their series clinical value these workers included some patients who were later proved not to have syphilitic aortic incompetence In 14% of 219 necropsies the diagnosis was proved to be wrong If, in this respect, the group that came to necropsy is representative of the entire series, a substantial element of error may have been introduced into the results However, the estimates of the effect of sex, age, angina, and heart failure on prognosis were broadly similar to ours.

Two recent American reviews have appeared in a British journal (1) Beerman (1953) summarises the difficulties in assessing prognosis, and (2) O'Brien et al (1955) present 578 cases of cardiovascular syphilis, of whom only 132 had aortic incompetence (70% were Negroes) They concluded that treatment with arsenic and bismuth had no demonstrable effect on survival, only 10 of their patients were treated with penicillin

Grimble (1955) reported 164 patients with aortic incompetence and aneurysm seen at Guy's Hospital between 1925 and 1944 In a small selected group of patients with aortic incompetence of comparable age without heart-failure adequate treatment with arsenic or with bismuth increased the mean survival from 25·5 months to 54·0 months after the onset of symptoms

From this review of previous work it is apparent that the effectiveness of arsenic and heavy-metal treatment has never been universally accepted (*Lancet* 1956) After excluding all patients dying within a year of diagnosis all patients with heart failure, and all patients aged more than 60 we have been left with two fairly comparable series of patients—"inadequately treated" (group 1) and "fully treated" (group 2b) The results indicate that, in these selected patients, the duration of life after the diagnosis of aortic incompetence has been considerably prolonged by treatment with arsenic and/or bismuth The results in the "partly treated" group (group 2a) are intermediate between those obtained in groups 1 and 2b (table IX) This is further evidence that the prolongation of life is really due to the treatment and not to some hidden bias unconsciously introduced in the selection of cases

No long-term study of the effect of penicillin on survival has yet been published. In view of the large numbers of penicillin-treated patients in the present series who are still alive our results can be provisional only Not until all the patients are dead can a firm conclusion be reached on the efficacy of penicillin With these reservations our results indicate that combined treatment with penicillin and either arsenic or bismuth is not more effective than a full course of either arsenic or bismuth alone Penicillin is, of course, much easier and safer to administer and need not be withheld from any patient, however ill. The survival-rate of patients treated with penicillin alone however, is not quite so good as that of those receiving arsenic and/or bismuth Until further and longer follow-up studies have been published, it appears unjustifiable to rely on penicillin alone. Probably it is best to give at least one full course of arsenic or bismuth to every patient in addition to penicillin

Summary

374 patients with syphilitic aortic incompetence are reported 222 patients died and 102 survive

Of the entire series 75% were alive after 1 year, 54% after 5 years 32% after 10 years, and 14% after 20 years. The mean survival of all those who died was 48 months from the date of diagnosis

Female and younger patients had a more favourable prognosis

49 patients were free from symptoms at the time of diagnosis: this group had a good prognosis, 84% being alive after 5 years

180 patients had cardiac pain at diagnosis It was commoner in females aged less than 50 and carried a relatively good prognosis 46% of the patients survived 5 years and 16% survived 20 years The mean survival of all those who died was 56 months from the date of diagnosis

111 patients had heart failure at diagnosis It was commoner in males and older patients and carried a bad

prognosis only 15% of the patients survived 5 years The mean survival of those who died was only 18 months from the date of diagnosis

The diastolic blood pressure was a good index of prognosis

In untreated patients the E S R was raised in 80% of patients without congestive heart-failure and in 64% of patients with congestive heart-failure The mean E S R before treatment was 32 mm and after penicillin 13 mm There was some evidence that an E S R above 50 mm was a bad prognostic sign

Calcification of the ascending aorta was noted in 35% of 64 radiographs personally examined It was commoner in elderly patients

After the exclusion of patients dying within a year of diagnosis, patients with heart-failure, asymptomatic patients, and patients aged more than 60 years, the mean survival of the patients who died was increased from 100 to 151 months by intensive treatment with arsenic and/or bismuth, after 10 years 60% of the "fully treated" group survived, compared with only 31% of the "inadequately treated" group This difference is statistically significant

Many of the patients treated with penicillin are still alive Conclusions in the present series must be regarded as provisional only There was no evidence that patients treated with penicillin and either arsenic or bismuth had a better prognosis than patients fully treated with either arsenic or bismuth alone Patients treated with penicillin alone, however, appeared to have a slightly poorer prognosis

It is therefore recommended that, on the information at present available, patients should receive at least one full course of either arsenic or bismuth and a full course of penicillin

We wish to thank Dr Maurice Campbell, Dr Evan Bedford, Dr Paul Wood, Dr William Evans, Dr Graham Hayward, Dr Wallace Brigden, Dr Kenneth Latter, Dr Wilfrid Oliver, and Dr James Campbell for permission to study patients under their care, Dr Bedford, Dr Wood, and Dr Evans for their valuable criticism of this paper, Dr Peter Kerley, Mr Ambrose King, and Mr J A Heady for much helpful advice, and the many general practitioners who kindly gave us information about their patients

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DISCREPANCIES IN THE ERYTHROCYTE-SEDIMENTATION TEST IN RHEUMATIC FEVER

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The reproducibility of the erythrocyte sedimentation (E S R) test was examined by Wintrobe and Landsberg (1935) in 9 cases (diagnosis not stated) The greatest standard deviation observed in multiple tubes containing similar oxalated blood was less than 1 mm, and Wintrobe and Landsberg concluded that E S R s may be considered to be significantly different when their difference is greater than 2 mm

For a year E S R s in this unit have been determined by two methods, each done in duplicate The degree of agreement in each pair of tubes was much less satisfactory than that noted by Wintrobe and Landsberg

TABLE I—E S R AT INITIAL EXAMINATION OF BLOOD

Case no	Arithmetical difference between duplicates (mm)		E S R (Westergren) (mm in 1 hr)
	Heparinised blood	Citrated blood	
1	0	3	12
2	2	0	16
3	1	10	105
4	0	2	15
5	5	0	48
6	6	0	70
7	0	0	70
8	2	0	50
9	0	0	55
10	0	0	18
11	5	0	122
12	2	0	43
13	0	0	71
14	0	0	80
15	11	1	126
16	6	1	58
17	7	1	32
18	7	0	62
19	6	0	8
20	4	2	56
21	0	0	72
22	12	3	100
23	2	0	67
24	0	2	18
25	11	1	52
26	9	2	32
27	3	5	63
28	42	1	67
29	5	2	36
31	12	1	39
32	12	0	117
33	1	1	71
34	2	6	79
35	11	3	99
36	2	1	31
37	7	3	71
38	36	11	84
39	9	0	29
40	0	1	7
41	3	1	28
42	1	0	90
43	0	0	8
44	17	1	81
45	2	3	43
46	1	0	12
47	6	0	73
48	47	0	116
49	3	0	127
50	12	1	64
51	0	1	54
52	0	2	64
53	20	0	38
54	1	1	100
55	0	1	10
56	35	2	85
57	20	2	63
58	11	1	92
59	35	0	103
60	3	0	41

The sample of blood from case 30 was lost by accident

Methods

60 consecutive patients admitted with either acute or subacute rheumatic fever were studied After an initial examination of their blood treatment was started, usually with aspirin Their blood was examined again on the fourth day of treatment, on completion of a week's treatment, and thereafter weekly

Blood was collected by venepuncture A syringe containing 1 ml of 3 8% sodium-citrate solution was filled to the 5 ml mark with blood, then the syringe was disconnected (the needle remaining in the vein), and 5 ml of blood was allowed to flow from the needle into a small siliconed container The bottom of the container was covered by a film of dried heparin (250 units) Each sample of blood was used to fill two Westergren sedimentation tubes Thus of the two methods used for sedimentation tests the first corresponded to that described by Westergren (1921), and the second was similar to the Westergren method except that the Westergren tube was filled with heparinised blood

Tubes were set up within 1 hour of collection of blood, tubes of any pair were always placed side by side in the same rack Readings were made at the end of 1 hour Correct filling of the tubes and reading of the results were personally supervised by one of us

TABLE II—SERIOUSLY DISCREPANT READINGS IN DUPLICATE ERYTHROCYTE-SEDIMENTATION TESTS

Case no	E S R (mm in 1 hr)				Fibrinogen (g per 100 ml)	P C V (%)
	Heparinised blood		Citrated blood			
	Tube 1	Tube 2	Tube 1	Tube 2		
Initial examination						
28	95	53	67	66	0 75	34
38	10	46	78	89	1 14	46
48	97	50	116	116	0 82	38
56	10	45	84	86	0 68	43
59	26	61	103	103	0 76	36
After 4 days treatment						
18*	106	83	83	82	0 78	37
32	55	101	103	102	0 82	36
36	82	59	68	70	0 67	40
44	65	47	80	80	0 87	38
58*	33	70	123	123	1 03	38
30	105	95	89	115	0 96	35
After 1—6 weeks treatment						
15	42	18	27	27	0 72	45
27	4	29	36	37	0 41	43
42*	95	47	130	130	0 63	35

* Cases in which the next or a later E S R test showed a similar serious discrepancy (more than 20 mm)

The remainder of the heparinised specimen was used to determine the packed cell volume (P C V) and the plasma fibrinogen level The gravimetric method of Foster and Whipple (1922), with minor modification, was used for estimating the fibrinogen level

Results

Readings at the initial examination of blood are shown in table I The first column shows the difference between the two sedimentation tubes filled with heparinised blood, the second column the difference between the two tubes filled with citrated blood, and the third column the E S R (Westergren) (mean of the two tests) The average arithmetical difference between the readings of the duplicates containing heparinised blood was 7 8 mm, and citrated blood 1 3 mm

Coincidentally with improvement in the rheumatic state and fall of the plasma fibrinogen level the discrepancies between the readings of duplicates became smaller and less numerous

A serious difference (more than 20 mm) between the readings of a pair of tubes containing similar heparinised blood was noted in 13 patients (table II) These major discrepancies were rare except during the week following admission In cases 18, 42, and 58 major discrepancies were found at two separate examinations In the remaining 10 patients though inconsistencies were noted at later examinations they did not reach 20 mm of difference

TABLE III—MULTIPLE E S R FOUND BY THREE METHODS OF TREATING BLOOD OBTAINED AT THE SAME VENEPUNCTURE

Case no	E S R (mm in 1 hr)											
	Heparinised blood				Citrated blood				Diluted heparinised blood			
	Tube 1	Tube 2	Tube 3	Tube 4	Tube 1	Tube 2	Tube 3	Tube 4	Tube 1	Tube 2	Tube 3	Tube 4
57	46	72	48	75	64	64	64	62	74	73	73	73
59	26	61	52	73	103	103	100	102	115	115	117	110
60	35	23	29	37	43	46	46	46	44	42	42	

There was only 1 instance (case 30) of a serious difference between the readings of a pair of tubes filled with similar citrated blood (table II)

Careful inspection did not show any abnormality of sedimentation Thus, when a serious difference existed between the readings of a pair of tubes, rather large cell aggregates formed and fell rapidly in one tube, while in the other the cell aggregates were smaller and the period of aggregation more prolonged

Discussion

These results imply that E S R tests with heparinised blood are not infrequently misleading when used to follow the course of rheumatic fever

The possibility that the discrepancies found were due to some unsatisfactory feature in technique must first be considered The results were examined to see whether the first tube filled tended to show either a higher or a lower E S R from that of the second tube, but there was no such trend (table II) Tubes of any pair were set up side by side in the same rack and were therefore exposed to the same extraneous physical factors (e g temperature) A pair of tubes and their contents would be identical, provided that the specimen had been properly mixed before the tubes were filled To test this the blood was collected from each tube after the reading at 1 hour and its P C V was determined This was done on 11 occasions when there was a serious difference between the readings of a pair of tubes, and proved that mixing had been satisfactory in all 11 cases

When 10 mg of oxalate per 5 ml of blood was used as anticoagulant, Wintrobe and Landsberg (1935) found that the E S R did not differ significantly from that of heparinised blood It therefore seemed likely that if heparinised blood showed inconsistent sedimentation oxalated blood would do so too In 2 cases in which a

TABLE IV—E S R IN BLOOD OF PATIENT AGED 24 WITH GONOCOCCAL ARTHRITIS

December	E S R (mm in 1 hr)							
	Heparinised blood				Citrated blood			
	Tube 1	Tube 2	Tube 3	Tube 4	Tube 1	Tube 2	Tube 3	Tube 4
17	70	61	76	110				
21	115	117	100	95				
28	93	78	57	97				
29	53	107	97		[illegible]	51	52	
30	50 40*	45 77*	[illegible] 38*	77 35*	[illegible]	[illegible]	[illegible]	54

Heparin 50 units per 5 ml of blood was used except for values marked * where 1 0 units per 5 ml blood was used On each occasion tubes 1 2 3 and 4 in that order were filled from the same sample of blood and placed in the same rack serious discrepancy was noted between the readings of sedimentation tubes containing heparinised blood another 5 ml of blood was obtained and collected in the oxalate mixture of Heller and Paul (1934) From each oxalated specimen four Westergren tubes were filled, the readings at 1 hour were 34, 17, 35, and 55 mm, and 58, 114, 108, and 61 mm

The column of blood in the Wintrobe tube is identical with that in the Westergren tube except that it is half the length (100 mm instead of 200 mm) In the shorter (Wintrobe) tube maximal sedimentation (due to packing) occurs more rapidly, and discrepancies at 1 hour would probably be less common than in Westergren tubes Therefore the frequency with which the classical Wintrobe method would show a lack of reproducibility cannot be inferred from the present results

The question whether the more reproducible results obtained with citrated blood were due to the effect of dilution or to the citrate ion was investigated, and it was concluded that dilution was the important factor In 3 cases multiple sedimentation tubes were filled with heparinised blood, citrated blood, and heparinised blood diluted with physiological saline solution (1 ml of saline solution to 4 ml of blood), all the blood having been obtained at the same venepuncture The results appear in table III

Of the present 60 patients with rheumatic fever 14 had a grossly inconsistent E S R at some stage of their illness This was found by setting up duplicate tubes, so the true incidence is almost certainly higher For example, in 1 case four tubes containing blood from the same sample showed readings (as mentioned above) of 34, 17, 35, and 55 mm Since six different pairs of these four tubes can be set up and only one pair agree, the chance of agreement is 1 in 6 (17%) Additional tubes from the same sample of blood might change that chance

Results obtained in a patient with gonococcal arthritis (table IV) indicate that inconsistency in the E S R is not confined to patients with rheumatic fever

Summary

In following the course of rheumatic fever E S R tests made with either heparinised or oxalated blood may be seriously misleading, results being obtained which are not reproducible

Repeated E S R tests were made both with citrated and with heparinised blood in 60 patients with rheumatic fever

In 13 patients (22%) there was at some stage in the disease a serious difference (more than 20 mm) between the readings of duplicate Westergren sedimentation tubes filled from the same heparinised sample of blood

Discrepancies persisted when oxalated blood was used instead of heparinised blood

In the shorter Wintrobe tube discrepancies would probably be less common (owing to earlier packing) than in the longer Westergren tube, therefore the frequency with which the classical Wintrobe method shows discrepancies cannot be inferred from the present results

In case 30 there was on one occasion a serious difference between the readings of a pair of tubes filled with citrated blood The more reproducible sedimentation of citrated blood seems to depend on dilution and not on the presence of citrate ions

Serious discrepancies between the readings of duplicate E S R tests are not confined to patients with rheumatic fever, they were found in a patient with gonococcal arthritis

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TREATMENT OF POST-HERPETIC NEURALGIA*

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PAIN is a subject of absorbing interest, but many patients with chronic pain are difficult people to assess, and the neurologist may feel justified in introducing some guile into his programme of cure Pain thresholds can be influenced by so many factors that he should at times be prepared to embark on what might be termed a game of bluff with his patients' higher cerebral mechanisms Thus he should not despise building up a certain atmosphere of the miraculous around his pain clinic, for this introduces a desirable physiological influence at a most important level

Among the more difficult varieties of chronic pain is post-herpetic neuralgia, which develops in about one case in ten of herpes zoster This complication cannot be correlated with the severity of the illness, but is much more likely in the elderly—the patients usually being over the age of 60, and often over 70

The pain seems to be a continuation of the discomfort felt before the rash appeared, and the patients may become demoralised by it It is arguable that all such patients have a low pain threshold, and for their excessive suffering we may, if we so wish, blame their parents, who during their early years failed to establish a healthy indifference to minor traumata and other painful states! However, these patients cannot be treated successfully by psycho-analysis

What we loosely term the psychogenic factor is a physiological process which is interfered with by frontal lobectomy Beecher (1956) calls it "the processing" of the pain mechanism It is a personal matter, and, as it is liable to take charge of the clinical picture if the pain continues for long, we should make a plea for intensive treatment, preferably with admission to hospital, within a very few weeks of the pain developing The elderly patient who has had severe pain for 5 or 10 years is not *easy to deal with*

Post-herpetic neuralgia resembles causalgia, which is associated, for example, with a partial lesion of a sensory nerve All who have experience of nerve injuries know the importance of full activity of the affected part if causalgia is to be avoided, and, in the same way, causalgia after herpes zoster is commoner in those who sit at home, doing little but nursing and protecting the sensitive area This is a common but fundamental mistake in dealing with any such pain, and we find that as soon as the rash is healed the affected tissues should be moved freely, and the scarred area rubbed General exercises help It is probable that the higher prevalence of pain in the elderly is correlated more with their inactivity than with their age We have all visited these sufferers in their homes, where, in a stuffy room, the patient sits crouching beside a fire, brooding over her pain And we shall do well in these circumstances to remove her from the unhealthy environment to the matter of fact atmosphere of a hospital ward For, although successful treatment usually depends more on physical than on psychological procedures, success breeds success in the treatment of chronic pain, and our results now seem to be so good, that the patient, soon after admission, comes to feel that it is just a matter of time before the nerves responsible are brought under control Among the many whose pain has a genuine physical basis, there are a few hysterics who are determined to make as much fuss as possible, and for them the concentrated treatment introduces a valuable element of discipline their symptom, which was once a protection, becomes a liability, so they cast it aside

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* Based on a communication to the Association of British Neurologists, Nov 16, 1956

Material and Methods

The present study concerns a hundred cases of post-herpetic neuralgia seen during the past 10 years or so—fifty referred to our neurosurgical colleagues and fifty referred to our neurological unit The average age in both groups was 66 years, and 60% were women In thirty-two of the surgical group, the trigeminal nerve area was affected, but in our group the number was twenty-three

The surgical group was somewhat negative from the therapeutic point of view, because surgery or alcohol nerve block was generally (and very wisely) avoided, but in recent years most of the medical patients have been admitted to hospital and submitted to concentrated treatment of one kind or another, with results which are so encouraging that we have come to look forward to admitting patients with post-herpetic neuralgia Certainly, our results are improving with experience

As has already been mentioned, the type of pain in these cases is one which is associated with a partial lesion of a peripheral nerve, and has features similar to those observed in causalgia There is a raised threshold to some forms of sensation, and, indeed, there may be complete anæsthesia of the scarred area (especially when the first division of the trigeminal nerve is involved) Often, however, there is also some hyperæsthesia in the scarred area, or at the edge which is overlapped by adjacent nerves (Weddell et al 1948) It has become evident that when hyperæsthesia is a prominent feature, the chances of cure are specially good

It is quite easy to remove the hyperæsthesia temporarily by blocking nerves or infiltrating the skin with procaine, and it is important to study, without delay, the effect of this procedure on the spontaneous pain In many instances this simple procedure gives remarkable relief for several hours, and frequent repetition of the procaine block often leads to increasing periods of freedom until relief may be permanent and the affected area no longer hyperæsthetic Procaine block of the nerves supplying the skin adjacent to the scarred area may be specially important Thus in ophthalmic herpes, block of the occipital nerves on the side involved may be beneficial, as well as the supratrochlear and supraorbital nerves on the opposite side

Hyperæsthesia can be abolished also by a mechanical vibrator It still does not seem to be widely known that a vibrator with a vulcanite applicator, held lightly on a hyperæsthetic area *for 5–10 minutes, acts* as a local anæsthetic, without the trauma of a needle, and removes cutaneous hyperæsthesia It does the same with a tender scar We used these appliances first for percussing neuromata in amputation stumps (Russell and Spalding 1950), and we now use them freely in the hospital ward, and when necessary lend them to the patients to take home Resting the sensitive area on a hard surface for half an hour has, by the action of direct pressure a similar effect in removing hyperæsthesia, and is especially useful where the trunk dermatomes are affected

Thus if there are areas of hyperæsthesia, remarkable benefit is derived from the removal of this sensitivity Presumably the nerve fibres concerned with firing hyperpathic sensations are very easily traumatised into inactivity by a vibrator

Vibrator ('Pifco massager') being applied by the patient (case 4) to the suboccipital region, for its local anæsthetic effect

This effect, although only temporary at first, on repetition soon becomes longer-lasting and eventually permanent The relief often provided by the removal of hyperæsthesia shows that, whatever the lesion is in the posterior-root ganglia, this is not where the distressing afferent impulses originate It is natural that, as the pain is relieved, the patient's confidence in the result of the treatment rises, and this improves matters still further Whichever method is used, repeated treatments are followed by disappearance of the hyperæsthesia, and this commonly leads to striking relief of spontaneous pain

This removal of all hyperæsthesia from the scarred and the adjacent areas may be the only treatment required, but sometimes pain persists and further steps are necessary

One of the most useful of these is to observe the effect of interspinous hypertonic saline, 0·4 ml of 6% saline being injected near the segment affected (Kellgren 1939) This may aggravate the pain temporarily, but may then be followed by relief for several hours When the face is involved, suboccipital injection is often surprisingly appropriate The ligamentous tissue into which these hypertonic saline injections are given lies only a short distance under the skin—deep injections are not given, and indeed might be dangerous

The ophthalmic cases may be difficult, and it may be helpful to shave the hair well clear of the anæsthetic zone, to give access to the adjacent areas Unlike the patient with *tic douloureux*, who will submit to anything, these patients may refuse to have their hair cut—"it's not so bad as all that"

Other methods, such as locally applied galvanism, procaine ionisation, sympathetic nerve block, and skeletal traction, may all be useful in certain circumstances In general, it is desirable to follow one treatment quickly with another, especially in the more difficult cases Some positive local action of a physical type, several times daily, may be desirable

We have no experience of extensive skin flap reflection, as advocated by Abbott and Martin (1951) and others, but this should be very successful if the flap includes a strip outside the scarred area, supplied by adjacent nerves In our opinion, X-ray therapy and alcohol nerve block should not be used in the treatment of herpes zoster at any stage X irradiation often makes matters worse in the chronic stage, and seems undesirable in the acute stage, because it helps neurotropic viruses to invade the nervous system Nerve-root section and alcohol nerve block also do not seem to us to be desirable for these cases Operations on the pain-tracts of the spinal cord are unlikely to give relief, while frontal lobe operations are an indication of defeat which we have so far avoided

Results

Patients seen within a few weeks of the acute stage are naturally the easiest to deal with, but even those who have suffered for many years respond to a determined attack " from all sides "

It is clear from follow-up studies that the great majority of the patients treated in recent years have been considerably relieved, and in some a spectacular cure has been achieved However, the methods used have been improving steadily and it seems more helpful to describe the treatment given to the last few patients treated They have not yet been followed for long, but with good early results there is generally some lasting relief

The following are the last five cases whose treatment has been completed

Case-reports

Case 1—A woman aged 64 developed ophthalmic herpes on the right side on Oct 23, 1955, and was admitted for 10 days to the Oxford Eye Hospital, where aureomycin was given After this illness, she complained of severe right frontal pain, and became irritable, depressed, and sleepless For this, many drugs, including pethidine, were prescribed, but no local treatment was given 2 months later, there was severe hyperæsthesia in the scarred area, which she had not dared to touch or wash on this account There was scarring in the right frontal region, along with keratitis and periorbital œdema In the scarred area, there was a mixture of sensory loss and marked hyperpathia She was depressed and miserable

The patient was admitted to Stoke Mandeville on Jan 6, 1956, and a vigorous policy was adopted of shampooing the scarred area and repeated massage with olive oil along with local treatment for the ocular inflammation The frontal area was massaged for 10–15 minutes three or four times daily There was considerable osteo arthritis of the cervical spine, and periods of neck traction (6 lb) while she was lying in bed added considerably to her comfort These simple measures were followed by remarkable relief and improvement in morale She was discharged on Jan 25, and 6 months later her condition was reported to have improved steadily since she left hospital

Case 2—A man aged 46 developed herpes zoster in the right occipital region in August, 1955 After this, there was persistent pain in the affected area with frequent sharp spasms of severe neuralgia He was admitted to Stoke Mandeville Hospital on Jan 20, 1956, and the only abnormality was marked tenderness over the scarred area Vigorous local massage was begun without delay On one occasion, 0 3 ml of 6% saline was injected into the interspinous ligament between the spines of the 2nd and 3rd cervical vertebræ, the pain was reproduced in the scarred area for 5 minutes, but then disappeared for several hours Treatment was then continued with a mechanical vibrator and massage to the sensitive area, each being applied three times a day for 10–15 minutes When he was discharged on Feb 2, the pain had all but disappeared, but he was supplied with a vibrator to use at home Seen on Oct 20 he had remained comfortable, except for some short periods of pain lasting 5–10 minutes once a day It was not considered necessary to readmit him

Case 3—A man aged 71 developed ophthalmic herpes zoster on the left side in November, 1952 Since then, he had had continuous pain in the left half of his scalp as though a nail were being driven through my head " Treatment with chlorpromazine and injections of vitamin B_1 (aneurine hydrochloride) and B_{12} (cyanocobalamin) had failed to give relief When he was admitted to Stoke Mandeville Hospital on June 20 1956, there was considerable scarring and some anæsthesia of the scalp in the left frontal region with a very tender area over the left eyebrow the frontal pain was also aggravated by pressure on the upper alveolar margin where two teeth had been extracted 2 years previously

Procaine block of the left supra orbital auriculotemporal and greater occipital nerves abolished the pain for the first time since its onset the sensitivity of the alveolar margin also disappeared He was then encouraged to apply a mechanical vibrator to the sensitive areas for 10 minutes every 2 hours while he was in hospital until his discharge on July 2 During this time he had *no* return of pain, but *it* returned 2 weeks after discharge—he had stopped treatment owing to pressure of work, but he was not prepared to come into hospital again until he had more spare time It is obviously desirable that a further period of intensive local treatment should be given

Case 4—A man aged 60 when first seen in July, 1950, had had severe ophthalmic herpes zoster a year previously Since then there had been a severe pain in the left frontal region, which was heavily scarred He had a hyperæsthetic zone over the upper edge of the scarred area, and tapping here caused a shooting pain above the left eyebrow He was first advised to press firmly with the wooden handle of a clothes brush over the sensitive zone for 10 minutes three times daily, and this gave considerable relief He also found that resting the sensitive frontal region on a table for 10 minutes had a relieving effect, and during the succeeding 5 years there was a steady tendency to improvement, provided he continued to apply local pressure as a numbing agent

He was, however, admitted to Stoke Mandeville Hospital on Sept 29, 1956, to see whether more could be done, for some pain had now spread to the suboccipital region on the left side This discomfort was relieved by injecting procaine into the left suboccipital muscles, and the long standing discomfort was abolished for 8 hours by blocking the supra orbital, supratrochlear and auriculotemporal nerves These injections were repeated two or three times, and the temporary relief was prolonged by using a mechanical vibrator which was provided for him to take home

Case 5—A woman aged 80 developed herpes zoster in the left mid thoracic zone in June, 1955, and complained of persistent severe pain in the scarred area There was also marked hyperæsthesia

She was admitted to Stoke Mandeville Hospital on Oct 27, 1956, and daily procaine blocks to the sensitive intercostal areas were given for 3 days Local massage was given frequently, and procaine by ionisation was applied twice daily for a week over the whole sensitive area After some further procaine nerve blocks, the hyperpathia almost disappeared and could be further relieved by vigorous massage which she was encouraged to apply herself several times a day

Discussion

These case records indicate that the first thing to do is to institute vigorous local treatment of one kind or another, and to combine this with local anæsthetic procedures, of which the mechanical vibrator is the most useful, for it can be applied by the patient himself as often as required

Some of our methods are probably having some effect by providing competing stimuli to the thalamus as well as by actually blocking afferent discharges However, in these cases it is important to use every trick of thalamic distraction one can think of Thus a competing stimulus may well explain the effect of counter irritation, or the remarkable relief, in some cases of causalgia, when cold is applied The electrical treatment of neuralgia, so much used 50 years ago, may have a similar basis In any case, it is clear that this wide approach to the problem of pain, however " organic " it may be, is well worth while

The methods described here are clearly applicable to many other forms of intractable pain, as has already been reported by Fischer Williams (1956)

Summary

A hundred cases of post herpetic neuralgia are considered, and the problems of treatment discussed

Post herpetic neuralgia can usually be relieved by concentrated treatment to reduce pain thresholds in the tissues adjacent to the scarred area

The removal of hyperæsthetic zones is important, and for this the repeated use of procaine nerve-block and of a mechanical vibrator, are specially valuable

The methods used in treating five recent cases are described

We are indebted to Mr J P Pennybacker for permission to refer to patients under his care

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A DIET RESTRICTED IN REFINED CEREALS AND SATURATED FATS:

ITS EFFECT ON THE SERUM-LIPID LEVEL OF ATHEROSCLEROTIC PATIENTS

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IN parts of the world where atherosclerosis is common the quality and quantity of the diet of the majority of the population differ significantly from those in countries where the disease is rare Atheroma may possibly be caused by a high intake of cholesterol, fat, calories, saturated fats (with relative deficiency of essential fatty acids), and degerminated carbohydrates (with deficiencies of vitamins and minerals) (Van Handel 1955)

Lowering of serum-cholesterol by a diet low in lipids has been reported by Keys (1952) Morrison (1955), similarly, used for atherosclerotic patients a low lipid diet supplemented with wheat germ Groen et al (1952) reported a fall in serum cholesterol in normal volunteers on vegetable diets, while Kinsell et al (1953) and Beveridge et al (1955) found that the serum-cholesterol was lowered by a high intake of certain oils which are rich in essential fatty acids The work of Bronte Stewart et al (1956) confirms that in short-term feeding experiments the serum cholesterol level is related to the source of the fat consumed An interesting new finding was the cholesterol depressing action of highly unsaturated marine oils

In the past 3 years we have routinely treated atherosclerotic patients with low-fat diets—i e, diets in which less than 20% of the total calories is derived from fat These diets reduced serum lipids in some cases but were without effect in others, or occasionally even raised the serum cholesterol Furthermore, the majority of patients became mentally depressed and physically weak during severe fat restriction (unpublished observations)

Therefore it was decided to abandon the low fat diet, but to restrict added fat to unsaturated soybean oil Legumes were added to provide a rich source of magnesium manganese, copper, and B vitamins including choline Peanuts and soybean flour provide additional unsaturated fats. Soybean products play an important rôle in the diet of most Oriental peoples A detailed discussion of the composition and the possible value of these food items in the prevention of atherosclerosis was published earlier (Van Handel 1955). The present study reports the effect of this new regimen on the serum cholesterol and phospholipid levels

TABLE I—PATIENTS WITH INITIAL SERUM CHOLESTEROL BELOW 250 MG PER 100 ML

	Serum-cholesterol (mg per 100 ml)			Serum phospholipids (mg per 100 ml)		
	Highest	Lowest	Average	Highest	Lowest	Average
Initial	240	160	215	280	175	240
Final	270	152	215	290	180	240

Methods

Estimations

Serum was extracted with Bloor's mixture Cholesterol was determined by the method of Fidler (1934) and lipid phosphorus by dry ashing with magnesium oxide (Van Handel 1954) Phosphorus was estimated by the method of Fiske and Subbarow (1925)

The Diet

Not allowed.—Lard and other animal fats, shortening, white bread, and foods made from degerminated flour and cereals

Restricted—Margarine and butter to 25 g a day

Allowed ad lib—Whole-wheat bread, liquid soybean oil as cooking fat, lean meat, milk, cheese, and eggs

Obligatory daily supplement—2–3 g of soy lecithin (the approximate amount which is lost in the degumming of 100 g of soybean oil), 25–50 g peanuts 25–50 g peas or beans, and 25–50 g 'Nurupan' (whole soybean flour)

Thirty-four patients followed the diet for periods ranging from 30 to 360 days Ten of them had been treated with a low-fat diet for from 3 months to several years before changing to this regimen All had previously shown clinical signs of coronary insufficiency, with or without myocardial infarction About half the patients were admitted to hospital for a period of 4 to 12 weeks Observations could then be made while they were under strict dietary control Of course, it is much more difficult to maintain control in outpatients, but a number of patients who did not follow the diet consistently have been excluded from this report

Results

In a group of sixteen patients with initial serum cholesterol levels under 250 mg per 100 ml, the diet had no significant effect (table I) The change of serum cholesterol was 0–10% They took the diet for 30–300 days (average 160)

TABLE II—PATIENTS WITH INITIAL SERUM CHOLESTEROL ABOVE 235 MG PER 100 ML

	Serum-cholesterol (mg per 100 ml)			Serum phospholipids (mg per 100 ml)		
	Highest	Lowest	Average	Highest	Lowest	Average
Initial	400	235	300	380	220	290
Final	250	172	228	282	180	250

Six of these sixteen had been taking a low fat diet for 90–300 days before they were transferred to the experimental diet This change did not cause a rise of serum lipids

Fourteen patients with initial levels of cholesterol over 235 mg per 100 ml showed a steady decrease in serum-cholesterol (table II) They took the diet for 30–330 days (average 110) Four of these fourteen had previously been treated with a low-fat diet and had maintained their high serum cholesterol during this period

Some typical data in a few patients, who responded well to the diet, are presented in detail in table III

Discussion

The present study was undertaken to evaluate the effect of a regimen low in saturated fatty acids and degerminated carbohydrates on patients with clinical

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TABLE III—SOME TYPICAL GOOD RESULTS. IN THE PERIOD MARKED "L" THE PATIENT WAS TAKING A LOW-FAT DIET

Patient	Day of experiment	Cholesterol (mg. per 100 ml.)	Phospholipids (mg. per 100 ml.)
Man aged 51	0	400	380
	30	350	292
	45	310	275
	75	260	265
	100	210	250
Man aged 58	−200 } L	307	
	0	300	250
	50	240	220
	100	230	210
	200	220	230
	332	232	210
Woman aged 55	0	314	320
	15	277	275
	80	255	260
	110	227	260
Woman aged 58	0	275	290
	90	223	230
	200	215	225
	300	200	220

atherosclerosis. The patients did not object to the substitution of soybean oil for solid fats. In most cases the whole family changed over to soybean oil as the source of cooking fat. Soybean flour was incorporated in several dishes such as soup, biscuits, and breakfast cereal, but some patients preferred to take it in a glass of milk or water. Not only those who were previously kept on diets very low in fat, but also the patients who had not previously followed a special diet, showed noteworthy improvement of disposition and of the ability to perform normal activities. Though no patient died, it would be premature to draw clinical conclusions, for we had no controls.

A steady drop of serum cholesterol was achieved and maintained during the many months of observation, but only when the initial values were high. A considerable number of our clearly atherosclerotic patients, on free diets, had serum cholesterols between 160 and 250 mg. per 100 ml. The blood lipids of these did not change significantly on the experimental diet.

The value attached to cholesterol-depressing diets is closely connected with the common belief that the lipids in atheromatous deposits derive from the plasma, but there is no strong experimental evidence for this assumption. The alleged atherogenic effects of fats in general, and of highly saturated fats (without cholesterol supplements) in particular, have not been confirmed by clear-cut experiments. In Java, where the highly saturated coconut oil is the main source of cooking fat, the incidence of clinical atherosclerosis is very low (deLangen 1935). To investigate whether saturated fats play a rôle in atherogenesis, data from such countries as France and Argentina, where the consumption of meat and dairy products is large and where unsaturated oils are used for cooking, should be compared with similar data from (non-Western) areas where coconut oil is the main source of cooking fat.

It is unlikely that a diet which merely substitutes unsaturated for saturated fats can prevent atherosclerosis; therefore our tentative diet includes other factors in addition to essential fatty acids.

Our results are compatible with the hypothesis that high blood lipids in atherosclerosis are caused or maintained by deficiencies in Western staple food.

Summary

A diet restricting animal fats and degerminated flour and with supplements of soy lecithin, soybean oil and flour, peanuts, and peas or beans, was successful in lowering the serum lipids in atherosclerotic patients where they had previously been high.

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HYPERNATRÆMIA AND HYPERCHLORÆMIA IN BULBAR POLIOMYELITIS

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THE association of high serum sodium and serum chlorine levels with scanty urinary excretion of sodium and chlorine is rare. The commonest cause is severe dehydration, as in some cases of diabetic coma and in enteritis of infants; in most of these the condition is only temporary, and excretion of sodium and chlorine begins again as soon as the dehydration is overcome.

In 1939 I observed 5 cases of hyperchloræmia and hypernatræmia associated with minimal urinary excretion of sodium and chlorine in patients with intracranial lesions of various types (Allott 1939). Since then hyperelectrolytæmia has been described in association with various forms of intracranial lesions: after the removal of a craniopharyngioma (Peters 1948), in various lesions of the frontal lobes (Sweet et al. 1948), in a case of bilateral occlusion of the anterior cerebral arteries, a case of craniotomy for chromophobe adenoma, and a case of hemiplegia (McCarty and Cooper 1951), in cases of severe head injury (Higgins et al. 1951, 1954), in encephalopathy following sulphonamide therapy (Luetscher and Blackman 1943, Goodale and Kinney 1949), in a case of total pituitary hypofunction (Engstrom and Liebman 1953), and in cases of cerebral disease most of which were described as "encephalomalacia" (Schoolman et al. 1955). In many of the published cases observations were very limited, being confined in some of them merely to a single observation or to raised serum electrolyte levels with no reference to urinary excretion.

I have recently had the opportunity, through the courtesy of Dr. J. P. Marsden, under whom the patients were admitted at Joyce Green Hospital, Dartford, of studying in detail two cases of poliomyelitis with cerebral involvement, one of which showed the full picture of hyperelectrolytæmia with suppression of the urinary excretion of sodium and chlorine, the other showing changes which may represent the early stages of this condition.

Both patients presented with severe bulbar poliomyelitis requiring artificial respiration with an intermittent positive pressure machine; both initially passed normal volumes of urine but in the first few days developed severe oliguria, which proceeded to polyuria, the urine containing a high concentration of urea but a very low concentration of sodium and chlorine.

Case-reports

Case 1.—An electrical engineer, aged 28, was admitted on Dec. 3, 1955, with severe occipital headache, sweating, and photophobia. Six days before admission he had had an acute attack of diarrhœa lasting two days.

On admission he had neck rigidity, slight weakness of his legs, and blood-pressure 140/80 mm. Hg. Next day he was hoarse and had difficulty in coughing and weakness of his arms and legs.

Progress

On Dec. 5 his blood-pressure had risen to 195/90 mm. Hg, his bladder was distended, and 330 ml. of dark urine, withdrawn by catheter, was slightly acid and contained a trace of protein but no cells.

By Dec. 6 his breathing was difficult, tracheotomy was done, and a positive-pressure respirator was affixed. His general condition was poor, and during the day he had two attacks of cyanosis, the first being attributed to difficulty with the apparatus but the second to a cerebral vasomotor upset. His blood-pressure during these attacks fell temporarily to 80/30 mm. Hg.

From Dec. 6 to Dec. 8 his urinary output was very scanty —170, 140, and 240 ml., with intakes of 2300, 3000, and 3400 ml. of fluid, for the three days. His systolic blood-pressure during this time was 90–110 mm. Hg.

His urinary output increased from 1200 ml. on Dec. 9 to 5600 ml. on Dec. 13 and remained copious after this. His blood-pressure meanwhile was 170/110–190/120 mm. Hg. His urine remained acid and contained only a trace of protein, with a very few red cells and casts. By Dec. 16 his blood-pressure had returned to normal, and it remained thereafter about 130/90 mm. Hg.

His blood-urea level had remained high throughout in spite of apparently adequate urinary excretion, but his serum electrolyte levels rose, with the onset of diuresis, to Na 169 m.eq. per litre, K 5.9 m.eq. per litre, Cl 130 m.eq. per litre, and HCO_3 24.8 m.eq. per litre on Dec. 17.

On Dec. 19 I was asked to see him because of these electrolyte abnormalities. He was now practically completely paralysed in all his limbs, there being only slight movements of his right hand and forearm, and respiratory distress was caused during brief interruptions necessary to adjust the respirator.

Chemical Observations (figs. 1–3)

Period I (hyperchloræmic phase).—From Dec. 14 to Dec. 29 there were high serum-electrolyte levels, with very scanty urinary excretion of sodium and chlorine. The blood-urea level was high, and the urinary urea concentration was also usually high—up to 3.5 g. per 100 ml. The intake of fluids (mostly by intragastric drip) was 3300–4500 ml. a day and the volume of urine usually 1500–2000 ml. a day. Until Dec. 16 the diet had consisted of milk and eggs, with various supplements, containing about 100 m.eq. of sodium, 60 m.eq. of potassium, and 50 g. of protein daily; but, because of the rising serum electrolyte levels, a diet of fat and carbohydrate without electrolytes was given from Dec. 17, the total intake of fluids being kept at the same level. The blood-urea level had been falling, so 'Casilan' 50 g. and later 100 g. daily was added to the diet from Dec. 20 but stopped again on Dec. 28, when the blood-urea level rose. This rise was probably due to mersalyl (see below). Between Dec. 28 and Jan. 2, the serum-sodium and serum-chlorine levels fell and the blood-urea level returned to normal. This was associated with increased urea clearance and the excretion of 48 g. and 56 g.

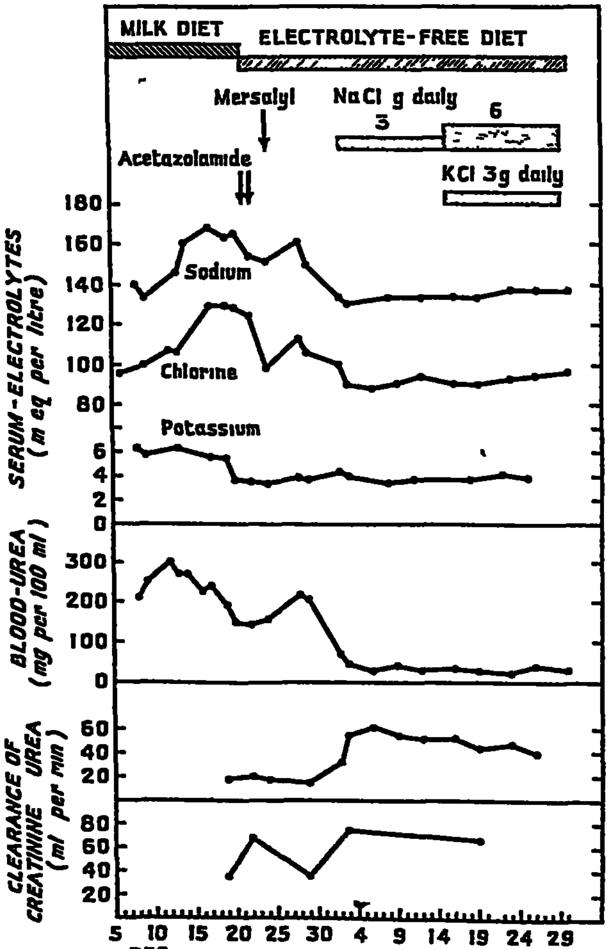

Fig. 1—Case 1: serum-electrolyte and blood-urea levels and clearance of urea and creatinine.

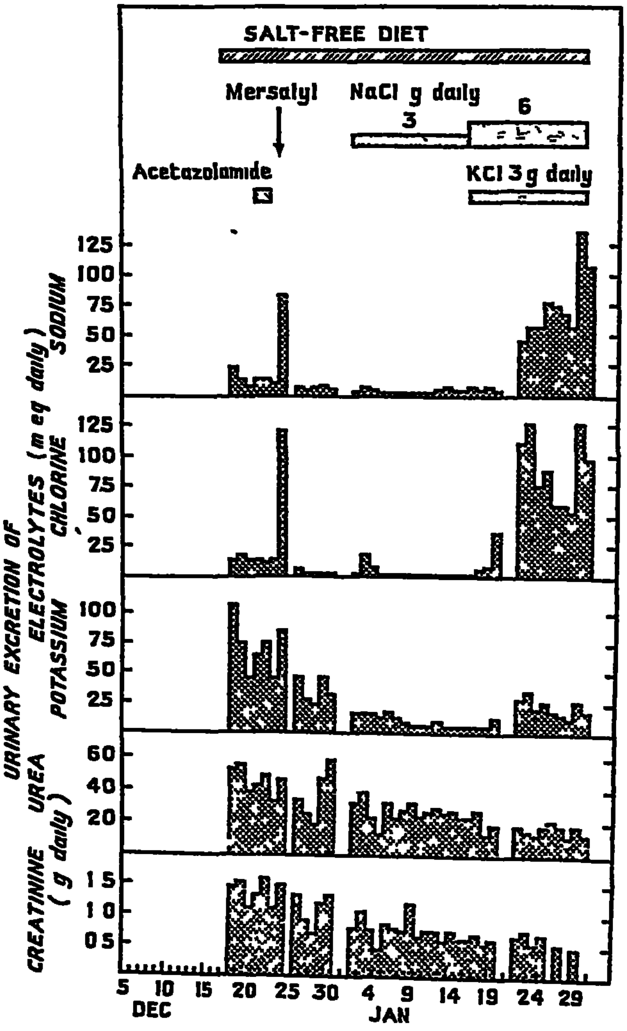

Fig. 2—Case 1: urinary excretion of electrolytes, urea, and creatinine.

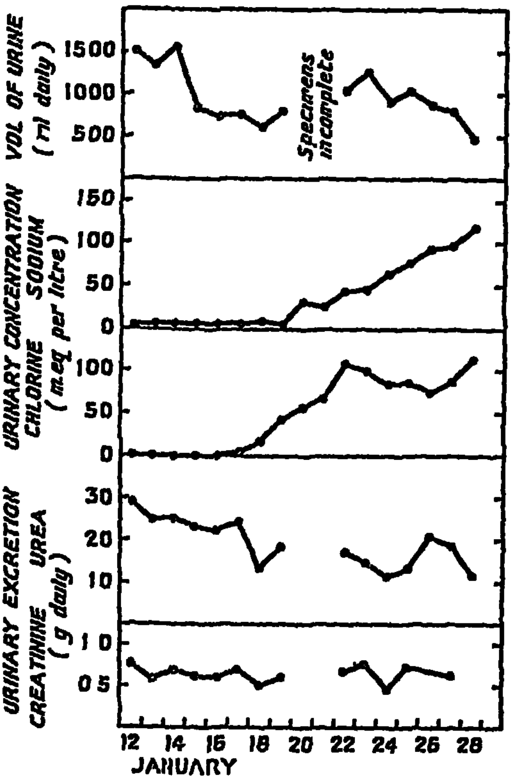

Fig 3—Case 1: resumption of excretion of electrolytes.

of urea on Dec 29 and 30, the output for the previous three days having been only 33 g, 25 g, and 19 g.

Period II.—From Dec 30 to Jan 16 the blood urea level was normal and the serum sodium level (about 134 m eq per litre) and the serum chlorine level (about 91 m eq per litre) on the low side of normal. The urinary urea concentration was usually 1·5–2·5 g per 100 ml. Salts were cautiously added to the diet (NaCl 3 g daily from Jan 3, later increased to 6 g daily, and KCl 3 g daily from Jan 15), but the excretion of sodium remained about 2–4 m eq daily, and, except for the two days immediately following the addition of NaCl to the diet, when 18 and 8 m eq were excreted, the excretion of chlorine was too scanty to be measurable—1 m eq or less daily. The excretion of potassium decreased from about 45 m eq daily at the beginning to 3–4 m eq daily at the end. It seems possible that this period covered the greater part of removal of waste tissues, the daily creatine output decreased from 1·65 g daily on Dec 29 to 0·32 g daily on Jan 17.

Period III (Jan 17–28).—The resumption of excretion of electrolytes on Jan 17 was preceded on Jan 15 by a sudden decrease in volume of the urine from 1200–1500 ml daily to 600–800 ml daily without change in the output of creatinine. The excretion of chlorine started on Jan 17 with a urinary concentration of 6 m eq per litre and increased continuously to 108 m eq per litre in six days. The excretion of sodium started on Jan 18 with 9 m eq per litre and continued to increase somewhat more slowly to 120 m eq per litre after eleven days. The excretion of potassium increased from about 5 m eq per litre to 25 m eq per litre. These results are shown graphically in fig 3.

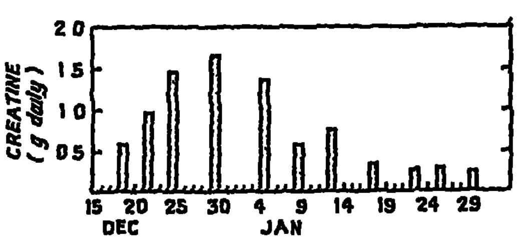

Fig 4—Case 1: urinary excretion of creatine.

Excretion of creatinine and creatine.—The excretion of creatinine fluctuated round about 1·2 g daily when observations were started and gradually decreased, as muscle mass decreased, to a mean of about 0·7 g daily by the end of the second month of illness. The excretion of creatine increased from 0·57 g on the fifteenth day of illness to a maximum of 1·65 g on the twenty-sixth day, and decreased to 0·32 g daily at the end of the seventh week. The findings are shown in fig 4.

Excretion of steroids.—The figures for the excretion of steroids are given in table I. The 17-ketogenic steroids and 17-hydroxycorticosteroids were determined by the methods of Appleby et al. (1955); the aldosterone was kindly estimated by Dr I. H. Mills, of St Thomas's Hospital, London. Although the first figures in both cases are above normal, they are probably not more than would be expected from the stress of the illness; and, when the excretion of steroids is expressed as mg per g of creatinine (if this is justifiable in a patient with gradually diminishing excretion of creatinine) the values on Jan 18, by which time the metabolism of Na and Cl had returned to normal, were at least as high as at the height of sodium retention. The aldosterone figure is definitely high: Dr Mills gives up to 2 µg daily as the upper limit of normal.

Effects of acetazolamide and mersalyl.—During the period of hyperelectrolytæmia the effects of acetazolamide and of mersalyl were investigated. Acetazolamide was given (250 mg on Dec 21 and 500 mg on Dec 22) without producing any change whatever in excretion of sodium and chlorine and producing only an insignificant change in excretion of potassium. Mersalyl 2 ml on Dec 24 increased the volume of urine from 1300 ml to 2650 ml and the excretion of sodium, chlorine, and potassium. The serum chloride level fell during the mersalyl day from 125 to 98 m eq per litre. The effect of the mersalyl is shown in table II. The excess fluid excreted was definitely hypotonic compared with the serum, and the net effect was disadvantageous and to increase dehydration: the blood urea level rose from 164 to 227 mg per 100 ml and the serum sodium level from 152 to 161 m eq per litre. Before the mersalyl was given, the urinary sodium and chlorine concentrations had been low, 6–12 m eq per litre representing the range of concentrations. After mersalyl diuresis they fell still lower to 1–7 m eq per litre and 0–3 m eq per litre respectively.

TABLE I—EXCRETION OF STEROIDS

Date	Daily excretion (mg)			Excretion expressed as mg per g of creatinine		
	17 K S	17 K G S	17 O H C S	17 K S	17 K G S	17 O H C S
Case 1						
Dec 19, 1955	16·7	25·3	45·9	11·2	17·0	30·8
Dec 21, „	Aldosterone = 15 µg					
Jan 3, 1956	10·0			12·2		
Jan 9, „	11·3	13·6	14·2	8·9	10·7	11·2
Jan 18, „	7·8	12·2	14·5	15·0	23·5	27·9
Case 2						
Jan 18, 1956	25·6	32·6	45·7	21·0	26·9	37·8
Jan 21, „	15·1	10·8	23·4	17·8	12·7	27·5

K S, ketosteroids. K G S, ketogenic steroids.
O H C S, hydroxycorticosteroids.

Clinical Progress

By Jan 18 the patient had improved to the extent that he had fair strength in his right hand and forearm and a slight return of power in his left hand. His legs were still completely paralysed, and his respiration had recovered to the extent that he could breathe without the respirator without distress for 5–8 minutes.

His respiratory paralysis gradually improved slightly, and by the end of January he could breathe without the respirator for 45–60 minutes, but at this time he had little power except in his right hand and forearm and his left hand.

TABLE II—EFFECT OF MERSALYL ON DAILY EXCRETION

—	Water (ml)	Na (m eq)	K (m eq)	Cl (m eq)
Average of previous 3 days	1480	10	59	14
Mersalyl day	2650	84	85	120
Excess due to mersalyl	1170	74	26	106

Case 2—A woman, aged 40, was admitted on Jan 13, 1956, with a week's history of backache, pains in the legs, and severe frontal headache The day before admission she vomited several times and noticed weakness in both legs

On admission she was fully conscious and coöperative, with blood pressure 140/80 mm Hg, nystagmus, weakness of her left arm, and paralysis of both legs Her blood urea level was 34 mg per 100 ml, and her serum electrolyte levels were normal

Progress

Next day her left arm was completely paralysed, she developed severe dyspnœa for which tracheotomy and an intermittent positive pressure machine were needed, and her blood pressure was 160/90 mm Hg

On Jan 15 her blood pressure was 100/80 mm Hg and urinary output 1200 ml, but next day, with the same blood-pressure, the urinary output decreased to 60 ml For the next three days she was semiconscious, with blood pressure 100/80–130/80 mm Hg, her daily urinary output increasing again to 430, 1640, and 1480 ml After this her general condition deteriorated, her urinary output gradually diminished, and she died on Jan 24 without fully recovering consciousness

Chemical Findings

The blood urea level rose from 39 mg per 100 ml on Jan 14 to 310 mg per 100 ml on Jan 20 The serum electrolyte levels were still within normal range on Jan 20 (Na 143 m eq per litre, Cl 96 m eq per litre), but the electrolytes in the urine had decreased from Na 15–35 m eq per litre and Cl 6–10 m eq per litre during the first three days to Na 4 m eq per litre and Cl 0 on the sixth day During the whole of her illness the urinary concentration of potassium remained high—35–79 m eq per litre during the first three days and 53 m eq per litre on the day before death The urea concentration in the urine varied throughout from 1 2 to 1 85 g per 100 ml

Discussion

Lower nephron nephrosis has been suggested by Schoolman et al (1955) as a possible cause of this chemical syndrome, but the picture differs from the diuretic phase of lower-nephron nephrosis in nearly every respect, in lower nephron nephrosis the tubules have lost their concentrating power and manifest this by excretion of a near glomerular filtrate, with a low urea concentration and usually a high electrolyte concentration In complete contrast the present patients had a very high concentration of urea with a very low sodium and chlorine content of the urine, showing that there was excessive reabsorption of sodium and chlorine

Dehydration

The simplest explanation of the chemical changes would be to regard the initial polyuria as an osmotic diuresis caused by the large amount of tissue breakdown products to be excreted, thus leading to dehydration, and to regard the absence of salt from the urine as due to salt deficiency, but this explanation encounters many difficulties

Many patients with hyperelectrolytæmia have been in coma, or with diminished thirst sensation, and Welt et al (1952) have shown that dehydration is a common cause of the condition In some of the many cases described by Schoolman et al (1955) dehydration was probably responsible

Although some dehydration was present and there was thirst during the hyperchloremic phase the present cases differ from cases of simple dehydration in the extremely scanty urinary excretion of Na and Cl McCance et al (1944) by simple dehydration in healthy persons, cut down the volume of urine from 1 34 ml a minute to 0 43 ml a minute with an increase in urinary urea from 1 04 to 3 98 g per 100 ml and an increase of urinary chloride from 86 to 219 m eq per litre Nadal et al (1941) by water deprivation in a person on a salt deficient diet, found urinary chloride values of 35 and 19 m eq per litre only when gross salt deficiency was produced by intestinal suction in an already salt deficient patient did the urinary sodium and chlorine fall to really low values, and this was associated with very low values of the electrolytes in the serum

McCance et al (1944) produced an osmotic diuresis in a dehydrated person by giving urea 35 g intravenously, the urinary sodium decreased from 125 to 17 m eq per litre as the urea increased from 2 9 to 4 8 g per 100 ml, but this amount of urea is very much more than was observed in either of the present patients, and the depression of urinary electrolytes very much less in case 2 the urinary urea increased only to 1 85 g per 100 ml the day before death, at which time the urinary Na was 7 m eq per litre and the urinary Cl 0 Unfortunately the total osmolar concentration was not determined

The abnormal tubular reabsorption in these patients was not confined to sodium and chlorine In another patient (not described here), who had very high serum-sodium and serum-chlorine levels with adequate urinary volume but negligible urinary concentration of these ions, sodium thiosulphate was given intravenously The glomerular filtration, calculated from endogenous creatinine, was about 160 ml a minute, but the thiosulphate "clearance" worked out at 2 2 ml a minute, showing that this foreign ion was also being abnormally reabsorbed

The distribution of fluid and electrolytes between the various body compartments may be disturbed, and Borst (1938, 1948) considers that the hyperelectrolytæmia observed from time to time after massive gastro-intestinal hæmorrhage is due to a diminution in volume of the circulating blood, and that this is responsible for the excessive renal reabsorption of sodium and chlorine, notwithstanding that there may sometimes be an excess of total extracellular fluid, even to the extent of œdema Borst (1951) has suggested that the findings in head injury are due to the diminished volume of circulating blood, but this is disputed by Higgins et al (1954)

In case 1 there was evidence of hæmoconcentration, the hæmoglobin increasing from 100% on admission to 106–108% during hyperelectrolytæmia The subsequent decrease to about 80% at the end of the hyperosmolar period was probably partly due to hæmodilution, but the effect of the infection in causing anæmia cannot be ruled out

The effect of mersalyl affords support for the theory that the diminished volume of circulatory blood is a factor the day mersalyl was given the blood-urea level had fallen to 150 mg per 100 ml and the serum sodium level to 154 m eq per litre After diuresis, with the loss of about 1200 ml of water, these levels rose again to 227 mg per 100 ml and 161 m eq per litre Borst and de Vries (1950), however, observed practically no response to mercurials in the patients with the syndrome due to a small volume of circulating blood

The blood electrolyte levels are related to changes in renal function The glomerular filtration rate, measured by endogenous creatinine clearance, rose from 35 ml a minute on Dec 19 to 69 ml a minute on Dec 22, as the serum sodium and serum chlorine levels were falling After mersalyl the creatinine clearance decreased again to 34 ml a minute on Dec 29, and the serum sodium and blood urea levels rose During the next four days, when the serum electrolyte levels fell to normal values the creatinine clearance increased to 79 ml a minute and the urea clearance to 36 ml a minute Throughout there was an inverse relationship between creatinine clearance and the levels of sodium, chlorine, and urea in the blood

During the four days from Dec 28 to Jan 2 the serum sodium level fell from 161 to 131 m eq per litre and the serum chlorine level from 112 to 92 m eq per litre These falls were not associated with any significant urinary excretion of electrolytes and must have been due to either dilution through expansion of the body-fluids or redistribution of fluids (and electrolytes) within the body Although the available data are insufficient for a definite decision between these alternatives, the second seems the more probable Even with as low a figure as 30 litres for total body water this dilution of 18% would mean a retention of 5 5 litres of water during the period Although urinary collections were incomplete during two days, there was no indication in the output of urine or in the intake of fluids to suggest such a retention

Although data of the output of salt during the first fortnight of illness are not available, the suggestion of salt deficiency might be regarded as supported by the fact that practically no chlorine and negligible sodium were excreted during a period in which 48 g of salt (820 m eq) was administered, but the findings differ from an ordinary salt deficiency in the intensity of the retention Further, in cases of severe salt deficiency the excretion of small quantities of sodium and chlorine usually begins almost as soon as salt is administered and long before a gross salt deficiency has been remedied The serum sodium (134–139 m eq per litre) and the serum chlorine (90–94 m eq per litre) were slightly low, but the return of chlorine and sodium to the urine was not associated with any significant change in these levels on Jan 19, by which time the urinary concentration of chlorine had increased to 41 m eq per litre, the serum-chlorine was still only 90 m eq per litre

The importance of potassium deficiency in poliomyelitis has been emphasised by Lans et al (1951) and Hall and Sherman (1953), and it might be suggested that the renal abnormality was due to potassium deficiency It is true that the excretion of electrolytes started again shortly after potassium chloride had been given, but this was probably merely coincidental the amount given before chlorine reappeared in the urine was only 6 g of KCl (80 m eq of potassium), and this quantity is quite insufficient to have significant effect on a real potassium deficiency

Antidiuretic Hormone

The association of hyperelectrolytæmia with diabetes insipidus has been well worked out by Engstrom and Liebman (1953) In one case of anterior and posterior pituitary deficiency following pregnancy the patient always had high levels of sodium and chlorine when not receiving vasopressin The values fell to normal when vasopressin was given, and the concentration, but not the total amount, of urinary sodium and chlorine increased In the case published by Peters (1948) of hyperelectrolytæmia following operation on a craniopharyngioma and in the cases published by Cooper and McCarty (1951) there was evidence of a postoperative acute diabetes insipidus

The possibility of interference with the production of antidiuretic hormone needs consideration in the present cases also In case 1 the early polyuria might have been due to lack of antidiuretic hormone, thus leading to dehydration, and excessive production of aldosterone (cf Bartter et al 1956, Muller et al 1956), the failure to excrete sodium and chlorine would then be due to continued excessive production of aldosterone It has been pointed out that the return of electrolyte excretion in the urine was preceded by a sharp diminution in the volume of urine (fig 3) Could this be due to a return of antidiuretic hormone and an associated decrease in aldosterone activity ? This cannot be regarded as proved but gives suggestions for further work

Kriss et al (1948) and Kaplan and Rapaport (1951) have shown that the excretion of sodium and chlorine is also controlled by the action of the splanchnic nerves on the renal tubules It is, of course, possible that some alteration in splanchnic activity is concerned in this syndrome, but there is no way of demonstrating this

Whatever the final decision about the cause of this condition, there are definite lessons for the management of severe cases of poliomyelitis, particularly in the severe bulbar form The serum electrolyte levels should be watched If the serum sodium and serum chlorine levels rise, salt should be discontinued and additional fluid given (The fluid intake in case 1 in the early stages was probably insufficient) When the serum electrolyte levels return to normal, salt should be added cautiously, but perhaps more rapidly than in case 1, and the possibility of a potassium deficiency must also be borne in mind

Astrup et al (1954) found serum sodium and serum chlorine levels usually normal or low in poliomyelitis Probably this hyperelectrolytæmia is a comparatively rare complication of poliomyelitis, but its existence, with the cessation of urinary excretion, makes the determination of serum-electrolyte levels necessary and emphasises the danger of relying solely on observations of urinary excretion by the Fantus test

Summary

Two cases of bulbar poliomyelitis showed a nearly complete suppression of urinary excretion of sodium and chlorine One of them also showed gross hypernatræmia and hyperchloræmia

Excessive excretion of aldosterone was present in one of the cases Reasons are given for considering that this chemical syndrome is due to some cause other than simple dehydration

These chemical changes may have been associated with interference with secretion of antidiuretic hormone, the consequent polyuria and dehydration may have led to the increased production of aldosterone, which in turn may have been responsible for the retention of sodium and chlorine

My thanks are due to Dr J P Marsden for allowing me to investigate the cases, Dr H G Close and the laboratory staff at Joyce Green Hospital for much assistance, Sister G Sims for her care in collecting specimens, and Mr P J Hawker and Mr J W Moreton for most of the analyses

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AMIPHENAZÓLE IN A CASE OF DRUG ADDICTION

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THE dangers of narcosis and respiratory depression have often prevented the full use of the pain-killing qualities of the opium alkaloids, and the risk of addiction is another bar to their continued administration Amiphenazole (2 4 diamino 5 phenylthiazole hydrochloride) has recently been found to stimulate the respiratory centre The concurrent administration of amiphenazole and morphine abolishes the depressant action of morphine on respiration (Shaw and Bentley 1955) Larger doses of morphine (200 mg) can safely be administered, so that the maximum analgesic action is obtained but respiratory depression is slight Moreover, the vomiting and constipation sometimes caused by morphine are often abolished when it is given with amiphenazole

The successful treatment of pethidine and 'Omnopon' addiction by amiphenazole has not yet been reported in this country

Case-report

A married woman of 26 fell ill with pulmonary tuberculosis in 1943 After hospital treatment she recovered and remained well until November, 1953, when she had an attack of pneumonia She was admitted to hospital in April 1954, with very extensive bilateral pulmonary tuberculosis with large thick walled cavities Under treatment with anti tuberculosis drugs there was some improvement Drug resistance developed and improvement was not maintained

In June 1956, she began to have repeated daily hæmoptyses and severe chest pain Her condition then steadily deteriorated and the prognosis became hopeless Pethidine gave some relief, but the symptoms were effectively controlled only by morphine Later, owing to gastro intestinal upsets, omnopon was given instead During the next four months she was given on an average 200 mg of omnopon and 300 mg of pethidine daily

The patient was depressed and confused, anorexia was extreme and she became even more emaciated Peripheral œdema developed She was persistently cyanosed even with almost continuous oxygen therapy During this time the patient became an obvious addict and demanded injections as soon as the effect of the previous one was wearing off, pleading pain, although we were seldom convinced of its presence

On Nov 17 we began treatment with morphine and amiphenazole During the next three days she was given a total of 2 842 g of morphine subcutaneously and 1 06 g of amiphenazole orally There was an immediate change in her condition She became mentally bright and alert, cyanosis disappeared her appetite improved and the œdema subsided Apathetic for months, she now became anxious to try a new antituberculosis drug and moved around freely in bed

For the next ten days no morphine was given The patient had no desire for further injections and required no sedation apart from a short-acting barbiturate at night Since then a small dose of morphine (16 mg) covered by amiphenazole (20 mg) has been required occasionally for obvious severe pain She now dislikes these injections, which is in marked contrast to her previous attitude

Comments

This patient had obviously become addicted to omnopon and pethidine This addiction was rapidly cured by amiphenazole without any withdrawal symptoms

It may be that amiphenazole should be given concurrently during prolonged medication with an opium alkaloid or the synthetic analgesics, pethidine and methadone hydrochloride Further investigation into the value of amiphenazole in the prevention and cure of addiction might be profitable

REFERENCE

Shaw, F H, Bentley, G A (1955) Aust J exp Biol Med Sci 33 143

Preliminary Communication

ERYTHROCYTE-POTASSIUM LEVEL IN RHEUMATOID ARTHRITIS

THE administration of adrenocortical steroids in man results in a net loss of potassium from the body and lowers the level of intracellular potassium Streeten and Solomon[1] have shown that the administration of corticotrophin or cortisone does not lower the potassium content of the erythrocytes but probably raises it Their investigations suggest that, as regards their content of potassium, the behaviour of erythrocytes towards adrenal steroids differs from that of other body cells

Sherwood Jones[2] investigated the distribution of electrolytes between erythrocytes and plasma in 3 patients with Addison's disease and in 2 patients with Cushing's syndrome They reported, however, normal levels of sodium and potassium in the erythrocytes

In view of a possible association between the adrenal steroids and the erythrocyte-K^+ level and the association of the collagen group of diseases with adrenal steroid metabolism, we decided to investigate the erythrocyte-K^+ levels of patients with collagen diseases

We report here the initial results obtained in patients with rheumatoid arthritis

METHOD

A simple standardised procedure was adopted suitable for routine laboratory analyses Estimations of the erythrocyte-K^+ level were based upon an indirect method requiring the determination of the whole blood K^+ level, the plasma-K^+ level, and the hæmatocrit reading Heparinised venous blood was used for the determinations The estimations were undertaken with as little delay as possible, and provided they were carried out within four hours of venepuncture, there was no significant loss of cell K^+.

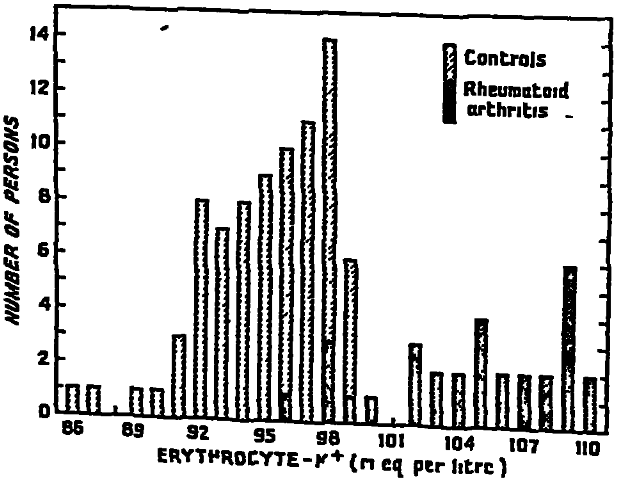
The whole blood K^+ was estimated in duplicate, the samples being prepared by diluting whole blood 1 in 1000 with distilled water The maximal acceptable deviation between duplicates was 0 5 m eq per litre for whole blood Flame photometer standards containing the appropriate sodium "background" gave complete linearity of scale over the working range of K^+ values

Plasma K^+ was estimated on 1 in 100 dilutions of plasma Hæmatocrits were determined in Wintrobe tubes by centrifuging for thirty minutes at 3000 r p.m in a governor-controlled centrifuge

SUBJECTS INVESTIGATED

The erythrocyte-K^+ level was investigated in the following groups

(1) "Controls" composed of medical students of either sex and patients with diseases other than of the collagen group or conditions known to be associated with electrolyte disturbance



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[1] Streeten D H P Solomon, A K *J gen Physiol* 1954 37 643
[2] Jones E S *Nature Lond* 1955 176, 269

(2) Patients of either sex with "active" or "quiescent" rheumatoid arthritis None were on steroid therapy

RESULTS

The distribution of erythrocyte-K^+ levels in the 80 "controls" is shown in the accompanying figure None of the "controls" had an erythrocyte K^+ level higher than 99 m eq per litre The distribution of erythrocyte-K^+ levels in 31 women with rheumatoid arthritis is also shown in the figure In this group 5 patients had erythrocyte-K^+ levels below 100 m eq per litre and 26 had 100 m eq per litre, or more Of 12 men with rheumatoid arthritis (see table) 3 had erythrocyte K^+ levels within the range of figures obtained for the "controls."

12 CASES OF RHEUMATOID ARTHRITIS IN MALES

Case no	Age (yr)	Erythrocyte K^+ level (m eq per litre)
1	30	98
2	55	101
3	44	104
4	53	106
5	46	107
6		104
7		105
8	66	98 5
9	50	100
10	65	102
11	60	98 5
12	66	106

No correlation was found between hæmatocrit reading, cell size, hæmoglobin content, age of patient, and erythrocyte-K^+ level

Clinical assessment of the patients suggested that the erythrocyte-K^+ level may be related to the degree of activity of the disease

CONCLUSIONS

The results obtained in this preliminary series indicate that patients with rheumatoid arthritis tend to have erythrocyte-K^+ levels higher than the accepted normal range The finding may be more constant in females than in males

The cause of the raised erythrocyte K^+ level is unknown Among other hypotheses, possible alterations in steroid metabolism, and their effects on the permeability of the erythrocyte, are being considered

A larger series of patients and a series of matched controls are under investigation in conjunction with the department of physical medicine of the Middlesex Hospital It is intended to study the relation of erythrocyte-K^+ levels to activity of disease and to steroid metabolism, and to assess the value of the investigation in the diagnosis of rheumatoid arthritis and the ability of the test to differentiate this disease from similar conditions

Our thanks are due to Dr A C Boyle and Dr. D Mattingl for referring patients to us and for their clinical assessment of the cases, and to Sir Charles Dodds for his interest in the work.

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Medical Societies

ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE

Toxoplasmosis

THE society met in London on Jan 17, with Prof R M GORDON, the president, in the chair, to discuss Toxoplasmosis

Prof P C C GARNHAM said that the prevalence of toxoplasma infection in man has been put as high as 50% in some communities, on the basis of serological tests, of which the dye test is the commonest The validity of this test has been doubted, and possibly man may acquire antibodies to sarcocystis passively from cattle, sheep, and pigs, which are commonly infected with that organism, such antibodies may give a positive reaction in the dye test for toxoplasma

Prof C P BEATTIE said that severe and fatal forms of toxoplasmosis first attracted notice, but these are rare Mortality in severe congenital forms is high, and children who survive are often mentally retarded, but it seems likely that even in congenital infections severe disease is the exception In the acquired disease the commonest manifestation is lymphadenopathy, with or without fever, and this may be mistaken for glandular fever except that the Paul Bunnell test is negative

The mode of transmission of the *infection to man* is unknown Many species of birds and mammals (including dogs and cats) have it, and tests indicate that persons handling animals are particularly prone to get it, no evidence of insect transmission has been found Man may become infected from man, or from imperfectly cooked meat No doubt there are many sources of infection, and transmission probably takes place by several routes

Dr I A B CATHIE said that it has been claimed that infection with *Trypanosoma cruzi* and trichomonas may give false positive dye tests, but he has not found this to be so, and has not encountered false positive complement-fixation tests in malaria or *Salmonella typhi* infections. Inactivation at 56°C for 30 minutes does not reduce the titre of the dye test antibody in human serum, and these antibodies, therefore, cannot be identified with properdin, but the sheep antibody is inactivated at 56°C, and therefore differs from the human antibody

Dr R LAINSON cited published work on the prevalence of this infection in animals, assessed by serological tests or isolation of the organism Isolation is the only sure proof of infection, and, since toxoplasma has not yet been cultivated on media free from living cells, isolation requires passage to "clean" laboratory animals Intraperitoneal inoculation of mice with brain tissue is convenient and satisfactory The morphology of strains isolated (there is only one species of toxoplasma) is uniform, and the strains are serologically and immunologically similar, though they may vary greatly in virulence Dr Lainson reported isolations from weasels ferrets, polecat ferret hybrids, and rats in England The carnivores may become infected by eating infected flesh possibly that of rabbits It appears that toxoplasma is a benign and well adapted parasite

Prof R J V PULVERTAFT showed a film of toxoplasma invading living cells or being phagocytosed by them

Dr J K A BEVERLEY remarked that a dye test of titre 1 in 500 or a complement fixation test of 1 in 16 may be taken as indicating active infection A rising titre is important, but the rise is not rapid A weak complement-fixation test may indicate old infection, and active infection can occur with a weak dye test, though subclinical infection can provoke high titres There is some evidence that pyrimethamine, the sulphonamides, and the sulphones are useful in treatment of the disease in animals

Dr J D FULTON described his method of isolating the organism for metabolic studies, glucose is the chief material used by it

Colonel J H WALTERS cited evidence which suggests that toxoplasmosis may be widely endemic in West Africa and said that it gives rise to a syndrome which may be mistaken for glandular fever

Dr BEVERLEY reported a laboratory infection from a contaminated hypodermic needle Dr CATHIE reported the case of a laboratory worker who had worked with toxoplasma for several years without the dye test becoming positive, and then suddenly the test became positive without the patient having had any illness or any other event which could explain it

THE RENAL ASSOCIATION

Azotæmic Renal Osteodystrophy

AT a meeting of this association on Jan 24, Dr S W STANBURY insisted that the clinical and biochemical investigation of the problems of azotæmic renal osteodystrophy should be based on a firm knowledge of the pathological state of the skeleton Neglect of histological study, which could often be made on biopsy specimens, had led to several serious misconceptions It was, for instance, universally assumed that osteitis fibrosa was the only osseous complication of uræmia in the adult By reference to the clinical and histological findings, in particular adult patients with chronic uræmia he was able to demonstrate both the development of florid osteomalacia and its presumptive cure by large doses of the vitamin D steroids Histological preparations of rachitic metaphyses were shown to support the claim that the uræmic child could develop true rickets This was certainly "rickets" when considered from the osteologist's viewpoint as "a failure of mineral deposition to keep pace with the endochondral growth of bone" Turning to the possible ætiology of the defective mineralisation, Dr Stanbury pointed out that the azotæmic patient wasted neither calcium nor phosphorus in the urine, but the intestinal absorption of both was defective As was the case with vitamin-D-resistant rickets (osteomalacia), this defect could be overcome by large doses of either calciferol or dihydrotachysterol, although the dangers of overdosage were considerable During successful treatment, calcium and phosphorus were retained in a ratio of approximately 2 to 1, and the osseous lesions were seen to heal radiologically Healing was accompanied by an increase in the level of blood citrate Reasons were given for believing that the metabolic defect represented an acquired insensitivity to vitamin D, for which it was unlikely that either systemic acidosis or elevation of the serum-phosphate could be held responsible A similar defect could occur in patients with lowered rates of glomerular filtration but without azotæmia, and also in nephrotic children No cause could be offered for the vitamin D resistance but it did not appear to be due to a simple failure to absorb the vitamin

The other osseous lesion occurring commonly in azotæmia was osteitis fibrosa, it could occur together with osteomalacia or independently The osseous changes were indistinguishable from those of primary hyperparathyroidism and, as in that condition, the presence of osteitis fibrosa was always accompanied by a reactive or reparative formation of new bone Clinically, renal osteitis fibrosa was best and earliest seen in the finger radiograph as erosions or ' scalloping" of the cortical surfaces of the phalanges It was probable to the point of certainty that a functional hyperparathyroidism was responsible for these lesions, but there was little direct evidence to indicate the cause of this secondary change From his personal experience of the condition, Dr Stanbury had two observations to make First, that the patient need not have rickets or osteomalacia prior to the development of hyperparathyroidism Secondly, one could not safely assume that the production of a positive calcium balance or even of hypercalcæmia would lead to regression of the parathyroid hyperplasia This may conceivably happen in some patients after vitamin D therapy, but in others hyperparathyroidism would continue and the lytic processes of osteitis fibrosa would release mineral from the recalcified skeleton This in turn could lead to extreme degrees of metastatic calcification

Prof C E DENT said that little had been added to our knowledge of this condition since Liu and Chu had described the major defect as being an inability to absorb calcium from the gut, with a negative calcium balance due to fæcal rather than urinary losses This resembled vitamin-D deficiency, but they had found that this vitamin did not correct the rickets or reverse the calcium balance, though A T 10 did. (The dose of A T 10, however, had been relatively much greater) Professor Dent had fully confirmed these findings but had found that calciferol could produce as good a response as A T 10 if given in corresponding amounts In one case he described in detail, the plasma-phosphorus rose but the calcium fell in spite of a strong positive balance, the urinary phosphate excretion rose with the plasma level, but the balance of phosphorus also became positive In azotæmia, pure rickets could occur with no evidence of osteitis fibrosa at necropsy, even when the essential renal lesion was glomerular The type of bone disease was therefore independent of the renal lesion It was usual to ascribe it to acidosis but giving alkalis with vitamin D produced no effect beyond that of the vitamin alone Renal hyperparathyroidism always responded equally well to this treatment, and this may be seen in as little as three weeks In one case, osteitis fibrosa healed but the renal rickets got worse, this was apparently due to a phosphate deficiency brought about by treatment with aluminium hydroxide, for it rapidly healed when this was stopped Another type of bone lesion seen was osteosclerosis

All three types of bone lesion seen in renal failure could also be seen in steatorrhœa, and resistance to vitamin D could then be demonstrated even when it was given parenterally It was possible that some anti vitamin-D factor was circulating in renal failure, as was originally suggested by Liu and Chu Such a substance might, like cortisone, partly reverse the action of vitamin D With adequate vitamin D therapy renal osteodystrophy always improved spectacularly even at a time when renal failure was progressing

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Reviews of Books

Hearing Defects in School Children

Scottish Council for Research in Education (publication no 38) London University of London Press 1956
Pp 110 10*s* 6*d*

THIS excellent monograph records very carefully the results of an investigation into hearing defects in children, mainly at ordinary schools

The authors stress the great importance of standardising the techniques of audiometry Most of the screening tests in ordinary schools have, unfortunately, to be carried out in a considerable level of background noise, but noises of up to 45 decibels can be present without affecting the threshold of hearing at any of the "speech" frequencies This noise level should be regarded as the maximum permissible in testing, even if the earphones are well designed

In attempting to correlate the degree of hearing loss with educational attainment, the committee found that a group of 12-year-old children with average hearing losses of over 20 decibels were retarded by 8 or 9 months in comparison with a corresponding control group of normally hearing pupils They concluded that even slight or moderate defects of hearing could constitute a serious educational handicap and that quite severe deafness had commonly escaped the notice of teachers Since many of these children could be cured or relieved by treatment, and since the educational handicap could be minimised by appropriate attention (even when medical treatment failed), audiometric testing of every child should be regarded as essential The wisdom of these conclusions will be evident to anyone who reads the text in full

Roentgen Signs in Clinical Diagnosis

ISADORE MESCHAN, M A, M D, professor and director of department of radiology at the Bowman Gray School of Medicine of Wake Forest College, Winston Salem North Carolina, U S A Philadelphia and London W B Saunders 1956 Pp 1058 £7

In this book of little more than a thousand pages, the author has provided a comprehensive survey of nearly every aspect of diagnostic radiology, and has in addition included chapters on radiographic techniques and radiation protection He has achieved this remarkable concentration of material by great economy of words in the text and by copious use of line drawings and diagrams in place of radiographs

In arrangement the work follows the pattern which is becoming increasingly popular in radiological textbooks—namely, of describing radiographic appearances, and then discussing the probable causes This method works well when the objective radiographic signs are clear and the possible causes few, but otherwise it may lead to confusion and repetition This danger, of which the author is obviously aware, is especially evident in the chapters on diseases of bone

This textbook will almost certainly become a standard work

Doctors in the Air

Wing Commander ROBERT MAYCOCK, A F C London Allen & Unwin 1957 Pp 145 15*s*

Doctors entering the Royal Air Force learn something of the stresses to which people who fly may be subjected, and during a short introductory course in aviation medicine at Farnborough see some of the many facets of the subject Probably few others appreciate the number of factors which must be reckoned with to ensure safety and even survival in the air

Wing Commander Maycock opens with a brief historical sketch of aviation, and logically progresses to problems of oxygen lack at altitude, *g* stress, and escape from high speed aircraft Chapters of autobiography indicate the wide range of the author's Service activities, and lead to discussion of further problems such as fatigue in aircrew and transport of casualties It is apparent how widely " applied physiology " enters into the design of a great deal of flying equipment, but technicalities are kept to a minimum

Though partly a personal narrative, the book clearly describes some of the important problems which had to be solved before man could safely fly fast and high, and it will bring to many readers some idea of the wide field covered by aviation medicine

La kinésithérapie dans le traitement des algies vertébrales

L CHARRIÈRE, professeur d'éducation physique, kinesitherapeute des Hôpitaux de Lyon Paris Masson 1956 Pp 156 Fr 1200

WITH the increasingly conservative attitude towards backache of all descriptions, the physiotherapy departments are taking an ever greater part in its treatment This unpretentious little book gives clear instructions on how exercises and postural therapy can be applied to these conditions The many diagrams are simple and to the point, although that of spondylolisthesis is incorrect and on the purely medical aspects the author is frequently open to criticism In his own field he is excellent, and physiotherapists will find this book worthy of study

The Human Machine

An Analysis and Description of the Human Body, and its Structure and Functions, in Terms of Inanimate Machinery

Sir ADOLPHE ABRAHAMS Harmondsworth Penguin Books 1956 Pp 200 3*s* 6*d*

It is the human machine in athletic activity which the author has really at heart, and the motor-car is the machine with which he compares and contrasts it The book will thus appeal chiefly to athletes and the athletically minded, who should find it instructive, illuminating, and salutary, with its ingenious analogies, its athletic erudition, and the cold douches of fact and common sense sprayed upon hoary myths and superstitions It seems odd to postulate " Nature " as the purposeful designer of the human frame and at the same time write off our hopes and fears as activities of our central nervous systems, but perhaps philosophy should be left to philosophers

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Blood Transfusion in Clinical Medicine (2nd ed Oxford · *Blackwell Scientific Publications* 1956 Pp 58[illegible] 45*s*)—The appearance of a second edition of this book by Dr P L Mollison will be welcomed by those in any way concerned with blood transfusion This edition will enhance the reputation quickly and deservedly won by the book when first published in 1951 The developments since then—in many of which Dr Mollison has himself had a hand—have necessitated extensive revision and the introduction of much new material One feature which distinguished the first edition has fortunately not been lost—the greater part of the book is based on the author's personal experience This work can be highly recommended

Diseases of the Heart (2nd ed Philadelphia and London W B Saunders 1956 Pp 1161 6 guineas)—The second edition of this well known textbook by Dr Charles K Friedberg maintains the high standard set by the first Three new chapters on graphic methods of cardiovascular examination have been added, and the section on cardiac surgery has been extensively revised to include the latest advances in surgery under direct vision, such as pump oxygenators, and hypothermia The book is up to date, and the exhaustive bibliography at the end of each chapter adds greatly to its value The author scrupulously gives a balanced picture on many controversial matters, commonly adding his own summing up This work is of great value to students and senior practitioners alike

Modern Operative Surgery (4th ed London Cassell 1955, vol 1, pp 1229 70*s* 1956, vol. 2, pp 2614 75*s*)—Many British surgeons were brought up on this work by the late Prof G Grey Turner Being accustomed to it they will be glad to greet the new edition, edited by Prof Lambert Rogers, as an old friend whose face has changed little The prefix " modern " should not, however, be allowed to mislead young surgeons Doubtless in an endeavour to present operative surgery over an era, procedures now outmoded are still described, though greater emphasis on current practice might be an advantage Perhaps future editions, of which there are likely to be many, will provide better illustrations and a fuller and more representative bibliography

Cardiopathies congénitales (2nd ed Paris Expansion Scientifique Française 1956 Pp 448)—The first edition of this comprehensive work by Prof P Soulié appeared in 1951 The author and his collaborators have now revised the text and added new chapters on scalar and vector cardiography, aortico pulmonary fistula, aortic stenosis, and arteriovenous aneurysms of the lung The book is in three parts The opening chapter of the first part deals with embryobiological anatomy, the second and third chapters with cardiac catheterisation and angiocardiography respectively There is a complete chapter devoted to cardiac shunts, cyanosis, and classification of the congenital cardiac anomalies The chapters in the second half of the book deal individually with the different forms of congenital heart disease The third part of the book is devoted to anæsthesia and surgical techniques, including cross circulation methods, pump oxygenators, and hypothermia This excellent and well illustrated textbook should be of great value to all students of congenital heart-disease

Nature of Viruses (London J & A Churchill 1956 Pp 292 42*s*)—The proceedings of the symposium on the biophysics and biochemistry of viruses held in London in March, 1955, under the chairmanship of Sir Charles Harington F R S, have now been published The editors for the Ciba Foundation, which organised the symposium, are Dr G E W Wolstenholme and Miss Elaine Millor

Hypotensive Drugs (London and New York Pergamon Press 1956 Pp 222 50*s*)—A conference on these drugs and the control of vascular tone in hypertension was held at the Wellcome Foundation, London, last April The proceedings have now been published under the editorship of Dr Michael Harington

THE LANCET

LONDON SATURDAY FEB 2 1957

Prognosis of Congestive Failure in the Elderly

Congestive heart-failure is one of the commonest reasons for the admission to hospital of people over the age of 65 In the absence of co-existing disease unrelated to heart-failure considerable and often dramatic improvement usually follows the application of the accepted principles of treatment for congestive failure at all ages, especially when it is coupled with an attack on any known underlying cause, such as anæmia, thyrotoxicosis or exacerbation of chronic respiratory infection It has long been apparent that if old patients could all receive the best standard of hospital care then the prognosis of congestive heart-failure would not be so poor as it is generally held to be

Bedford and Caird[1] point out that little has been written about the prognosis of congestive failure in the elderly, and they have made a detailed study of the condition in 231 patients of 65 or over, who represent 14% of all admissions to the geriatric unit at Cowley Road Hospital, Oxford during the forty-six months from July 1 1949, to April 30 1953 The patients were divided into nine ætiological groups normotensive hypertensive, aortic, rheumatic pulmonary, syphilitic thyrotoxic, anæmic and miscellaneous In considering patients of this age myocardial ischæmia was presumed to be a constant ætiological factor "Normotensive" meant normal blood-pressure and no evidence of any of the conditions in the other groups Thus, the underlying cause of failure was myocardial ischæmia alone for it was impossible to assess the contribution of precipitating factors in any group because many patients were too ill to give a reliable history 229 patients were successfully followed for one and two years, 162 patients for three years and 92 for four years and the corresponding survival-rates were 36% 27% 20%, and 16% These figures are impressive but as Bedford and Caird remark the outcome of a single episode of congestive failure is probably even better than these findings indicate since any hospital series is heavily loaded against survival because it contains many examples of recurrent or resistant failure and a high proportion of patients with some other lethal disease which determines the prognosis Some of the prognostic conclusions which Bedford and Caird have derived from their analysis seem at first sight to conflict with orthodox teaching Thus if an elderly patient survives an episode of congestive failure and the few months that follow it his expectation of life is not materially shortened Though 64% of the deaths took place in the first twelve months after the initial failure the expectation of life of those patients who survived for a year was at least equal to the normal, and moreover the age of the patient was not of prognostic significance In view of these findings it is obviously important to tackle with vigour the first bout of congestive failure in an old person and not simply to regard it from the onset as "terminal cardiac failure" Again as a generalisation, the prognosis in failure does not depend on the cause of the heart-disease For example the poor prognosis formerly accorded congestive heart-failure due to calcareous aortic stenosis is shown to be false when this condition is assessed by modern diagnostic criteria, and Bedford and Caird's findings support those previously recorded by Kumpe and Bean[2] and Lewes[3]

It is not surprising that the survival-rate was better in the normotensive group than in the hypertensives at all ages in the Oxford survey. What is surprising is the greater number of deaths among hypertensive women, despite the better prognosis of hypertension in women than in men at all ages This difference may be due to the excess of women who die from hypertensive heart-failure in the 70s as demonstrated by Clawson[4] or possibly to a greater incidence of auricular fibrillation in women In normotensive patients the cardiac rhythm did not affect the prognosis; but only 9% of hypertensive subjects with auricular fibrillation survived two years compared with 33% of hypertensives with normal rhythm Bedford and Caird's figure of 6% of patients with congestive failure due to rheumatic disease of the mitral valve indicates the care they took in establishing the diagnosis Rheumatic heart-disease is not rare in the elderly but it may be hard to recognise When at the turn of the century, rheumatic fever and its severe complications were more common than they are today the seriously affected patients were easily recognised, and most of them died before the age of 40 Those with less badly damaged hearts have survived to old age, most of them with mitral incompetence rather than stenosis and nearly half with normal rhythm When symptoms begin late in life often with few physical signs, the underlying condition may readily be overlooked. The prognosis in the rheumatic group, however, is much the same as that of normotensive congestive failure

An analysis of the causes of death is essential to a better estimate of prognosis In Bedford and Caird's series 146 patients died in hospital and 101 were examined post mortem In 33% death was attributed to bronchopneumonia arising either during the episode of congestive failure (8%) or after the heart-failure had resolved and the patient was under treatment for some dissociated condition (25%). Death due to resistant or recurrent attacks of failure accounted for 16% and pulmonary embolism for 14% The figure for embolism may be too low since some of the very sudden deaths were not followed by necropsy and may have included a number of massive pulmonary embolisms Surprisingly cardiac infarction accounted for only 5% but it was included as a cause of death only when the infarction occurred in the last few days of life and when it was confirmed by electrocardiography necropsy, or both Co-existing lethal disease accounted for 7%, and remote causes such as uræmia and cerebrovascular accidents for 14% The high proportion of deaths due to bronchopneumonia is partly a reflection of failure to prevent detect, or treat this condition in elderly patients with congestive failure, and the high death-rate from pulmonary embolism is a challenge yet to be met BEDFORD and CAIRD believe that there is a prima-facie case for giving anticoagulants to all elderly patients in congestive failure, though they admit that many things may complicate the situation and make the treatment unsuccessful It is plain that further experience and knowledge are needed, particularly in the important matter of treatment in the home

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[1] Bedford P D Caird F I Quart J Med 1956 25 407

[2] Kumpe C. W., Bean, W B Medicine, Baltimore, 1948 27, 139

[3] Lewes D Brit med J 1951 i 211

[4] Clawson B J In Hypertension, Minneapolis 1951

Practitioner and Local Authority

“ LET's face it, Clinics Are Unethical ” said RICHARD COBBLEIGH at the end of the brisk exchanges which followed his contribution to the Widdicombe File[1] The correspondence which we published under the title Clinicosis illustrated several different views of the work done in local-authority clinics, but few of those who wrote to us would deny that young COBBLEIGH's remark points to one of the big obstacles to reconciliation between therapeutic and preventive medicine as now practised by general practitioner and local-authority doctor Nor can anyone be entirely satisfied with a system which evokes so many expressions of dissatisfaction the clinic doctor is often aggrieved by the restrictions placed on the treatment he can give at the clinic, the general practitioner argues that the work would more properly and effectively be done by him, and, unhappily, each side sometimes accuses the other of not pulling its weight To all this a satisfactory solution is unlikely to emerge without adoption of some integrating policy Indeed, the uneasy relations between general practitioner and local authority have created such a situation as we had in mind when we referred lately to the need for a return to planning[2]

We welcome therefore a useful step in this direction by the medical officer of health for Staffordshire, Dr GERALD RAMAGE, who has prepared a reasoned analysis[3] of the problem of the general practitioner and the local authority's personal health services He has compared, in an objective way, the views of general practitioners and local-authority doctors on the work they do, and, in the light of these opinions, he discusses the difficulties to be overcome In assessing the value to the community of the local authority's services, RAMAGE refers especially to the defects and illnesses of childhood the clinic workers undoubtedly discover many abnormalities in the children they see, among them conditions that are much the better for early treatment It has often been suggested (by GEORGE et al,[4] for example) that, in child-welfare clinics, the advisory work of the clinic doctors could be taken over by health visitors, and their medical duties by general practitioners But many mothers who take their children to these clinics do so because they know that there they can see and talk to a doctor who is not too busy to give time to comparatively minor troubles, and attendances might fall away if the child-welfare clinics were staffed only by health visitors On the other hand, an increasing number of general practitioners are now running ‘ well-children ” sessions for their own patients, and, as more and more of them are able to do so, the child-welfare clinics will become empty and the health visitors will be free to give more direct help to general practitioners And the same could happen in antenatal and other clinics But it is unlikely to happen for a long time, unless general practitioners are given some financial reward for providing these extra services As things now are, and as RAMAGE's inquiry illustrates, it is doubtful whether the present size of general practitioners' lists allows them time for anything but a gesture at preventive work The figures given in the Cohen report on general practice for the length of the practitioner's working week were higher than those derived from a more recent investigation[5] but what is perhaps more important than hours of work is the practitioner's ability to order his day's affairs around fixed sessions which he can attend with certainty Group practice is the environment that will do most to help him in this way, *and it is in group practice that doctors* may have the ampler accommodation needed for *effective “ clinic ”* work

If the general practitioner becomes able and willing to take on much of the work of the clinics, what changes should be made in consequence in the executive direction of the local-authority services? In the second part of his paper RAMAGE explores the possibilities of control other than by the local health authority, and his comparison between the administrative structure and functions of the executive council and the public-health department is very much in favour of the council For many reasons most general practitioners think poorly of local authority organisations and would be unwilling to serve under them, they dislike an authority which has power to determine the doctor's relationship with his patients, and which gives the doctors it employs so little say in its organisation The proposal to merge the present local-authority services with one of the other existing branches of the National Health Service has been resisted on the grounds that such a union could not cater for school medical services and other special *departments* of the local authority welfare service Alternatively, local authority work might be done by general practitioners if executive-council duties were transferred to the local authority's control, and this, it is said, would make it easier for practitioners to take over the duties of the local-authority doctors, though the plan would be unworkable unless the practitioners were thoroughly satisfied with the arrangements RAMAGE puts forward a programme whereby practitioners could take over by stages the work now being done by clinic doctors and whereby increasing help could be provided for practitioners who run their own clinics Under such a scheme many of the “ public-health doctors ” would ultimately disappear, though there would, of course, always be whole-time posts for other important health-department duties The responsibility of the local authority for the provision of premises could be extended to include a contribution for suitably designed practice premises, and the doctor practising preventive as well as therapeutic medicine should have access to

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1 *Lancet* 1956 ii 781
2 *Ibid* Jan 5 1957 p 31
3 Ramage, G *Med Offr*, 1957, 97 31
4 George, J T A, Lowe C R McKeown T *Lancet*, 1953, i, 88
5 Crombie D L Cross K W *Brit J prev Soc Med* 1956 10, 141, see annotation, *Lancet* 1956, ii, 1312

premises provided for him without paying rent as does the specialist who works in a hospital

Few will dispute RAMAGE s final conclusion—namely that the general practitioner *could* become responsible for the antenatal maternity, infant-welfare, and school branches of the preventive services And if one can judge by the correspondence in our columns most doctors think he *should* do so From this point it could be argued the course is fairly clear more general practitioners must be given the opportunity to prevent as well as treat disease and to take over the work of the clinics and administrative difficulties must be resolutely overcome But there may be complications Under the present arrangements patients can choose whether to seek the advice of their family doctor or that of the clinic doctor for a particular condition and if the family doctor becomes the patient s only source of immediate help there may be dangers in such a monopoly of medical advice Whatever the medical profession may think there is no doubt that many people in this country value the alternative source of advice provided by local-authority clinics, and it would be wrong to disregard this public opinion. If the clinics go the picture of the popular all-embracing family practitioner may be disturbed by an outcry in defence of the clinics, as something the public likes rather than something it still urgently needs Moreover, there may be another administrative formula that would be more acceptable it might be better to separate the personal health services of the local authority from its other duties to the community and transfer them to suitably modified executive councils of the National Health Service This is of course just one of several possibilities (another is the plan proposed by Professor FRASER BROCKINGTON[6] for making the medical officer of health the coördinator of the medical team with general practitioners the first and most important agents in public health) Nevertheless here might be the beginning of an opportunity to link organised preventive medicine with general medical practice at the level where the link would be strongest Doctors health visitors and others now employed by local authorities could be ' seconded to group practices and practice groups, there to work with general practitioners, to teach them and to learn from them In this way " public health might quickly come to have a real meaning in general practice

Treatment of Coarctation of the Aorta

COARCTATION of the aorta should seldom be overlooked if the femoral pulse is sought whenever increased pulsation in the neck brachial hypertension, or unexplained aortic incompetence are detected What is to be done when the diagnosis is made? CAMPBELL and BAYLIS[7] have studied 130 patients with coarctation and they have tried to answer this question by assessing the prognosis In this series 6 patients died who had seemed quite well a year or two before and 4 of them were between twenty and thirty years old Altogether 16 patients died from causes including congestive failure rupture of the aorta bacterial endocarditis and intracranial hæmorrhage all well recognised in this condition[8,9]: and some patients died after operation Symptoms were uncommon in the earlier decades of life though 4 patients had cerebrovascular accidents before the age of twenty, and the blood-pressure after rising sharply until the age of seventeen subsequently remained almost steady Even in the fourth decade the average diastolic pressure did not exceed 110 mm Hg and it is often lower than is generally supposed There was aortic incompetence in nearly a quarter of the cases and stenosis in a further 6 CAMPBELL and BAYLIS regard incompetence as the consequence of bicuspid valves rather than rheumatism and its effects are often slight, with little depression of the diastolic pressure though the incompetence may become more apparent as age advances Absence of symptoms is no guarantee against sudden death and the age of the patients when first seen (only 6 were over thirty-five) suggests a high mortality from the age of twenty onwards For these reasons CAMPBELL and BAYLIS now recommend resection in most children, and they feel it should not be long delayed after eight years Aortic incompetence is an added indication. CRAFOORD[10] and GROSS[11] put the best age for operation at between ten and twenty years because the aorta is then of adequate size and is still free from degenerative changes The mortality of resection was 9% in CAMPBELL and BAYLIS s series and in 648 reported cases they found it to be rather less—7% In CLELAND et al s series[12] of 40 patients who were operated on 3 died including 1 who had a dissecting aneurysm and for whom operation was advised as a desperate resort CLELAND et al suggested that a mortality-rate of less than 10% may now be anticipated in practised hands and the figure is now probably even lower—CAMPBELL and BAYLIS suggest 5% in uncomplicated cases and after GROSS s last 100 operations there were only 2 deaths

After a successful resection, the pressure falls in the arms and rises in the legs but, despite claims to the contrary, COUNIHAN[13] has found that it does not become normal In 20 patients he found that the postoperative pressures remained higher than would have been expected in normal persons of the same age The obvious explanation—that the stricture was incompletely relieved—was rejected by COUNIHAN for a number of reasons The collateral circulation disappeared after operation and the femoral pulse-wave measured by sphygmograms became synchronous with or just preceded that in the radial artery Femoral systolic pressure equalled or exceeded brachial systolic pressure in all except 1 patient, in whom it remained 10 mm lower In 12 cases measurements were made at operation of the aortic diameter at the site of the anastomosis and proximal to it, even when these were identical hypertension persisted. COUNIHAN concluded that the more nearly uniform the aortic calibre after the operation the lower the systolic pressure became—but it always remained above normal WRIGHT et al [14] examined 10 patients soon after operation and again after periods up to seven years In most of them the femoral systolic pressure continued to rise slowly, and to a lesser extent the radial pressure fell As WRIGHT et al put it, ‘ the residual coarctation ” tended to improve slightly during this time, but unlike COUNIHAN’s patients 5 still had femoral systolic pressures significantly lower than brachial pressures after a number of years, and presumably a degree of stricture remained

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[6] See leading article Lancet 1956 i [illegible]

[7] Campbell M Baylis J H Brit Heart J 1956 18 47

[8] Abbott M. Amer Heart J 1928 3 574

[9] Reifenstein G H Levine S A Gross R E Ibid 1947 33 146

[10] Crafoord C Minerva Cardioang Europea 1955 suppl 1, p 1 9

[11] Gross R E Circulation, 1953 7 757

[12] Cleland W P Counihan T B, Goodwin J F Steiner R E Brit med J 1956 ii 379

[13] Counihan T B Clin Sci 1956 15 149

Why the blood-pressure does not fall to normal is unknown, but nevertheless what fall there is is sufficient to encourage the belief that the complications of coarctation are abolished or much reduced The operative risk is still appreciable, and it is unlikely to improve greatly unless resection is advised before the onset of complications, or before the development of degenerative changes in the wall of the aorta make a difficult operation far more so And even after successful resection, the risk of bacterial endocarditis upon a bicuspid valve remains

Annotations

INFLATION AND BETTERMENT

IF a Government believe that the nation is in critical danger from inflation, and if they are taking difficult and unpopular measures to check it, there is force in their appeal to all sections of the community not to ask for more money Stabilisation of the purchasing-power of the pound would be an advantage for which most of us would be ready to pay a considerable price The policy of our post-war Governments, however, has been directed rather towards slowing inflation than towards stopping it indeed, if unemployment threatens, we may soon see a degree of reinflation permitted This policy may be right or wrong, but if money is to go on declining in value—even if slowly—rational and decent means must be found for adjusting remuneration accordingly

In some countries wages are linked with a cost-of-living index, which alleviates the effects of inflation but also goes far to ensure its continuance In our own country, too, recent responses to wage claims, when not governed wholly by expediency, have been based on this principle Thus we have all read with mixed feelings that administrative and clerical staff earning less than £1200 a year in the National Health Service have been awarded “ a 3% increase in salary on the basis of the rise in the cost of living since February 1, 1956,” [15] while dispensing assistants have had an increase of 5% to allow for the rise since the previous September

In commenting on a similar increase of 3% recommended by the Railways Tribunal “ to match the rise in the cost of living since the last increase,” the *Economist* [16] says that an approximately correct decision has been given for the wrong reasons Wages can be increased each year, without promoting inflation, provided the percentage increase is no more than that of the nation’s real income thus if (as in a good normal year) the national income goes up by about 3%, everybody’s remuneration can go up by 3% without harming the economy This is in line with our own view [17] that the only satisfactory way of financing the National Health Service is that it should be “ accorded, as of right, a defined proportion of each year’s national income ”—of which in turn defined proportions would be used for paying the various groups of people who work in it “ Betterment,” provided the nation continued to prosper, would then be automatic

MOSQUITOES AND MYXOMATOSIS

MYXOMATOSIS was first described in 1898 in Uruguay [1] but not until 1927 was the deliberate infection of wild rabbits suggested as a means of reducing their number in Australia The attempts were only partly successful, apparently because of the absence of insect vectors, for without vectors the disease will spread only when the rabbits are in close contact After the late war further efforts led to the rapid spread of myxomatosis in the Murray valley Investigations into the mechanism of transmission then pointed to the rapid dispersal of infection by the movement of infected mosquitoes, and other vectors in Australia were black flies and stickfast fleas It was thought that the virus did not develop in the mosquito and that transmission was purely mechanical, the insect contaminating its proboscis with virus from the skin lesions of an infected rabbit and transferring it to healthy rabbits up to 25 days later

In Britain, no officially authorised attempt has ever been made to introduce myxomatosis, but when it had spread quickly across Europe in 1953, it reached England (though by what means is not known) and the first case was confirmed at Edenbridge, in Kent, in October, 1953 By the end of 1955 it had reached almost every parish in England, Scotland, and Wales

Late in 1954 an investigation began into the possible insect vectors in this country The rabbit flea is the principal vector, but the activities of mosquitoes were also studied In the part of the country where the first outbreak took place, by far the most prevalent mosquitoes were the woodland aedes, and it seemed reasonable to expect that this common mosquito would find a regular and easily available source of blood in the wild rabbit This possibility was examined by Muirhead Thomson,[2] who showed that, though aedes mosquitoes would feed readily on rabbits in the comatose stage of myxomatosis, they seemed reluctant to feed on healthy wild rabbits By exposing rabbits in cages in woods where the aedes abounded, it was shown that the mosquitoes were not attracted to healthy domestic rabbits which remained uninfected despite months of exposure Though aedes mosquitoes could be infected with virus by feeding on infected rabbits, their unwillingness to feed on healthy rabbits seemed to make them unimportant vectors of the disease

In Australia, anopheles mosquitoes have figured largely in the spread of myxomatosis, and the possible role of *Anopheles atroparvus*, which is the main vector of malaria in Northern Europe, was also considered [3] in Britain It proved to be an extremely efficient vector, capable of carrying the infection through the winter, and, theoretically at least, bridging the gap between the virtual elimination of a rabbit population and the appearance of the healthy progeny of an odd survivor But there is no evidence that anything of this kind does, in fact, happen under natural conditions One possible explanation is that *A atroparvus* rarely bites in the open and lives in dark stables, cowsheds, or piggeries for most of the year But as pigs and stables become fewer, and cowsheds become light and well ventilated, it is becoming increasingly difficult to find this species of mosquito where formerly large numbers would have been expected *A atroparvus* prefers the blood of domestic animals to that of wild rabbits, and Muirhead Thomson concludes that it has little to do with the spread of myxomatosis among wild rabbits in Britain In some places, however, it may help to spread the disease among domestic rabbits. it has been shown that a single bite can infect, and that one mosquito can infect several rabbits in a short time

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[14] Wright, J L Burchell H B Wood E H, Hines, E A Clagett O T *Circulation*, 1956 14 806

[15] *Brit med J* Jan. 5 1957, suppl p 12

[16] *Economist*, Dec 15, 1956 p 949

[17] *Lancet* Jan 5 1957 p 31

[1] Sanarelli G *Rif med* 1898 14 ii 217

[2] Muirhead Thomson, R C *J Hyg Camb* 1956, 54 461

[3] Muirhead Thomson R C *Ibid* p 472

Though Australian workers believe that spread by mosquitoes is purely a mechanical transfer, Andrewes et al[4] have shown that mosquitoes of this species can remain infective for up to 220 days—much longer than was previously thought The fact that anopheles may remain infective for so long (whereas in the mouthparts of dead mosquitoes the virus survives for only a few days) suggests that there may, in fact, be limited multiplication of the virus But if there is "biological" transmission, it is certainly very different from that of yellow-fever and insect-borne encephalitis viruses

METABOLIC RÔLE OF ZINC

THE belief that zinc is essential to normal development rests in part upon the work of Todd Elvehjem, and Hart,[5] who showed that trace amounts were necessary for the well being of growing rats, but its fundamental importance to all animals became apparent only after Keilin and Mann[6] had demonstrated that the enzyme, carbonic anhydrase, contains 0 33% of the element as an inherent part of the molecule Zinc is now known to have other functions, which have lately been reviewed by Vallee[7]

Of the normal daily intake of 10–15 mg, the greater part is excreted in the fæces, the fraction absorbed maintains a total body store of about 2 g, distributed differentially throughout the tissues In the plasma, zinc (at a concentration of 124 ± 16 µg per 100 ml) is, like calcium, partly bound in non ionisable form to the plasma proteins (about a third is in this form), and partly in loose association with protein in an ionisable form suitable for transport Normal erythrocytes contain 1 44 mg per 100 ml of packed cells, and, at least in health, the slight fluctuations in this figure can be correlated with carbonic anhydrase activity, but no such specific function has been associated with either the protein bound zinc of the serum or the protein-zinc complex which has been isolated from human leucocytes Isotopic zinc (^{65}Zn) is rapidly taken up by the liver kidney, pancreas, and pituitary, but it accumulates more slowly in the bone-marrow and in the circulating red cells High levels are also found in the retina and iris and in the prostate, and it is known that the element can pass across the placenta

Besides its part in the carbonic anhydrase system, there is evidence that zinc, in association with protein, figures prominently in other metabolic changes The zinc isotope which accumulates in the pancreas is secreted in the pancreatic juice and this secretion also contains a highly specific carboxypeptidase enzyme which, like carbonic anhydrase, is inhibited by zinc-binding agents This enzyme has been crystallised as a zinc protein complex, in which the presence of zinc is essential for activity Three other enzymes, alcohol dehydrogenase, glutamic dehydrogenase, and lactic dehydrogenase, each dependent on diphosphopyridine, have also been shown to be zinc-protein complexes

Crystallisation of insulin as a zinc complex has suggested that this element may be an essential part of the active hormone But the experimental evidence does not support this view, for zinc can be replaced here by nickel, cobalt or cadmium, and the amorphous form of insulin which presumably does not contain any metal, has equal physiological activity Yet zinc undoubtedly modifies the action of insulin, since the addition of zinc chloride to insulin before injection delays the action of the hormone Reports of a similar action on gonadotrophin preparations are interesting and justify further investigation

Empirically, it has been found that low serum-zinc levels are often associated with the pyrexia of infection, increased levels are apparently without significance Serum levels are also low in untreated pernicious anæmia, but as there is no corresponding fall in total erythrocyte zinc, the mean corpuscular zinc concentration rises In other anæmias, polycythæmia and leukæmia, the changes in the zinc content of the red cells parallels the hæmatocrit value and the hæmoglobin concentration

Chemical methods for the determination of trace amounts of zinc are not yet as precise as is desirable in work of this kind There is reason to hope, however, that new physical methods including the use of the radioactive isotope ^{65}Zn and the possibility of measurement by flame photometry, may provide a reliable laboratory aid to future advance in this interesting and important field

TOLBUTAMIDE

THE first sulphonylurea to receive a clinical trial in the treatment of diabetes mellitus was carbutamide (B Z 55)[1] The initial German claims that it had a powerful hypoglycæmic action in certain types of diabetes were confirmed, but its limitations also became apparent It was usually of no value in the young patient with severe diabetes, it was definitely contra-indicated in the treatment of diabetic ketosis, and it was ineffective in the presence of complications such as infection Further, carbutamide had a definite action on the bone marrow in a certain proportion of cases, and a special warning was issued about this danger[2] Other less serious side effects included skin rashes and interference with thyroid function

The second sulphonylurea to be investigated was tolbutamide, which has a methyl group in place of the *p* amino group of carbutamide, and many reports have now appeared[3] There are certain differences in pharmacological properties between carbutamide and tolbutamide The hypoglycæmic effect persists, though tolbutamide is slightly less active,[4] but the bacteriostatic action is lost[5] Of greater importance is the question of bone marrow toxicity, and this is always more difficult to assess The dangers of carbutamide in this respect were not fully appreciated until some time after its introduction The evidence so far suggests that tolbutamide is considerably less dangerous than carbutamide, though it is not entirely innocuous since it too may produce leucopenia[6] Both substances suppress the uptake of radio iodine, but tolbutamide is less active in this respect[7–12] Clinically this side effect has not so far been important, but clearly this anti thyroid action must be borne in mind if lengthy treatment is needed Skin rashes are occasional complications with both carbutamide and tolbutamide [12,13]

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[4] Andrewes C H Muirhead Thomson R C, Stevenson J P *Ibid* p 475

[5] Todd W R Elvehjem C A Hart E B *Amer J Physiol* 1934 107 146

[6] Keilin D Mann T *Biochem J* 1940, 34 1136

[7] Vallee B L *J Amer med Ass* 1956 162 1053

[1] See *Lancet* 1956 ii, 180

[2] Duncan L J P Nabarro J D N Oakley W G Wolff F W *Brit med J* 1956 ii 454 See also Page O C et al *New Engl J med* 1957 256 74

[3] Levine R Duncan G G *Metabolism* 1956 5 721

[4] Beaser S B *Ibid*, p 933

[5] Moreau R Deuil R Sarrazin A, de Traverse P M Martinet, M *Pr med* 1956 64, 1261

[6] Fulmer H S Dube, A H Lloyd C W *Metabolism* 1956 5 940

[7] Renold, A E Winegrad A I Froesch E R, Thorn, G W *Ibid* p 757

[8] Brown J Solomon D H *Ibid* p 813

[9] Mortimore G F, Di Raimondo, V C Forsham P H *Ibid* p 840

[10] McGavack T H Seegers W Haar H Erk V *Ibid* p 919

[11] Kuhl W J *Ibid* p 953

[12] Heineman, A Cohn C, Weinstein M Levine, R *Ibid* p 972

The hypoglycæmic action of the two drugs apparently depends on the same principle [14], and there is no evidence that a diabetic patient who does not respond to one compound will react favourably to the other The way these substances produce hypoglycæmia is still uncertain, and the position has not been greatly clarified since we commented [1] on this subject six months ago

There are certain characteristic differences between the actions of insulin and sulphonylurea in producing hypoglycæmia Insulin increases the glycogen content of muscle, unlike sulphonylurea, which, on the other hand, increases hepatic glycogen [15,16] It is thought that the sulphonylureas may act by decreasing the release of glucose from the liver [7,17], but this view is not universally accepted These compounds are ineffective after total pancreatectomy, but small doses have a definite hypoglycæmic action when injected into a pancreatic artery No effect on the blood sugar level follows injection into the portal vein [18] Other evidence points to the fact that they can act only in the presence of some functioning pancreatic tissue and supports the view that tolbutamide has a direct action on the islets of Langerhans [19]

The persisting uncertainty about both the mechanism of action and the hazards of long continued administration means that the use of tolbutamide should be restricted to carefully planned therapeutic trials Its widespread use, even in the type of diabetes that might respond, is certainly unwise Many of the patients who might respond are overweight and can often best be treated by dietetic measures alone In more severe cases the attraction of treatment by mouth should not outweigh the fact that insulin is still the physiological replacement

PESTS AND PESTICIDES

MANY chemical substances used to control insect pests and plant weeds are toxic to man and other mammals, and the widespread use of these substances is an occupational hazard to sprayers and factory workers There is also a potential danger to the general population from food which may contain minute amounts of these substances, applied at some stage during its growth, preparation, or preservation These problems have been recognised by many governments, and the views of an international panel of experts, set up under the auspices of the World Health Organisation, have lately been published [20] Chemically, the pesticides fall into two large groups the chlorinated hydrocarbons, which include dicophane (D D T), chlordane, dieldrin, and endrin, and the organophosphorus compounds, of which parathion, T E P P, malathion, and chlorthion are examples The mechanism and the symptoms of poisoning are quite different in the two groups, but the fundamental actions of individual members of each group are similar

Those who are anxious to have the most effective materials they can get must also ensure that these can be used with safety to both man and animals Clearly, information on the toxicity, safe methods of use, and the treatment of poisoning must be readily available before effective field programmes can be planned Animal experiments provide basic information on comparative toxicity But the methods of applying an insecticide in different environments may result in unexpected poisoning Thus, dieldrin poisoning has been troublesome among workers in Venezuela, where it is used to control the vector of Chagas's disease, but dieldrin has been used in Africa and Indonesia for malaria control with no untoward effects For several reasons, the difficulties of getting up to date information, and therefore of controlling adequately the use of insecticides, have become greater during the past few years An increase in the number of insect species attacked and the development of resistance by the insects have led to an increase in both the quantity and variety of chemicals used In 1946 resistance was reported in only 1 species of insect, but by 1956, 34 species were known to be resistant to these insecticides—a change which emphasises the need for laboratory investigation and careful field studies before making recommendations about the use of such substances

The clinical signs of early poisoning by either the organophosphorus or hydrocarbon compounds are not specific The late signs of poisoning by organophosphorus compounds are due to the accumulation of acetylcholine at nerve ganglia and motor end-plates of muscles—muscle fasciculation, bronchospasm, abdominal pain, terminal convulsions, and coma In serious poisoning by the chlorinated hydrocarbons, there is incoordination of movement, irritability, with intermittent clonic tonic convulsions, and finally respiratory failure Specific tests can establish the diagnosis of poisoning by the organophosphorus compounds (depression of the blood cholinesterase activity is a characteristic action of this group) But no satisfactory laboratory test has yet been devised for detecting poisoning by any of the chlorinated hydrocarbons, except dicophane In dicophane poisoning, dichlorophenylacetic acid (D D A) is excreted in the urine

The routine animal experiments which are carried out before any new substance is recommended as a pesticide may also throw light on the mode of action of the new compound It is often found, however, that laboratory animals show considerable species differences in their susceptibility The W H O report recommends that greater emphasis be given to studies of human beings who have been exposed to pesticides, and the report also devotes many pages to the discussion of measures for the protection of operators handling pesticides Points of particular importance are that the workmen should be made fully aware of the risks involved, and if men exposed to organophosphorus compounds are found to have a low blood-cholinesterase level, further exposure must be forbidden even though no symptoms or signs of illness are apparent

Though the amounts of pesticides present in milk flour, meat, fats, and water are insufficient to produce symptoms of acute or chronic poisoning, no one knows what damage may follow the continued absorption of small amounts over long periods For this reason volatile chemicals should be used as far as possible and the amount applied should be kept down to a minimum It is known that dicophane, dieldrin, and gammabenzene hexachloride are eliminated in the milk of lactating animals, and dicophane has been found in human milk For this reason, these substances should not be used as insecticides in dairies or be added to cattle feeding stuff. Another consideration is the effect on domestic animal and fish—for example, when applying insecticides for the control of malaria or molluscicides for the control of bilharziasis, the concentration of insecticide in the water must be well below the level which would harm the fish The W H O study group decided that no recommendations could yet be made about the maximum safe limits for residues of pesticides on food, because of the shortage of reliable information

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13 Unger R H, Davidson J W *J Amer med Ass* 1956 162 147
14 Beringer A, Kolbl E *Wien med Wschr* 1956, 106 792
15 Miller, W L, Dulin, W E *Science*, 1956, 123 584
16 Wick A N, Britton B, Grabowski, R *Metabolism* 1956, 5, 739
17 Purnell, R Arai, Y, Pratt, E, Hlad, C Elrick, H *Ibid*, p 778
18 Colwell, A R jun, Colwell, J A, Colwell A R *Ibid*, p 749
19 Goetz, F C, Gilbertsen, A S, Josephson, V *Ibid*, p 788
20 *Tech Rep Wld Hlth Org* 1956, no 114 Toxic Hazards of Pesticides to Man

Special Articles

INDIVIDUAL REACTIONS TO CHANGE
AS SEEN IN SENIOR MANAGEMENT IN INDUSTRY*

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In these days the idea is current that the greater part of nervous breakdown is due to intimate rather than external causes But many psychiatrists are now coming to believe that stress related to the simple business of living and working may be of at least equal importance And of the breakdowns which occur, a great number are directly related to a failure to adapt successfully to change or the need for change For this reason management is a most promising field for mental hygiene

Man, we learn *from the Koran,* is incapable of perfection , and in its low level of accuracy and large number of errors human performance compares ill with that of most forms of machinery This, however, is the price we pay for two qualities in which the human organism far excels any machine of its creation—namely, *complexity* and the capacity for *self-regulation and profiting from experience* In man alone there have developed from these qualities such attributes as initiative foresight, responsibility and appreciation of human relationships But unfortunately these attributes which are essential for leadership in any major enterprise remain scarce, and they are very unevenly distributed That their correlation with intelligence in the academic sense is relatively low explains many of the mistakes in personnel selection

Like man industry must adapt to changing conditions Within its organisation it will have a considerable division of labour, and, in terms of cybernetics, will include regulators, discriminators predictors, and integrators, linked to a certain number of generalisers It is the generalisers that are *responsible,* ultimately, for the direction of change , and the future of industry depends on their selection, training and distribution, in place and time, and on maintaining the fickle flame of their efficiency—for they are only human

One of the trends in business organisation is the increase in the proportion of administrative to operational staff If twenty men drawing only moderate salaries and working at half pressure could be as effective as ten men working at full pressure, this might not matter so much, but it is not so If they can be obtained a smaller number of men earning more pay and doing much more work in the same time will produce far better results

INSECURITY

It is with the causes of inefficiency in the components of the regulating mechanism—the senior managers and directors—that I shall now deal

If I have any complaint of boards of directors or groups of senior executives it is that they are far too considerate when one of their number falls into my hands Their consideration often takes the form of concern lest he should lose his job and the dignity and authority that go with it They will bemoan the pace of modern industry, and if given the opportunity, they will furtively *compare* the patient s case with their own These men have recognised that it may be their turn next The strain of doing a job for which they are no longer fit, their determination to hang on to what they have got, is written all over them They are insecure In my view their value as generalisers is often limited, for they share with the neurotic the urge to save their own skins If the generaliser is no longer able to identify his own aims with those of the firm in an enlightened self-interest, if he is preoccupied with holding on to his personal status and the *status quo,* this attitude will extend to his work and he will albeit unconsciously, resist change

Most people in industry are well adjusted preserve a good balance between their industrial and private lives and generate no unhealthy inward tension so that if their task is well designed for them and if it is one that gives an opportunity to make use of their abilities, attitudes and interests, they will work at maximum efficiency In their case modification of their work may create a temporary but healthy tension which has the function of keeping them alert during the period of adaptation In those who are less well adjusted however, even the suggestion of change and the threat of being called upon to do or to understand something beyond their abilities brings the threat of breakdown They are unable *consciously* to accept the reasons for their uneasy feeling about the new idea and rationalise their position and convince themselves that all change is perilous and all chance unsound " Their response is not always clearly evident They may in fact appear very enthusiastic until the implications of the proposed change in terms of personal reorientation have sunk in The delayed change of heart after a day or two is a known characteristic of this group

Among those in senior positions in an organisation the tendency to hold on to power as such is apt to increase as real capacity diminishes Use is frequently made by the insecure of the fact that the man who is trying to get a new idea across has to use many times as much energy as the man who wishes merely to obstruct him passively The sense of power through refusal learnt in the cradle is experienced again with new and ego-sustaining satisfaction

Where resistance to change is of emotional rather than rational origin the ways of overcoming it may *sometimes* have to be oblique in the extreme If one is to be a bringer of change and progress, a good deal of time has to be spent *on just this process for* a cause will rarely sell itself entirely on its own merits Means must constantly be found for providing spiritual gain for those who are to support it

MATURITY AND INERTIA

Only a small proportion of humanity has the capacity the energy, and the wish to act as generalisers Yet many find themselves either thrust into this position or are there *by* a passive operation of promotion The human brain in the most intelligent *groups* is not *mature* until the age of 25, at which time there is still much more to be learnt But after 25 there is a very slow decline in the speed *of thought* and the capacity for learning Between 25 and 35 the seeds of a man s best ideas are laid down even if they flourish much later After 35 maturity and experience must compensate for the gradual but definite slowing of mental activity which is *taking place* A few, with sound brains and well-trained habits of mind, can maintain their originality well into the senium, but in one whose ability has never been adequate, or whose decline has been more rapid than usual, the mental mechanisms by which he keeps up with his work and conceals the truth from himself and others are fully in operation by 40 The most powerful weapons protecting him are *tradition* and *promotion by seniority* Too often the advice which should be given to a firm is " It would be economical to pension this man off generously—to pay him to stay away " But by that time of life the currency acceptable to him is not so much cash as prestige

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* From an address to members of the Duke of Edinburgh's study conference on the Human Problems of Industrial Communities within the Commonwealth and Empire, July 14 1956

It is unfortunately not yet possible to get spare parts for the human machine, and the brain in particular can lose components but never replace them Nor can one easily scrap the machine and find a new one at once, for it takes time to train a senior manager for the particular needs of the organisation he is to control I should not like to give the impression that I always consider the more change the better, or think that continual change is necessarily healthy On the contrary, the formation and maintenance of stable routines is an essential But it is evidence of high morale in a human group that there is no mental set against the possibility of change, that new thought can be generated without having to overcome too much inertia of mind and that the capacity to adapt to change has not been lost In the same way continual changes of staff as well as methods may have an adverse effect on morale There seems, however, to be nothing whatever to be said for inbreeding at the top end of management, and the practice of introducing chairmen and heads of departments from outside must surely keep managers in competitive trim If a firm, through such a policy, tends to lose personnel because they cannot feel secure, the loss in experience may be made up by a gain in initiative

THE RESPONSE TO STRESS

Breakdown occurs in both the successful and the unsuccessful, and in that the former adapt better to change, their outlook is usually better In fact some very successful men with a very sure touch in their business affairs require in their private lives to be propped up by psychiatrists, astrologers, diets, and wives, and this is clearly worth doing

A feature of some successful executives is the intermittency of their drive They will accomplish a great deal in a few short weeks, after which they are less in evidence until another quantum of energy is available It is characteristic of them that they respond to change, even when they have not themselves initiated it, with a burst of energy Their moods are often quite predictable to their secretaries, though not to themselves This intermittency is consistent with a high intellect and is a liability which those gifted with the ingredients of success must often accept Few are able to live through an active progress to senior positions without showing some signs of strain, but these are usually self-limiting

Inability to adapt to one's circumstances creates a sense of inadequacy, of inward tension and insecurity This tension, which may be brought about by many other kinds of psychological stress, is the common basis of neurotic breakdown Where a person can face his own inadequacy—be he ugly, clumsy, stupid, or merely lacking in drive—and change his circumstances, even at the loss of prestige or pay, so that he can cope with them, he will not break down Perhaps I should say, *would* not break down, for I have yet to meet him One and all, we are bolstered up by self-deceptions and comforting ideas which we are not in the habit of examining very carefully

Some causes of tension in managers are

(1) *Sudden change to a task requiring rapid and complex adaptation in a man who has been too well organised for too long*

(2) Failure to accept with resignation a position inconsistent with ambitions

(3) Decline of ability to keep up with a job which is too responsible and calls for more initiative than can be found without strain

(4) Conflict between identification with firm's interests and competing interests at home

(5) A degree of intermittency in drive which has allowed the individual to take on more when "high" than he can cope with when "low"

(6) The cumulative effects of a type of drive which makes delegation difficult and prevents a reasonable relationship of work to leisure

(7) Increasing uneasiness at the prospect of retirement for which no mental preparations have been made

The tension generated shows itself in various ways, all of which have an indirect effect on efficiency

(1) Poor sleep, bad temper, continual grumbling, longer hours of work but less achieved Symptoms usually attributed to overwork

(2) Repeated minor sickness Consulting specialists and self medication, often accompanied by an interest in life assurance and financial security

(3) Procrastination Working from in tray to out-tray and losing sight of long term aims Working by the clock rather than by the interest of the job

(4) Feeling of frustration and persecution by colleagues. Complaints of lack of cooperation

(5) Increase in alcoholic intake and verbal output Technical jargon and catch phrases replace original thought

There is a tendency to underrate the importance of alcohol as a contributory cause in breakdown at the senior levels It provides a readily available and socially acceptable escape from the sense of insecurity, and the premium put on extraversion and interpersonal relations in business predisposes to its use in excess There might be some question whether firms are getting their money's worth out of the bonhomie generated by their expenditure under this heading

BETTER SELECTION AND ALTERNATIVE PLACEMENT

How is it possible to bring into the regulating mechanism of a firm a sufficient proportion of people who are capable of exercising foresight and of applying it in the form of change ? Also to get them into this position while in their prime and to get them out of it before the onset of the *defensive decline* described above, if they are not capable of keeping up the pace Two possibilities at least are worth considering—*better selection,* and *alternative placement* for those whose initiative is waning

Managers capable of going to the top are scarce Probably, in the immediate future a lower proportion will come from the universities, for these are at present saddled with an excess of expert examinees, intellectually precocious but immature in character, who have had (in relation to their contemporaries) their peak performance in the years between the "eleven plus" and the General Certificate of Education It is fortunate that industry is offering opportunities to those who have failed to get into universities and who have reached maturity on the job There are also the sons of middle class parents who (because of taxation or the means test for educational grants) cannot be sent to the university but can be accepted for training in industry from the outset Again, the technical and research branches of industry can contribute a large quota to senior management A firm which can take ten possibles, and, having given them all special opportunities for rapid training, can produce one first class manager, is not making a bad bargain if three more can find satisfactory places lower down in the pyramid

Though they are fallible and have caused disappointment, selection methods can help Applied psychology is still inclined to lay too much stress on brightness as opposed to other less measurable qualities It is apt, too, to be excessively preoccupied with the exclusion of those who may actually break down as opposed to those who will merely be inefficient and who in fact are far more expensive in the end But that some organised selection is better than none is now being realised by those firms who are getting the left-overs from those who do select Selection does not have to be 100% successful to be a good investment

The selection of the future administrator is a continuous process, and while a promising entrant is learning his job he must be frequently re assessed, for there is no method of selection as reliable as the long-term observation of the individual's reaction to a succession of real situations There is no reason why it should not be recognised as continuing throughout his career in industry

Senior managerial staff who are unable to maintain initiative may be valuable in a position in which they can use their experience In the larger organisations it should be possible to have a staff structure designed so that those who have a chance to go on to the very top should not be as well paid as those who, having got so far in the general administration, may prefer to take a more specialised post with higher pay, earlier retirement, and as high sounding a title as is considered possible The way to the top would thus be hard, with the option at any time of compromising for the more specialised but more lucrative post with less influence on general policy

There remains the problem of the inadequate but ambitious, the dogs in the administrative manger Experiments with methods by which members of a group of seniors make an annual report, without consultation, on the fitness of each of their colleagues, are of great interest in this country, because when a Briton is asked to pass judgment of this kind he usually will do his best to be objective and will not at once seek to form a voting bloc The results of such experiments, carried out with due care for secrecy and anonymity, indicate that the method might be useful if it became the established custom to ask for assessments of this kind and to correlate them statistically over a period of years While it remains the custom to " carry " those who have become drunken, idle or prematurely incompetent the cost will remain high Financial security is desirable as age advances, but to assure personal prestige as well as material security is more than the economy can bear

From the point of view of one whose news of the battles of industry is mainly derived from the casualties left on the field, it appears that the ideal of management is a body of individuals who see their own advancement, and the satisfaction of their personal drive, in pursuing the aims of their organisation, who are conscious of the responsibility of recruiting young men to their number on a basis of merit alone, and who have an established system of using the experience of those who can no longer stand the pace of change As the pace of competitive industry accelerates there can be no room for traditional self-deceptions, and direction must surely be placed in the hands of those who can not only accept but will welcome change

CLUBS FOR " MIXED " HANDICAPS

MOST of the voluntary organisations for the disabled have been formed to help people with a particular handicap or disease Thus there are societies which look after the welfare of spastics, of people with poliomyelitis, or of the blind The St Raphael Clubs are unusual in that they are open to nearly all handicapped people, from teenagers to old-age pensioners, regardless of their disability

The first club was started ten years ago by the parents of some handicapped children in Norwich The name was chosen because the angel Raphael was sent to help the sons of Noah in their adversity Ten clubs have now been set up, including those at Hexham, Romford, King's Lynn, Colchester, Swaffham, Lowestoft, and Wayland, a rural area of Norfolk

The clubs offer recreation and social help to handicapped people The limitations of disability are lessened by the fun and satisfaction of doing things (however small) together, and of meeting old friends and making new contacts—not always an easy thing for the disabled Companionship underlies everything done in every St Raphael club A one ailment club can breed an odd sort of preoccupation But at a St Raphael club the patient with poliomyelitis, for instance, is shown the problems and courage of spastics, arthritics, and the blind

The clubs are run as much as possible by the members themselves, but much of the work is of course done by the least handicapped and by able bodied supporters Surgeons, almoners, and occupational therapists help with their special knowledge, organisations such as the Red Cross, the Churches, and the W V S help in many ways, and transport is provided by Rotary and Round Tables

The Norwich club has a membership of 110 and an average attendance of 75 at its weekly meetings It has its own premises, a small redundant school which was bought a few years ago after great efforts by the members and their supporters There is a large hall, now complete with piano and stacking chairs, a small lounge with easy chairs and a television set (given by the local Round Table), a room with a billiard-table and workshop tools, and a kitchen Other organisations of handicapped people, such as the Invalid Tricycle Association, are allowed to use the rooms when free On Saturdays the club is open from 3 P M until after 9 P M Older members hold their weekly meetings on a different day from the younger generation Entertainments vary from film shows and outings to concerts and short plays A small choir leads a monthly religious service held by members and their friends Some members make and sell toys, and for the past two years the club has held a competition and exhibition of handicrafts, to which the other St Raphael clubs have contributed It has also found jobs in offices for several members, and a local firm has provided piece work to be done at the club itself

The Hexham and Wayland clubs serve country areas, and their membership is less than 50 But the need they meet is perhaps even greater than in larger towns Thus the Hexham club includes blind people, who in Norwich, where the numbers are larger, have an organisation of their own

Each club is recognised by the authorities for the receipt of grants Members pay 6*d* per meeting—held weekly in Norwich, monthly in the smaller clubs For blind members there are special grants

Public Health

Nursing-homes in London

THE report for 1955 of the medical officer of health for the county of London [1] includes an account, by the late Dr E B Argles, of nursing-homes in the county Whereas in 1937 170 nursing-homes were registered the number had fallen to 108 in 1945, 63 in 1947, and 48 in 1953 Rising costs, says the report, have alarmed the users as well as the owners of nursing-homes Accommodation which before the late war cost 5–8 guineas a week today costs 11–25 guineas, but this is not a disproportionate increase when compared with rises in costs

Confinements in nursing-homes numbered 1001 in 1952 compared with 3107 in 1947 This large drop is not due wholly to the fall in birth-rate from 20 9 per 1000 population in 1947 to 15 3 per 1000 in 1952 Most homes have found that in the post-war years less use has been made of their operating theatres, whereas more beds are being used for medical cases and particularly for the treatment of chronic sick or senile patients " Establishments which provide care for the aged by ordinary unskilled staff fill a real need, and there are good reasons why some of the smaller nursing homes should turn their attention to this type of elderly person who so often fails to find the accommodation for which he or she is seeking "

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[1] London County Council Report of the County Medical Officer of Health and Principal School Medical Officer for the Year 1955 Issued from County Hall S E 1 Pp 193 2s 6d

Before Our Time

"DOCTOR"

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THE word "doctor" has no less than twelve different meanings, but only two of these concern medical men[1]—a degree in a university and the name given to a medical practitioner

As a degree it was first used in the medical school of Salerno[2] about the middle of the 11th century It was next used in the law school of the University of Bologna[2] in the middle of the 12th century as a degree superior to that of magister, and soon afterwards it was introduced at Paris,[3] first in the divinity school and later for law and medicine Oxford University,[3] which was founded about 1167, gave a doctorate in divinity, and sometime in the 13th century one in law and medicine Cambridge University,[4] which was founded about 1209, also gave a degree of doctor in these subjects Until the University of Durham was founded in 1832 these were the only two universities in England which could grant the degree of doctor in physic, but the other universities in the British Isles—St Andrews (founded in 1411), Glasgow (1451), Aberdeen (1494), Dublin (1591), Edinburgh (1583)—all gave degrees in medicine

At the present time Oxford confers the degree of doctor in seven faculties An estimate of the respective numbers in each faculty, obtained from the University Calendar, is divinity, 99, civil law, 31, medicine, 234, letters, 58, science, 68, music, 29, philosophy, 883 The total of these figures (1402) is probably on the low side, since if the doctor removes his name from the "books" it is omitted from the calendar But it will be seen that of some 1400 who have a doctor's degree and can call themselves Doctor, fewer than 250 are doctors of medicine

Outside the universities, degrees in divinity, civil law, and medicine were formerly conferred in this country by the Pope After Henry VIII assumed the post of "Supreme Head of the church and clergy as far as the law of Christ will allow" (Act, 25 Henry VIII, c 21) in 1534, these powers were transferred to the Archbishop of Canterbury, and the degrees are now called the Lambeth doctorates[5] Thomas Cranmer did not confer any degrees in medicine, but, of the 451 Lambeth degrees given between 1663 and 1848, 31 were in medicine and 13 of the recipients do not seem to have had a medical qualification The last degree in medicine was conferred in 1880[6]

The other common use of the word is for a medical practitioner, and its first recorded use is by Langland[1] Chaucer used it in 1386, saying "With us ther was a Doctour of Phisyk"[7] The older word for a medical practitioner was a leech, and this is noticed as early as the year 900[1] Chaucer said in 1386 "What nedeth hym that hath a parfit leche To sechen other leches in the toun"[1,8] Both words seem to have been used in the succeeding centuries, but in the 17th "leech" was applied to veterinary practitioners

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When the Royal College of Physicians was founded in 1518, its fellows and licentiates did not call themselves Doctor unless they had the degree of doctor of medicine in either Oxford or Cambridge or one of the universities in the British Isles

Surgeons about this date in London were members either of the Barbers Company, which contained both barbers and surgeons, or of the Guild of Surgeons which was less influential and poorer than the Barbers Company[9] These two united in 1540 when Henry VIII granted a charter to them as the Barber Surgeons Company[9] The members of the company rarely if ever had the degree of doctor of medicine and did not call themselves Doctor The Surgeons separated from the Barber Surgeons Company in 1745 and formed their own company This was dissolved in 1796 and a royal charter was granted to the new College of Surgeons in 1800 During the 360 years since the foundation of the Barber Surgeons Company, few surgeons would have had the degree of doctor of medicine, and surgeons would not have been addressed as Doctor

The rise of the apothecary began to cause difficulties in the profession An Act of Parliament in 1815 gave the Society of Apothecaries the right to appoint a court of examiners to examine all apothecaries to ascertain the skill and abilities of such persons in the science and practice of medicine and their fitness to practice as an apothecary Further, in 1827 the society asked for proofs of training in midwifery which neither of the Royal Colleges demanded, so that the holder of the diploma of L S A might have had a better all round qualification than the licentiate of the Royal College of Physicians or the member of the Royal College of Surgeons Between the years 1815 and 1883 no fewer than 31,000 men were licensed to practise by the Society of Apothecaries and it was thought that five sixths of the London students in 1822 were studying for general practice as surgeon apothecaries[10] Many of these men, who were not licentiates of the Royal College of Physicians, called themselves Doctor, and this custom caused a good deal of ill feeling, especially when the Medical Act was passed in 1858 This Act required, among other things, that all should register their qualifications with the General Medical Council *The Lancet*, the *British Medical Journal*, and the *Medical Times* of 1860 contain many letters complaining that licentiates of the Society of Apothecaries called themselves Doctor whereas those of the Royal College of Physicians were not allowed to do so—which made the general public tend to regard the licentiate of the Society of Apothecaries (L S A) as superior to the licentiate of the Royal College

The matter was brought to a head when an action was brought against Hubert Edward Kelly, who lived in Pinner, because, although he had registered only the qualifications of M R C S, L S A, he styled himself Doctor The action was dismissed by the magistrate and was heard on appeal in the Court of Exchequer before the Lord Chief Baron and two other barons The Lord Chief Baron, in dismissing the appeal, said "If a man is registered, he may call himself what he pleases," and "the Act (Medical Act of 1858) is to prevent any man practising medicine who is not registered"[11] This case was complicated by Kelly having produced documents which showed that he had the degree of Erlangen University, and, though he had not registered this degree, he was clearly entitled to call himself Doctor

The Royal College of Physicians paid no attention to this decision, and in 1862 published its by law in English which said

"No Fellow, Member, or Licentiate of the College shall assume the title of Doctor of Medicine or use any other designation, name title, or distinction implying that he is a Graduate in Medicine of a University, unless he be a Graduate in Medicine of a University"[12]

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[1] New English Dictionary
[2] Rashdall, H Medieval Universities (edited by F M Powicke and A B Emden) London, 1936, vol i, pp 76, 87, 271
[3] *Ibid*, vol iii p 11
[4] *Ibid*, p 277
[5] *Lancet*, 1896, i 1146
[6] Private communication from the Librarian, Lambeth Palace
[7] Chaucer G (1386) Complete works (edited by W W Skeat) *Oxford 1894 Prologues line 411*
[8] *Ibid*, Somnour s Tale, line 248
[9] Young S Annals of the Barbers Company London 1890, p 47 et seq
[10] Horner, N G The Growth of the General Practitioner of Medicine in England London, 1922, p 36
[11] *Lancet*, 1860, ii, 524

There the matter rested until after 1884 when the two Royal Colleges agreed to set up a Conjoint Board to conduct the examinations in medicine, surgery, and midwifery under conditions which satisfied the requirements of the General Medical Council and to grant a Conjoint diploma[13] Having done this, the two colleges considered whether they could not grant a degree instead of only a diploma Their proposal was rejected in 1889 by the Royal Commission upon the Higher Education in London[14] Two years later a proposal to delegate "pass degrees" to a joint board, nominated partly by the senate of London University and partly by the two Royal Colleges, was rejected by convocation[15] Three years later the two colleges approved a plan to found a second university in London to be called the Gresham University, which would have been a teaching university independent of London University[16] This scheme was eventually rejected by a Royal Commission in 1900 when a new constitution was granted to London University The two colleges were each given two representatives on the senate, and under the constitution "powers were granted to the Senate to make arrangements to conduct jointly with the Senate examinations in such portions of the subjects in the course of study for a medical degree as may be agreed upon between the Senate and those Colleges" (Statute 123)[17] This statute has never been acted on, and after careful consideration in 1903[18] and again in 1910 and 1911,[19] the Royal College of Physicians "decided that it was inadvisable that the College should take any further steps to promote the scheme of a Conjoint Examination contained in the report dated 1910" This ended the efforts of the twenty-six years on the part of the two colleges to grant degrees to their licentiates and members

In 1905 the secretary of the Royal College of Surgeons wrote to the Royal College of Physicians saying that his college received many complaints from its members about the by-law forbidding them to use the title of Doctor, and hoping that the Royal College of Physicians might see its way to withdraw its prohibition[20] The matter was carefully considered by the Royal College of Physicians but in April 1906, the comitia decided by a large majority to make no change in its by-law[21] However in July, 1911, the comitia again considered the matter because of more complaints by its licentiates and because of the impossibility of preventing licentiates from using the title of Doctor if they defied the college As a result the by-law was amended in 1912[22] and now reads

> "No Fellow, Member or Licentiate of the College shall append to his name the title of Doctor of Medicine or the letters M D or any other letters indicating that he is a Graduate of a University, unless he has obtained a degree entitling him to do so"

The meaning of the by-law may be summarised in the words which the Chief Baron used in 1860 "If a man is registered he may call himself what he pleases" At the time the by-law was passed the whole medical profession and its press was deeply concerned with the struggle over the Lloyd George National Insurance Act and *The Lancet* did not comment on it until nearly five months later[23] The concluding sentence of its annotation runs

> "Previously the distinction between practitioners who did or did not hold University degrees was rather an invidious one as it tended to the idea that their professional skill and knowledge were similarly unequal, which was by no means necessarily the case now without fear of any reproach for using a forbidden term, the Licentiates of the Royal College of Physicians and the Members of the Royal College of Surgeons can adopt the professional title which is generally understood by the public to indicate that they are duly qualified practitioners of medicine"

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Now that forty-four years have elapsed since the by-law was altered, the general practitioners all call themselves, or are called by their patients, Doctor, whether they have the degree of doctor of medicine or not The newly qualified house officers are treated in a very unequal fashion In some teaching hospitals both the house-physician and house surgeon are called Mister In others the house-physician is called Doctor and the house-surgeon Mister In the great majority of non-teaching hospitals, I understand that, both are called Doctor, though in some the house-surgeon is called Mister Although the Royal College of Surgeons had striven so hard to get the by-law altered so that its members might be called Doctor, its fellows and those of the sister college of Edinburgh refuse to be called Doctor and insist on being called Mister, as though that were a superior degree

This curious practice which does not exist in any other country (so far as I know), except in those Dominions of the British Commonwealth which follow the practice of the Royal College of Surgeons, seems to arise from the old antagonism between the Royal College of Physicians and the Barber Surgeons Company after its formation in 1540 The members of the company rarely if ever had a degree of doctor of medicine, and their general education was certainly inferior to that of the physicians. Further, judging by the rules which William Harvey, in 1633, laid down for them at St Bartholomew's Hospital they were under the domination of the physicians[24] Nowadays, when the general education and qualifying examinations are perforce the same for both physicians and surgeons, it seems peculiar that the distinction should still exist, and that the surgeons should still seek to preserve the insignia of their inferiority in the Middle Ages This practice seemed most peculiar when an elderly anæsthetist (now dead), who had always been styled Doctor, was elected a fellow of the Royal College of Surgeons and insisted on being addressed as Mister The fellows of the Royal College of Obstetricians and Gynæcologists, and all who aspire to become Members of that College, also refuse to be called Doctor and seem to glory in being called Mister This is more difficult to understand seeing that fifty years ago they all called themselves Doctor The custom seems to have started about the time of the foundation of the college and it is difficult for an elderly physician, who is proud to call himself Doctor, to understand why the change was made

The practice causes a good deal of confusion among patients and the general public who cannot understand why a properly qualified doctor should not be so called It also causes some inconvenience to themselves if they travel in countries where all medical men are called Doctor Is it too much to hope that one day everyone who has a registrable qualification will be called Doctor and that this curious survival will cease ?

I have to thank the Registrar, Sir Harold Boldero for permission to consult the Annals of the Royal College of Physicians of London and Mr L M Payne, F.L.A., for his great assistance in searching the records

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[12] Annals of the Royal College of Physicians of London 1862
[13] *Lancet* 1884 ii 741 972
[14] *Ibid* 1889 i 1[illegible]
[15] *Ibid* 1891 i 1110
[16] *Ibid* 1894 i 967
[17] *Ibid* 1900 i [illegible]
[18] Annals of the Royal College of Physicians of London 1903
[19] *Ibid* 1910 1911
[20] *Ibid* 190[illegible]
[21] *Ibid* 1906
[22] *Ibid* 1912
[23] *Lancet* 1913 i 12[illegible]
[24] Moore N History of St Bartholomew's Hospital London 1918 vol ii p [illegible]

In England Now

A Running Commentary by Peripatetic Correspondents

THROUGH hell and high water we uphold the cause of Freedom In our mountain fastness we are quite used to swinging our little motor cars around the hairpin bends and down the 1 in 4 gradient that leads to the village We do not clutter up the valley with warning signs and suchlike cossetting Our cats' eyes blink contentedly by the hearth, our white lines stay by the dartboard We have the room and the time to enjoy the pattern of sunlight on the fells, to swerve round the sheep in the road, to stop for a chat on the corner We would be thought plain daft if we waggled our arms about with fancy signals as it says in the *Highway Code* Likely cause a nasty accident

The well-meaning efforts of the old grannies on the councils of other areas fire us with proud contempt We hoot with derision at their steep-hill triangles on a simple 1 in 8, we shriek drovers' oaths at the sight of their cattle-crossing signs, we sail airborne over their silly little humped-back bridges So it was when we set out with a tank full of basic ration to return our heir to school Convention demands that out of a pile of dubbined rugger boots, squash racquets, tuck, electrical gadgets, and general haberdashery, all duly numbered and name-taped, we should emerge in decent habit to pay our respects to the Housemaster before abandoning the offspring

We always try to grant the last wishes of the condemned, so that was why we took the coast road Tide-tables mean even less to our valley than road-signs We greeted with growing hilarity a succession of boards which told us that the road was impassable at high-water, that duck-shooting was strictly reserved, and that bathing was dangerous We pressed on in the usual way towards the wheeling seagulls At the edge of the saltings we ran slap into a sheet of water, but, as it was only a few inches deep, I whistled a cheery hornpipe and surged on round the bend The bow wave was piling up, and so was my better half's anxiety The heir, of course, was delighted Then with a strangled splutter the exhaust sank below the surface and we hove to A quick glance at the daily paper predicted a 31 feet tide with high-water in another half-hour By the way the sea was sluicing across the road it was doing its best to comply through the floorboards

The heir and I ripped off our shoes and socks, rolled up our Sunday-best trousers, and stepped out into an ice-cold January flood My wife bundled up her fur coat and high heels to sit cross-legged at the wheel while we pushed our mock amphibian towards the distant shore Some unfeeling engineer had tar-sprayed the road with granite chippings, so sharp that they penetrated even the stocking anæsthesia of the freezing waves But Fate was kind once we had done our penance Henry Ford's hardy product shook itself and spat seaweed out of the silencer We wrung the water out of our pants and arrived in the quadrangle looking more like the end of term than the start We dumped the body and drove away like mad Of course the brakes would not work, but apart from that minor distraction we kept a vigilant eye on the road-signs all the way home The price of Freedom without doubt

* * *

Into the middle of a dull surgery came Mary, all smiles and looking very well She sat down and said " A've given o'er wark " Wondering what was coming next I gave a non-committal "Yes," and she continued "and a've brought this for thee," holding out a pound note Still nonplussed, I asked her why I should have it and she explained that she had just come from the post-office and this was half of her first retirement pension " Dost thou not remember ? " she said

And then indeed I did Mary's winter coughs were always accompanied by some degree of asthma, but about twelve years ago she had a particularly resistant wheeze and she became very despondent She thought that her time had come and that she would never get back to work again "I shall never live to draw me pension, and think of all them stamps a've bin puttin' on for all these years," she moaned. To cheer her up I suggested that we should make a bargain If I kept her alive until she could draw her pension we should share it between us—fifty-fifty I had forgotten, but she had remembered and here was her thank-offering " It's for thee," she said, " to give to any charity that thou likes "

There are still a lot of nice folk about

* * *

A very clearly marked feature in many neurotics is an inability to make decisions This can be elegantly demonstrated by the coal-cellar test

The patient is ordered to fill a coal scuttle in a well lit cellar He cannot decide which lump is the most suitable to put in the scuttle, and characteristic pawing movements are observed A viewing window of one way glass is a convenience The test is now repeated in total darkness Since the lumps cannot be seen, there is no hesitation as to which to reach for, and the performance may be greatly speeded up

The ratio of time-in-the-light to time-in-the dark is taken, and a value greater than unity indicates neurosis Resentment will increase filling-time, but since this is likely to be felt more keenly in the dark than in the light, a time-ratio greater than unity will always be significant

* * *

Outside our front gate a small dog came abruptly into contact with a small car from which an even smaller man sadly emerged We watched as its last few breaths were quickly spent in the gutter " Daddy," asked Jo (aged 3) " Did that doggie run across the road and bump into that man's car and get bleeded ? " " Yes," said Bill (5), " and now he will go to a hospital and be made all better like Daddy does Daddy, will you make him all better ? " " What a silly doggie," concluded Jo, deep in thought " Oh, no," explained Bill " It's not his fault, his Mummy and Daddy should have stopped him, shouldn't they, Daddy ? " " Daddy," said the youngest, giving me no chance to get in, "what will they do to that doggie ? " At last I had the opportunity of explaining that my hospital didn't take dogs, and, anyway, he was beyond my skill " Well, what will they do with him ? " There was no escape " I expect they will take him away and bury him " " Oh, but that's unkind," said Bill at once That was lost on me, and I sought enlightenment He explained " Because that will make him even more dead " Quite defeated, I went for help to the kitchen " But that's a very sensible remark," said my wife, and returned to the washing up

The psychological damage from this incident does not seem to be as deep as I had feared Over the bath later that week I was asked à propos of absolutely nothing " Daddy, when I'm as old as you are, how old will you be ? " *Rapid calculations on the wall led me to con*clude " 51 " (28 minus 5 plus 28 I think) " And when I'm 51, how old will you be ? " (Deep thought) " 74 " " And when I'm 74, how old will you be ? " (More deep thought How Much Longer O Lord ?) " 97 " " And when I'm 97 how old will you be ? " Seeing no end to this, and in an admittedly unguarded moment " I shall probably be dead " No damage, however, this was greeted with uproarious laughter and much jumping about " And when you're 97 how old shall I be ? " he ended up " You'll probably be dead, too," I said Enormous amusement at this, both of them quite incapably convulsed with mirth

What about it, Sigmund ?

* * *

In Wales family connection used to be shown by placing the word " ap " (the son of) before a name, and traces of this remain in Parry, Pugh, and Pritchard, sons of Harry, Hugh, and Richard When this method was discredited, the English " son " took its place, but after the name, and John's son and Hugh's son became Jones and Hughes But the remote valleys tended to become over populated with one family and it became necessary to invent a method of naming the subspecies as it were so the occupational system was evolved—Mr Thomas the Post or Hughes the Milk Sometimes, however, the nicknames have a more topical basis In our village Owen John Williams is an auctioneer and is known as Owen John the Going Gone, while Thomas Jones, who has only two central incisors left, one up and one down, is Thomas Jones Central 'Eating

Letters to the Editor

HYPERTENSION: PRESYMPTOMATIC DIAGNOSIS AND TREATMENT

SIR,—Formerly it was held that hypertensive patients become accustomed to their high blood-pressure, which is then necessary to maintain the circulation. Even today many authorities say that hypertension should not be reduced unless it is causing symptoms.[1–3]

But we are in an era when the emphasis is on early diagnosis and early treatment and it is hard to see why hypertension should alone be left untreated until it reaches a stage when nothing much can be done about it. In most cases of hypertension the rise in blood-pressure at first is transitory, labile, and asymptomatic. Why then should we not try to detect it at an early stage and keep the blood-pressure down by comparatively simple measures? Surely we should look on hypertension as a reversible illness, which, like an attack of asthma, should be brought under control as quickly as possible, though we cannot guarantee that it will not recur. We are not unduly nervous about telling a patient that he is suffering from tuberculosis, valvular heart-disease, or diabetes. Why then should we continue to teach that it is best not to tell the hypertensive patient that his blood-pressure is raised? I agree that the actual blood-pressure readings should not be mentioned; but I believe that the patient should certainly be told that he has a mild elevation of blood pressure, that he should follow certain simple restrictions on his activity and diet, and take some drugs for a time.

On the principle that high blood-pressure, like other disorders, should be treated as soon as it is discovered, I am at present studying a series of eleven cases, of which the following is representative.

In February, 1955, Dr A, aged 51, complained of headache with a tired feeling at the end of the day. The only abnormality found was a blood pressure (B.P.) of 168/106 mm. Hg. The B.P. recorded 4 months earlier had been 130/84. Though there were no other symptoms or complications I decided to treat him with comparatively mild hypotensive agents. He was given reserpine 0·25 mg. twice a day, and 'Theogardenal' (phenobarbitone and theobromine) one tablet twice a day, and advised to reduce his sodium intake by half. The B.P. was recorded on alternate days and in 2 weeks it fell to 140/90. The dose of reserpine was reduced to 0·1 mg. twice a day and stopped after another 2 weeks. The blood-pressure has since remained about 140/90.

The other ten patients have all had a diastolic pressure persisting above 100 mm. Hg for several weeks, and have been treated on the same lines. All have responded, though one showed a recurrence after 4 months and another after 7 months. These episodes of recurrence yielded to similar treatment. In only one case pentolinium tablets had to be used to bring the pressure down initially, the milder hypotensives not having acted.

Of the eleven patients, three were women and eight men, their ages ranging from 42 to 56. They have been under observation for periods varying from 4 to 21 months.

The classification of essential hypertension into benign and malignant is completely misleading. It should be given up. The term "benign" can properly be applied to a condition which has hardly ever been known to cause death, but hardly to essential hypertension in which about 90% of the patients die sooner or later of the well-known complications. For too long this totally inappropriate terminology has led physicians to ignore the presence of hypertension and adopt an attitude of expectancy with folded hands until complications set in, by which time it is practically impossible to reverse the changes. With a diastolic pressure fixed at about 130 mm. Hg, the measures required are more complex and more doubtful in their results, and there is the additional danger that thrombotic complications may be precipitated by over-zealous treatment.

The idea that once a mild hypertensive is started on a regime of dietetic control and drug therapy he is likely to require these for many years, is probably incorrect. A large series of cases should be studied the world over to obtain data regarding the late results of early treatment of asymptomatic hypertension. In such studies workers in India can play as large a part as those in the West. Of the many fallacies surrounding essential hypertension, perhaps the most serious as that there is no hypertension in the rice-eating peoples of the East or that hypertension is a disease of Occidental civilisation. Physicians who have worked in India know that high blood-pressure is exceedingly common in India both in the cities and in the countryside.

Madras Medical College,
Madras, India.

K. S. SANJIVI.

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[1] [illegible] M. L. Int. med. J. 19[illegible], ii, 11[illegible]
[2] F[illegible] A. M. Med. Clin. N. Amer. 19[illegible], 40, 132.
[3] Wil[illegible] In Price's Text Book of the Practice of Medicine. London, 1956, p. [illegible]11.

THE PLIGHT OF HOSPITAL PHARMACY

SIR,—As chairman of the committee that examined some aspects of hospital pharmacy for the Central Health Services Council a few years ago, I must thank you for your timely survey of its staffing problems (Jan. 19).

You rightly identify inadequate salary scales as a main cause of the shortage of hospital pharmacists, and there is no doubt that there will be no significant increase in recruits until salaries improve. But in pharmacy, as in other sections of the health service, that is by no means the whole story. In some respects the problem is akin to that faced by general practitioners. They are asking for higher remuneration, but over and above that they look for better conditions of practice. Dissatisfaction does not show itself so obviously among general practitioners because for them the alternative to grinning and bearing it is a major operation such as emigration to Canada. For pharmacists there is the simpler alternative of moving into one of the other branches of pharmacy, and that is what they are doing. Like the general practitioner, the hospital pharmacist looks for a professional career that is progressive and satisfying as much as financially rewarding, and too many hospitals fail to provide it.

A campaign to increase recruitment cannot succeed if it is linked only with better salaries. It will be necessary for management committees to consider in consultation with their chief pharmacist how far the inadequacies of their pharmacy departments may be responsible for shortage of staff. Many of them need substantial replanning. A large number of them were never properly designed when the hospital was first built and have been left for years to grow haphazardly. Moreover, it should go without saying—but often does not—that the chief pharmacist has the authority and responsibility which must be accorded to the head of a department if he is to do full justice to his work. He must have the effective voice in the purchase of his materials and engagement of his staff. He should be able to report direct to the management committee and to attend its meeting when pharmaceutical affairs are discussed. One of his chief duties should be to tender advice to the medical staff about prescribing efficiently and economically, and he should have access to the medical committee for that purpose.

The salary scale for pharmacists should depend more upon the complication of the work in their department than on the size of the hospital. It should bring a pharmacist up to a good competence at forty or so and beyond that there should be a sufficient number of well-paid senior posts throughout the service to attract good men to a hospital career As you emphasise, special rewards for higher qualifications are likewise important for this purpose More pharmacists can be recruited into hospitals only when it is generally understood by those in authority that the present staff shortages are due to a general neglect of the hospital pharmaceutical service, which is slowly running down because no-one is tackling the fundamental defects The service can be rebuilt, but only if it is given a new deal and a new look in all its aspects

House of Commons,
London S W 1
HUGH LINSTEAD

PRESCRIPTIONS FOR DIABETICS

SIR,—The medical subcommittee of the British Diabetic Association has now clarified with the Ministry of Health some financial alleviations for diabetic patients on the new prescription regulations

To be brief, a Ministry letter of Nov 27, 1956, states that the supplies of needles, spirit, testing tablets, and —most important—insulin can be prescribed for three months or more depending on the doctor's view in the individual case One shilling only per item would be payable, irrespective of the quantity ordered

British Diabetic Association,
152 Harley Street,
London W 1
R D LAWRENCE
Chairman, medical subcommittee

HYPOPITUITARISM AND GONADAL DYSGENESIS

SIR,—I feel sure that many of your readers who, like myself, are not experts in the pathology and biochemistry of the hormone deficiency diseases, would welcome some reassurance about the paper by Dr Jackson and Dr Hoffenberg in your issue of Dec 15

This describes the case of an old man who was admitted to hospital for treatment of hepatomegaly and piles The authors state that he was suffering from dwarfism, mental deficiency, epilepsy, severe anæmia, and considerable œdema of the legs and sacrum They explain how cretinism was suspected and go on to describe an insulin tolerance test which resulted in hypoglycæmic coma and death

One must presume that the insulin tolerance test was used in preference to the exhibition of thyroid because of some advantage such as greater safety or greater certainty of the result, which might be reflected in greater certainty of treatment, and hence, greater advantage to the patient Unfortunately this point is not made clear in the article

One would also be interested to know whether the patient was held to have died accidentally, as the result of an accidentally produced hypoglycæmic coma, or whether the death was held to be due to a pre existing condition

I ask these questions because the authors themselves make it clear that the patient was incapable of coöperation (and therefore incapable of giving consent to an experiment), because the photograph (fig 1 in the paper) seems to indicate considerable distress on the part of the patient (however, the photograph may well be misleading) and because the article makes no reference to the efforts which must have been made to alleviate the patient's condition

In cases of this kind, where the scientific interest is great and the end result to the patient of little scientific importance, it is only too easy to give the false impression that the scientific interest is the only one involved, I feel sure that the authors would welcome an opportunity to correct this impression in this case

London, N 1
R E W FISHER

*** We have shown this letter to the authors of the article Their reply follows —ED L

SIR,—We should like to assure your correspondent that the humane aspects of this case were not overlooked, but that only the basic scientific facts were given in the published report Actually at the time of investigation of this case (1952) we were quite unaware of its great scientific interest, which became apparent to us later while studying problems of sexual differentiation We stress that the investigation referred to was *not* purely academic, but was pertinent to the handling of the case

Shortly before seeing this patient we had investigated two cases of adult cretinism, and we felt fairly sure that we were dealing with another one An insulin tolerance test was considered valuable to rule out the possibility of hypopituitarism which we (mistakenly) felt was very unlikely At the time it was considered dangerous to exhibit thyroid alone in hypopituitary cases, so that this investigation was undertaken as a routine One of us was present during the insulin test and administered intravenous glucose as soon as possible after the coma, which rapidly restored the blood sugar but the patient remained unconscious and was found to be hypothermic He died two days later, having never fully recovered consciousness, despite our best attempts at resuscitation Hypopituitary patients are well known to be subject to such a mode of death He did not die in hypoglycæmic coma, although we readily admit and deplore the fact that this episode appeared to have started the train of events which led to his death, which, however, could not have long been delayed in any case

Regarding the photograph, the patient was weak and unable to stand without assistance His appearance of distress is easily explained by his efforts, which were required for only as long as it took to work the camera shutter

We openly acknowledged our error of judgment in this case, but we really hope that we have vindicated our ethical integrity

W P U JACKSON
R HOFFENBERG

DANGEROUS CONTAMINANTS IN STORED BLOOD

SIR,—I am greatly relieved that Dr Drummond (Jan 12) thinks that experts can sample blood bottles with a very low contamination rate I wish he could persuade the authors of *Notes on Transfusion*, issued by the Ministry of Health, that this is true, for that booklet makes it mandatory to mark as "Dangerous for Patients" every blood bottle 24 hours after it has been sampled Some regional transfusion directors refuse to accept this directive, and insist that blood must be used even when more than 24 hours have elapsed after the bottle has been entered[1] I am glad that Dr Drummond thinks (as indeed I do) that this practice is safe, but it is to my mind scandalous that any regional transfusion director should enforce the use of a bottle of blood which, according to the Ministry's advisers, is dangerous for patients—the more so since, if the patient died, the pathologist would have the greatest difficulty in justifying the action forced on him by the regional transfusion officer

There seems to be no general agreement on how deaths associated with transfusion should be classified I submit that one should discriminate between deaths due solely to transfusion and those associated with disease treated by transfusion For example, during a transfusion given very rapidly because of torrential hæmorrhage the citrate anticoagulant might lower the ionised calcium level enough to cause heart failure, the ensuing death should not be ascribed to the transfusion I think this difference will explain the difference between the frequency of transfusion deaths accepted by Dr Aidin and myself Deaths due solely to transfusion can be classified into (*a*) hæmolytic reactions due to serological incompatibility, stale blood, or blood damaged by heating or freezing, (*b*) bacterial contamination, (*c*) cause unknown

Bacterial contamination itself is often of no importance, for the entry of a few bacteria at the time of administration is harmless, as is shown by the excellent results obtained by the open method The problem is different with stored blood, for, though pathogens hardly grow at

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[1] *Lancet*, 1955, i, 205

+4°C, some saprophytes do so with generation times of the same order as that found by Dr McEntegart (Nov 3)—and also with the lag period he found. Such bacteria cannot kill by colonising the patient, but may do so by causing a reaction to their own body proteins or to their metabolites, and they may kill in this way even if they themselves have first been killed so that Dr Marsh's (Jan 12) criteria for deciding whether death was due to bacterial contamination are not valid. It does follow, however, that blood contaminated with a few saprophytes is dangerous only after the bacteria have had a chance to multiply, and Dr McEntegart thinks that this period of relative harmlessness may be as long as 14 days. If this be so, I cannot see any rationale for doing stained films on all blood bottles which are to be issued.

In this hospital, if the patient becomes ill after transfusion, the transfused blood is cultured at 20°C and at 37°C—and so far out of some 25,000 bottles no reactions attributable to bacteria have been encountered. Can Dr Aidin (Dec 22) or Dr Stark Murray (Jan 19) tell us how many patients have been saved from contaminated blood by their stained film procedure? Or, for that matter, can anybody else who has been working in England during the last ten years? *Experientia docebit*

Central Middlesex Hospital
London N W 10

GEORGE DISCOMBE

A MISSED FRACTURE

SIR,—I read with considerable misgiving the report under this heading (Jan 19).

Firstly, the coroner has no power to criticise anyone; his job is to determine the cause of death and nothing more. Such criticism should be disputed on the spot, for it may well be quoted in subsequent claims for damages.

In this particular case one should not be too sure that the casualty officer failed in his duty. He was sent an old lady with an injury to her arm, he dealt with this and returned her to the care of her own doctor. It is admittedly to be regretted that he did not diagnose the fractured femur, but neither did he find a fractured skull, diabetes mellitus, and a host of other possibilities. If a casualty officer, or any doctor, thoroughly examined and investigated every patient he saw, he would never leave his surgery or consulting room.

The final sentence is even more ominous. The public has a right to be treated—and nothing more. It has no right to expect "completeness," and in particular no right to be cured—as many seem to think.

Newcastle General
Hospital

J F STONE
Senior casualty officer (surgical)

HYPOTHERMIA

SIR,—I wonder whether the initiators of artificial hibernation know about their predecessor who practised this therapy (though in a primitive form) during the 1914–18 war. The information comes from one no less than Mahatma Gandhi,[1] who was suffering at that time from severe dysentery.

> "Whilst I lay thus ever expectant of death, Dr Tadwalker came one day with a strange person of Maharashtra. He is not known to fame, but the moment I saw him I found that he was a crank like myself. He had come to try his treatment on me. He had almost finished his course of studies in the Grant Medical College at Bombay without taking the degree. Later I came to know that he was a member of the Brahmo Samaj. Sjt Kelkar, for that is his name, is a man of an independent and obstinate temperament. He swears by the ice treatment which he wanted to try on me. We gave him the name of 'Ice Doctor.' He is quite confident that he has discovered certain things which have escaped qualified doctors. It is a pity both for him and me that he has not been able to infect me with his faith in his system. I believe in his system up to a certain point, but I am afraid he has been hasty in arriving at certain conclusions. But whatever may be the merits of his discoveries, I allowed him to experiment on my body. I did not mind his external treatment. It consisted in the application of ice all over the body. Though I am unable to endorse the effect that he claims his treatment had on me, it certainly infused in me a new hope, and the mind naturally reacted on the body. I began to have an appetite and to take a gentle walk for five or ten minutes."

The event took place whilst "the deadly war in Europe was still going on."

St John's Hospital
Budapest

GEORGE LEVART

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[1] Mahatma Gandhi. His Own Story. Edited by C F Andrews. London 1931 p 29.

A NEW CLINICAL ENTITY?

SIR,—The epidemic of aseptic meningitis which has been observed in different parts of England,[1–4] and which seems to involve pronounced pleocytosis in the cerebrospinal fluid (C S F)[5] has also been prevalent in different countries on the Continent.

Between June and November last year innumerable cases of aseptic meningitis, sometimes with exanthem, were reported in Belgium. The manifestations were roughly the same as those so described by your correspondents.

1 Definite meningeal symptoms, with or without the now well known rubella-like exanthem, fever, headache, back and neck stiffness, severe muscle pains, vomiting, photophobia, sometimes conjunctivitis, and, characteristically, a very pronounced pleocytosis with cell counts ranging from 50 to more than 3000 cells per c mm. Recovery was the rule, but there was a notable tendency to relapse.

2 A kind of "summer influenza fever," sometimes accompanied by rash, in which no meningeal symptoms were clinically obvious, though lumbar puncture sometimes revealed C S F involvement.

As was pointed out in this journal,[6] there was no "striking evidence of involvement of the substance of the brain and cord", but mixed infections with poliomyelitis virus were recorded in Belgium, and proved by laboratory findings.

This disease seemed to be very easily transmissible and we know of many multiple family or secondary cases, as described by Dr Pickles[2] and Dr Lyle.[3] Between July and November we isolated 156 virus strains—122 from stools, 28 from C S F, and 6 from throat. These viruses were cytopathogenic for monkey-kidney cells but not for HeLa cells. That all these viruses were of the same strain can be presumed from the results of cross neutralisation tests: any virus isolated was neutralised by any patient's convalescent serum, as well as by rabbit serum after immunisation with one strain chosen as reference.

The identity of these similar strains was evidenced by the following tests: no neutralisation occurred, either by monkey anti-poliomyelitis sera, or by those standard rabbit anti-E C H O virus sera (received from Dr A Sabin) which corresponded to types 7, 8, 10, 11, or by rabbit anti-E C H O virus sera, ranging from type 1 to type 14 (9 excepted). However, indubitable neutralisation was always observed with anti-E C H O-9 serum.

Inversely, among standard E C H O viruses received from Dr A Svedmyr and Dr J L Melnick, ranging from type 1 to 14, type 9 only was neutralised by patients' sera, and by rabbit antisera corresponding to Belgian strains.

79 of the patients showed the same rise of neutralising antibodies, between acute and convalescent sera, towards Belgian virus strains and towards E C H O virus 9.

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1 Tyrrell D A J, Snell B *Lancet* 1956 ii 1028
2 Pickles W N *Ibid* p 1047
3 Lyle, W H *Ibid* p 1042,
4 *Ibid* p 947
5 *Ibid* 1956 i, 789
6 *Ibid*, 1956, ii 1091

Neutralisation results seemed to be confirmed by complement-fixation tests

The same outbreak of aseptic meningitis was also observed in the Netherlands[7,8] and in Switzerland[9], from a Swiss stool specimen we have isolated an ECHO-9 virus, and one strain received from the Netherlands[7] proved to be also of type 9

Dr F Dekking, of Amsterdam,[8] has also typed several strains as ECHO 9 and has found them to cause myositis in suckling mice At the beginning of this epidemic we inoculated suckling mice with different stool specimens, without ever provoking clinical symptoms Possibly pathogenicity for suckling mice is enhanced by several passages on tissue cultures, so we are now going to proceed to new inoculations of suckling mice with tissue-culture passaged strains as inoculum Anyway, the Belgian reference strain was not neutralised by Dr G Dalldorf's standard anti-Coxsackie sera, corresponding to the types A1–17 and A19 and to types B1–5

Whatever antigenic or clinical correlation may be found later on between Coxsackie and ECHO groups, we feel justified meanwhile, in suggesting that the aetiological agent of the Belgian outbreak of aseptic meningitis was a single strain of virus, antigenically identical with the American ECHO-9 standard virus strain

Considering the epidemiological and clinical similarities, one may be tempted to wonder whether the same agent was not responsible for both the British and the Continental outbreaks of aseptic meningitis

Such aseptic meningitis caused by ECHO viruses have already been described by several workers[10–14] Mainly prevalent in the U S A are types 4 and 6[13 15 16] Other types of ECHO viruses have been found associated with some rather isolated cases of aseptic meningitis[13 14 17] Moreover, Neva and Enders[12] isolated in 1954 an agent, afterwards identified as ECHO 6,[18] during an outbreak of exanthem without meningitis in Boston

University of Ghent EMILE NIHOUL
Institut Pasteur Brussels LISE QUERSIN-THIRY

SIR,—With reference to the series of articles and letters that has appeared—under various names—since last May, it may be of interest to record that we described a similar outbreak that occurred in two villages of the Meon Valley in 1948[19]

There was a total of 29 cases, 8 of whom were admitted to hospital between Sept 23 and Oct 27 The outstanding symptoms were moderate pyrexia, severe frontal headache, vomiting, and pain and stiffness in the back of the neck

A positive Kernig's sign was a fairly constant feature The pyrexia subsided with the disappearance of symptoms in a few days Of the patients treated in hospital, 4 exhibited a transient rash, 5 complained of photophobia and 2 had severe insomnia

The cerebrospinal fluid showed an increased cell count in all cases investigated, but there was no paresis at any stage Virus investigation yielded negative results

S CHALMERS PARRY
Winchester ROBERT A GOOD

PLEURAL BIOPSY

SIR,—Closed pleural biopsy, to which you refer (Jan 19), is likely to prove a safe and useful diagnostic procedure Through the kindness of Mr Abrams and Mr J W Jackson, of Harefield Hospital, I have used a needle which allows of aspiration of fluid and biopsy of the parietal pleura in one operation I hope to report a number of such biopsies later The following case is an example

A young airman was admitted with erythema nodosum and a pleural effusion The composition of the fluid was compatible with underlying tuberculosis, no organisms were found microscopically Biopsy of the parietal pleura showed granulation tissue, highly suggestive of tuberculosis A diagnosis was thus established within a few days

I am grateful to Dr Drew Thomson and Dr A C Pollard, of the Middlesex Hospital, for the histological report

Royal Air Force Hospital,
Wroughton Swindon,
Wiltshire P MESTITZ

PSYCHOTHERAPY IN GENERAL PRACTICE

SIR,—Dr Neville Davis's letter of Jan 19 was read with particular interest by the group of four general practitioners at Darbishire House Health Centre where for the past eighteen months Miss Madge Dongray, a trained social worker, has been giving full time assistance with some of the medicosocial problems arising in day-to-day practice Since for all of us this was a new experiment in collaboration, it may be useful to describe how we set about it

It was agreed at the outset to refer to the social worker problems which worried or puzzled the doctors and in which her specialised knowledge and experience[1] might prove helpful This method differed from that of Dr Davis and Mr Heimler in that we did not specially select problems of "mental health" but left each doctor to decide for himself where he felt the need of help

Many of the problems thus referred were practical difficulties—concerned, for example, with the care of the aged, employment, housing, and finance—in which help could be given to the doctor and the patient in using the social services more effectively At the end of ten months, however, we found that in just over half the cases discussed between doctor and social worker the most significant factor was directly connected with mental and emotional health This group of 72 cases was roughly classified as

1	Psychiatric illness with suspected psychotic features	13
2	Severe neurosis	6
3	Chronic anxiety state	4
4	Less severe anxiety or depression as a more or less persistent factor	5
5	Sudden emotional crises (either at recurrent intervals or in reaction to special circumstances)	14
6	Behaviour problems in children	11
7	Mental deficiency	4
8	Gross marital dysharmony of long standing	5
9	Problem families	10

Many of these cases presented somatic symptoms such as headache, palpitations, and vomiting, although we are not sure whether they could be correctly classified as "psychosomatic"

Dr Davis's experiment in three corner consultation gives food for thought At our centre, where the patient is introduced to the social worker by the doctor, much thought has been given to the way in which the doctor should propose this consultation to the patient, and also to the content of the social worker's interviews with the patient and of her discussions with the doctors either individually or as a group We are learning to understand the importance of feeling—both in the patient and in ourselves—and to examine how our own attitudes, expectations, and anxieties influence the extent to which

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7 Verlinde, J D Personal communication
8 Dekking F Personal communication
9 Rebmann E Personal communication
10 Melnick J L *Amer J publ Hlth*, 1954 44 571
11 Melnick J L *Ann, N Y Acad Sci* 1955, 61 754
12 Neva F A, Enders, J F *J Immunol* 1954, 72 307
13 Honig, E J, Melnick J L Isacson P Parr, R Myers, I L, Walton M *J exp Med* 1956, 103 247
14 Davis, D C, Melnick, J L *Proc Soc exp Biol*, N Y 1956, 92 839
15 Kibrick Cited by G H Werner *Pr méd* 1956, 64, 1859
16 Sabin, A B Personal communication
17 Committee on ECHO viruses *Science*, 1955 122 1187
18 Werner G H *Pr méd* 1956 64 1859
19 A Small Epidemic with Meningeal Symptoms Simulating Leptospiral Infection *Publ Hlth, Lond* 1949, 62, 163

[1] Miss Dongray formerly worked as a hospital almoner and in 1952 completed a year of study and practical work under supervision in the child guidance department of the Tavistock Clinic, London

we can help the patient One of us at least admits to a considerable increase in tolerance since the experiment began

Although at present the "listening" function may be left too often with the social worker, the fact that the doctor has to decide when and how to refer tends to increase his awareness of the emotional content of his interviews as well as of the significance of the patient's social background the fact that, in many cases which were previously baffling, real help can be given makes careful and generous listening worth while

Like Dr Davis, we have found that many patients are substantially relieved by one interview, while some need more and a few have been taken on by the social worker for long-term assistance Others need referral to a psychiatrist or to the child guidance clinic or other special sources of help, but there is evidence that the nature of the initial interviews plays an important part in determining whether he can make good use of this specialist aid The wisdom of interviewing relatives and generally understanding family tensions which affect the patient's health has also been evident

Unlike Dr Davis and Mr Heimler, we have attempted work in which children are involved, because we feel this is extremely important for prevention and because it is the particular interest of the social worker Interviews with parents of children often result in an easing of tension, with benefit to the child We have a further line of defence in the psychiatrists attached to the family-welfare service and the child-guidance clinic, who give generously of their time in discussing cases where it is not strictly necessary to refer the patient for psychiatric consultation or child guidance but where the doctor and social worker need advice and support

Medical students spending a fortnight of their final year with the practitioners are also taking part in case-conferences with the doctor and social worker, at which our method of working is demonstrated and debated.

We, too, feel that "the journey is just begun"

HENRY W ASHWORTH
HUGH DAVIE
H GOLDIE
J LENTEN
MADGE DONGRAY

Darbishire House Health Centre,
Manchester

SIR,—Your leading article of Dec 29 and the subsequent correspondence have far greater implications than might at first be evident

Dr Davis has described how, working with relatively simple techniques, we helped some 70% of the patients in our series to make a partial or apparently satisfactory adjustment to their environment In 1955 I reported[1] on 41 people, seen at the request of the National Assistance Board, who had been drawing National Assistance for at least two years, and of whom 20 returned to work The method used, in essence the same as that practised in conjunction with Dr Davis, rehabilitated many patients who otherwise might still be "on the dole" Likewise from the economic standpoint it may be worth mentioning Dr Davis's impression that the amount of drugs prescribed for the patients we studied was considerably less than that prescribed for similar patients who were not included in the experiment

From every point of view it seems desirable that all who deal with the emotionally disturbed—including not only doctors but officers of the National Assistance Board and Ministry of Labour officials—should appreciate the importance of recognising persons who may derive benefit from this type of work As such recognition would produce a demand for help for far greater numbers than at present, I personally believe that everybody dealing with people in this category should have some guidance in interpersonal relationships, and especially in recognition and appreciation of their own emotional responses, as Dr Davis has brought out in his letter This may be utopian, but a beginning must be made somewhere

London, N 12

EUGENE HEIMLER

TREATMENT OF SORE THROAT

SIR,—In the three letters from general practitioners last week, I was glad to find general agreement on the general practitioner's authority to speak on sore throat But two of your correspondents attribute to me opinions which were not voiced in my letter of Jan 19

I did not state that all cases of sore throat should be treated with penicillin On the contrary I went to some lengths to distinguish tonsillitis from pharyngitis, and advocated the universal use of penicillin therapy only for tonsillitis The common cold is often accompanied by sore throat, which may be the presenting symptom, but this is quite different from the acute inflammation accompanying tonsillar infection, which is also distinguished by cervical adenitis and pyrexia Tonsillitis is often unilateral—an indication of its separate entity and distinguishing it from the general inflammation accompanying catarrhal infections Hence my plea for discrimination, on clinical grounds alone, when deciding whether or not to use antibacterial drugs in this condition

I think that the paper by Chapple et al[1] effectively answers Dr Fry's plea for a demonstration that oral penicillin shortens the course of acute sore throats This paper is an excellent example of the usefulness of such practical investigations in general practice

It is hardly surprising that I have not met a nasty stomatitis caused by penicillin lozenges, since I never employ this utterly useless form of medication When referring to oral penicillin therapy in my letter I was careful to qualify this with the word "swallowed" I fear that this must have escaped Flying Officer Smith's notice, since there was no reference to penicillin lozenges in my letter I am surprised that he should resurrect the old bogy of induced penicillin resistance The hæmolytic streptococcus is remarkably immune to this phenomenon, and, even after ten years' widespread use of penicillin, iatrically induced drug resistance is virtually confined to our hospital wards If this was due to inadequate dosage, our hospital staffs would have much *to answer for!*

Twickenham

DAVID WHEATLEY

SERUM-LIPIDS AND ATHEROSCLEROSIS

SIR,—The ætiological and therapeutic problems of atherosclerosis are so admirably dealt with in two articles in your issue of Jan 19, that it seems almost improper to criticise them It is, however, a sad comment on our times that the "references" are so numerous but, nevertheless, so defective By this I mean that only papers in the English and American languages are mentioned, though much valuable work has been published in Europe, particularly in Germany It is surprising that neither the name Schettler[2] nor the work of Küchmeister et al[3] receives mention Both these groups have reviewed the subject in much detail, and have called attention to the value of certain lecithins (from soybean) and 2 4-5 polyoxyethylene sorbitol mono oleate in causing atherogenic serum to become normal Of course, it is not certain that such a state of affairs implies that the atherosclerotic process is being prevented or improved, but there is no doubt that the preparation mentioned exerts the type of action claimed by these authors It appears that the constituents exert an indirect effect on the cholesterol/phospholipid ratio, causing it to approach the normal 1 0 certainly the serum changes that follow administration of the preparation cannot be due simply to the small amounts of lecithins, &c

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[1] Heimler F *Med Offr*, 1955, 94, 351

[1] Chapple P A L, Franklin L M, Paulett J D, Tuckman J, Woodall J T, Tomlinson, A J H, McDonald, J C *Brit med J* 1956, i 705

[2] Schettler, G *Ergebn inn Med* 1955, 6, 278

[3] Küchmeister, H, Goldeck, H, Hammers, H *Med Klinik*, 1956, 51, 35

It is to be hoped that this line of approach will be pursued

London, W 1 A PINEY

SARCOIDOSIS

SIR,—We are glad to have Dr Consden's criticism (Jan 12) of our paper on bacterial residues in sarcoidosis[1] and would like to make further observations on the points he raised

We have stained by the Ziehl Neelsen method extracts of normal human skin, subcutaneous tissue, brain, liver, lung, kidney, heart, and skeletal muscle, and subcutaneous rheumatoid nodules, as well as several chemicals such as oleic and stearic acids and cholesterol When decolorised with acid alcohol (10% HCl in alcohol) none of these was acid fast In this we do not agree with Dr Consden We find that when decolorisation is completed in two stages in a carefully controlled manner, as suggested by Philpot and Wells,[2] and as mentioned in our original paper,[1] using 25% sulphuric acid followed by alcohol, these substances are not acid fast We would suggest that each stage of decolorisation should be for at least half an hour

On the other hand, the extracts of the four cases of sarcoid were each strongly acid and alcohol fast and resisted decolorisation with 25% H_2SO_4 followed by alcohol for a period of 24 hours in each stage

Dr Consden states that, if mycolic acid were present, it would certainly form only a very small proportion of the total fatty acids We do not know the source of this information as we are not aware of published work besides ours which deals with the fatty acids found in sarcoid lesions It should be borne in mind that the fatty-acid content of sarcoid lesions may bear no resemblance to that of normal tissue or to that of tubercle bacilli and that we dealt with tissue that in no way histologically resembled normal

The more important findings were that the extract from each case of sarcoid was shown to be, on infra red spectrophotometry, a long chain fatty acid Each spectrum closely resembled the published spectra of mycolic acid[3,4] Randall et al[5] claimed that each fraction of the extracts of tubercle bacilli is identifiable by spectrophotometry In our original article[1] the spectra had only one absorption band in the region 1180–1320 cm^{-1} In fatty acids containing up to 21 carbon atoms, there are many bands forming a progression in this region[6] This evidence rules out the possibility of fatty acids of up to 21 carbon atoms

Each sarcoid extract isolated had a melting point in the range 54–58°C (the melting point of mycolic acid is 54–59°C[7–9]) and was a white powder

In two of the lesions studied (lung and cervical gland) we had sufficient material to extract these tissues after pulverisation, according to the classical methods of Anderson and other workers[4, 9–11] Using these methods, most if not all other closely related substances associated with mycolic acid, such as palmitic, oleic, stearic, and phthioic acids, are removed during the fractional separation We were left in each case with a white powder, whose melting point and spectrum were similar to those of mycolic acid

Taking all these facts into consideration it would seem to us justifiable to regard this organic substance as mycolic acid, as it is a white powder at room-temperature, has a melting-point between 54 and 58°C, is isolated by classical methods from tissues by a method that separates closely associated substances from it, is strongly acid-fast, and above all has the spectrum of a long-chain fatty acid that is extremely similar to mycolic acid

We would emphasise again that these positive results have been obtained on only the four examples of "sarcoid" that we have examined, and we are anxious to obtain more material for investigation

W G STRAWBRIDGE
Cardiff S E NETHERCOTT

SIR,—The studies by Mr Nethercott and Dr Strawbridge on the chemical composition of sarcoid nodules are interesting and suggestive, but the authors presume a degree of specificity for their findings which may not be justified

Contrary to their statement, a lipid of the mycolic acid type with the same infra red spectrum has been described as a normal component of the human body[1] It seemed then, as it does now, that tuberculoid reactions and the chemical extractions for mycolic acid have the same level of only partial specificity Where there is a tuberculoid granuloma, there should be a compound resembling mycolic acid, but if such a compound can come from such diverse cells as spermatozoa and mycobacteria, it conceivably can have yet a third source in sarcoidosis

Department of Pathology,
Memorial Center,
New York JOHN W BERG

RECURRENT MOTOR PARALYSIS

SIR,—The interesting case described by Dr Breen and Dr Emond in your last issue suggests a possible diagnosis of myasthenia gravis Admittedly, the disorder is rarely seen before the age of 10 years, but I have met with cases between 4 and 7 years, and examples are described for example, by F R Ford at 5 and 6 years and even younger[2] The manifestations of myasthenia in children are often atypical, but facial paralysis is not infrequent and involvement of the diaphragm is known to occur If and when the symptoms reappear, a neostigmine test should confirm or disprove myasthenia gravis

London, W 1. C WORSTER DROUGHT

DILUTION OF INULIN

SIR,—When, some time ago, I became interested in the study of renal function, I turned in vain to the available literature to determine the correct diluent and dilution for 10% inulin to render it isotonic for intravenous or subcutaneous administration

As supplied by Messrs Kerfoot, pyrogen free 10% inulin is a supersaturated solution in distilled water that requires dilution for constant infusion if the solution is to remain stable without recrystallisation during the course of an experiment

Using serial dilutions of the 10% inulin solution in distilled water, and heparinised washed human red cells as an "*osmometer*," I found that the undiluted 10% inulin solution was isotonic with human red corpuscles, there was an increase in the packed cell volume of the red cells with a dilution of 7 5%, and hæmolysis became visible when dilutions of 5% or higher were used

This indicates that the 10% solution of inulin as supplied may be used undiluted shortly after dissolution by heating for priming doses, but should be diluted with 0 9% sodium-chloride solution for sustaining infusions I have found it convenient to calculate the amount of 10% inulin necessary per minute to sustain a plasma level of 40 mg per 100 ml, and to make up this to 1 ml per minute with isotonic saline solution

I hope that these results will be of value to any two confronted with the same problem as was I

Department of Medicine,
University of Cape Town E DOWDLE

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2 Philpot F J, Wells A Q *Amer Rev Tuberc* 1952 66, 28
3 Kubica G P, Randall H M, Smith D W *Ibid*, 1956, 73, 529
4 Noll H, Bloch, H *J biol Chem* 1955 214, 251
5 Randall H M, Smith, D W Colm, A C, Nungester, W J *Amer Rev Tuberc* 1951 63 372
6 Jones R N, McKay, A F Sinclair, R G *J Amer chem Soc* 1952 74 2575
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8 Asselineau J, Lederer E *Bull Soc Chim biol Paris* 1949 31 492
9 Anderson R J *Chem Rev* 1941 29, 225
10 Noll H Bloch H *Amer Rev Tuberc* 1953, 67 828
11 Bloch, H, Sorkin, E Erlenmeyer, H *Ibid*, p 629

1 Berg J W *Arch Path (Lab Med)* 1954, 57 11,
2 Ford F R Diseases of the Nervous System in Infancy and Childhood Springfield, Ill, 1952

MÉNIÈRE'S DISEASE

SIR,—In connection with your leading article last week I would like to emphasise the enormous help that has been derived as to the nature and causes of attacks of Meniere's vertigo by the careful post-mortem study of the findings in fatal cases of acute apoplectiform vertigo in patients with myelocytic leukæmia This was obvious from my article with Mr Rickard Lake entitled Acute Ménière's Symptoms in Splenomedullary Leucocythæmia in *Medico Chirurgical Transactions* (1900, 83, 185) In this we were greatly helped by Dr Louis Waldstein, then resident in London though not practising The most striking cases from the literature of the subject were referred to, and our communication was followed on the same evening by one on an analogous case by F W Mott (later Sir Frederick Mott)

London N W 1   F PARKES WEBER

SHORTAGE OF RADIOGRAPHERS

SIR,—Dr Illingworth (Jan 5) has given his views on the causes of the shortage of radiographers As some of his statements are inaccurate and misleading,-I should like to reply

Firstly, the dissatisfaction felt by radiographers towards their "inadequate remuneration" is by no means confined to "a few male radiographers" There is overwhelming evidence at the society's headquarters that this dissatisfaction is universal throughout the profession At a meeting held recently in London to discuss the disastrous salary award made in November, the number of women attending greatly outnumbered the men and they were by no means silent observers but showed a keen interest by their questions and suggestions

Secondly, the Society of Radiographers has no regulations governing the age at which a student radiographer may commence training although no student may qualify before reaching the age of 20—a reasonable age, bearing in mind the responsibility of the radiographer when dealing with sick and injured patients, more especially now that the danger of excessive radiation is so much to the fore

Thirdly, the Society of Radiographers, along with other professional societies, has been required to submit to the Minister of Health its syllabus of training, educational standard details of examinations, and the composition of its board of examiners These have been approved by the Minister More recently the educational requirements were broadened in order to assist recruitment, and this step was also approved by the Minister

The Society's board of examiners is composed of radiologists, radiotherapists, physicists, and X-ray technologists, many of whom are not members of the society, together with radiographers This board is virtually an autonomous body, and it is ludicrous to suggest that the society, makes its examinations too difficult, thus limiting entry into the profession Dr Illingworth himself has for some time been one of the society's examiners

It is universally accepted that those who understand the principles underlying the construction of apparatus use it to the best advantage, and the syllabus in physics and apparatus was drawn up with this in mind It is the duty of this society to see that radiographers have this basic knowledge, especially when they have to handle complicated and very costly apparatus which is capable of doing irreparable harm to both the patients and themselves

It is to the advantage of the radiologist and the medical profession generally to have a fully staffed department of highly qualified, competent radiographers able to carry out their duties efficiently, and to pay proper attention to the care and comfort of the patient and thus enable diagnosis to be confirmed or to record progress with the minimum radiation exposure to the patient

Finally, the post of superintendent radiographer is essential as on this radiographer falls the responsibility of the day to day administration of the department Even in departments where a full-time consultant radiologist is appointed, a great deal of responsibility falls on the superintendent radiographer, and in the majority of hospitals where the consultant is only part-time the superintendent radiographer often has to accept the responsibility of running the department and for the care and welfare of the patients as well as maintaining a high standard of radiography

The standards of training required by the Society of Radiographers are reputed to be the best in the world and in no small way contribute to the high standard of the radiological services of this country Nothing should be done to lower this standard or the service to the patients

Society of Radiographers,
32 Welbeck Street London, W 1   MARY VAUGHAN
President

SIR,—I can but suppose that Dr Illingworth wrote with his tongue in his cheek Should this not be so, it must be inferred that he would favour the complete disbandment, not only of the Society of Radiographers, but of all auxiliary medical examining bodies If physics is superfluous to radiography, is it any more necessary for training for the radiological diploma ?

A superintendent's duties are varied, and the smooth running of the department and the contentedness of the staff depend possibly more on his handling than on any other factor He provides the liaison between the radiologist and the remainder of the staff If Dr Illingworth feels himself capable of taking over the technical and administrative duties of the superintendent radiographer in addition to those of radiology in a reasonably large department, then I must take off my hat to him

Almost all superintendent radiographers must, of necessity, be capable of carrying out "running repairs" As a correspondent has already said, we are not all within easy reach of the servicing engineer, nor can we afford to let a major piece of apparatus lie idle Incidentally, these "running repairs" save managements some hundreds of pounds annually—a fact which most managements are totally unaware of

General Infirmary,
Salisbury   K CRUICKSHANK

RETURN TO PLANNING

SIR,—Arising out of your leading article and correspondence to date on this matter, two big points appear to have arisen, firstly, the plight of the young married registrars or senior hospital medical officers, often with children, whose remuneration is so inadequate, secondly, the whole question of merit awards

Surely if there is to be a return to planning, there should be an abolition of all merit awards, which must inevitably encumber the supertax paying consultant Let these vast sums of money handed over as merit awards (the large portion of which is handed back in tax to the Government) be spread amongst the well-deserving registrars and senior medical officers

Windsor   D MAXWELL

PROLONGED PYREXIA IN CHILDREN

SIR,—In reply to Dr Wallis, who wrote last week, my reasons for not considering brucellosis as a diagnosis were not the upper respiratory symptoms or the one negative agglutination test, but the occurrence of these cases of pyrexia starting at a time when an epidemic of influenza was present in the town and surrounding countryside Moreover none of the patients had a rash, palpable spleen, or neutropenia, and the temperature chart did not show an undulant type of fever The milk is pasteurised non-tuberculin tested

In the absence of serological proof, it is possible to suggest that the epidemic in the children's home, although following an identical clinical pattern, was different from that in the surrounding area If this is so, it is a most remarkable coincidence

Chipping Norton
Oxon   F E JAMES

RAISED C S F -SUGAR LEVELS

SIR,—I wonder if any of your correspondents can give me some information about raised levels of sugar in the cerebrospinal fluid (C S F)

We deal with a large number of C S F s, as this is a fever hospital and a poliomyelitis unit Off and on over the past few years we have come across the odd C S F sugar above the normal limits—usually about *120–140* mg per *100* ml— and, as the C S F pressure was raised, it was assumed that this merely *reflected the blood sugar level at the time* Unfortunately no blood sugar estimations were performed In every case a repeat C S F after clinical recovery gave a result within normal limits Recently, however, we had a very high result—180 mg per 100 ml —and a blood sugar taken simultaneously was only 88 mg per 100 ml The patient, a case of bulbar poliomyelitis, has not yet sufficiently recovered to make a repeat lumbar puncture worth while

I know of no reference to such unusual results

Rush Green Hospital,
Romford, Essex

F BRAFIELD

CARDIAC ARREST

SIR,—*Some recent papers on cardiac arrest on the* operating-table,[1-3] and the letter from Professor Stammers last week setting the modern treatment in its historical perspective, have focused attention on this dire calamity May I plead for four practical measures which would lessen the mortality of the condition

1 The surgeons and anæsthetists in each hospital should draft a short plan for action to be taken in case of sudden cardiac arrest, and this should be displayed in the operating-suite and be familiar to all who work there, especially the junior surgeons and anæsthetists

2 All surgeons, no matter what their specialty, should, together with their junior colleagues, go to the post mortem room, say, once a year to familiarise themselves with the technique of transthoracic cardiac massage on the cadaver

3 Each operating theatre should be equipped with a drum containing the sterile instruments, retractors, syringes, and ampoules needed in the emergency

4 Each theatre suite should be provided with an electrical defibrillator

To be fully prepared to meet the emergency is to be more than half-way towards its successful management

Southend on Sea

J ALFRED LEE

A NEWSPAPER FOR THE PARTLY SIGHTED ?

SIR,—In everyday work in a general practice one is struck by the number of patients who have become "partly sighted" in their late sixties and early seventies Sudden and permanent deterioration in vision may follow a stroke of one type or another, or slow deterioration may be due to cardiovascular degeneration embracing conditions responsible for retinal failure

Often the patient is intelligent and mentally active but forced into early retirement by the physical infirmities consequent upon cerebrovascular degeneration At one moment the patient may be at the head of a large business or in control of a school, and the next he is bedridden, eclipsed and useless The plight of these people is the worse because their one link with the rest *of the world has been severed They can no longer read*

I have several such patients who struggle with the daily nationals and their favourite journals but can read only the headlines How many are heard to say "I can read the headlines, but I cannot make anything of the rest ?"

The purpose of my letter is to ask if it is possible to print a weekly newspaper all in headline type for these patients There are, I calculate, at least 100,000 people in Great Britain whose sight is sufficient to read large headline type but not sufficient to read ordinary letter press What a boon it would be to these people to be able to read all the news themselves and feel that once again they are in touch with the outside world

A large magnifying glass is not the solution to this problem The field of vision is reduced too greatly and there is too much peripheral distortion to make reading anything but a labour

Is there a newspaper printed all in headline type ? If not, could any institution be persuaded to try the experiment ? What an opportunity for a repressed journalist to publish ten thousand words in headlines and to feel he is doing good at the same time

Sheffield

E C ATKINSON

A "POST-ACUTE" HOSPITAL

SIR,—According to a newspaper report cited in your news columns last week, Mundesley Sanatorium is to be taken over by the East Anglian Regional Hospital Board as a "post acute" hospital

"Acute" means "coming sharply to a crisis, not chronic" *(O E D)* We already have "sub acute" and "hyper-acute" (or, for the purist, "super acute"), but "post acute" seems to be new I take it that post subacute and post chronic patients will not qualify for admission, so let us hope that early ambulation on the Norfolk beaches will meet with good patient acceptance from the post-acutes

Institute of Diseases
of the Chest
London, S W 3

J R BIGNALL

YOGURT IN GASTRO-ENTERITIS OF INFANCY

SIR,—We have read Dr Raffle's letter[1] with interest as we have used yogurt for the treatment of gastro enteritis in a number of patients We have found *that* commercial yogurt preparations differ in their efficacy, and possibly this is due to variation in the microflora between the different yogurt preparations

The normal yogurt today consists of a roughly equal mixture of *Lactobacillus bulgaricus* and *Streptococcus thermophilus L bulgaricus* is the organism originally publicised by Metchnikoff, but it has been shown by numerous investigators[2-4] that *L bulgaricus* not only cannot proliferate in the gut but rapidly dies out For lactobacillus therapy, therefore (as distinct from yogurt as a food), *L acidophilus*, which can be regarded as a normal inhabitant of the intestine, should be used Either a pure culture of *L acidophilus* (acidophilus milk) or a yogurt containing an appreciable proportion (e g , 10%) of *L acidophilus* should be used for the treatment of gastro enteritis and similar complaints

Although the attitude of practitioners generally towards cultured milks is very mixed, there is considerable experimental evidence that for some complaints (e g , gastro enteritis, colitis, constipation, biliary disorders, flatulence, malaise, migraine, nervous fatigue) cultured milks, and especially acidophilus milk, can be extremely valuable[4-6] Yogurt and acidophilus milk can often be taken by those who cannot take ordinary milk It thus has value as a food for those unable to digest milk The curd formed in the stomach by cultured milks is much finer than that formed by milk[6,7]

Many examples of the value of cultured milks supported by sound experimental evidence are given in the literature We may quote in this connection the observations of Comly[8] and Mayon White[9] on deaths of infants from methæmoglobinæmia as the result of bacterial reduction of nitrate in water, and the use of yogurt as a

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[1] Wylie, W D *Brit J Anaesth* 1956 28, 551

[2] Milstein B B *Ann R Coll Surg Engl* 1956 19, 69

[3] McMillan, I K R , Cockett, F B , Styles P *Thorax*, 1952 7, 205

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[1] Raffle E J *Lancet* 1956 ii, 1106

[2] Rettger, L P Cheplin H A Intestinal Flora London, 1921

[3] Cruickshank R *Brit J exp Path* 1928 9 318

[4] Rettger L P , et al Lactobacillus Acidophilus and its Therapeutic Applications London 1935

[5] Davis J G *Food* 1952 21 249 284

[6] Davis J G *J Soc Dairy Tech* 1956 9 69 117 160

[7] Davis J G *Bull Hosp St Cruz Barcelona* (in the press)

[8] Comly H H *J Amer med Ass* 1947 129, 112

[9] Mayon White R M *Lancet*, 1951, i, 931

remedy A particularly interesting paper on cultured milks in relation to stomach conditions in humans of various ages is that by Orla Jensen et al[10]

J G DAVIS
D LATTO

London W 1

SOCIAL STRESSES SEEN IN GENERAL PRACTICE

SIR,—The family doctor sees certain symptoms and complaints recurring under similar conditions He can, if he looks for them, recognise particular social conditions which favour particular kinds of illness The following are three examples, all of them (as it happens) chiefly affecting men 40 to 60 years of age

Football Matches

People of all social classes have become weekly devotees of the local football game and, fit or not, will attend a match in any weather

Some patients, though suffering from a feverish cold or acute bronchitis, thus expose themselves against their better knowledge to damp cold weather They may even be compelled to be absent from work for this reason, or, by following their urge, turn trivial illnesses into more serious ones

More important are those with coronary disease The football-grounds are often further from the car-park or bus-stop than they usually have to walk, they hurry and become members of the herd, rushing to their stands, and often have to climb many steep steps, enduring a physical effort they would do their utmost to avoid at any other time In addition, their emotional excitement leads to further strain I find that patients who usually need perhaps 2–3 glyceryl trinitrate tablets a day may have to take 8 during each match I have records of several patients in whom a first or a fatal attack of coronary thrombosis can be directly attributed to attendance at a match

Lodge Meetings

Looking at the history of middle-aged patients with nervous breakdown, hypertension, or coronary disease, it is surprising how many regularly attend Masonic meetings and break down in preparing themselves for high office in their lodge At an age when they are out of mental training for such work, they have to learn by heart long passages of ceremonial formulæ and speeches Sometimes for a year or more, their free time, and often long night hours, are devoted to memorising long passages, and this can lead to continuous anxiety Ambition, pride, and fear of failure usually keep them going until their object is achieved, and then they break down in utter exhaustion, often with an anxiety state or coronary thrombosis The ceremony itself, with perhaps two hours in a locked or closed room, causes acute anxiety symptoms

These lodge activities are rarely disclosed spontaneously by the patient themselves, but once attention has been drawn to them (usually by their wives) the strain is admitted Such a strain is undoubtedly more significant in breakdowns than has been realised The family doctor can often prevent these men, when they are seen in time, from doing something which will be detrimental to their health Perhaps some lodges would allow their members to read their ceremonial addresses and not insist that everything must be spoken from memory

Income-tax Difficulties

In my third group are those who fear, or are actually in trouble with, the income-tax authorities Their symptoms of sleeplessness, nervousness, lack of concentration, and feeling run down, are so characteristic that one can almost ask them outright whether they have any income-tax troubles An interesting point is that these people do not start worrying until they are in fear of being found out or are already in difficulties The severity of symptoms is not always in proportion to the gravity of the offence It seems particularly to depend on the length of time taken to settle the problem with the authorities and even if the material effect of the settlement is less ruinous than had been feared, the effect on physical and mental health is often devastating No treatment is likely to do much good until the authorities have reached their decision, and the only help a family doctor can give is friendly advice to disclose everything in order to save the patient's best asset, his health

I offer these as illustrations of social strains which are obvious when once observed and which perhaps need more attention than they generally receive

Manchester   R FRIEDLAENDER

VAGITUS UTERINUS

SIR,—Mr Russell's article (Jan 19) reminded me that I encountered this phenomenon about 1926 During a forceps delivery, before the head was visible, the baby "squawked" The midwife, never an encouraging type, muttered in my ear "you've done it all right, this time, doctor!" However, all ended well

Middlesbrough   JOHN CAHILL

THE FUTURE OF NURSING

SIR,—I was relieved to see the letter from Miss M M Edwards last week and the views she has expressed on the right relationship between doctor and nurse

As district nurses we willingly work under the direction of a doctor in carrying out the treatments he orders and reporting to him on his patients We would not have it otherwise, recognising that the doctor has medical knowledge, skill, and responsibilities far beyond those of a nurse, and that he is her respected colleague

General practitioners, from whom 90% of the district nurse's patients are referred, have, since the Queen's Institute was first organised nationally 70 years ago, worked in harmonious partnership with district nurses These nurses feel no need, even when they are district nurse midwives and health visitors, to proclaim that "they are practitioners in their own right"

When their relationship is unquestioned, from long experience it is found that the doctor readily leaves to the nurse, with or without consultation, full responsibility for the nursing comfort, morale, hygiene, and health teaching of his patients, and for obtaining social help He knows that the nurse will keep him informed of the patient's progress, and of when his medical help is needed urgently Both work with one objective, but it is the doctor who shoulders the ultimate and greater responsibility

The training of a doctor is extensive and requires to be of a high university level for the knowledge and skill he must attain It is wasteful if he undertakes work, except in expediency, which a nurse could do The training of a State-registered nurse is less extensive, and it is in my opinion doubtful if it requires to be of a university level even for the few leaders of the nursing profession It seems that the motives suggesting that there should be more nurses with university degrees are mainly "to keep up with the Joneses" in other countries, many of which have universities of very different standards from those in this country It seems wasteful that the precious places in the few universities of Great Britain should be taken up by potential nurses

The well trained mind, capable of critical analysis, is of undoubted value to any nurse whose work requires her to administer or to teach If, as is the case with a few district nurses, she happens to have a degree before becoming a nurse, she yet may have no desire to administer or to teach Even if she does desire it, a specially designed advanced nursing course after registration seems likely to be more helpful than her previous university degree

It is wasteful also, if State registered nurses whose basic education requires to be good and whose training is long and comprehensive, are used for work, except when unavoidable, which a State enrolled assistant nurse could undertake A considerable increase in the employ-

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10 Orla Jensen, S, et al *J. Danish Acad Sci Lit* 1945 111 4

RAISED C S F -SUGAR LEVELS

SIR,—I wonder if any of your correspondents can give me some information about raised levels of sugar in the cerebrospinal fluid (C S F)

We deal with a large number of C S F s, as this is a fever hospital and a poliomyelitis unit Off and on over the past few years we have come across the odd C S F sugar above the normal limits—usually about 120–140 mg per 100 ml —and, as the C S F pressure was raised, it was assumed that this merely reflected the blood sugar level at the time Unfortunately no blood sugar estimations were performed In every case a repeat C S F after clinical recovery gave a result within normal limits Recently, however, we had a very high result—180 mg per 100 ml —and a blood sugar taken simultaneously was only 88 mg per 100 ml The patient, a case of bulbar poliomyelitis, has not yet sufficiently recovered to make a repeat lumbar puncture worth while

I know of no reference to such unusual results

Rush Green Hospital
Romford, Essex

F BRAFIELD

CARDIAC ARREST

SIR,—Some recent papers on cardiac arrest on the operating-table,[1-3] and the letter from Professor Stammers last week setting the modern treatment in its historical perspective, have focused attention on this dire calamity May I plead for four practical measures which would lessen the mortality of the condition

1 The surgeons and anæsthetists in each hospital should draft a short plan for action to be taken in case of sudden cardiac arrest, and this should be displayed in the operating-suite and be familiar to all who work there, especially the junior surgeons and anæsthetists

2 All surgeons, no matter what their specialty, should, together with their junior colleagues, go to the post mortem room, say, once a year to familiarise themselves with the technique of transthoracic cardiac massage on the cadaver

3 Each operating theatre should be equipped with a drum containing the sterile instruments, retractors, syringes, and ampoules needed in the emergency

4 Each theatre suite should be provided with an electrical defibrillator

To be fully prepared to meet the emergency is to be more than half way towards its successful management

Southend-on Sea

J ALFRED LEE

A NEWSPAPER FOR THE PARTLY SIGHTED ?

SIR,—In everyday work in a general practice one is struck by the number of patients who have become "partly sighted" in their late sixties and early seventies Sudden and permanent deterioration in vision may follow a stroke of one type or another, or slow deterioration may be due to cardiovascular degeneration embracing conditions responsible for retinal failure

Often the patient is intelligent and mentally active but forced into early retirement by the physical infirmities consequent upon cerebrovascular degeneration At one moment the patient may be at the head of a large business or in control of a school, and the next he is bedridden, eclipsed and useless The plight of these people is the worse because their one link with the rest of the world has been severed They can no longer read

I have several such patients who struggle with the daily nationals and their favourite journals but can read only the headlines How many are heard to say "I can read the headlines, but I cannot make anything of the rest ?"

The purpose of my letter is to ask if it is possible to print a weekly newspaper all in headline type for these patients There are, I calculate, at least 100,000 people in Great Britain whose sight is sufficient to read large headline type but not sufficient to read ordinary letter press What a boon it would be to these people to be able to read all the news themselves and feel that once again they are in touch with the outside world

A large magnifying glass is not the solution to the problem The field of vision is reduced too greatly and there is too much peripheral distortion to make reading anything but a labour

Is there a newspaper printed all in headline type ? If not, could any institution be persuaded to try the experiment ? What an opportunity for a repressed journalist to publish ten thousand words in headlines and to feel he is doing good at the same time

Sheffield

E C ATKINSON

A "POST-ACUTE" HOSPITAL

SIR,—According to a newspaper report cited in your news columns last week, Mundesley Sanatorium is to be taken over by the East Anglian Regional Hospital Board as a "post acute" hospital

"Acute" means "coming sharply to a crisis, not chronic" (*O E D*) We already have "sub acute" and "hyper-acute" (or, for the purist, "super acute"), but "post-acute" seems to be new I take it that post subacute and post chronic patients will not qualify for admission , so let us hope that early ambulation on the Norfolk beaches will meet with good patient acceptance from the post-acutes

Institute of Diseases
of the Chest,
London, S W 3

J R BIGNALL

YOGURT IN GASTRO-ENTERITIS OF INFANCY

SIR,—We have read Dr Raffle's letter[1] with interest as we have used yogurt for the treatment of gastro enteritis in a number of patients We have found that commercial yogurt preparations differ in their efficacy, and possibly this is due to variation in the microflora between the different yogurt preparations

The normal yogurt today consists of a roughly equal mixture of *Lactobacillus bulgaricus* and *Streptococcus thermophilus* *L bulgaricus* is the organism originally publicised by Metchnikoff, but it has been shown by numerous investigators[2-4] that *L bulgaricus* not only cannot proliferate in the gut but rapidly dies out For lactobacillus therapy, therefore (as distinct from yogurt as a food), *L acidophilus*, which can be regarded as a normal inhabitant of the intestine, should be used Either a pure culture of *L acidophilus* (acidophilus milk) or a yogurt containing an appreciable proportion (e g , 10%) of *L acidophilus* should be used for the treatment of gastro enteritis and similar complaints

Although the attitude of practitioners generally towards cultured milks is very mixed, there is considerable experimental evidence that for some complaints (e g , gastro enteritis, colitis, constipation, biliary disorders, flatulence, malaise, migraine, nervous fatigue) cultured milks, and especially acidophilus milk, can be extremely valuable[4-6] Yogurt and acidophilus milk can often be taken by those who cannot take ordinary milk It thus has value as a food for those unable to digest milk The curd formed in the stomach by cultured milks is much finer than that formed by milk[5,7]

Many examples of the value of cultured milks supported by sound experimental evidence are given in the literature We may quote in this connection the observations of Comly[8] and Mayon-White[9] on deaths of infants from methæmoglobinæmia as the result of bacterial reduction of nitrate in water, and the use of yogurt as a

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1 Wylie W D *Brit J Anaesth* 1956, 28 551
2 Milstein B B *Ann R Coll Surg Engl* 1956, 19 69
3 McMillan, I K R , Cockett, F B , Styles P *Thorax* 1952, 7, 205

1 Raffle E J *Lancet*, 1956 ii 1106
2 Rettger, L F , Cheplin, H A Intestinal Flora London 1921
3 Cruickshank R *Brit J exp Path* 1928 9 318
4 Rettger L F , et al Lactobacillus Acidophilus and its Therapeutic Applications London 1935
5 Davis J G *Food* 1952 21 249 284
6 Davis J G *J Soc Dairy Tech* 1956 9 69 117 160
7 Davis J G *Bull Hosp St Cruz Barcelona* (in the press)
8 Comly H H *J Amer med Ass* 1947 129, 112
9 Mayon-White, R M. *Lancet*, 1951, i, 931

remedy A particularly interesting paper on cultured milks in relation to stomach conditions in humans of various ages is that by Orla Jensen et al[10]

J G DAVIS
D LATTO

London, W 1

SOCIAL STRESSES SEEN IN GENERAL PRACTICE

SIR,—The family doctor sees certain symptoms and complaints recurring under similar conditions He can, if he looks for them, recognise particular social conditions which favour particular kinds of illness The following are three examples, all of them (as it happens) chiefly affecting men 40 to 60 years of age

Football Matches

People of all social classes have become weekly devotees of the local football game and, fit or not, will attend a match in any weather

Some patients, though suffering from a feverish cold or acute bronchitis, thus expose themselves against their better knowledge to damp cold weather They may even be compelled to be absent from work for this reason, or, by following their urge, turn trivial illnesses into more serious ones

More important are those with coronary disease The football-grounds are often further from the car-park or bus-stop than they usually have to walk; they hurry and become members of the herd, rushing to their stands, and often have to climb many steep steps, enduring a physical effort they would do their utmost to avoid at any other time In addition, their emotional excitement leads to further strain I find that patients who usually need perhaps 2-3 glyceryl trinitrate tablets a day may have to take 8 during each match I have records of several patients in whom a first or a fatal attack of coronary thrombosis can be directly attributed to attendance at a match

Lodge Meetings

Looking at the history of middle-aged patients with nervous breakdown, hypertension, or coronary disease, it is surprising how many regularly attend Masonic meetings and break down in preparing themselves for high office in their lodge At an age when they are out of mental training for such work, they have to learn by heart long passages of ceremonial formulæ and speeches Sometimes for a year or more, their free time, and often long night hours, are devoted to memorising long passages, and this can lead to continuous anxiety Ambition, pride, and fear of failure usually keep them going until their object is achieved, and then they break down in utter exhaustion, often with an anxiety state or coronary thrombosis The ceremony itself, with perhaps two hours in a locked or closed room, causes acute anxiety symptoms

These lodge activities are rarely disclosed spontaneously by the patient themselves, but once attention has been drawn to them (usually by their wives) the strain is admitted Such a strain is undoubtedly more significant in breakdowns than has been realised The family doctor can often prevent these men, when they are seen in time, from doing something which will be detrimental to their health Perhaps some lodges would allow their members to read their ceremonial addresses and not insist that everything must be spoken from memory

Income-tax Difficulties

In my third group are those who fear, or are actually in trouble with the income-tax authorities Their symptoms of sleeplessness nervousness, lack of concentration, and feeling run down, are so characteristic that one can almost ask them outright whether they have any income tax troubles An interesting point is that these people do not start worrying until they are in fear of being found out or are already in difficulties The severity of symptoms is not always in proportion to the gravity of the offence It seems particularly to depend on the length of time taken to settle the problem with the authorities and even if the material effect of the settlement is less ruinous than had been feared, the effect on physical and mental health is often devastating No treatment is likely to do much good until the authorities have reached their decision, and the only help a family doctor can give is friendly advice to disclose everything in order to save the patient's best asset, his health

I offer these as illustrations of social strains which are obvious when once observed and which perhaps need more attention than they generally receive

Manchester R FRIEDLAENDER

VAGITUS UTERINUS

SIR,—Mr Russell's article (Jan 19) reminded me that I encountered this phenomenon about 1926 During a forceps delivery, before the head was visible, the baby "squawked" The midwife, never an encouraging type, muttered in my ear "you've done it all right, this time, doctor!" However, all ended well

Middlesbrough JOHN CAHILL

THE FUTURE OF NURSING

SIR,—I was relieved to see the letter from Miss M M Edwards last week and the views she has expressed on the right relationship between doctor and nurse

As district nurses we willingly work under the direction of a doctor in carrying out the treatments he orders and reporting to him on his patients We would not have it otherwise, recognising that the doctor has medical knowledge, skill, and responsibilities far beyond those of a nurse, and that he is her respected colleague

General practitioners, from whom 90% of the district nurse's patients are referred, have, since the Queen's Institute was first organised nationally 70 years ago, worked in harmonious partnership with district nurses These nurses feel no need, even when they are district nurse midwives and health visitors, to proclaim that "they are practitioners in their own right"

When their relationship is unquestioned, from long experience it is found that the doctor readily leaves to the nurse, with or without consultation, full responsibility for the nursing comfort, morale, hygiene, and health teaching of his patients, and for obtaining social help He knows that the nurse will keep him informed of the patient's progress, and of when his medical help is needed urgently Both work with one objective, but it is the doctor who shoulders the ultimate and greater responsibility

The training of a doctor is extensive and requires to be of a high university level for the knowledge and skill he must attain It is wasteful if he undertakes work, except in expediency, which a nurse could do The training of a State registered nurse is less extensive, and it is in my opinion doubtful if it requires to be of a university level even for the few leaders of the nursing profession It seems that the motives suggesting that there should be more nurses with university degrees are mainly "to keep up with the Joneses" in other countries, many of which have universities of very different standards from those in this country It seems wasteful that the precious places in the few universities of Great Britain should be taken up by potential nurses

The well trained mind, capable of critical analysis, is of undoubted value to any nurse whose work requires her to administer or to teach If, as is the case with a few district nurses, she happens to have a degree before becoming a nurse, she yet may have no desire to administer or to teach Even if she does desire it, a specially designed advanced nursing course after registration seems likely to be more helpful than her previous university degree

It is wasteful also, if State registered nurses, whose basic education requires to be good and whose training is long and comprehensive are used for work, except when unavoidable, which a State enrolled assistant nurse could undertake A considerable increase in the employment of assistant nurses working in partnership and with the guidance of State-registered nurses seems to be essential

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[10] Orla Jensen S, et al *J Danish Acad Sci Lit* 1945 111 4

The future of the nursing service will be strengthened if the concern of doctors in the training of the State-registered nurse is welcomed and encouraged, and if the latter concern themselves more than at present with the wider training of the assistant nurse

Let each one choose the career within his or her ability or in which can be found satisfaction, recognising the other's greater knowledge rather than considering lowering the standards of each

Queen's Institute of District Nursing,
London, S W 1
E J MERRY

SUCCESSFUL ABSENTEES

SIR,—Your readers have noted with interest the innovation at St Andrews University (reported in your columns last week) whereby the final examinations may be passed in the absence of the candidate This innovation has no doubt been designed to benefit those who have also taken their medical course in absentia

Westminster Medical School,
London, S W 1
ANDREW SHERRINGTON

SYRINGE CARRIER

SIR,—Most people with experience of syringe carriers for dry sterilisation will agree with Dr McDonald and Mr Pirnie (Jan 26) that the syringe carrier suggested by Dr Lerman (Jan 12) is unlikely to solve the problems of the *anæsthetist But one cannot allow their dogmatic* attack upon multiple syringe carriers to go unchallenged

In our experience a properly designed multiple syringe container is the only answer to the many problems, organisational, technical and financial, involved in running a syringe service which will cover all hospital departments, small outlying hospitals, the general practitioners, and the laboratory itself After some years of using the Kingston type of multiple syringe carrier,[1] and issuing it to some hundreds of users, we find it has none of the disadvantages alleged by Dr McDonald and Mr Pirnie

Firstly, it need not " contain a fixed set of syringes which may or may not accord with the demands of varying circumstances " Just because our normal pack contains a variety of syringes—2, 5, 10, and 20 ml —it answers most demands But the normal pack can easily be changed to meet special needs As our anæsthetists do not all have the same views as to what is best we have now had a certain number of boxes made with sides in distinctive colours (red, blue, and green) and by altering the clips can issue packs with all one size—and the theatre carries a stock of each Other users have other needs and can have a box specially packed to meet them

Secondly, in our experience with this type of box, which was designed with these points in view, the contents are *not* "rendered potentially non sterile on first opening" Nor can the needles or syringes be contaminated by " air, droplets, or hands " As for the " life " of one boxful our turnover of *3500* syringes a week *ensures that* this is not prolonged, but we do not in any case require all the syringes to be used before a box is returned It is a very simple operation to replace a *few* used *syringes* and sterilise the lot

Thirdly, in the Kingston box the sign of sterility is the continued presence of the cotton wool plug round the needle To use the syringe this seal must be removed, and once removed it is quite clear that the syringe has been used (or at any rate taken out and exposed to air even if, for any reason, not used) In practice, after turning these boxes over hundreds of times, after their use by all grades of medical and nursing staff, after use for all hospital purposes, we are quite certain of their sterility and continuing sterility

The problems of a syringe service which neither multiple nor single pack will absolutely abolish—the needle that looks sharp but is not, the plunger that has stuck, the imperfect fitting of needle to syringes—all remain unless one uses an extravagant number of people on the job Our multiple pack has reduced these to a minimum because it saves time, and it has reduced costs because breakages are only about one per cent of all the syringes issued

Kingston Hospital,
Surrey
D STARK MURRAY

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[1] Murray D S *Lancet* 1954, i, 1274

Parliament

The Right Kind of Bed

MOST old people lead contented lives with their families or friends but, as Lord AMULREE pointed out in the House of Lords on Jan 22, many of the small group of old people who live alone fall into the unfortunate administrative gap between the National Health Service Act and the National Assistance Act 40% of the old people who applied for admission to hospital, he said, belonged to this group, and after their hospital treatment it was difficult to find anywhere for them to go They were not sick, they were suffering from profound disability, and though local authorities were providing more accommodation for people who were on the borderline between being really fit and in need of hospital accommodation, there was still not enough As a result, many people were forced to remain in hospital, occupying beds which were urgently needed for the care of the sick, and which cost £12–15 a week each

Lord Amulree did not for a moment advocate a return to the old poor law, but one principle in it which he thought was valuable was that people in need of care and attention, whether sick or well, were under the same authority One of the disadvantages of the present division was that old people were often reluctant to go into a welfare home because for them it still had, however mistakenly, a flavour of the workhouse Another was that the welfare authorities would not accept people who were not fit In his view, while *accommoda*tion was so straitened, it should be used for the people who really needed it In 1954, 65,000 old people were living in these *homes* compared with 47,000 in 1945 Were there some people living in these homes unnecessarily? Could some of them, with the help of better domiciliary services, *not live on their own, and free the homes* for the less fit? Indeed, if the right people were kept in the beds we had, he doubted if any big increase was needed

We should get away from the terms " acute sick " and " chronic sick " A more useful division, he suggested, was people who were sick and needed medical care and treatment, and people who were disabled and needed different care and attention He also thought it would help if regional boards and local authorities made joint appointments so that the same doctors looked after old people in hospitals and the local-authority homes, and if the welfare services could be transferred to the health committee of the local authority

Lord COTTESLOE, in his work as chairman of the North West Metropolitan Regional Hospital Board, had seen something of the difficulties which arose from shortage of accommodation He agreed that the wrong people were often in what beds there were To his mind the greatest cause for concern was the substantial number of mental-hospital patients who should never have gone into a mental hospital at all but should have found a place in a welfare home Once these people had been sent to a mental hospital it was difficult to transplant them to a home He was anxious that we should be careful that for the future no old people who were merely a little confused should find their way into the mental hospitals

The EARL OF HOME, the secretary of State for Commonwealth Relations, replying for the Government, offered some support for Lord Amulree's view In 1955 some 4500 elderly people who no longer needed full hospital treatment occupied hospital beds On the other hand, there were 2000 old people who would be *better* in hospital than in the premises in which they were housed So by transfers, and if additional premises and home helps were available, some 2500 beds could be used to better purpose for others in more urgent need

Reviewing what had been done for old people he said that in the past nine years 70 geriatric units had been started, while the number of elderly outpatients had risen from 7000 in 1950 to 27,000 in 1955 Local authorities had opened 900 small residential homes The home-nursing service made 12$^1/_2$ million visits a year to old people We could thus, he thought, conscientiously say that we were not neglecting the old But it would be unrealistic against the background of the national income to expect that there should be a great increase in capital investment Further help for the elderly must rest on greater efficiency in organisation, greater coördination of the efforts of hospitals, doctors, and welfare authorities, and greater appreciation by the local authorities of the needs of the old In 1954–56 the Ministry of Health's officers made a survey of the services for the elderly sick throughout England and Wales The results had been assessed on a national basis and the Minister proposed to issue memoranda with suggestions arising from the survey and to send them to all hospitals and local authorities

QUESTION TIME

Doctors' Remuneration

Mr **Marcus Lipton** asked the Minister of Health what negotiations were pending to increase the salaries of doctors —Mr **Dennis Vosper** replied The Secretary of State for Scotland and I have agreed to meet representatives of the profession towards the middle of February For the present, I have no statement to make

Mr **John Rankin** asked the Minister if he was now prepared to accept the contractual obligation implied in the Spens report as the basis of all future salary negotiations with the medical profession? Mr **Vosper** I am advised that no legal contractual obligation exists Mr **Rankin** Does the Minister not realise that now he has properly decided to meet the doctors in negotiations over their claim for higher remuneration, it will be necessary for him to face up to what are called the implications, alleged or otherwise, of the Spens reports? Would it not be wise of him to take this matter into consideration in the negotiations? Mr **Vosper** I have just said in my original reply that no legal contractual obligation exists That opinion was conveyed to the doctors at an earlier meeting, and when they meet in February they will be well aware of the position Mr **Rankin** Is the Minister not aware that this is one of the points which has caused every scalpel in Scotland at least to be drawn during the week end and that there will be no satisfactory issue unless the matter is dealt with? The doctors do not accept the explanation he has given Mr **Vosper** I have already said that I will meet the doctors, and I shall look forward to that meeting, but I shall not be meeting them on the basis that a legal contractual obligation exists

Cigarette-smoking

Mr **Lipton** asked the Minister whether he would appoint a select committee to consider what immediate and practical steps can be taken to reduce cigarette smoking —Mr **Vosper** replied I do not consider that a select committee would be an appropriate body for this purpose

Mr **Somerville Hastings** Short of appointing a Royal Commission, does not the Minister feel that the evidence is sufficiently strong for something definite to be done by his department? Ought not young people and children in the schools at any rate to be warned of the dangers of cigarette smoking? Mr **Vosper** I do intend to look further into this matter and to take the advice of those concerned I do not believe at the moment that a select committee would be the right vehicle The Minister of Education has of course, recently issued further advice to the schools

Prices of Pharmaceutical Products

Replying to a question Mr **Vosper** said that the current negotiations with the pharmaceutical industry concerned the prices of proprietary preparations Discussions had recently been concluded and in the light of these the industry had revised their proposals, which he was now considering

Prescription Charges

Mr **S S Awbery** asked the Minister if he was aware that many chronic sick cancer patients diabetics those suffering from ulcers and others with long standing complaints are not receiving the treatment they need and which was intended by the National Health Act, 1948, that chemists are reporting a reduction of 50% in the prescriptions since the new charges were made on Dec 1 Mr **Vosper** I have no evidence from professional organisations or elsewhere that patients are not receiving the treatment they need, or that there has been such a reduction in prescriptions dispensed

Number of Patients and Hospital Salaries

Mr **C J A Doughty** asked the Minister which officials of mental hospitals were responsible for the discharge of patients, on what basis they were remunerated, and whether their remuneration was related in any way to the number of patients in the hospital —Mr **Vosper** replied No official is authorised to discharge a patient in a mental hospital, but any two members of the hospital management committee when ordering the discharge of a temporary or certified patient must do so with the advice in writing of the medical superintendent The salary of medical superintendents is generally based on length of service in their clinical grade and not on the number of patients Mr **Doughty** It therefore follows does it not, that if beds in a mental hospital are empty, the officials responsible for the discharge of patients suffer no financial loss? Mr **Vosper** Yes, that is true

Mr **N N Dodds** asked the Minister on what basis the salaries of senior nursing officers in mental institutions were fixed —Mr **Vosper** replied The salaries of both matrons and chief male nurses in mental and mental deficiency hospitals are determined by the status of the hospital and the number of staffed beds for which the officer is responsible The classification of deputy matrons and deputy chief male nurses for salary purposes is governed by that of their chiefs

Health of Immigrants

Captain **H B Kerby** asked the Minister of Health if he was aware that Great Britain was the only Commonwealth country that any immigrant could enter without producing a certificate of good health, and what steps he proposed taking to safeguard Great Britain from imported communicable diseases Mr **Vosper** replied The existing Public Health (Ships) and (Aircraft) Regulations, 1952, give wide powers to port medical officers to deal with any case or suspected case of communicable disease arriving in this country In addition, alien immigrants may be medically examined under the Aliens Order, 1953

Obituary

JOHN McGRATH

M Sc, M D N U I

The death, on Jan 11, of John McGrath, professor of pathology and bacteriology and dean of the faculty of medicine in University College, Dublin, leaves a gap in Irish medical life

Born in co Waterford in 1901 he was educated at Clongowes Wood College, graduating B SC at University College, Dublin, in 1921 The following year he proceeded M SC and he graduated in medicine in 1925 He spent some years abroad in postgraduate study in Vienna Heidelberg, and Mannheim before returning to Dublin where he was appointed assistant pathologist and biochemist at St Vincent's Hospital with which he was to be associated for the next quarter of a century

In 1929 he was appointed lecturer in medical jurisprudence in University College and also State pathologist and in 1933 he was called to the Irish Bar It was in forensic medicine that he became, perhaps, most widely known, and there can have been few courthouses in the country in which he had not given evidence He studied every case with scrupulous attention to detail, and the Irish courts were fortunate in having at their disposal a man of such vast experience whose evidence was always so clearly expressed

He was an exceptionally good lecturer, and for many years he was external examiner to Dublin University and to the Queen's University of Belfast In 1952 he was appointed to the chair of pathology and bacteriology at University College, Dublin and last year he was elected dean of the faculty of medicine Unfortunately, almost immediately afterwards he became seriously ill

He was a member of the Royal Irish Academy, of the senate of the National University of Ireland and of the

Medical Registration Council, and he had been president of the section of pathology of the Royal Academy of Medicine in Ireland During the early thirties he was one of those responsible for the foundation of the Medical Research Council of Ireland, of which he remained treasurer until his death He was the first chairman of the National Blood Transfusion Association and was for many years pathologist to the National Maternity Hospital He was a former assistant editor of the *Irish Journal of Medical Science*

Such a busy professional life might well have left little scope for other activities, but his term as president of the Royal Zoological Society of Ireland—which controls the Dublin Zoo—was outstandingly successful He was a keen fisherman and an enthusiastic photographer, and until lately one of his greatest pleasures was winter sports He could speak with authority of most parts of Europe, for his holidays were almost always spent in travel, yet few can have known their own countryside so well

CHARLES NOON

O B E , F R C S

Mr Noon, senior consulting surgeon to the Norfolk and Norwich Hospital, died on Jan 19 at the age of 71

He was born in Leicester, where his father, the late Samuel Bilson Noon, practised as a solicitor He was educated at Blairlodge, Stirlingshire, and studied medicine at St Bartholomew's Hospital After qualifying in 1910 he spent the next three years in house-posts at Barts, and his chiefs included Holburt Waring, Horder, Charles Gordon-Watson, and Francis Champneys In 1914 he took the F R C S and the following year he was appointed chief assistant to the gynæcological department at Barts

Noon first went to Norfolk when, early in the 1914–18 war, he was put in charge of the surgical division of the Norfolk War Hospital at Thorpe, and in 1919 he was appointed O B E for his surgical work among the casualties from the Western front The same year he was appointed assistant surgeon to the Norfolk and Norwich Hospital, and he was also surgeon in charge of the Ministry of Pensions orthopædic clinics and surgeon to the Ministry's limb-fitting centre at Norwich In the next few years he joined the staffs of other local hospitals, including the Norwich Maternity Hospital, the Patrick Stead Hospital, Halesworth, St Andrew's Hospital, Thorpe, and the Jenny Lind Hospital, Norwich His private practice grew quickly, but he found time to keep up with advances in general medicine, for he was interested not only in surgery He was the first surgeon to use radium at the Norfolk and Norwich Hospital

During the late war he was group adviser to the Norfolk area of the Emergency Medical Service, and in 1943 he was appointed deputy regional adviser in surgery to the Ministry of Health He retired from his hospital appointment in 1955, but he continued to sit as a member of the hospital management committee

A colleague writes

Noon was what we Norfolk people call a *character* I shall never forget him going round the wards with the inevitable bowler on the back of his head, illustrating his observations on the patients from his wealth of aphorisms Nor shall I forget his rare clinical acumen and his ability quickly to size up his patients He had a pungent wit and could be outspoken in committee, and he had strong views on the Welfare State and what he considered bureaucratic medicine At a first meeting his manner might seem abrupt, but those of us who knew him well knew also that nothing would prevent him from obeying any call for help He was a keen and discriminating collector of first editions, old silver, and ivory

Mr Noon married in 1921 Cecily, daughter of Mr F W South She survives him with their son, Mr C F Noon, F R C S

IVY EVELYN HASLAM

M D Lond , M R C P

Dr Haslam, who died on Jan 11 at the age of 79 was the first woman to take the M R C P when, in 1909, women were admitted to the examination

As Ivy Woodward she was educated at Bromley High School, Bedford College, and the London School of Medicine for Women After qualifying in 1903 she held house-appointments at the Royal Free Hospital and at the Belgrave Hospital for Children Later she became assistant to the clinical pathologist, curator of the museum, and demonstrator in morbid histology at the Royal Free She was also clinical assistant at the New Hospital for Women and the Royal Hospital for Diseases of the Chest before she was appointed medical registrar at the Royal Free Hospital In 1908 when she took the M D Lond she qualified for the gold medal

In 1910 she married Dr A C Haslam, who practised at Bromley, Kent After her marriage she gave up regular medical work She had two sons and three daughters (who survive her), and her family became her main concern, but throughout her life she never lost her interest in medicine She also found time for wide cultural interests, especially in literature and language After her husband's death in 1927 she moved to Gerrard's Cross, and to support her growing family she took up infant-welfare and school-inspection work Between 1931 and 1948 she held appointments as medical officer to infant-welfare clinics in Camberwell and Wandsworth In 1948 she retired from all medical work and moved to London

H K W , a fellow student at the Royal Free, writes

Ivy Woodward's charming personality, keen sense of humour, and tolerance of other peoples' point of view made her popular with her colleagues and with her patients As one of the visiting physicians at the Royal Free said, at a time when medical women were not accepted as they are today, " Her kindness and consideration for her patients are remarkable " It was regrettable that after her marriage she was able to do only a limited amount of medical work, a great loss to the profession of one so gifted

ARTHUR HENRY CROOK

M A , M Chir Camb , F R C S

Mr A H Crook, formerly orthopædic surgeon to the Eastbourne group of hospitals, died on Jan 19 at the age of 72 He was born at Southampton in 1884 From Cambridge he obtained an exhibition scholarship to Guy's Hospital After qualifying in 1908 he held house appointments at Guy's, and in 1911 he took the F R C S and in 1912 the M CHIR The same year he settled in practice in Eastbourne, and soon afterwards he was appointed assistant medical officer to the Princess Alice Hospital there During the 1914-18 war he served with the Royal Navy in Antwerp, Gallipoli, when he was mentioned in dispatches, and later on the Somme and in Ireland

On his return to his practice he took up his work at the Princess Alice Hospital, and in 1932 he became surgeon there In 1936 he was due to retire, but the post of fracture surgeon was created for him and he held it till 1951 Up to last year he occasionally acted as a locum In 1933 he helped to found the Eastbourne Sailing Club, and was in turn vice-commodore, commodore, and vice president for life He leaves a widow, three sons, and a daughter

Mr RUFUS THOMAS

C A B writes

In the long struggle over conditions of service of whole time consultants Rufus Thomas took a leading part His long service to the Whole Time Consultants' Association, first as secretary and then as president, was recognised when he was made honorary member of the association He gave evidence before the Royal Commission on Taxation of Profits and Income, and there and elsewhere he always presented his case in clear precise words and in a kindly and persuasive manner

Notes and News

THE REMUNERATION CLAIM

Representatives of the Negotiating Committee are to meet the Minister of Health on the morning of Wednesday, Feb 20 The full committee will meet on the afternoon of that day

WORLD HEALTH ORGANISATION

Poland, Albania, and Bulgaria have informed the Director General that they intend to resume active participation in W H O this year

Dr A T *Shousha, regional director for the Eastern* Mediterranean, will be succeeded on Sept 1 by Dr A H Taba

FAMINE IN IRELAND

The Great Famine of 1845–52 was not the first nor the last period of acute distress in Ireland It has, however left an enduring mark on popular memory because of its duration and severity Memories still linger in Irish oral tradition A new study by a group of specialists in the period [1] contains seven sections, of which that by Sir William MacArthur, dealing with the medical history, may prove the most interesting to medical and other readers

The cause of the famine was a fungus disease of the potato which appeared in the form of black spots on the leaves, with, on the under surface a whitish mould containing the spores These were conveyed to other potato plants by wind and insects particularly when the weather was warm and damp The potato was almost the sole food of about a third of the population, and a main article of diet of a much larger proportion On the heels of each famine there came an epidemic of fevers—mainly typhus and relapsing, both conveyed by the common louse of man On one occasion cholera added to the disaster Well over half a million people died In the better classes relapsing fever was almost unknown, whereas typhus was contracted by many doctors and clergy from their attendance on the sick, and by members of the gentry who were *infected* in crowded assemblies either while presiding as magistrates, sitting on relief committees, attending as jurors, or helping to relieve the overwhelming distress by which they were surrounded One out of every thirteen doctors died at their posts

AUSTRIAN BIOGRAPHIES

Theodor Billroth once wrote to Johannes Brahms "I have never met a great researcher who was not basically an artist of a sort" The truth of this statement is borne out by reading (in German French, or English) the concise biographies of 51 distinguished Austrian doctors that are contained in an interesting book [2] compiled by Professor Schönbauer and Dr Marlene Jantsch The proceeds will be used to provide subventions for scientific publications

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University of Cambridge

Dr J D Lever, university lecturer in anatomy, has been elected to a staff fellowship at Trinity College on his appointment as college lecturer

Queen's University, Belfast

At the summer graduation Air Marshal Sir James Kilpatrick will receive the honorary degree of LL D in recognition of his services for medicine in the Royal Air Force

University of Birmingham

On Dec 14 the following degrees were conferred

M D—Roy Astley, B D Bower M G Fitzgerald, T A Phillips, Rachel F W Sillett G F Trobridge

M B, Ch B—Margaret J Aldridge G H Berry K G Branch D C Colwell J H Croft, C M David G H Davies Marion K Donovan, A M Evans G S Farmer, I M Fletcher D M Gardiner, N H N Gardner N R Houlston J W E Johnson P W Lee, Barbara S M Marshall D H Tarkett

Mr A L T Easton has been appointed lecturer in obstetrics and gynæcology

Sir Solly Zuckerman F R S, will give the Sir Josiah Mason lectures during the 1957–58 session He is to speak on control of population growth

Royal College of Obstetricians and Gynæcologists

At a meeting of council held on Jan 26, with Sir Charles Read, the president, in the chair, the following were elected to the membership

D C Aird, G B Batchelor, R A T Boland, G D D Cable, Mahomed Ismail Cassimjee, J S W Chambers Probhat Kumar Choudhuri, C A B Clemetson K I *Digwood* Ammud Freier, W J Garrett William Gault, William Gavin, Ivan Goldman C J Goosen, Bernard Kirsch, Margaret A Lakeman E W Little, H H McCrostie, J G Markus, A E B Matthews T T E Michael A B Miller Arun Kumar Mitra, Jessie M B Muirhead A G Muttuthamby, A B L Peake, A C C Pinion L J Rice, Ray Richards T J Ryan, G J W Stump Sarosh Meher Thanevala, K F G Wilson, Robert Yule

North of England Obstetrical and Gynæcological Society

The following officers have been elected for 1957

President Mr F Stabler vice presidents, Dr E A Gerrard, Mr P Malpas, Mr H Agar Mr G R MacDonald Dr W Hunter, hon treasurer, Mr C H Walsh, *hon general secretary*, Mr T J Burk, hon reporting secretary, Miss U M Lister

Royal *College of Physicians of London*

Prof J R Squire will deliver the Oliver Sharpey lectures *on Tuesday and* Thursday, March 12 and 14, on the functions of the plasma proteins Dr L C Hill will give Lumleian lectures on Tuesday *and Thursday, April* 2 and 4, on systemic lupus erythematosus All lectures will be held at 5 P M at the college, Pall Mall East, S W 1

Course on Child and Family Psychiatry

The department of child psychiatry of the Ipswich and East Suffolk Hospital is holding a course on this subject from April 8 *to* 12 The course has been recognised by the Ministry of Education for school medical officers and by the Ministry *of Health* for maternity and child-welfare officers Further particulars may be had from 11, Fore Street, Ipswich

International Congress on Occupational Health

This congress will be held at Helsinki from July 1 to 6 Subjects chosen for discussion at the plenary sessions include industrial noise, evaluation of invalidity, industrial hygiene norms, and human engineering Further particulars may be had from Dr Pertti Sumari, secretary general of the congress, Tyoterveyslaitos, Haartmaninkatu 1, Helsinki, Finland

Preventing Delay of Ambulances

From Feb 1 ambulances bringing emergency cases into Edinburgh from the country are being *met at the outskirts* of the city by a gong fitted escort car or ambulance, manned by a driver who knows the district well, who will lead the incoming ambulance to the hospital by the quietest and quickest route A similar scheme was introduced in Glasgow at the beginning of the year

Visit to Baltic and U S S R

The Society for Cultural Relations with the U S S R hopes to organise for its *medical* section a *Baltic* cruise which will visit Copenhagen, Stockholm, and Helsinki, and spend 6–10 days in Leningrad and Moscow during September *Doctors,* medical students, or members of their families—whether or not they are members of the society—are invited to *apply* for further particulars to the secretary, 14, Kensington Square, London, W 8

Wellcome Trust

The Trust has announced *further* benefactions, amounting *to* £173,500, which bring the total distributed over the past twelve months to £401,500 The latest awards include the following

Up to £35 000 to the University of Edinburgh *for* the cost of *rebuilding animal* houses at the Institute of Animal Genetics

Up to £60 000 to the University of Leeds towards the cost of building research laboratories *for medical physics* and urology on the site of the Leeds General Infirmary

Up to £35 000 to the Royal College of Surgeons of England for the completion of the Wellcome Museums at *the* college

Up to £13 000 to the University of Manchester for the cost of a mobile radiographic and laboratory unit for use primarily in field work on the rheumatic diseases

Up to £15 000 to the University of St Andrews for the cost of adding Wellcome Laboratories of Pharmacology to the Gatty Marine Laboratory

The trustees have agreed, in principle, to present a motor cruiser to the Medical Research *Council* to assist communication between the council's laboratories at Yajara on the Gambia River and the branch laboratory some 70 miles further up the river This vessel would be adaptable as a mobile research laboratory for use in field studies in the interior of the Gambia territory

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[1] The Great Famine Studies in Irish History 1845–52 Edited by R Dudley Edwards professor of modern Irish history University College Dublin and T Desmond Williams professor of modern history University College, Dublin Dublin Browne & Nolan 1956 Pp 517 30s

[2] Österreichische Ärzte als Helfer der Menschheit Notring Jahrbuch 1957 Wien 1 Paperback 40, clothback 60, Austrian schillings

Fellowship for South African Medical Graduates

The Eli Lilly medical research fellowship ($3000 p a) is open to South African doctors who wish to work in the United States Further details can be had from Dr H A Shapiro, P O Box 1010, Johannesburg, South Africa

International Hospital Federation

This federation is to hold a congress at Lisbon, from June 3 to 7 The main theme will be International Cooperation for Hospital Development—the Hospital of the Future Further particulars may be had from the secretariat of the federation, 10, Old Jewry, London, E C 2

Central Council for Health Education

The council's summer school will be held at Bangor, from Aug 20 to 30 The subject will be the promotion of health and techniques of health education Further details may be had from the medical director of the council, Tavistock House, London, W C 1

Royal Statistical Society

Frances Wood Prize —This prize (50 guineas) is offered for the best investigation, on statistical lines, of a problem which bears directly or indirectly on economic or social conditions Further particulars may be had from the hon secretaries of the society, 21, Bentinck Street, London, W 1 The closing date for submission of essays is Sept 30

International Embryological Conference

This conference, which is sponsored by the *Journal of Embryology and Experimental Morphology*, will be held in the department of anatomy of the University of Cambridge from April 10 to 13 Copies of the programme may be had from Mr D R Newth, PH D , department of zoology, University College, London, W C 1

N H S Superannuation Concession

Medical and dental practitioners and part time specialists in the National Health Service who elected to receive a contribution of 8% of their superannuable remuneration towards payment of premiums on their insurance policies instead of joining the service's superannuation scheme may now be allowed to substitute for the original policies recognised for purposes of the option, annuity policies which would qualify for the new income tax relief afforded under section 22 of the Finance Act, 1956 Recognition of the substituted policies and payment of the Minister's contribution in respect of them will be subject to the following conditions

Where the original policy is made into a paid up policy, that policy shall not be assigned or otherwise surrendered before maturity date A breach of this condition would lead to the discontinuance of the 8% contribution

Where the original policy is surrendered all the money derived therefrom shall be used in the purchase of the substituted policy

Applications for approval to substitute policies should be sent to the Health Services Superannuation Division, Government Buildings, Honeypot Lane, Stanmore, Middlesex

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Prof W C W Nixon has been elected a member of the World Health Organisation's expert advisory panel on maternal and child health

The Distillers Company (Biochemicals) Limited have moved their sales division to Broadway House, The Broadway London, S W 19

Appointments

Cadogan, E P M B Madras, D I M assistant psychiatrist (S H M O), Storthes Hall Hospital, Kirkburton, near Huddersfield

Couch R S C, M D Lond M R C P, F F R, D M R D assistant radiologist St Thomas s Hospital London

Davies R G M D Lond D P H M O H and school M O, Huddersfield

Evans O L M B Lpool, D P H M O H, Leominster, Bromyard, Kington and district

Gorf C P M D Dubl, M R C P I, D P M consultant psychiatrist and physician superintendent Menston Hospital near Leeds

Lancaster N P M D Manc, D P M consultant psychiatrist, Bristol mental hospitals

Lister, Jeremy M R C S, D C H assistant psychiatrist (S H M O), Cefn Coed Hospital, Swansea

Mill W A, M S Lond F R C S consultant E N T surgeon, Royal Masonic Hospital London

Milne, A C M B Aberd, F F A R C S, D A consultant anæsthetist, northern group of hospitals and department of surgical neurology Edinburgh Royal Infirmary and Bangour Hospital

Taylor R M M B Manc D P M assistant psychiatrist Birmingham (mental C) group of hospitals

Diary of the Week

FEB 3 TO 9

Tuesday, 5th

Royal College of Physicians of London, Pall Mall East, S W 1
5 P M Dr D D Reid Environmental Factors in Respiratory Disease (First of two Milroy lectures)

Royal College of Surgeons of England, Lincoln's Inn Fields, London, W C 2
3 45 P M Dr G T Allen Histological Variations in Basal Cell Tumours (Erasmus Wilson demonstration)

Royal Society of Medicine, 1 Wimpole Street, London, W 1
8 30 P M *Orthopædics* Mr Denys Wainwright Transcervical Fracture Mr R H Maudsley Relief of Pain in Paget's Disease Mr B H Brock Hydrocortisone Therapy in Tennis Elbow

British Postgraduate Medical Federation
5 30 P M (London School of Hygiene and Tropical Medicine, Keppel Street, W C 1) Dr N B Myant Biliary Excretion of Thyroid Hormone

St Mary's Hospital Medical School, *Paddington*, W 2
5 P M Mr David Gordon Unusual Lesions of the Vulva

Royal Army Medical College, Millbank, *London*, S W 1
5 P M Dr J T Scales Metals and Plastics in the Treatment of *Disease*

Institute of Dermatology, Lisle Street, W C 2
5 30 P M Dr R T Brain Electrotherapeutic Techniques

Wednesday, 6th

Royal Society of Medicine
5 15 P M *History of Medicine* Dr Douglas Guthrie Whither Medical History ? (Presidential address)
8 P M *Surgery* Mr M Hobsley Surgical Significance of the *Internal Architecture of the Liver* Mr K F Wood Carcinoma of the Adrenal Cortex without Endocrine Effects Mr Henry Wapshaw Diagnosis of Acute Pancreatitis Mr B N Catchpole Massive Thrombophlebitis Mr O Daniel Serious Postoperative Bleeding Due to Acquired Defects of the Coagulation Mechanism

Postgraduate Medical School of London, Ducane Road, W 12
2 P M Dr Alick Isaacs Influenza and Adeno Viruses

Institute of Dermatology
5 30 P M Dr R W Riddell Laboratory Procedures for Mycotic Infections

Institute of Diseases of the Chest, Brompton, S W 3
5 P M Mr T Holmes Sellors Surgical Treatment of Pulmonary Stenosis

Midland Medical Society
8 15 P M (Birmingham Medical Institute, 154, Great Charles Street, Birmingham, 3) Dr H W Donovan, Dr C F Hawkins, Prof E Brodie Hughes Dr L Nagley Relief of Pain

Liverpool Medical Institution, 114 Mount Pleasant, Liverpool 3
8 P M Prof J H Dible Pathology of Peripheral Ischæmia

Manchester Medical Society, Medical School, University of Manchester
4 30 P M Mr T W Hibbert Wines and Sherries

Medico Chirurgical Society of Edinburgh
8 30 P M (Royal College of Surgeons, 18, Nicolson Street) Dr J R Paterson, Dr John Macaskill Cataract Operations

Thursday, 7th

Royal Society of Medicine
8 P M *Neurology* Dr Denis Hill, Dr B G Parsons Smith, Dr J A V Bates Changing Values in Electroencephalography

Royal College of Physicians of London
5 P M Dr Reid Environmental Factors in Respiratory Disease (Second of two Milroy lectures)

University College, Gower Street, W C 1
5 15 P M Prof Franz Bergel, D SC Chemical Aspects of Psychopharmacology

British Postgraduate Medical Federation
5 30 P M (London School of Hygiene and Tropical Medicine) Dr H M Sinclair Vitamins in Nutrition

University of St Andrews, Queen's College, Small's Wynd, Dundee
5 P M Dr Sheila Sherlock Hepatic Coma

Friday, 8th

Postgraduate Medical School of London
10 A M Prof F R Winton Renal Circulation

Institute of Laryngology and Otology, 330, Gray's Inn Road W C 1
3 30 P M Mr C Gill Carey Tinnitus

United Kingdom Committee for the World Federation for Mental Health
5 45 P M (County Hall, Westminster Bridge S E 1) Dr Margaret Mead Mental Health in a Changing World

Midland Centre for Neurosurgery, Holly Lane, Smethwick near Birmingham
8 P M Sir Francis Walshe, F R S Ætiology and Nature of the So called Traumatic Neurosis

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Corrigendum *A New Acetabular Reamer for Arthroplasty* —The device described by Mr R B Duthie (*Lancet*, 1956, ii, 1085) is manufactured in Great Britain by Zimmer Orthopædic Ltd , Bridgend, Glam , and not by an American company

THE DISINTEGRATIVE ACTION OF THE NERVOUS SYSTEM*

William Phillips
M.D., B.Sc. Wales, F.R.C.P.
PHYSICIAN TO THE UNITED CARDIFF HOSPITALS

Sherrington's first masterpiece, his Silliman memorial lectures, was published in 1906 as *The Integrative Action of the Nervous System*. It is therefore the fiftieth anniversary of the publication of a book which will remain a landmark in the history of medicine. 1956 marks also the centenary of the birth of another great neurologist, born only the year before Sherrington, Sigmund Freud, and so I felt it not inappropriate today to discuss a topic which I believe will become of increasing importance as advances in medicine mop up small pockets of resistance in localised fields of pathology.

* * *

That the nervous system itself might be a source of disease is no new idea, and as far back as 1868 William Gull said "there is a neuropathology from the brain", but in this and in many other ways that remarkable clinician was much ahead of thought in his day. Since Gull's time, many have expressed the same sort of view and none in more intriguing a fashion than did Wilfred Trotter (1941) in his essay on the Insulation of the Nervous System, where he reflects that

> "It may be worth suggesting, however, that the problem (the reason for the curious embryology of the nervous system) has also a functional side and that the epiblastic origin of an organ that is ultimately to be deeply embedded in mesoblastic tissues possibly has the function of contributing its strangeness and therefore its effectiveness, to the nervous system as a whole. This quasi-hostility between neural and somatic, between brain and body, is a suggestive and perhaps a disturbing thought."

Morley Roberts (1926) in his *Malignancy and Evolution* said "the body is composed of differentiated cell colonies living in a state of hostile symbiosis in precarious and uneasy balance so that balance between organs and tissues may be easily lost—the brain is a morbid overgrowth and tumour its tremendous size may not only be one of the causes of malignancy but ultimately the cause of extermination of the human race." But this was based on philosophic speculation and somewhat strained analogy, however disturbingly the last clause may read today.

Even when the initial novelty of seeking out psychosomatic relationships had been overcome, those interested particularly in this subject were slow to investigate such possibilities except where mechanisms capable of producing local changes seemed likely, from their knowledge of physiology, to be possible and an analysis (Engel 1954) of the first fifteen volumes of the journal *Psychosomatic Medicine* showed that 80% of the 206 articles were devoted to the circulatory system, skin, gastro-intestinal tract, respiratory system, pain, and metabolic disturbances. I wonder how many of our teaching hospitals and great special hospitals could with all the good will in the world derive from their existing case-notes material of real value to a serious student of such matters. I would not myself be optimistic in this regard. What indeed can one expect in the way of appreciation of the patient as a person, of his hopes and fears, aims and beliefs, when one encounters a rugged patient introduced by a highly trained senior registrar as an interesting example of disseminated sclerosis commencing at 59 and finds that the description "porter" on his case-notes had been of so little interest, and resulted in so little inquiry, that the vision of a man balancing a hundredweight of baskets in a tall chimney on his head for the working hours of upwards of forty years had quite escaped comment?

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While the endocrine glands are subject to most of the ordinary pathological changes—for example, tuberculosis and neoplasm—one of the striking features of the common endocrine disorders is the remarkable circumstance that disorder or atrophy is the main feature of their pathology. I find it difficult from clinical experience to accept the view that conditions such as thyrotoxicosis, myxœdema and many of the disorders of menstruation, diabetes mellitus, and the like, often commence in a localised disturbance in the glands concerned, without preceding central disorder, and it would be my conviction that emotional disturbances are the main, if not for practical purposes the sole, origin of such central derangement.

In two such different conditions as rheumatoid arthritis and diabetes mellitus there is much to compare. Of the first, Bauer (1956) has said from an experience of 300 patients studied over twenty-five years, that "no significant lead had emerged as to cause or cure—an impasse which faced all investigators of the disease." I think the walls of our college will approve his conclusion that "rest emerged as the keystone of treatment, and the definite natural tendency for the disease to remit cast doubts on the many reported 'cures'." An immediate analogy can be drawn between a chronic relapsing joint condition, which is in some sense modified by adrenocorticotrophic hormone or cortisone, and the state of the diabetic patient controlled by insulin. I regard the insulin treatment of diabetes as the most perfect example of how scientific medicine has succeeded in blinding itself to the existence of the patient while at the same time boasting of his survival. To most treatment of diabetes is treatment of a blood chemistry unrelated to treatment of a person except in so far as he is expected to fall in with quite rigid authoritarian dictates as to his food and other habits for the rest of his life—all of course with most kindly intentions. Yet, consideration of experimental evidence might long ago have introduced an element of caution into this outlook. I have elsewhere summarised (Phillips 1953a) the experimental pointers to objections to the concept of diabetes as a simple endocrine lack from disease of special tissues in the pancreas.

Concerning the possibility that emotional factors may be responsible for diabetes there is, of course, much literature, some of it critical and suggestive (Daniels 1948). I have encountered four patients with severe diabetes where the experimental situation seems in part paralleled—four patients in whom an abrupt onset followed periods of intense emotional stress and in whom by good fortune prompt diagnosis was possible by reason of the nature of the presenting symptoms. In all immediate high insulin dosage was used and efforts were made to deal with the psychological situation. After progressive diminution in their insulin requirements, all in the course of four to eight weeks became free from glycosuria without insulin, and they have remained so on ordinary diets, living ordinary lives since; two of them I judged to have made an emotional adjustment more from developed traits in their own make-up than by my help. I think the reason why I have only four such patients is that until recent years I had not recognised the implications of the response of the first patient, whom I saw in a military hospital. Now, were I seeing many diabetic patients, I should be increasingly interested in what is going on in the patients'

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* From the Bradshaw lecture for 1956, delivered to the Royal College of Physicians of London on Nov. 8.

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lives and minds There are evidently further analogies in thyrotoxic glycosuria

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The *study of peptic ulcer*—a disorder which because a pain or other symptom causes the patient usually to be aware of variations in his state quite quickly—is of great value in teaching the doctor the importance of body-mind relationship The correlation of its important complications with acute periods of stress is frequent, although it by no means follows that the essential information is available to any clumsy, untutored approach Success often seems to attend competent surgical treatment of the patients whose ulcers are bothering them mainly because of the effects of the fibrosis of healing, but in this extraordinarily important disorder the evaluation of therapy must surely be long-term

Browning and Houseworth (1953) interested themselves in the development of new symptoms following medical and surgical treatment of duodenal ulcer They noted a significant decrease in ulcer symptoms following gastrectomy but also a parallel increase in other illness, whereas in the medically treated patients, who were often incompletely relieved of their ulcer symptoms, there was no redistribution of symptoms The most important point which emerged from their study was that the longer the period of follow-up, the more significant the differences in the two groups appeared The earlier a physician with the interest and skill necessary to recognise the nature of the causative stress can help to secure graceful adjustment to the general life situation, the more the gross permanent effects of ulcer scarring can be prevented or minimised

Grace (1953) and his co-workers studied patients with duodenal ulcer to estimate the significance of this kind of statement, using two groups matched for stage in the disease and in many other ways, and found that, of the patients they had treated without using dietetic measures or new or old antispasmodics, about two thirds after three years showed X-ray evidence of complete healing, whereas, of the comparable patients treated in other clinics with conventional drug and dietetic treatment only one-third were similarly healed The evidential basis for accepting a stress causation of peptic ulcer so amply demonstrated in the studies by Stewart Wolf (1949) on patients with gastric fistulæ, will be well known to you, of it, Wolf has said

> "Among stimuli sustaining gastric hyperfunction, troublesome life situations were found to be prominent and surprisingly potent, often outweighing the effects of powerful pharmacodynamic agents In treatment of duodenal ulcer, getting to know the patient and offering him help and encouragement in dealing with his day-to day challenges and problems appear to offer more than do diets and antacids alone"

The varying course of illnesses such as thyrotoxicosis and ulcerative colitis—both again amenable in different ways to medical and surgical approaches in therapy—parallel with extraordinary precision the natural history of peptic ulceration, and in these conditions I think that the onset, rate of improvement, and relapses during treatment, are conditioned by stress exclusively

* * *

I would like now to touch on a concept which seems possibly important Whether genetic or other constitutional factors are essential before the mind can produce somatic damage is unlikely to be determined at all easily, and it *does not* really *matter* in this discussion whether the amount of added stress necessary to produce somatic changes in an individual has to be little or great It is in quite another direction that the practical importance of the situation lies I put forward the proposition that in some patients the life situation is incompatible with his personality in such degree that unaided he can make no adjustment, in others, partial adjustment is possible, while in a third group adjustment is more or less readily achieved I suspect that conditions such as some psychoses may come into the first group, and likewise many examples of ulcerative colitis, while others are at the more severe end of the second group. Possibly again in the first group, or in the more severe part of the second, illnesses such as disseminated scleros may need to be placed In the more benign part of the middle group, and perhaps in *all* parts of the third group, come the peptic ulcerations, asthma, thyrotoxicosis and diabetes, while migraine, for example, and psoriasis will most often be in the first group I am satisfied that in the whole of the third group, and in very much of the second group, already enormously rewarding therapeutic opportunities are ignored by preoccupation with local lesions and peripheral ideas of ætiology My conviction would be that with sufficient skill in investigation, many, if not most, of the first group will also become amenable to non-mechanistic approach in treatment

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One of the most disturbing features of the failure of modern medicine, especially academic medicine, to face up to the implication of Freud's major discovery is the extraordinary ignorance one finds of what he actually thought and said There can be little excuse for ignorance of his life now that the brilliant and devoted biographical study by Ernest Jones—soon, I hope, to be completed—has appeared Were Freud's works not available in the happiest of English translations, one could excuse more readily ignorance of them, and I find it odd, for example, that few seem to have noticed that the fourteenth edition of the *Encyclopædia Britannica* (1929) contains a most precise article on psycho analysis by Freud himself His account of the subject matter of psycho analysis is an extremely succinct and important one Now, over thirty years later, much could be said of the validity of the details of his exposition, but it is certain that in the history of medicine his name will live as long as that of any of the mighty originals we honour That the theory of psychology and the rigid system of treatment he built up are both unlikely to survive unaltered does not detract from his greatness, and, at this distance, they can be seen as the inevitable effects of the cultural atmosphere of the times and places in which he spent his formative years

* * *

Prejudice and bias aside, two important kinds of difficulty prevent easy recognition of the effects of emotion on the tissues On the one hand, the causative disturbance may be unrecognisable except by the trained observer, or, though less subtle, may still be beneath consciousness, or on the *other hand* there may be *no* symptoms to attract the patient's notice Between these difficulties come those disorders which, though apparent enough, do not make the patient think of an emotional origin—simply because the time-relationship is not impressed on him either by previous experience or by immediacy of effect

I have said elsewhere (1953b) that for *most people* the state of health is not a very conscious matter unless sharp deviations from the customary state take place, and many will fail to recognise those differences of personality which to others are their distinguishing marks To feel well in the conventional sense is an *exaggeration*, when well one feels nothing of one's health unless in response to external stimulus In many circumstances, quite gross changes of mental comfort can occur without the patient considering even the possibility that his reaction has been other than ordinary If long experience has brought home to him that his usual response to worry or upset has been, say, abdominal discomfort, diarrhœa, frequency of micturition, or headache, then an unusual severity of such symptoms may make him aware that a particularly severe stress has been responsible, but even so apparently simple a correlation is by no means usual—and in the definition of stress it is prudent to remember Plutarch's remark that it is "man's nature to resent evil words more than evil deeds, for it is more easy to submit to injury than insult"—and in considering response to stress, to recall Shakespeare's famous lines "Give sorrow words, the grief that does not speak whispers the o'er fraught heart, and bids it break."

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An almost insuperable difficulty arises where a response is bizarre, and I shall illustrate this by a few words on multiple lipomatosis. The ætiology of this curious disorder has been little discussed, though Heilmann and Sonneck (1953), describing a case in which the lipomatosis seemed to follow electric shock, refer to others attributed to head injury, particularly injury to the base of the skull.

When I first saw the condition twenty-five years ago, even the patient's subsequent suicide did not make me reflect on why he had developed an enormous number of lipomata. Early in the war, I saw a second patient who in six weeks had developed numerous lipomata about the arms, thighs, and trunk. There were so many large ones in the forearms that, when he presented arms, a tourniquet effect made him relax his grip quite quickly, and on two such occasions his rifle clattered to the ground. He presented an antecedent intense anxiety state based on readily understandable factors, and when we had relieved his emotional disorder he reminded us that no further lipomata had appeared, but again I thought little of the matter. On returning to civil life, I was almost at once presented with a third problem of this kind—the combination of an intense exhaustion and anxiety state in an exceedingly active and responsible young man with gross lipomatosis of acute onset, mainly affecting the arms. Twenty-nine lipomata were neatly excised while he was having a short course of modified prolonged narcosis, and I was greatly intrigued to find that, with the relief of his psychogenic disorder, no further lipomata appeared. I waited with some eagerness for another comparable patient, and within the last fortnight I have seen one. Unfortunately it is some seven years since his lipomata appeared, so that critical study of the life situation at the relevant time will be difficult, but it is clear that in this instance a man of 63 developed the condition in circumstances which caused him soon afterwards to retire prematurely from his occupation. Tentative exploration of the last patient has not gone further, but I would suggest that this slight personal experience of four patients with multiple lipomatosis cannot be dismissed as irrelevant to my main theme. I would agree at once that the development of benign fatty tumours seems a very odd way for the body to express its discontent, but if these observations have substance, then I would suggest that there is no tissue in the body which may not react in a similar way.

The effect of stress on body resistance to infection is difficult to define although one suspects some close connection when one encounters, for example, a patient who has had pneumonia several times in thirty years, always immediately after severe stresses. *Recurrent* herpes, simplex and zoster, in my small experience, has always been so correlated, and this view is shared by others (Weichselbaum 1956). When one feels that a real improvement has taken place in a patient's personal adjustment to life it is intriguing to hear comments such as "It's odd I haven't had another attack because, if this had happened to me before treatment I'm certain I would have had a very bad attack—I suppose it's because I had begun to feel happier and easier." This remark was made by an intelligent patient who had failed to show her expected somatic reaction when her daughter was killed tragically the day after what was to have been a final discussion of her health.

There are those who insist that patients with disseminated sclerosis are apt to show a uniform type of personality. My co-editor, Hugh Garland, for example, writes:

> "early examples of disseminated sclerosis, when there can be little possibility of personality changes having arisen through gross disease of the brain, show many striking features. Usually physically attractive, these people are almost invariably polite, quiet, pleasant and devoid of aggressive talk or behaviour, they dislike quarrels or arguments, or any show or display of temper. In the author's view it is this type of person, and probably only this type, which develops disseminated sclerosis, and in such people it is very commonly the fact that prior to the onset of the first symptoms, there has been clear evidence of emotional stress. It may well be that trauma, parturition and the other factors mentioned above operate by some similar mechanism." (Garland 1953.)

When one considers the difference in the possibility of regeneration in damaged nervous tissue as compared with tissues where normally mitosis is active and replacement constant and frequent (Leblond and Walker 1956), it seems clear that, if stress damage arises in the nervous system, the only recovery to be expected is the removal of the effects of immediate neuroglial or similar reaction. Schwab and Prichard (1950) studying a hundred parkinsonian patients with special interest in psychosomatic effects in stable, vulnerable, and difficult personalities concluded that there is a close correlation between personality and the effects of environmental stress. They found that, while all patients were temporarily worse with short-lived stress, only 12% of the 42 patients in the stable group showed permanent aggravation of their disorder when exposed to long-continued or severe stress, whereas 33 (27%) of the vulnerable and 25 (56%) of the difficult-personality groups were so affected. Others have suggested that some patients with parkinsonism may be showing reaction to stress in the very centre of the integrating mechanism, and many examples of chronological correlation between exacerbations and stress are on record. Again, I had never considered this possibility until quite recently when I was a little chagrined by a patient's unprompted and quite categorical account of her correlation not only of an exacerbation in the parkinsonism but also of its origin with clear-cut episodes of severe stress.

The more one studies such matters, the more one realises how extraordinarily blind our preconceptions make us. We tend to see only what we expect to see, and it is hardly surprising that many can practice over a long period of years without ever realising that mental factors can induce a physical disease. Particularly is this understandable when one considers how very much more careful and understanding an approach is required to elicit this type of history. We may recall what Oliver Wendell Holmes said in 1883 about the futility of much of medical practice:

> 'many a suicide would have been prevented if the doctor's wife had visited the victim the day before it happened. She would have seen in the merchant's face his impending bankruptcy while her stupid husband was prescribing for his dyspepsia and indorsing his note; she would recognize the love lorn maiden by an ill adjusted ribbon—a line in the features—a droop in the attitude, a tone in the voice—which mean nothing to him, and so the brook must be dragged tomorrow.'

It cannot be said too often that when one is studying the possibilities of psychosomatic ætiology to ask a patient whether anything may be worrying him is a waste of

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The study of peptic ulcer—a disorder which because a pain or other symptom causes the patient usually to be aware of variations in his state quite quickly—is of great value in teaching the doctor the importance of body-mind relationship The correlation of its important complications with acute periods of stress is frequent, although it by no means follows that the essential information is available to any clumsy, untutored approach Success often seems to attend competent surgical treatment of the patients whose ulcers are bothering them mainly because of the effects of the fibrosis of healing, but in this extraordinarily important disorder the evaluation of therapy must surely be long-term

Browning and Houseworth (1953) interested themselves in the development of new symptoms following medical and surgical treatment of duodenal ulcer They noted a significant decrease in ulcer symptoms *following gastrectomy but also a parallel increase in* other illness, whereas in the medically treated patients, who were often incompletely relieved of their ulcer symptoms, there was no redistribution of symptoms The most important point which emerged from their study was that the longer the period of follow-up, the more significant the differences in the two groups appeared The earlier a physician with the interest and skill necessary to recognise the nature of the causative stress can help to secure graceful adjustment to the general life situation, the more the gross permanent effects of ulcer scarring can be prevented or minimised

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The varying course of illnesses such as thyrotoxicosis and ulcerative colitis—both again amenable in different ways to medical and surgical approaches in therapy—parallel with extraordinary precision the natural history of peptic ulceration, and in these conditions I think that the onset, rate of improvement, and relapses during treatment, are conditioned by stress exclusively

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I would like now to touch on a concept which seems possibly important Whether genetic or other constitutional factors are essential before the mind can produce somatic damage is unlikely to be determined at all easily, and it does not really matter in this discussion whether the amount of added stress necessary to produce somatic changes in an individual has to be little or great It is in quite another direction that the practical importance of the situation lies I put forward the proposition that in some patients the life situation is incompatible with his personality in such degree that unaided he can make no adjustment , in others, partial adjustment is possible , while in a third group adjustment is more or less readily achieved I suspect that conditions such as some psychoses may come *into* the first group, and likewise many examples of ulcerative colitis, while others are at the more severe end of the second group Possibly again in the first group, or in the more severe part of the second, illnesses such as disseminated sclerosis may need to be placed In the more benign part of the middle group, and perhaps in all parts of the third group, come the peptic ulcerations, asthma, thyrotoxicosis and diabetes, while migraine, for example, and psoriasis will most often be in the first group I am satisfied that in the whole of the third group, and in very much of the second group, already enormously rewarding therapeutic opportunities are ignored by preoccupation with local lesions and peripheral ideas of ætiology My conviction would be that with sufficient skill in investigation, many, if not most, of the first group will also become amenable to non-mechanistic approach in treatment

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One of the most disturbing features of the failure of modern medicine, especially academic medicine, to face up to the implication of Freud's major discovery is the extraordinary ignorance one finds of what he actually thought and said There can be little excuse for ignorance of his life now that the brilliant and devoted biographical study by Ernest Jones—soon, I hope, to be completed—has appeared Were Freud's works not available in the happiest of English translations, one could excuse more readily ignorance of them , and I find it odd, for example, that few seem to have noticed that the fourteenth edition of the *Encyclopædia Britannica* (1929) contains a most precise article on psycho analysis by Freud himself His account of the subject matter of psycho analysis is an extremely succinct and important one Now, over thirty years later, much could be said of the validity of the details of his exposition, but it is certain that in the history of medicine his name will live as long as that of any of the mighty originals we honour That the theory of psychology and the rigid system of treatment he built up are both unlikely to survive unaltered does not detract from his greatness, and, at this distance, they can be seen as the inevitable effects of the cultural atmosphere of the times and places in which he spent his formative years

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Prejudice *and* bias aside, *two* important kinds of difficulty prevent easy recognition of the effects of emotion on the tissues On the one hand, the causative disturbance may be unrecognisable except by the trained observer, or, though less subtle, may still be beneath consciousness , or on the other hand there *may* be no symptoms to *attract* the patient's notice Between these difficulties come those disorders which, though apparent enough, do not make the patient *think* of an emotional origin—simply because the time-relationship is not impressed on him either by previous experience or by immediacy of effect

I have said elsewhere (1953b) that for most people the state of health is not a very conscious matter unless sharp deviations from the customary state take place, and many will fail to recognise those differences *of personality* which to others are their distinguishing marks To feel well in the conventional sense is an exaggeration , when well one feels nothing of one's health unless in response to external stimulus In many circumstances, quite gross changes of mental comfort can occur without the patient considering even the possibility that his reaction has been other than ordinary If long experience has brought home to him that his usual response to worry or upset has been, say, abdominal discomfort, diarrhœa, frequency of micturition, or headache, then an unusual severity of such symptoms may make him aware that a particularly severe stress has been responsible, but even so apparently simple a correlation is by no means usual—and in the definition of stress it is prudent to remember Plutarch's remark that it is " man's nature to resent evil words more than evil deeds , for it is more easy to submit to injury than insult "—and in considering response to stress, to recall Shakespeare's famous lines " Give sorrow words , the grief that does not speak whispers the o'er fraught heart, and bids it break "

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I would like now to touch on a concept which seems possibly important Whether genetic or other constitutional factors are essential before the mind can produce somatic damage is unlikely to be determined at all easily, and it does not really matter in this discussion whether the amount of added stress necessary to produce somatic changes in an individual has to be little or great It is in quite another direction that the practical importance of the situation lies I put forward the proposition that in some patients the life situation is incompatible with his personality in such degree that unaided he can make no adjustment , in others, partial adjustment is possible , while in a third group adjustment is more or less readily achieved I suspect that conditions such as some psychoses may come into the first group, and likewise many examples of ulcerative colitis, while others are at the more severe end of the second group. Possibly again in the first group, or in the more severe part of the second, illnesses such as disseminated sclero may need to be placed In the more benign part of the middle group, and perhaps in all parts of the third group, come the peptic ulcerations, asthma, thyrotoxico and diabetes, while migraine, for example, and psoria will most often be in the first group I am satisfied that in the whole of the third group, and in very much of the second group, already enormously rewarding therapeutic opportunities are ignored by preoccupation with local lesions and peripheral ideas of ætiology My conviction would be that with sufficient skill in investigation, many, if not most, of the first group will also become amenable to non-mechanistic approach in treatment

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One of the most disturbing features of the failure of modern medicine, especially academic medicine, to face up to the implication of Freud's major discovery is the extraordinary ignorance one finds of what he actually thought and said There can be little excuse for ignorance of his life now that the brilliant and devoted biographical study by Ernest Jones—soon, I hope, to be completed—has appeared Were Freud's works not available in the happiest of English translations, one could excuse more readily ignorance of them , and I find it odd, for example, that few seem to have noticed that the fourteenth edition of the *Encyclopædia Britannica* (1929) contains a most precise article on psycho-analysis by Freud himself His account of the subject matter of psycho analysis is an extremely succinct and important one Now, over thirty years later, much could be said of the validity of the details of his exposition, but it is certain that in the history of medicine his name will live as long as that of any of the mighty originals we honour That the theory of psychology and the rigid system of treatment he built up are both unlikely to survive unaltered does not detract from his greatness, and, at this distance, they can be seen as the inevitable effects of the cultural atmosphere of the times and places in which he spent his formative years

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Prejudice and bias aside, two important kinds of difficulty prevent easy recognition of the effects of emotion on the tissues On the one hand, the causative disturbance may be unrecognisable except by the trained observer, or, though less subtle, may still be beneath consciousness , or on the other hand there may be no symptoms to attract the patient's notice Between these difficulties come those disorders which, though apparent enough, do not make the patient think of an emotional origin—simply because the time relationship is not impressed on him either by previous experience or by immediacy of effect

I have said elsewhere (1953b) that for most people the state of health is not a very conscious matter unless sharp deviations from the customary state take place, and many will fail to recognise those differences of personality which to others are their distinguishing marks To feel well in the conventional sense is an exaggeration , when well one feels nothing of one's health unless in response to external stimulus In many circumstances, quite gross changes of mental comfort can occur without the patient considering even the possibility that his reaction has been other than ordinary If long experience has brought home to him that his usual response to worry or upset has been, say, abdominal discomfort, diarrhœa, frequency of micturition, or headache, then an unusual severity of such symptoms may make him aware that a particularly severe stress has been responsible, but even so apparently simple a correlation is by no means usual—and in the definition of stress it is prudent to remember Plutarch's remark that it is "man's nature to resent evil words more than evil deeds, for it is more easy to submit to injury than insult"—and in considering response to stress, to recall Shakespeare's famous lines "Give sorrow words, the grief that does not speak whispers the o'er fraught heart, and bids it break."

* * *

An almost insuperable difficulty arises where a response is bizarre, and I shall illustrate this by a few words on multiple lipomatosis. The ætiology of this curious disorder has been little discussed, though Heilmann and Sonneck (1953), describing a case in which the lipomatosis seemed to follow electric shock, refer to others attributed to head injury, particularly injury to the base of the skull.

When I first saw the condition twenty-five years ago, even the patient's subsequent suicide did not make me reflect on why he had developed an enormous number of lipomata. Early in the war, I saw a second patient who in six weeks had developed numerous lipomata about the arms, thighs, and trunk. There were so many large ones in the forearms that, when he presented arms, a tourniquet effect made him relax his grip quite quickly, and on two such occasions his rifle clattered to the ground. He presented an antecedent intense anxiety state based on readily understandable factors, and when we had relieved his emotional disorder he reminded us that no further lipomata had appeared, but again I thought little of the matter. On returning to civil life, I was almost at once presented with a third problem of this kind—the combination of an intense exhaustion and anxiety state in an exceedingly active and responsible young man with gross lipomatosis of acute onset, mainly affecting the arms. Twenty-nine lipomata were neatly excised while he was having a short course of modified prolonged narcosis, and I was greatly intrigued to find that, with the relief of his psychogenic disorder, no further lipomata appeared. I waited with some eagerness for another comparable patient, and within the last fortnight I have seen one. Unfortunately it is some seven years since his lipomata appeared, so that critical study of the life situation at the relevant time will be difficult, but it is clear that in this instance a man of 63 developed the condition in circumstances which caused him soon afterwards to retire prematurely from his occupation. Tentative exploration of the last patient has not gone further, but I would suggest that this slight personal experience of four patients with multiple lipomatosis cannot be dismissed as irrelevant to my main theme. I would agree at once that the development of benign fatty tumours seems a very odd way for the body to express its discontent, but if these observations have substance, then I would suggest that there is no tissue in the body which may not react in a similar way.

The effect of stress on body resistance to infection is difficult to define, although one suspects some close connection when one encounters, for example, a patient who has had pneumonia several times in thirty years, always immediately after severe stresses. *Recurrent* herpes simplex and zoster, in my small experience, has always been so correlated, and this view is shared by others (Weichselbaum 1936). When one feels that a real improvement has taken place in a patient's personal adjustment to life it is intriguing to hear comments such as "*It's odd I haven't had another attack, because, if this had happened to me before treatment I'm certain I* would have had a very bad attack—I suppose it's because I had begun to feel happier and easier." This remark was made by an intelligent patient who had failed to show her expected somatic reaction when her daughter was killed tragically the day after what was to have been a final discussion of her health.

There are those who insist that patients with disseminated sclerosis are apt to show a uniform type of personality. My co-editor, Hugh Garland, for example, writes:

> " . . . early examples of disseminated sclerosis, when there can be little possibility of personality changes having arisen through gross disease of the brain, show many striking features. Usually physically attractive, these people are almost invariably polite, quiet, pleasant and devoid of aggressive talk or behaviour; they dislike quarrels or arguments, or any show or display of temper. In the author's view it is this type of person, and probably only this type, which develops disseminated sclerosis, and in such people it is very commonly the fact that prior to the onset of the first symptoms, there has been clear evidence of emotional stress. It may well be that trauma, parturition and the other factors mentioned above operate by some similar mechanism." (Garland 1953.)

When one considers the difference in the possibility of regeneration in damaged nervous tissue as compared with tissues where normally mitosis is active and replacement constant and frequent (Leblond and Walker 1956), it seems clear that, if stress damage arises in the nervous system, the only recovery to be expected is the removal of the effects of immediate neuroglial or similar reaction. Schwab and Prichard (1950) studying a hundred parkinsonian patients with special interest in psychosomatic effects in stable, vulnerable, and difficult personalities concluded that there is a close correlation between personality and the effects of environmental stress. They found that, while all patients were temporarily worse with short-lived stress, only 12% of the 42 patients in the stable group showed permanent aggravation of their disorder when exposed to long-continued or severe stress, whereas 33 (27%) of the vulnerable and 25 (56%) of the difficult personality groups were so affected. Others have suggested that some patients with parkinsonism may be showing reaction to stress in the very centre of the integrating mechanism, and many examples of chronological correlation between exacerbations and stress are on record. Again, I had never considered this possibility until quite recently when I was a little chagrined by a patient's unprompted and quite categorical account of her correlation, not only of an exacerbation in the parkinsonism but also of its origin with clear cut episodes of severe stress.

The more one studies such matters, the more one realises how extraordinarily blind our preconceptions make us. We tend to see only what we expect to see, and it is hardly surprising that many can practice over a long period of years without ever realising that mental factors can induce a physical disease. Particularly is this understandable when one considers how very much more careful and understanding an approach is required to elicit this type of history. We may recall what Oliver Wendell Holmes said in 1883 about the futility of much of medical practice:

> " . . . many a suicide would have been prevented if the doctor's wife had visited the victim the day before it happened. She would have seen in the merchant's face his impending bankruptcy while her stupid husband was prescribing for his dyspepsia and indorsing his note. *She would recognize* the love lorn maiden by an ill adjusted ribbon—a line in the features—a droop in the attitude, a tone in the voice—which mean nothing to him, and so the brook must be dragged tomorrow." •

It cannot be said too often that when one is studying the possibilities of psychosomatic ætiology, to ask a patient whether anything may be worrying him is a waste of

time To ask whether he considers himself a worrier, or whether his family so judge him, will usually produce a relevant and unemotional response To ask how worry or upset affects him will similarly produce some useful information, although often thought and inquiry from relatives will be needed before even this question can be answered with even partial accuracy, but letting the patient talk and go on talking is the method of choice The hostility induced by Freud's emphasis on sexual aspects of psychogenesis has left a legacy of half-acceptance of his main principles, interpreted in a way that allows only the bizarre and exceptional circumstance to be effective in ætiology, whereas in general the everyday ordinary unsettled difficulties of personal inter-relationships are far more important

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Attempting to determine the relationship of specific attitudes and emotions to bodily disease, Grace and Graham (1952) tried to define situations chronologically associated with symptoms, and obtain a description of the patient's attitude at the time They emphasised the necessity of getting from the patient a clear unambiguous statement of what he felt had happened to him and what he wanted to do about it *at the time of the occurrence of the symptom* They said that in their series "all patients with the same symptom complex described their attitudes towards the situation which precipitated it in essentially the same way" In urticaria, for example, the patients saw themselves as mistreated, either in words or deeds, and were preoccupied with what was happening rather than thinking of retaliation or of solving their problem In eczema, the feeling was of being interfered with or prevented from doing something, together with inability to think of a method of dealing with frustration the preoccupation being with interference and the people or situations frustrating the patient This contrasts with the preoccupation of the person with migraine, who strives to carry out a planned programme or reach some clear objective, the headache occurring with cessation of effort and being unrelated to success or failure here the typical statements quoted were "*I had to get it done,*" "*I had to meet a deadline,*" "I had a million things to do before lunch," "I was trying to get all these things accomplished"

Grace and Graham propose that emotion be defined as an attitude with its associated physiological changes Such generalisations—and there are many comparable ideas—are in my view still unjustified, but each seems to have its significant element of truth and value

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Though many doctors and patients are quite unaware of psychosomatic relationships, some patients have intuitive awareness of quite surprising precision

> The husband of a patient whom I had known for a long time was telling me of his wife's eventual death, and, speaking of his adjustment to circumstances, remarked that he himself had had far less urticaria and paroxysmal tachycardia in the past year He was not my patient, and I had known nothing *of these disabilities*, *but a casual inquiry* produced the striking answer that he knew that his urticaria was an invariable response to grief, and, so far as he had determined, to no other circumstance, while the paroxysmal tachycardia was always produced by anger and by nothing else

The individual's pattern of reaction to a given emotion may well be constant for a short or long period, but in another patient the same reaction may be caused by quite a different circumstance This view is well illustrated by some recent experience with patients with psoriasis

I do not myself practice, and know only too little of, dermatology, but for some time I have had the habit of asking a patient who happens to have psoriasis, always at the end of a consultation—whether he has any views about its cause Four consecutive patients have attributed exacerbations of their psoriasis to emotional stress The first had found a feeling of injustice would be responsible within twelve to twenty four hours for fresh lesions, the second found her skin react to upset about illness in others within twenty four hours, a third correlated it precisely with pleasurable marital sexual experiences, while the fourth had discovered that pleasurable planning of business activity, while awake at night, was similarly responsible I have described these patients in a little more detail recently and also enlarged on the theme of how to get the information from the patient (Phillips 1956)

A delightful and significant experiment, entitled The Patient Sits Down, is described by White (1953) who, in a cardiological practice, noted how patients seated themselves in his consulting room He distinguished between patients who promptly sat down and leaned back in the chair, and those who sat on the edge of the chair, drew the chair close to the desk, and then sat down on the edge of the chair, or who drew the chair close to the desk, sat down on the edge of the chair, leaned forward, and rested the elbows on the desk He then studied whether removing the desk, so that no physical barrier existed between him and the patient, would have any effect on their seating habits He made the interesting observation that over 50% of patients sat at ease when there was no desk, in contrast with about 10%, when a desk was present Subsequent inquiries from individual patients suggested that this apparently trivial procedure produced not only a feeling of increased ease but also increased recollection of details previously forgotten about illnesses

It is difficult in a busy day to avoid the temptation to cut a patient short and to arrive at an opinion on too short a history and an adequate physical examination My experience is that one can seldom obtain even a sketchy view of the patient as a whole if less than forty minutes is taken over the history, and I am therefore shocked when I hear that there are already too many doctors My view would be that standards of medical practice will deteriorate progressively unless doctors have enough time to consider patients as individuals The implication is that more doctors are required, and that they should each be responsible for a smaller number of patients The total cost of a health service might well be little affected by such a change, for when public and profession had become reorientated in therapeutics, it might save much useless drug therapy and needless absence from work

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I define psychiatric competence as the *ability* to relieve a child's enuresis by discussing with the child's parents—without seeing the child and best without discussing enuresis—their conflicts in important spheres of adjustment To some this definition will appear little short of outrageous I believe that careful examination of the definition leads to important principles in therapeutics I do not expect that doctors will quickly achieve such competence unless their interest be unusual, *but* I do suggest that many, five minutes after a consultation has started, have said to themselves "*only child*" Some no doubt will have gone further, simply because they have become aware, in some way, difficult to define, that a certain sort of person, is talking to them and have allowed a thought to flit through their minds, although the patient has talked only about his palpitation and chest pain, "I wonder has he an enuretic *child*"—and been right!

Present day trends in search for methods of relieving emotional tension and its effects are in certain well defined directions Firstly, and least used, is formal psycho analysis Next come short methods of psycho

therapy, consisting usually in more superficial studies of underlying tensions and perhaps little more than establishment of chronological correlation between stress and effect This is probably the commonest kind of approach Then come methods entirely mechanistic in concept, derived from experimental psychology, popular in limited informed circles and enthusiastically advocated by many completely ignorant of psycho pathology Next come methods which rely entirely on drugs which have either a general sedative effect or for which some special local effect within the nervous system is claimed—a method, of course, often used with another more fundamental approach Then come the very important neurosurgical approaches And finally the possibilities of group therapy appear to be of increasingly wide applicability and effectiveness

In assessing the place and relative values of these different ways of treatment, great difficulties arise at once The formal analysts tell us nothing of their failures and little enough of their successes Their method, as it would seem at present to be defined, makes it impossible that any analyst can treat in a working life time more than an insignificant number of patients Since treatment is recommended to last some five years, and during this period should occupy an hour a day for five or six days each week, any correlation between result and method must be extremely difficult to determine The analysts appear to forget that they are not treating patients in a vacuum All the ordinary impacts of life, all man's normal tendencies to try to do something about his own situation for himself, and all the influences of casual conversation, of reading, or of the psychotherapeutic effect of music and the arts, of worldly success or of emotional contentment, are by no means completely kept away from a patient because he is being psycho analysed Even had I the knowledge so to do, I could not here discuss the place or methods of psycho analysis, and I shall merely say that I agree entirely with Ida McAlpine's (1956) assessment in her Tribute to Freud, emphasising nevertheless a conviction that as a research method it has important and possibly unique contributions to make But clearly, from a practical standpoint, conditions as common as those we are considering can never be routinely treated by classical analysis The conditioning and comparable methods derived from pure psychology seem to me, even if successful in removing symptoms, to be symptomatic therapy, and general objections to exclusively symptomatic treatment apply forcibly to most of these mechanistic methods One feels they are little removed from treatment of the Charcot type of hysterical manifestation by crude suggestion—often enough immediately successful in relieving, for example, a hysterical paralysis, but failing to prevent later continued illness or calamities such as suicide Drug treatment is often a necessary adjuvant, but as a sole method it is in general very disappointing, as a sober recent review by Leiberman and Vaughan (1956) indicates Neuro surgical relief has been of enormous benefit to thousands of patients, but so far, at any rate, it has in the main been used far more in psychotic illnesses and very severe obsessional states, while in psychosomatic problems little experience has been gained

The fields in which group psychotherapy has been used extensively now include many common problems ranging between examples coming squarely into the definition of preventive action and those equally evidently in the domain of curative medicine Slavson (1956), speaking from a wide experience states that it was met with "singular receptivity not only from professionally trained persons or patients but from the general community as well Group psychotherapy uniformly evoked favourable response and unresistive acceptance from the intelligent men in the street, from newspapers, popular magazines and other media of communication, giving testimony to its acceptability" He goes on to say

> "It has been my conviction for many years that while the intelligence of masses cannot be trusted, their intuitive and instinctive responses are unfailing Aggregates weaken the ego and rational understanding but sharpen instincts the term 'group' has always held a special fascination for man partly because his survival in nature was conditioned by association in group life and partly because group living presented the individual with special and arduous difficulties Thus, all appeals to group action in group association command *ipso facto* attention"

You will not need to be reminded of Trotter's celebrated essay (Trotter 1916)

I have only once had the opportunity of examining some thousands of patients referred to me as an anonymous office-holder with unknown predilections and interests, and perhaps only the first thousand of these came fully into this definition At the Military Hospital, York, at the time of Dunkirk, I made a careful analysis of the first thousand patients referred to me, all with "organic" labels Of these I found that 30% had no trace of organic defect and had disabilities which were entirely functional, 40% had some organic signs but had a disability which was wholly functional, while 30% could receive an "organic" label—including, however, in this group peptic ulcer, asthma, and numerous other conditions which, I need hardly say, I placed in the "organic" category with considerable cynicism This "organic" group included 9 patients with post-encephalitic parkinsonism, 6 of whom—the only 6 correctly diagnosed—had been referred to me by a psychiatric colleague recently translated to an academic sphere!

If, as this and many comparable experiences, suggest, more than a third of all human illness contains an emotional element important enough to need recognition in treatment, it may be that the method of group therapy will prove the most practical means of extending psychotherapy on a sufficiently broad scale In contrast with the basic therapeutic principle in individual psychotherapy—the fresh exposure of the patient under more favourable circumstances to emotional situations formerly incompetently handled—in group therapy the environment is more variable, its effect on the patient more intricate, and the therapist's control on environmental factors less complete The simplest group treatment is the explanatory lecture in which the causation and mechanism of symptoms is explained To the friendless and isolated, preoccupied with troubles, it often brings considerable relief to realise in a group setting that many others have to contend with similar disabilities

One of the extraordinary things about group experience is the sharp reminder the therapist receives that words mean different things to different sorts of people, since untutored members of a group will quickly identify with astonishing precision the significance of quite ordinary remarks in group discussion, often to the initial discomfiture of a worker who may have spent hours in individual psychotherapy and missed the significance, in this way group therapy is an important educative method for the therapist The group is a testing place for social reality, for the patients become aware of discrepancies between their fantasies and the feelings they evoke in their fellows So many patients report that they have improved not only in the relief of symptoms but also in social relationships outside the group, and so often does this happen in patients in whom other methods have failed after long trial, that in most important clinics group therapy seems at present to be an extremely interesting approach

An old and much respected friend, Dr Hugh Barber, recently wrote

> "To understand the personality or constitutional make up of our patients is more in the realm of an art It is learned

time To ask whether he considers himself a worrier, or whether his family so judge him, will usually produce a relevant and unemotional response To ask how worry or upset affects him will similarly produce some useful information, although often thought and inquiry from relatives will be needed before even this question can be answered with even partial accuracy, but letting the patient talk and go on talking is the method of choice The hostility induced by Freud's emphasis on sexual aspects of psychogenesis has left a legacy of half-acceptance of his main principles, interpreted in a way that allows only the bizarre and exceptional circumstance to be effective in ætiology, whereas in general the everyday ordinary unsettled difficulties of personal inter-relationships are far more important

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Though many doctors and patients are quite unaware of psychosomatic relationships, some patients have intuitive awareness of quite surprising precision

> The husband of a patient whom I had known for a long time was telling me of his wife's eventual death, and, speaking of his adjustment to circumstances, remarked that he himself had had far less urticaria and paroxysmal tachycardia in the past year He was not my patient, and I had known nothing of these disabilities, but a casual inquiry produced the striking answer that he knew that his urticaria was an invariable response to grief, and, so far as he had determined, to no other circumstance, while the paroxysmal tachycardia was always produced by anger and by nothing else

The individual's pattern of reaction to a given emotion may well be constant for a short or long period, but in another patient the same reaction may be caused by quite a different circumstance This view is well illustrated by some recent experience with patients with psoriasis

I do not myself practice, and know only too little of, dermatology, but for some time I have had the habit of asking a patient who happens to have psoriasis, always at the end of a consultation—whether he has any views about its cause Four consecutive patients have attributed exacerbations of their psoriasis to emotional stress The first had found a feeling of injustice would be responsible within twelve to twenty four hours for fresh lesions, the second found her skin react to upset about illness in others within twenty four hours, a third correlated it precisely with pleasurable marital sexual experiences, while the fourth had discovered that pleasurable planning of business activity, while awake at night, was similarly responsible I have described these patients in a little more detail recently and also enlarged on the theme of how to get the information from the patient (Phillips 1956)

A delightful and significant experiment, entitled The Patient Sits Down, is described by White (1953) who, in a cardiological practice, noted how patients seated themselves in his consulting room He distinguished between patients who promptly sat down and leaned back in the chair, and those who sat on the edge of the chair, drew the chair close to the desk, and then sat down on the edge of the chair, or who drew the chair close to the desk, sat down on the edge of the chair, leaned forward, and rested the elbows on the desk He then studied whether removing the desk, so that no physical barrier existed between him and the patient, would have any effect on their seating habits He made the interesting observation that over 50% of patients sat at ease when there was no desk, in contrast with about 10%, when a desk was present Subsequent inquiries from individual patients suggested that this apparently trivial procedure produced not only a feeling of increased ease but also increased recollection of details previously forgotten about illnesses

It is difficult in a busy day to avoid the temptation to cut a patient short and to arrive at an opinion on too short a history and an adequate physical examination My experience is that one can seldom obtain even a sketchy view of the patient as a whole if less than forty minutes is taken over the history, and I am therefore shocked when I hear that there are already too many doctors My view would be that standards of medical practice will deteriorate progressively unless doctors have enough time to consider patients as individuals The implication is that more doctors are required, and that they should each be responsible for a smaller number of patients The total cost of a health service might well be little affected by such a change, for when public and profession had become reorientated in therapeutics, it might save much useless drug therapy and needless absence from work

* * *

I define psychiatric competence as the ability to relieve a child's enuresis by discussing with the child's parents—without seeing the child and best without discussing enuresis—their conflicts in important spheres of adjustment To some this definition will appear little short of outrageous I believe that careful examination of the definition leads to important principles in therapeutics I do not expect that doctors will quickly achieve such competence unless their interest be unusual, but I do suggest that many, five minutes after a consultation has started, have said to themselves "only child" Some no doubt will have gone further, simply because they have become aware, in some way, difficult to define, that a certain sort of person, is talking to them and have allowed a thought to flit through their minds, although the patient has talked only about his palpitation and chest pain, "I wonder has he an enuretic child"—and been right!

Present day trends in search for methods of relieving emotional tension and its effects are in certain well defined directions Firstly, and least used, is formal psycho analysis Next come short methods of psycho

therapy, consisting usually in more superficial studies of underlying tensions and perhaps little more than establishment of chronological correlation between stress and effect This is probably the commonest kind of approach Then come methods entirely mechanistic in concept, derived from experimental psychology, popular in limited informed circles and enthusiastically advocated by many completely ignorant of psychopathology Next come methods which rely entirely on drugs which have either a general sedative effect or for which some special local effect within the nervous system is claimed—a method, of course, often used with another more fundamental approach Then come the very important neurosurgical approaches And finally the possibilities of group therapy appear to be of increasingly wide applicability and effectiveness

In assessing the place and relative values of these different ways of treatment, great difficulties arise at once The formal analysts tell us nothing of their failures and little enough of their successes Their method, as it would seem at present to be defined, makes it impossible that any analyst can treat in a working lifetime more than an insignificant number of patients Since treatment is recommended to last some five years, and during this period should occupy an hour a day for five or six days each week, any correlation between result and method must be extremely difficult to determine The analysts appear to forget that they are not treating patients in a vacuum All the ordinary impacts of life, all man's normal tendencies to try to do something about his own situation for himself, and all the influences of casual conversation, of reading, or of the psychotherapeutic effect of music and the arts, of worldly success or of emotional contentment, are by no means completely kept away from a patient because he is being psycho analysed Even had I the knowledge so to do, I could not here discuss the place or methods of psycho analysis, and I shall merely say that I agree entirely with Ida McAlpine's (1956) assessment in her Tribute to Freud, emphasising nevertheless a conviction that as a research method it has important and possibly unique contributions to make But clearly, from a practical standpoint, conditions as common as those we are considering can never be routinely treated by classical analysis The conditioning and comparable methods derived from pure psychology seem to me, even if successful in removing symptoms, to be symptomatic therapy, and general objections to exclusively symptomatic treatment apply forcibly to most of these mechanistic methods One feels they are little removed from treatment of the Charcot type of hysterical manifestation by crude suggestion—often enough immediately successful in relieving, for example, a hysterical paralysis, but failing to prevent later continued illness or calamities such as suicide Drug treatment is often a necessary adjuvant, but as a sole method it is in general very disappointing, as a sober recent review by Leiberman and Vaughan (1956) indicates Neurosurgical relief has been of enormous benefit to thousands of patients, but so far, at any rate, it has in the main been used far more in psychotic illnesses and very severe obsessional states, while in psychosomatic problems little experience has been gained

The fields in which group psychotherapy has been used extensively now include many common problems ranging between examples coming squarely into the definition of preventive action and those equally evidently in the domain of curative medicine Slavson (1956), speaking from a wide experience, states that it was met with "singular receptivity not only from professionally trained persons or patients but from the general community as well Group psychotherapy uniformly evoked favourable response and unresistive acceptance from the intelligent men in the street, from newspapers, popular magazines and other media of communication, giving testimony to its acceptability" He goes on to say

> "It has been my conviction for many years that while the intelligence of masses cannot be trusted, their intuitive and instinctive responses are unfailing Aggregates weaken the ego and rational understanding but sharpen instincts . the term 'group' has always held a special fascination for man partly because his survival in nature was conditioned by association in group life and partly because group living presented the individual with special and arduous difficulties Thus, all appeals to group action in group association command *ipso facto* attention"

You will not need to be reminded of Trotter's celebrated essay (Trotter 1916)

I have only once had the opportunity of examining some thousands of patients referred to me as an anonymous office-holder with unknown predilections and interests, and perhaps only the first thousand of these came fully into this definition At the Military Hospital, York, at the time of Dunkirk, I made a careful analysis of the first thousand patients referred to me, all with "organic" labels Of these I found that 30% had no trace of organic defect and had disabilities which were entirely functional, 40% had some organic signs but had a disability which was wholly functional, while 30% could receive an "organic" label—including, however, in this group peptic ulcer, asthma, and numerous other conditions which, I need hardly say, I placed in the "organic" category with considerable cynicism This "organic" group included 9 patients with post encephalitic parkinsonism, 6 of whom—the only 6 correctly diagnosed—had been referred to me by a psychiatric colleague recently translated to an academic sphere!

If, as this and many comparable experiences, suggest, more than a third of all human illness contains an emotional element important enough to need recognition in treatment, it may be that the method of group therapy will prove the most practical means of extending psychotherapy on a sufficiently broad scale In contrast with the basic therapeutic principle in individual psychotherapy—the fresh exposure of the patient under more favourable circumstances to emotional situations formerly incompetently handled—in group therapy the environment is more variable, its effect on the patient more intricate, and the therapist's control on environmental factors less complete The simplest group treatment is the explanatory lecture in which the causation and mechanism of symptoms is explained To the friendless and isolated, preoccupied with troubles, it often brings considerable relief to realise in a group setting that many others have to contend with similar disabilities

One of the extraordinary things about group experience is the sharp reminder the therapist receives that words mean different things to different sorts of people, since untutored members of a group will quickly identify with astonishing precision the significance of quite ordinary remarks in group discussion, often to the initial discomfiture of a worker who may have spent hours in individual psychotherapy and missed the significance, in this way group therapy is an important educative method for the therapist The group is a testing-place for social reality, for the patients become aware of discrepancies between their fantasies and the feelings they evoke in their fellows So many patients report that they have improved not only in the relief of symptoms but also in social relationships outside the group, and so often does this happen in patients in whom other methods have failed after long trial, that in most important clinics group therapy seems at present to be an extremely interesting approach

An old and much respected friend, Dr Hugh Barber, recently wrote .

> "To understand the personality or constitutional make up of our patients is more in the realm of an art It is learned

by experience which begins with sympathy and understanding rather than with theory and preconceived ideas

"It may be unfortunate scientifically but in practice it is common sense which will help our patients if we study their personalities in thought rather than in words The time is not yet come, and possibly it never may, when the whole of medical practice is based on exact science" (Barber 1956)

He will not take it amiss, I feel certain, if I comment that this can be criticised in that knowledge of human constitution is already usefully formalised by the studies of W H Sheldon (1940, 1942) and his school, which, while by no means removing the art from the physician's appraisal, teaches the inexperienced methods of distinguishing differences between individuals The studies of Sheldon and his associates on human temperament and human physique afford a most important and suggestive group of studies in constitutional differences

Their original thesis was that if human beings could be described in terms of their most deep seated "similarities and differences, it might prove not impossible to differentiate between heredity and the effects of environment" In the study of temperament, they started with 650 alleged traits of temperament which they reduced finally to a short list of 60 traits which seemed to incorporate all the *ideas* in the 650 All could be defined in the sense of having an opposite, and the individual traits were expanded to a 7 point graphic rating scale An initial survey of 20 students studied analytically for a year and all observed repeatedly in social settings in the same period with notes made on informal occasions and in analytical sessions, afforded a pilot study for a full scale appraisal of personality variation in university students

They distinguished three main groups of temperament which they called viscerotonia, somatotonia, and cerebrotonia The emphasis in the first group seemed to be on the gut, in the second on muscle and activity, and in the third on concentration and attention The degree in which each element could be identified in individuals was assessed

I would place both this study of temperament and the study of physique almost as obligatory reading for the informed doctor

* * *

The years since 1906 have seen a bewildering advance in the understanding of the complexities of biochemistry As to the metabolic activity of the proteins of the brain, for example, Gaitonde and Richter (1956) say that the evidence

" leads to the conclusion that the proteins of the brain *in vivo* are in a state of rapid dynamic change The half life of the methionine bonds in the brain proteins of about fourteen days, implies a half life of less than one day for a whole protein molecule of 80,000 molecular weight containing 15 methionine units If similar considerations are applied to the bonds of the 20 other amino acids and to the labile bonds of the phospholipid units in the lipoproteins, it would appear that the half life of some at least of the lipoproteins, which are the main organic constituents of the brain, must be of the order of seconds rather than days This may be relevant to the problem of the engram, or the permanent trace that is left when nerve tissue is stimulated"

It is clear from this sort of work that it will be the enzyme chemists, those interested in the cell and its anatomy, physiology, and pathology, and ultimately the quantum biologists, who will discover the mechanism of memory, for submolecular events are at work It is extraordinary how often some hitherto ignored or unknown substance has come to assume striking biological importance Interaction between most of these and substances now long studied in the physiology of the pituitary gland and associated neural areas has been almost always shown to occur There seems to be almost a rule that there is the potentiality at least of central control over the most remote peripheral mechanisms, a circumstance perhaps most clearly shown by Verney's demonstration of osmoreceptors (1947) and by his work on the effects of emotion on urinary secretion (1946)

An example of a substance whose importance has been relatively recently and still only partially appreciated is 5 hydroxytryptamine, of particular interest to the cardiologist since for the first time a relatively simple substance appears to be responsible for a valve lesion The right sided cardiac lesions apparently produced by the high blood levels of circulating 5 H T released from gut or hepatic argentaffinomata are themselves of profound interest The nature of the endocardial response produced suggests intriguing possibilities, especially when one considers that chemically 5 H T is related to plant growth hormones, that it is found in platelets and in concentration in the centrencephalon, that it is also released with the clotting of blood, and that it may be responsible for the fatal vasoconstriction of pulmonary embolism, renal cortical necrosis, and important effects on circulatory hæmodynamics both generally and locally in renal and coronary circuits No sufficient explanation of the usual localisation of rheumatic valve damage to the left side of the heart and the relatively unusual involvement of the valves of the right chambers has ever been found, and such explanation should also show why it is that the right sided lesions occur only in patients in whom there is also severe left sided damage It now seems less odd to me that when I first heard before the war that Flanders Dunbar (1943) and her associates were contrasting, from the point of view of their personality and make up, patients with rheumatic heart disease with those suffering from a variety of other disorders The idea then partly incomprehensible and partly fantastic now seems a little less outrageous

All the substances so far known to have profound local influences are capable of influence as to their amount and production by central events, and speculations could be continued in many directions for it is clear, as Dale (1943), and Page and McCubbin (1956), indicate, that much more will be discovered about this highly significant chemical

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In 1918 Freud wrote a paper, Should Psychoanalysis be Taught at the University? He considered and advocated the advisability from two points of view—that of psycho-analysis and that of the university My own university regards a chair of mental health as a most urgent requirement Pressure comes most strongly from those university teachers and members of governing bodies who have seen tragic consequences of medical ignorance of psychology and psychiatry and also have witnessed remarkable results from highly skilled psychiatry Putnam (1899) in his famous Shattuck lectures, entitled Not the Disease Only but also the Man, made the point that "the physician is an educator," and goes on

"We all hear of the triumphs of surgery, and every doctor feels a personal pride in spreading the news of them abroad but there are not so many who know that there are men, as yet few in number, but of equal genius, who with equal devotion and study have been searching for means to change little by little the trend of the forces that work in the mind and are thus silently laying the foundations of a new departure in therapeutics This is education of a high order but such studies as these must yield conclusions that the well trained doctor will find useful in his daily practice The doctor is most obviously an educator in dealing with the training of children To learn to do this sort of thing, to speak and comprehend the mental language of all sorts and conditions of men, is one of the many important tasks which the physician will in time learn to perform"

Putnam considered "a thorough preliminary course in psychology and philosophy far above a knowledge of botany or zoology, and following close on chemistry and physics, in the preparation for the work of the general practitioner"—and this fifty seven years ago In my view, a university without a chair of mental health fails to recognise the paramount importance of knowledge of this subject in the education of all who have to deal with people either in work, in the family, in schools or other experience Only one university, as far as I know (that of British Columbia), has a chair of psycho analysis, but it is noteworthy that the North American universities have the most lively regard for the importance of mental health and education, and Dame Olive Wheeler, who has spent recent vacations lecturing at a number of them on these topics, tells me that the interest and critical appreciation of her audiences are outstanding One looks forward to the time when all faculties and all teachers at every level of education will have a common meeting place in university departments of mental health staffed with people representing many approaches and disciplines, and not bound to rigid doctrinaire systems

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Medicine has to consider itself in the social setting of its time and I would think no one is more aware than a doctor of the changes in every aspect of life in the past fifty years The rate of change has been such that the situation for the practising doctor has become truly frightening His is the only profession in almost universal direct contact with the general public, and any thinking doctor will be aware that, if he has been qualified five years and has not been reading regularly, he is distinctly out of date In my view, if he has been qualified ten years and has not read regularly, he is dangerously uninformed The situation of anyone who left medical school twenty years ago and is still working on the teaching he received as a student without postgraduate education from journals, books, or meetings, is, unless he be a very unusual man, almost medieval as far as important parts of medical practice are concerned The rate of change is increasing and if Sarnoff (1956), for example, is correct—and I see no reason to doubt the general validity of his suggestion—the next twenty years will see the events of the past fifty years completely eclipsed by such advances as the availability of nuclear and solar energy, automatic instantaneous translation of languages, television in world-wide interindividual communication, revolution in all forms of aerial transport, beneficent automation, vast arrays of new synthetic materials, new sources of food and new methods of expanding harvests, new forms of electronic light to remove perils of night driving and flying, wide extension of the use of computors in recording and accounting, improved weather forecasting and even climatic control, universal education, a revival in religion, outlawry of war, and an avalanche of improvements in preventive medicine and the probable extension of human life span to almost a century Few would assert that many of these items will seem imaginative in twenty years' time The forecast is, perhaps, a little more precise than some would allow, but Sir George Thomson's *Foreseeable Future* (1955) does not differ very materially from it I am glad to see that Thomson believes "the old ways of thought inherited from the Greeks and Hebrews and modified at the Renaissance will gradually change" For me it is a matter of amazement that intelligent people should still consider there has been the slightest proof for the thesis that a classical education trains the mind in some unique fashion

The task of the practising doctor is already frighteningly complex, but if emotional factors already clearly determined in many frequent and important chronic disorders are also found of causative or other significance in diseases now thought to be the archetypes of "organic," then indeed will clinical differentiation become a nightmare unless medical education has changed fundamentally its bias against systematic knowledge of the workings of the mind, its ignorance of the constitution of emotions, and its discreditable running away from reality

The rate of change in the world is such that the famous comment of the author of the *Instincts of the Herd in Peace and War*, who for so unhappy a reason must be much in mind at present, is especially apposite "Conservatism then is functional in a practical art, but let this fact remind us that in science it is necessarily meaningless and always and wholly harmful" I suggest that before one dismisses mental factors in the ætiology of disease as the irrelevant irresponsible vapourings of the uncritical, attention be given to studies such as those of Guetzkow (1951), Asch (1951, 1952, 1955), and Miller and Dollard (1941) on the effects of group and social pressure on opinions, for these are significant and disturbing and highly relevant in their implications In all these matters, the view expressed when the Duke of Edinburgh at his conference last July, emphasised the place of humility and respect in interpersonal relationships of all kinds, must surely stand the test of time

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Medicine before long will be faced with a public demanding a drug or alternative treatment for every discomfort, in the literal sense of the word, which may occur in life People are preoccupied with ends and not means Anxiety about security in home, work, social status, and national security is reaching pathological proportions, and every change in industrial method or material, in forms of energy or even astronomical theory, produces fresh hysterical herd reactions—for most of science and scientific changes are incomprehensible to the masses, and equally frightening Are we as a profession in general clearer in our views on mental health and the treatment of mental illnesses than we were three hundred years before Sherrington's Silliman Lectures? In *Macbeth* Shakespeare's physician is seen to be a cautious doubting man preferring the evidence of his own senses to the reports of others, competent in case-recording—even forestalling *Alice Through the Looking Glass* ("the horror of that moment," the King said, "I shall never never forget" "Oh yes you will," the Queen said, "unless you make a memorandum of it"), aware that sleep-walking can be due to nervous disturbance from ordinary as well as from bizarre happenings, and very conscious of the risks of suicide At the same time, with many a modern doctor, he suggests it is either for the Church or for the patient to deal with the problems of mental health, and, in the last resort, how like he is to most of us who prefer someone else to deal with the problems of mental health in our patients

Where then do Sherrington and Freud come closest together—the one philosopher and poet, as well as in Fulton's words "the most profound student of the nervous system the world has yet known," and the other initially biologist and neurologist, the main architect of our beginning understanding of the mind? The final sentences of *Man on his Nature* seem to me relevant and most noble words .

> "Natural knowledge has not forgone emotion It has simply taken for itself new ground of emotion, under impulsion from and in sacrifice to that one of its 'values,' Truth Its view of the world and of itself is based upon the purview of what by its lights it can accept as true In that way much that is comfortable in other religions lapses If you will, man's situation is left bleaker One feature of that situation is that the human mind such as it is, is left the crown of mind to which human life in all its needs has direct access Compared with a situation where the human mind beset with its perplexities had higher mind and higher personality than itself to lean on and to seek counsel from, this other situation where it has no appeal and no resort for help beyond itself, has an element of tragedy and pathos Ours is a situation which transforms the human spirit's task, almost beyond recognition, to one of loftier responsibility It elevates that spirit to the position of protagonist of a virility and dignity which otherwise the human figure could not possess It raises the lowliest human being conjointly with the highest, Prometheus like, to a rank of obligation and pathos which neither Moses in his law giving nor Job in all his suffering could surpass We have, because human, an inalienable prerogative

of responsibility which we cannot devolve, no, not as once was thought, even upon the stars We can share it only with each other "

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" boys and girls whose precociousness suggests that they are likely winners of scholarships, are taken as young as possible and crammed with specialist knowledge like geese The harmful effects of this system are twofold In the first place, the late developer is penalized If, as I believe, the evolution of man from his sub human ancestors has largely been achieved by progressive delay in development, prolongation of childhood and retardation of maturity, the premium which we place on precociousness works directly against the processes which have made man what he is and may make him into *Homo sapientior* It is certainly to the good that there should be provision for rewarding the precocious, but surely not to the point where scholarships will be awarded to babies if they can converse before they are two years old, From their performance when at school it is clear that neither Newton nor Darwin would have won scholarships on our existing system, and that is serious

" The second harmful result of precocious specialization is that general subjects are displaced from a boy's or girl's education, perhaps for ever The effect of this bears more heavily on science than on the humanities, because if a boy spends in dissecting the dogfish and frog the time when he might be acquiring a grounding in English by the most critical method, which is by means of latin prose, it will be increasingly difficult for him to go back afterwards and make up for what he missed On the other hand, the boy who has had a grounding in the humanities is in the fortunate position that he can at any time broaden himself by simply walking into a laboratory, if only he will In my experience that is the source of the best scientists of all Incidentally, this is my contribution to the problem of increasing the supply of scientists, for there is no need to wait until all the schools have science masters, and fully equipped laboratories, if the universities will make scientists of students with a good general education "—MR GAVIN DE BEER in the Rickman Godlee lecture for 1956 delivered at University College Hospital

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RHEUMATOID ARTHRITIS WITH CHRONIC LEG ULCERATION

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A GROUP of six patients with unusually chronic ulceration of the leg associated with a rheumatoid type of arthritis is here described Reasons are given for regarding these as manifestations of disseminated lupus erythematosus

Case-reports

Case 1 —A housewife, then aged 28, began to develop rheumatoid arthritis in 1950, 2 months after an attack of salpingitis which had settled down after treatment with penicillin and sulphonamides In 1952 she had a rash on the upper part of the front of her chest, 3 weeks after starting gold therapy 3 weeks later, the rash having subsided, gold injections were re started and continued for 14 weeks, when they were discontinued owing to the reappearance of the rash This subsided within 2 weeks of stopping the injections In 1954 subcutaneous swellings began to appear on the backs of her elbows During the period March, 1954, to March, 1955, she received two courses of bee sting therapy applied to the skin overlying her affected joints In June, 1955, an ulcer began to develop on each ankle, and in February, 1956, she had dry pleurisy lasting a week

Examination —In April, 1956, she was underweight (6 st 10 lb) and crippled with rheumatoid arthritis, many subcutaneous "rheumatoid" nodules were present on the extensor surfaces of her arms and over her scapulæ There was a clean-based ulcer 7 5 × 5 5 cm on the outer side of her right ankle and one 3 × 2 5 cm on the outer side of the left ankle The finger nail folds showed many elongated telangiectases

Investigations —Urine deposit—a few red cells and white cells Culture sterile Blood urea 27 mg per 100 ml Urea clearance 50% and 31% of normal Intravenous pyelogram normal Blood counts showed persistent hypochromic anæmia White cell counts normal Blood for lupus erythematosus (L E) cells strongly positive Plasma proteins 7 8 g per 100 ml (albumin 3 5 g, globulin 4 3 g) Electrophoretic pattern raised γ globulin and α_2 globulin Blood Wassermann reaction negative

Progress —The smaller ulcer healed in 7 weeks with bed rest and local treatment The larger ulcer healed only after pinch grafting, but 12 weeks later it broke down and the whole graft was lost At the same time a fresh ulcer appeared just below the outer side of the left knee

Case 2 —A housewife, then aged 51, first developed symptoms of rheumatoid arthritis in 1943 From 1951 to 1954 she was treated with courses of phenylbutazone and gold In 1953 nodules appeared over her elbows, and early in 1955 an ulcer developed on her left ankle

Examination —In February, 1955, she was obese and crippled with rheumatoid arthritis, with "rheumatoid" nodules on the backs of the arms and hands An ulcer 10 × 6 cm was present on the outer side of the left ankle and one about 2 cm across on the medial side of the base of the left first toe X ray examination of the chest showed an area of segmental collapse at the right base which persisted in spite of active treatment In May and October she had two attacks of constant lower abdominal pain associated with nausea and vomiting, and a temperature of 101°F on one occasion, apart from slight tenderness, no other abnormal findings were made clinically or radiologically In August she had an attack of loss of consciousness lasting 2 minutes While lying in bed she became cyanosed but there was no clonic phase and she was not incontinent On recovery she complained of severe right sided headache Heart and central nervous system were subsequently normal, as were the electro encephalogram and skull X ray films

Investigations —Urine normal Blood counts showed constant hypochromic anæmia and leucopenia Blood for L E cells strongly positive on two occasions and negative on two A positive finding was not associated with any exacerbation of her condition Plasma proteins 7 7 g per

100 ml. (albumin 3·8 g., globulin 3·9 g.). Electrophoretic strip showed a raised α_2 globulin and a slightly raised γ globulin. Wassermann reaction negative.

Progress.—No healing at all could be induced in these ulcers in spite of 9 months in hospital. Grafting failed, as did local injections of hydrocortisone. Systemic steroid therapy was not given owing to her age, and the marked osteoporosis resulting from her immobility.

Case 3.—A man first developed symptoms of rheumatoid arthritis in 1947, at the age of 40. In 1949 he had dermatitis following two courses of gold injections. In the same year an ulcer developed on the outer side of his right ankle, and in 1954 on the medial side of his right first toe. Also in 1954 nodules appeared over his elbows. In June, 1955, he was found to have left-sided papillœdema and right-sided optic atrophy. At the time it was thought that this might be secondary to a toxic hydrocephalus, either in association with the arthritis, or due to phenylbutazone.

Examination.—In December, 1955, he had crippling rheumatoid arthritis, "rheumatoid" nodules over the elbows, and a clean based ulcer 5 × 6 cm. over the outer side of the right ankle and one about 1 cm. across over the medial side of the right first toe.

Investigations.—Urine normal. Persistent normochromic anæmia. White cells normal. Blood for L.E. cells positive. Plasma proteins 6·9 g. per 100 ml. (albumin 4·4 g., globulin 2·5 g.). Electrophoretic pattern showed a raised α_2 globulin. Wassermann reaction negative.

Progress.—No change in the appearance of the ulcers during 2 weeks in hospital.

Case 4.—A lorry driver developed symptoms of rheumatoid arthritis in 1946 at the age of 40. In 1952 nodules appeared over the elbows, and in October, 1955, an ulcer developed on the right lower leg. Previous treatment for the arthritis included gold, phenylbutazone, and corticotrophin (A.C.T.H.), with no recorded drug eruption.

Examination.—In December, 1956, he had gross arthritis with rheumatoid nodules and a clean-based ulcer 2·5 cm. in diameter over the medial side of his right lower leg. All tendon reflexes were brisk, with bilateral extensor plantar responses. There was superficial sensory loss over the dorsum of the left foot. Cerebrospinal fluid was normal. X-ray films of the cervical spine showed spondylosis, but those of the lumbar spine showed no abnormality. Dr. R. Gilliatt considered that the neurological findings were probably due to the patient's cervical spondylosis.

Investigations.—Persistent microscopic hæmaturia. Renal function tests and pyelogram normal. Cystoscopy by Mr. E. W. Riches showed hyperæmia of the prostatic urethra of sufficient degree to account for the hæmaturia. Blood count normal. Blood for L.E. cells negative on eight occasions. Plasma-proteins 6·1 g. per 100 ml. (albumin 3·4 g., globulin 2·7 g.). Electrophoretic pattern showed grossly raised α_2 globulin.

Progress.—There was no healing on bed rest and local applications alone. Healing began and continued slowly to completion over 12 weeks on daily corticotrophin (A.C.T.H.) gel intramuscularly.

Case 5.—A housewife first developed symptoms of rheumatoid arthritis at the age of 20 in 1934. She had gold dermatitis in 1935. A severe relapse of her arthritis followed pregnancy in 1943 and about the same time nodules began to appear on the backs of her hands and elbows. In 1953 an ulcer rapidly developed over her left ankle. The following year she developed soreness of the eyes and has since been under Mr. Derek Ainslie's care for the treatment of episcleritis and scleritis.

Examination.—In April 1954, she had very severe arthritis, "rheumatoid" nodules over the elbows and backs of hands and a clean based ulcer 10 × 9 cm. over the medial side of her left ankle.

Investigations over the years 1952 to 1956 have shown recurrent urinary infections. Pyelogram normal. Blood counts have shown a persistent normochromic anæmia. White cells normal. Blood for L.E. cells negative on the one occasion tested. Electrophoretic pattern showed raised α_2 globulin. Wassermann reaction negative.

Progress.—Two attempts at grafting in July and August, 1953 failed. No local treatment was of any avail. The ulcer eventually healed in March 1956 4 weeks after beginning oral cortisone. 2 weeks later, however, a fresh ulcer developed on the medial side of the left ankle. This ulcer was still present in September, 1956, in spite of continued oral cortisone (25 mg. b.d.).

Case 6.—This man, then aged 45, first developed symptoms of rheumatoid arthritis in 1945. In 1947 he had nodules over the left elbow for 6 months. At the time he was told that they were "rheumatoid." Raynaud's phenomena in the hands and feet began in 1952. In 1953 he had gold dermatitis and in April 1954, an ulcer appeared on the medial side of the right ankle.

Examination.—In November, 1954, he had severe arthritis, dusky erythema, and telangiectases at the bases of the finger-nails, and a clean based ulcer 2·5 cm. in diameter over the medial side of the right ankle.

Investigations.—Urine deposit: occasional red cells on admission; subsequent deposits normal. Blood counts showed mild hypochromic anæmia. Blood for L.E. cells (November, 1954) negative; (September, 1956) positive. Plasma-proteins 6·0 g. per 100 ml. (albumin 3·6 g., globulin 2·4 g.). Electrophoretic pattern showed a raised α_2 globulin.

Progress.—The ulcer slowly healed over 12 weeks' treatment in hospital, during which time he received hydrocortisone subcutaneously into the base of the ulcer (25 mg. twice weekly).

Histology of the Ulcers

Biopsies were made in cases 1, 2, 5, and 6. They may be considered together.

The histological features were best shown by the biopsy specimen from the edge of the deep ulcer in case 5. At the margin of the ulcer its floor was formed by inflammatory vascular granulation tissue, but this soon gave place to necrotic tissue which extended in places to the deep limits of the specimen, which was 0·75 cm. thick. Irregular band-like areas of necrosis of the fibro-fatty subcutaneous tissue and dermis extended some distance beneath the apparently intact skin, and the presence of necrotic tissue at the deep limit of removal of the specimen made it hardly surprising that grafts failed to take over the ulcer. The necrotic areas, though so extensive and involving fatty tissue in addition to collagen, had at their margins palisaded rows of elongated histiocytes characteristic of the nodules of rheumatoid arthritis. Necrotic fat cells were seen in places surrounded by histiocytes or foam cells, and a few giant cells were present. In the areas intervening between necrotic zones there was considerable fibroblastic proliferation and infiltration with lymphocytes and plasmacytes. Smaller biopsies from the ulcer floor of this patient at a later stage showed only non-specific chronic inflammatory changes with a granulation lining to the ulcer.

Small biopsies from the margin of the ulcerated area in cases 1, 2, and 6 showed necrotic collagen bounded by a palisade of histiocytes and fibroblasts together with occasional giant cells flooring the ulcer, but without any extensive necrosis in the deeper tissues.

Discussion

We have been struck by the similarity of the clinical pictures presented by these six patients. All had severe, crippling and apparently typical rheumatoid arthritis with many subcutaneous nodules; and the appearance of the ulcers was so uniform that, after seeing the first few patients, we felt that cases could be recognised by an examination of the ulcer alone.

In most cases the ulcers were on the lower third of the leg either on the inner or on the outer surface; in one case the upper part of the leg, just below the knee was involved and in another the toe and foot. We have not been able to witness the onset, but it seems that the earliest sign is a painful induration about 1 cm. across, which in the course of a week or two breaks down to form a punched out ulcer. In case 1 an ulcer 3 weeks old was already deeply punched out, about 1·5 cm. across, with smooth regular edges. There was no slough and the floor appeared to be formed by the subcutaneous tissue. Around the ulcer was a dark red flush extending about 3 cm, with very little palpable induration and no surrounding œdema Larger ulcers retain these characteristics The largest have been 10 cm across, always with smooth even outlines The floor is uneven, with a varying amount of whitish slough which can usually be easily removed, and comparatively little pus Granulations do not form readily Surrounding erythema and induration are not prominent, and subcutaneous œdema is slight or absent Pain is a constant feature, sometimes severe

Varicose veins, antecedent phlebitis, and other evidence of vascular stasis in the legs, were not found In only one of these patients did the ulcer heal with rest in bed and local treatment with antiseptics or antibiotics, and it seemed clear that neither local infection nor vascular stasis was playing an essential part The leg pulses and the skin-temperature were normal

Laine and Vainio (1955) reported twelve cases of skin ulceration among about two thousand patients with arthritis Their description of torpid ulcers resulting from breakdown of a cutaneous nodule fits in with our observations, but they do not seem to have been struck by any other features in their cases Skin ulceration is not a recognised feature of rheumatoid arthritis and in all our cases further investigation has yielded more information In four of the six, L E cells have been found in the peripheral blood, four have had drug eruptions in the past, a multitude of other symptoms of great variety were all compatible with the diagnosis of disseminated lupus erythematosus

The distinction between rheumatoid arthritis and disseminated lupus erythematosus is perhaps not so clear or so valid as terminology would imply, on the other hand, the diagnosis of disseminated lupus erythematosus covers a wide variety of clinical syndromes There is a great deal of difference between our cases and the more acute syndromes with skin eruptions, grave systemic upset, and a high mortality, even though the underlying pathological mechanism may be closely similar Harvey et al (1954), in a comprehensive review, do not include skin ulceration of this kind as a feature of disseminated lupus erythematosus All our patients had "rheumatoid arthritis" as their severe and dominating feature, all are running a chronic course, and only in case 2 has the general health been much affected This seems to indicate a relatively benign and slow progress of the disorder Our view that the skin ulceration is a part of the general illness is supported by its failure to improve with ordinary local treatment and by the recovery which followed steroid therapy in three patients

The mechanism of the ulceration is not certain Laine and Vainio suggest that the ulcers result from the breakdown of rheumatic nodules, but this does not seem to be so in our cases We did not find any notable induration in the base of the ulcers, and in no case had the patient been aware that a subcutaneous nodule of the usual type preceded the ulcer In case 2 several ordinary rheumatic nodules had broken down, discharging on the surface through a small slit-like sinus, and sufficed to emphasise the different picture thus produced Histological studies suggest that collagen necrosis may be the primary lesion, it may be of course that the primary lesion in the skin is the same as that which originates a rheumatic nodule in the deeper tissues, forming an ulcer in the one case and a proliferative tissue reaction in the other Our histological findings are compatible with this explanation, but evidently more biopsies, preferably of early lesions, are required It is noteworthy that all our patients had many subcutaneous nodules this is perhaps of significance since most series of rheumatoid arthritis give a frequency for nodules of no more than about 20% of cases

That we have observed six cases of this kind in the space of 2 years suggests that they are not extremely uncommon In view of their site it may well be that they are usually regarded as due to vascular stasis to which the immobility produced by arthritis contributes We believe, however, that though vascular stasis may play a minor part in producing the lesion, the distinction from ulceration due to stasis can be clearly drawn by the absence of all evidence of venous stasis and the failure, usually, of the ulcers to make any notable response to rest in bed The distinction is an important one, partly because of the disseminated character of the underlying disease, partly because of the entirely different treatment requirements Steroid therapy, which regularly produces a response in disseminated lupus erythematosus, is probably the only measure likely to help the ulcers

In three cases we were particularly struck by the failure of grafting These were all granulating satisfactorily and appeared to be ideally suitable, so that the failure of grafting was surprising It perhaps suggests that auto-antibodies may be responsible for the destruction of the graft, on the other hand, histological examination suggested that the grafts failed because an ulcer which appears to be granulating well still has necrotic collagen in its base

Summary

Six patients are described, in all of whom a rheumatoid type of arthritis was followed by painful ulceration of the leg Further observation permitted the diagnosis of disseminated lupus erythematosus

Owing to the multi faceted clinical picture shown by these cases, they have been seen by many members of the staff of the Middlesex Hospital Thanks are due to them for permission to extract details from their records and particularly to the staff of the Bland Sutton Institute of Pathology and the Courtauld Institute of Biochemistry for their work on the special investigations

Cases 1, 2, and 6 were shown at a meeting of the dermatological section of the Royal Society of Medicine on Oct 18, 1956

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STEVENS-JOHNSON SYNDROME

A REPORT OF FIVE CASES AND A DISCUSSION ON ÆTIOLOGY AND TREATMENT

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THOUGH much has been written about erythema multiforme exudativum (Stevens Johnson syndrome) the ætiology is still in doubt, and the efficacy of treatment is by no means established Five cases are here presented, four of which I saw in the medical wards of two hospitals, the fifth was not seen, but her records were found in reviewing cases of erythema multiforme in one of these hospitals They are reported for the following reasons

(1) Two cases were fatal—an uncommon outcome

(2) In one case necropsy and microscopic examination revealed changes not previously described

(3) The difficulties of ascribing this (or indeed any) condition to drug allergy are demonstrated

(4) The difficulties of ascribing curative properties to any drug, and the tendency to repeated self limited attacks with eventual complete remission, are illustrated

Case-reports

FIRST CASE

A motor driver and oil storeman aged 25 was admitted to hospital on Nov 24, 1949, complaining of pain in the left side of the chest and productive cough for 8 days He had been off work for 4 weeks because of a severe "chest cold"

This had apparently cleared up, and he had been up and about for a few days when he developed the pain in his chest, which was pleuritic Since then a troublesome cough had appeared, with copious pinkish sputum On the day before admission, the pain in the left chest was replaced by an aching pain across the front of the chest, not aggravated by deep breathing or coughing His nose had been blocked, and had bled several times He had no other symptoms His previous health had been good, he had never been given sulphonamide drugs, and there was no personal or family history of allergy His father had died of "nephritis and hypertension" and his sister had died in her thirties of "coronary thrombosis" unconfirmed by electrocardiogram or necropsy

Examination

His temperature was 100 8°F, pulse rate 86 per min, and respiration rate 25 per min on admission There were no rashes or palpably enlarged lymph-glands His nose was blocked and his voice nasal in character, his face appeared rather bloated A whitish membrane covered the tongue and fauces, and the tonsils were enlarged There was diminished movement at the left lung base and medium râles were heard at both bases

The blood pressure (B P) was 145/80 mm Hg No other abnormality was made out, and the urine was normal

Treatment and Progress

He was given crystalline penicillin 125,000 units 3 hourly intramuscularly, his temperature varied between 102°F and 98°F The nasal congestion increased until on Nov 28 the nose was blocked with blood clot, and the fauces, uvula, palate, and tongue were covered with raised yellowish white papules with surrounding œdema and erythema The chest signs were unchanged, and radiography had shown prominent hilar shadows and some loss of translucency in the right costophrenic sinus The white cell count was 6000 per c.mm with a normal differential count Bacteriological examination of the sputum and throat swabs revealed no specific pathogens Agglutination tests for the enteric group and brucella were all negative

The conjunctivæ became inflamed to the extent of chemosis The voice was reduced to a croak, and the breathing was stertorous Necrotic ulcers on the fauces became confluent, and shallow necrotic ulcers appeared over the buttocks and elbows These lesions began as vesicles, became hæmorrhagic, and then broke down to form ulcers with dry black bases, varying from $^{1}/_{8}$ to $1^{1}/_{2}$ in in diameter The fauces and uvula became so necrotic that the latter seemed on the point of sloughing off, and a few hæmorrhagic lesions appeared on the lips The conjunctivitis remained acute and subconjunctival hæmorrhages appeared Cultures of further throat swabs produced a growth of *Staphylococcus pyogenes*, and no diphtheria or Vincent's organisms were detected The blood was sterile and contained no cold agglutinins The white cell count rose to 12,000 per c.mm with a preponderance of polymorphs, and the hæmoglobin fell from 80 to 60% (Sahli) The erythrocyte sedimentation rate (E S.R) (Wintrobe) was 58 mm in one hour The blood Wassermann reaction was "? negative" and Meinicke "negative" As the illness progressed, a little albumin was found in the urine and a few granular casts There was slight œdema of the ankles and a left sided pleural effusion appeared Aureomycin (chlortetracycline) 250 mg orally 6 hourly was given from Dec 2 to Dec 5, and then promethazine 25 mg orally t i d The penicillin was continued and mouth washes given He died on Dec 9 after gradual weakening of respiration

Necropsy

There was congestion and ulceration of the entire respiratory tract The lungs, particularly the lower lobes, were studded with large yellowish necrotic zones which were firm and honeycombed Both lower lobes were covered with a fibrinous exudate The hilar lymph glands were fleshy, large, and hæmorrhagic

The heart was large (500 g) but, apart from mild atheroma in the coronary arteries, was normal A large ulcer (again with a yellowish tinge) was found in the jejunum, and there were many superficial ulcers in the ileum The liver was very large (3000 g) but appeared normal in texture The spleen was also large (700 g) and covered with a fibrinous exudate On section the whole spleen appeared to be in a state of infarction with numerous yellowish necrotic areas again with a honeycomb appearance The kidneys were a little larger than normal and the right contained a few recent infarcts

Histology

Lungs —The essential lesion in the lungs seems to be fibrinoid necrosis of the capillaries and complete destruction of lung tissue in the affected areas These areas are seen as foci of necrotic cellular debris with a surrounding granulomatous reaction with giant cells

Kidneys —In the right kidney there are typical segmental and focal lesions of polyarteritis nodosa involving the interlobular arteries, with infarction of the corresponding segments of parenchyma The glomeruli have the appearances of periglomerular granulomata described by Davson, Ball, and Platt (1948)

Spleen —In the spleen there are multiple and sometimes confluent necrotic foci of varying size with surrounding granulomatous reaction, as well as occasional segmental fibrinoid necrosis of trabecular arteries

Skin —The lesions of the skin and mucous membranes are essentially infarcts

Lesions of polyarteritis nodosa are confirmed microscopically in the testes, skeletal muscles, myocardium, and peripheral nerves

The pathological diagnosis is Wegener's granulomatosis A more detailed description of this case will be published in a journal of pathology.

SECOND CASE

An unmarried woman clerk aged 33 was admitted to hospital on June 19, 1950, with a history of joint pains for 10 days and scattered skin lesions for 7 days After 2 days of vague stiffness in the limbs, she had severe aching pains in the arms, and her hands and wrists began to swell, at the same time an eruption appeared on the buttocks The pain continued for 3 days and then improved She was then given salicylates by her doctor, and next day her pains were again severe and seemed to flit from joint to joint On admission she complained little of joint pain, however, but mainly of ulceration of the mouth which had appeared the previous day At the same time a rash had appeared on both hands and the right elbow, and below the left breast There had been no cough and no urinary upset, and menstruation was normal 6 months previously she had had an attack of joint pains and mouth ulceration lasting only a few days

At 18 she had had radiotherapy for thyrotoxicosis but the result was poor For 2 years before admission she had been taking thiouracil, never less than 50 mg daily, and for many months 75 mg Otherwise her health had been good and she had never taken sulphonamide drugs There was no personal or family history of allergy

Examination and Investigations

Her temperature was 101 4°F, pulse rate 120 per min, and respiration rate 27 per min on admission She was flushed and her eyes were prominent, but there was no conjunctivitis Enlarged lymph glands were noted in the retro auricular regions and in the posterior triangles of the neck The right lobe of the thyroid gland was enlarged and firm Scattered macules and vesicles were present over the scalp and forehead, and on the dorsa of the hands and wrists A few of the vesicles were hæmorrhagic, and under the left breast there was a weeping maculo papulo vesicular eruption There were a few hæmorrhagic vesicles over the right olecranon, and a further twenty over the sacrum and buttocks ($^{1}/_{4}$ in in diameter) The remaining areas of skin were flushed but otherwise normal

There was a hæmorrhagic vesicle on the lower lip, and sordes on the inner aspect of the lips The tongue was coated with a brownish fur, and ulcerated, most deeply at the right border The upper pole of the left tonsil bore a yellowish slough, and there were small ulcers over gums and fauces The joints seemed normal apart from some pain and tenderness in the knees and a doubtful effusion into the left knee Apart from the expected manifestations of thyrotoxicosis, the cardiovascular system was normal There was no evidence of pulmonary disease The external genitalia appeared normal The white cells numbered 3500 per c mm on admission and 50% were polymorphonuclear cells Platelets were present in normal abundance

Treatment and Progress

Penicillin 125,000 units 8 hourly was given from June 19 to 30 and promethazine, 25 mg t i d from June 19 to 26, and 25 mg daily till July 1 After 2 days her general condition had greatly improved, and after 5 days she was apyrexial

The condition of her mouth and skin improved steadily and the blood picture remained the same

Thyroidectomy was later performed by Mr T Murray Newton and although *3 months* had elapsed since thiouracil was stopped, the gland was still very vascular and showed the changes characteristic of thiouracil therapy *Her subsequent* health has been good

THIRD CASE

This patient was not seen by me but her records were found among those of cases of erythema multiforme admitted to the Western Infirmary, Glasgow

An unmarried girl of 23 *was* admitted from an island of the Outer Hebrides on Nov 12, 1941 She was then suffering from the *fourth* of a series of attacks—the first three having been *in* February, July, and September of the same year Each consisted of ulcerative stomatitis, conjunctivitis, vesicular and pustular lesions on the trunk and limbs, and an apparently *severe anæmia*

Evidently she was severely ill each time Her own doctor was very anxious about her and suspected agranulocytosis In the absence of local *facilities*, in war time, he was forced *to* risk *giving her* sulphonamides, and the results appeared *good Eventually* she was referred to hospital because it *was feared that* a further attack might prove fatal She had had a child a year previously, and the puerperium was complicated by a "somewhat toxic spell" Her doctor could not be sure whether he gave her sulphonamides at that time but thought he might well have done so

She spent only 3 days in hospital and the notes are not very full Her hæmoglobin was 55% (Sahli) but there is no record of further blood examinations A chest radiograph and a *fractional gastric* analysis were normal

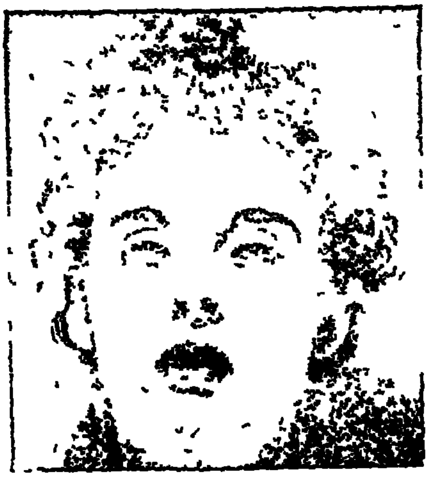
In 1951 her doctor was able to tell me that she had had one further *attack* and had thereafter remained well There was no allergic background, but her half sister had a mild erythema multiforme, *followed* by pulmonary tuberculosis from which she died

FOURTH CASE

A shop manageress aged 23 was admitted to hospital on *Dec 23, 1953* A week before, malaise, sore throat, headache, and cough had developed She had sweated unduly and her voice had become hoarse 4 days before admission her eyes became painful and inflamed, and her mouth and lips became swollen and ulcerated On the night before admission she was delirious There was no history of dysuria or of urethral or vaginal discharge She had had sulphonamides for 3 days and two *injections of* penicillin Her previous health had been good

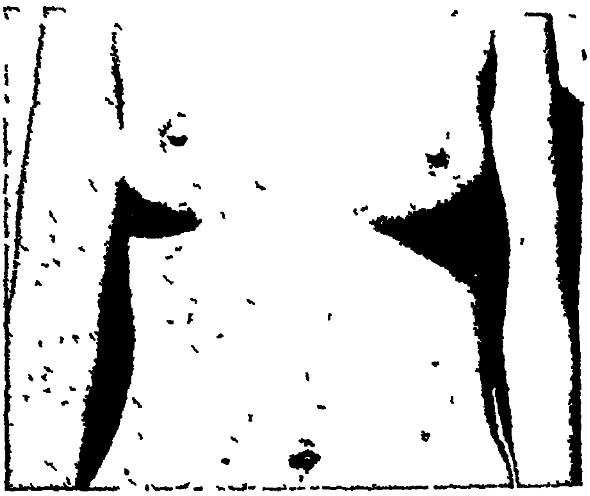
Examination

Her temperature was 100 6°F and she looked *ill* There was ulcerative stomatitis and hæmorrhagic crusting of the lips and buccal *mucosa* The conjunctivæ were much injected and œdematous No enlarged lymph glands were found Her limbs and trunk were covered with scattered erythematous circular lesions up to 1 cm in diameter These are *shown in the figure Some were of the* "*iris*" *type No* abnormality was made out in the chest on admission, but 3 days later clinical and radiological signs of left basal collapse and consolidation appeared The skin lesions did not ulcerate, but several became bullous Her mouth was very uncomfortable, and eating and speaking caused pain



Treatment and Progress

On the day after admission the temperature returned to normal, and in the next week reached 99°F only twice A course of cortisone by intramuscular injection was begun on Dec 24—100 mg t i d for 1 *day, 100 mg b d* for 2 days, and then 100 mg daily During this period the skin lesions persisted but there was some improvement in the conjunctivitis The mouth remained grossly ulcerated



Skin lesions in case 4

On Dec 29 the temperature rose suddenly to 103°F and corticotrophin (A C T H), 25 mg t i d intramuscularly, was substituted for cortisone 4 days later she was very much better The mouth was almost healed and the skin lesions were fading The eyes were almost back to normal Corticotrophin gel was then given (20 mg daily for 15 days) and there was no recurrence of symptoms She was also given crystalline penicillin, 500,000 units intramuscularly on Dec 29, followed by procaine penicillin 300,000 units b d *for 5 days*

The white cell count on admission was 7400 per c mm *with a normal* differential count On Dec 29 this had risen *to* 13,000 per c mm The E S R (Wintrobe) was 4 mm in *one hour on Dec 29* Blood culture was sterile and two *buccal swabs showed no* specific flora on direct examination and *culture* A repeat chest radiograph on Jan 7, 1954, showed *that* the basal shadow on the left side had disappeared

FIFTH CASE

A woman aged 18 was admitted *to hospital on* April 17, 1954 She had been married in February, 1954 Cystitis had *troubled* her for 5 weeks before admission From April 3 *to 7 she had* had a course of sulphadimidine On April 14 she began to complain of sore throat, painful eyes, and a rash, and on April 15 a course of chloramphenicol was begun

Examination

On admission she was very ill and semicomatose The temperature was 101°F and there were signs suggesting *bilateral* bronchopneumonia *There was a generalised* macular rash with bullæ, and gross ulceration of the mouth and fauces She had chemosis and purulent conjunctivitis There were no vulvar lesions She was put in an oxygen tent and given *aureomycin 100 mg intravenously* This was repeated after 4 hours, when she was also given oral aureomycin 1 5 g, *followed* at 6 hourly intervals by 1 g and then 0 5 g The drug was then continued at the rate of *0 5 g 6 hourly* until April 19

Treatment and Progress

The white cell count was then 8000 per c mm with only 38% of polymorphs A course of corticotrophin (25 mg 6 hourly) was begun, but after 200 mg had been given her condition continued to worsen and cortisone was *substituted* At first only 10 mg 4 hourly could be given, but after 1 day this was increased to 25 mg 4 hourly By that evening the patient was desperately ill, with a blood pressure *of 55/?* An intravenous infusion of noradrenaline was given with some temporary improvement in the blood pressure *On April 23 the dose of cortisone* was *raised* to 300 mg a day, *but she died the same evening* The blood urea then was 380 mg per 100 ml

Post mortem Findings

There was mucopus in the trachea and bronchi, and nodular congested areas in both lower lobes Brownish grey pus *could be expressed* from these areas There was no pleural eaction The abdominal viscera, endocrine organs, heart, nd brain appeared normal

Histological examination revealed no arterial abnormality

Discussion

Thomas (1950) suggested the division of Stevens Johnson syndrome (erythema multiforme exudativum) into two groups—major and minor The "major" type is associated with long-continued fever and severe conjunctivitis, the "minor" with predominantly skin lesions All five of the above cases seem to belong to the "major" category, though perhaps case 2 was intermediate

None of the patients had the genital lesions which have often been described, but this does not seem to be an essential part of the syndrome The tendency to recurrence is well illustrated by case 3 and to a lesser extent by case 2 However, even after severe and repeated attacks, eventual complete remission seems likely (case 3)

Fatal cases of this syndrome are rather rare, and cases 1 and 5 are therefore of special interest The atypical pneumonia is a common accompaniment of the syndrome, but the histological and macroscopic changes in case 1 have not been previously described In the few published accounts of necropsies following Stevens Johnson syndrome I have not been able to find any reference to arterial lesions

The clinical picture of Wegener's granulomatosis is described by Johnsson (1948) Rhinitis is the initial symptom, followed by a necrotic process in the nose, throat, and respiratory tract The patient appears to have a septicæmic illness with a high sedimentation-rate Terminally there is uræmia and hypertension No characteristic rash is described by Johnsson, but in a review by Fahey et al (1954) and in a recent article (Walton and Leggat 1956) patients are described with petechial rashes and with hæmorrhagic necrotising lesions, particularly over the elbows Ulceration of the mouth and chemosis are also mentioned by these authors

It may therefore be argued that case 1 was, clinically as well as pathologically, one of Wegener's granulomatosis rather than Stevens Johnson syndrome, but I feel that the clinical diagnosis of Stevens Johnson syndrome was undoubtedly justified Both conditions are thought to have an allergic background, the tissues becoming sensitive to products of necrosis, to drugs, or eventually to many stimuli There is no suggestion of drug allergy in this case One may look upon it as a case of Wegener's granulomatosis presenting as Stevens-Johnson syndrome, or of Wegener's granulomatosis simulating Stevens Johnson syndrome

Polyarteritis is also found in certain cases of "drug sensitivity"—to sulphonamides (Hartroft 1944, More et al 1946), thiourea (Gibson and Quinlan 1945, Dalgleish 1952), and phenylbutazone (O'Brien and Storey 1954) A case of Stevens Johnson syndrome following phenylbutazone therapy has been described (Steel and Moffatt 1954) It is always difficult, however, to prove that drug allergy is really responsible In case 2 the long-term treatment with thiouracil was considered as a possible causal factor, and attempts were made to prove sensitivity to this drug

Standard textbooks on allergy are not at all helpful in this respect It is generally agreed that though the formation of "haptens" provides a convenient theoretical explanation of drug allergy, there are apparently no circulating antibodies, and therefore the conventional methods of skin testing are useless However, an article by Rajka and Hegyi (1950) suggested that the "distant reversed Prausnitz Küstner (P K) reaction" is a reliable means of demonstrating drug allergy

First the P K method of demonstrating transferred sensitivity was tried (Prausnitz and Küstner 1921)

In this method the skin of the back of a normal person is used Intradermal injections are made—two of 0 1 ml of the supposedly sensitive person's serum, and two of 0 1 ml of normal serum 24 hours later 0 02 ml of the suspected agent is injected into one "sensitised" and one control site, and 0 02 ml of normal saline into the other two sites A positive reaction is characterised by the development of a weal and flare into the one area where the allergen is in contact with the sensitised skin All the other control sites should show no reaction

Three normal people were thus tested with the serum of case 2 An injectable form of thiouracil was difficult to obtain since this drug is almost insoluble in water It seemed reasonable to suppose, however, that the serum of a patient under treatment with thiouracil would contain enough of the drug, either free or combined with serum protein Such a serum was used in 0 05 ml doses as the second injection in these tests, and none of the three tests was positive

The distant reversed P K reaction was then tried

Here, a patient under treatment with the suspected drug is injected intradermally with 0 05 ml of the potentially sensitive person's serum A control injection of normal serum is also given, and a positive reaction is characterised by a weal and flare which is confined to the test site

This test was carried out on three patients who were having thiouracil, using the serum of case 2 The first gave a negative result, the other two gave an apparently positive result with weal and flare definitely exceeding those at the control sites However, when similar tests were made in persons who had never had thiouracil, a similar picture was obtained Apparently some non-specific irritant had appeared in the serum of case 2, though it had been stored under aseptic conditions in a refrigerator No control of this type is mentioned by Rajka and Hegyi

It is interesting here to mention the findings in a case of undoubted methylthiouracil sensitivity encountered at the same time Fever, tachycardia, and considerable malaise developed when this patient took methylthiouracil Propylthiouracil was tolerated normally It was proved beyond doubt by repeated (accidental) exhibition of methylthiouracil that this was a specific sensitivity Yet here again the direct P K reaction (three tests) and the distant reversed P K reaction (four tests) were negative

The results of these tests suggest that the distant reversed P K test as proposed by Rajka and Hegyi is of no help in proving or disproving drug allergy Further disadvantages are evident from their article—the reactions were never positive in all test subjects and no indication is given of what proportion may be expected to give satisfactory results It is doubtful whether the differences between the sizes of the weals and flares in positive and control sites were significant, and the possibility of non-specific positive results such as I have found was apparently not considered

It is suggested therefore that a very critical approach should be made in attributing cases of Stevens Johnson syndrome to drug allergy Case 1 had no sulphonamides or other probable allergen Case 2 had only thiouracil. Case 3 seemed to improve when sulphonamides were exhibited in one of her attacks Case 4 had no potentially sensitising drugs Case 5 might have been due to sulphonamides but the time relationship makes this unlikely. It seems probable that the infections for which the various antibacterial agents were given could be the precipitating cause of the syndrome

Aureomycin and chloramphenicol have been said to produce improvement in some cases of Stevens Johnson syndrome These antibiotics did not seem to help in case 1 or case 5 but of course these patients were desperately ill when the course of treatment was begun Cortisone and corticotrophin are reported to "cure" the syndrome (Caldwell 1953), and this is adduced as further evidence of an allergic basis for the condition.

It is not, however, certain that the anti-allergic properties of these drugs are necessarily responsible for the " cures ", or indeed that the improvement was not due to spontaneous remission Thus in case 4 an exacerbation occurred while cortisone treatment was continuing The subsequent improvement followed the simultaneous administration of penicillin and corticotrophin, and it is impossible *to give credit to one rather than to the other*

Hence the cause of this syndrome is still obscure The hypothesis of drug allergy has not been supported by *any convincing proof*—and indeed it is shown that this mechanism is very difficult to prove The apparently satisfactory responses to antibiotics and to cortisone and corticotrophin are also suspect in a disorder which is usually self-limiting, and is liable to apparently spontaneous remissions and relapses

Summary

Five cases of Stevens Johnson syndrome are described Two were fatal, and one showed unusual post-mortem changes

One followed a long course of thiouracil therapy The difficulties of proving drug allergy are described

The cause of this syndrome remains obscure, and the therapeutic efficacy of antibiotics, cortisone, and corticotrophin are not proven

The cases were under the care of the late Dr D S Stevenson, the late Dr W R Snodgrass, and Sir John McNee in the Western Infirmary, Glasgow, and of Dr J S Parkinson and Dr W Mackay in Hope Hospital, Salford The supplies of cortisone and corticotrophin used in cases 4 and 5 were provided by Dr J S Parkinson I am indebted to Dr J Stewart for the necropsy and histological reports in case 1, and to Dr J D Hepplestone for those in case 5 Dr A J Macleod kindly provided a report on the progress of case 3

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RADIOACTIVE VITAMIN B_{12} IN THE DIAGNOSIS OF NEUROLOGICAL DISORDERS

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SUBACUTE combined degeneration of the spinal cord is caused by deficiency of vitamin B_{12} (Castle's extrinsic factor), the absorption of which is impaired by lack of *intrinsic factor* In patients with the typical history of peripheral paræsthesiæ associated with paresis, clear neurological signs, megaloblastic anæmia, and achlorhydria, the diagnosis is not in doubt, but such a clear clinical picture is by no means always found At times a good response to vitamin B_{12} has been used as a criterion in the diagnosis of subacute combined degeneration, and latterly the serum-vitamin-B_{12} level has been used for the same purposes Unfortunately the estimation of the serum-vitamin-B_{12} level is technically difficult, and the result is valueless if the patient has received parenteral vitamin B_{12} Furthermore, the serum level may be low because of a defect of absorption unrelated to the production of intrinsic factor

The most satisfactory way of establishing the diagnosis is to demonstrate that the patient cannot absorb vitamin B_{12} This vitamin contains cobalt and can conveniently be labelled with its radio isotopes, ^{60}Co or ^{58}Co, and there are four possible techniques which may be used

(1) Radioactive vitamin B_{12} is given and eight hours later a blood sample is taken (Booth and Mollin 1956) This technique necessitates a high dose (5 μC) of material labelled with ^{58}Co, and venepuncture after an interval which makes it impracticable for outpatients

(2) Arias et al (1955) assessed the radioactivity of the liver with a collimator ten days after an oral dose of radioactive B_{12}, after a subcutaneous dose, and after an oral dose with intrinsic factor This test is long and cumbersome, and surface counting over the liver may be inaccurate

(3) Radioactive vitamin B_{12} is given by mouth and the radioactivity of the stools measured over four to nine days, the amount absorbed being calculated by subtraction (Halstead et al 1956) The technical disadvantages are obvious

(4) Schilling et al (1955) estimated the urinary excretion in the twenty four hours following an oral dose of vitamin B_{12} labelled with ^{60}Co They showed that in 18 controls, 7–22% of the ingested radioactive material was excreted in the urine in twenty four hours Of 31 patients with achlorhydria but without blood dyscrasia, 24 excreted amounts equal to those in the control series, the remaining 7 excreted smaller but appreciable amounts In 35 patients with pernicious anæmia the excretion was usually 1% or less (maximum 2 3%)

We have applied this last technique to the investigation of neurological disorders, using vitamin B_{12} labelled with ^{58}Co, which has a half-life of seventy two days and is virtually free from risk In our series no patient under 45 was tested and the dose was of the order of 0 5 μC

Methods

Because of the relatively long half-life of ^{58}Co the tracer doses for use over a month or two can be dispensed in a single batch The radioactive vitamin B_{12} is diluted to give 0 5 μC per ml , and inactive B_{12} is added to bring the concentration to 3 μg per ml Accurate 1 ml quantities of the solution are transferred to glass ampoules, which are then sealed off At the same time a 1 in 1000 dilution of this solution is prepared as a standard for the estimation of the radioactivity in urine when the test is performed The preparation is carried out with sterile glassware, and the ampoules are boiled for ten minutes after sealing as a further precaution against contamination with micro organisms that might metabolise the vitamin B_{12} The standard is also made up in *N*/10 hydrochloric acid to preserve sterility, and sufficient cobalt chloride is added to it to impart a definite pink colour to the solution This makes it easily recognisable, and may also reduce the liability to adsorption on to the glass The standard solution is divided into several portions, which are kept in well-stoppered bottles until needed One bottle will serve for several tests, but fresh bottles should be used from time to time to avoid the possible accumulation of errors due to evaporation and contamination, and it is wise, on opening a fresh bottle, to check the old standard against the new

When a test is to be performed, the contents of one ampoule of the prepared solution of activity 0 5 μC are transferred to a suitable drinking-vessel and made up to 100 ml. with water The procedure is then as follows

(1) *Zero Hour* —Light breakfast, but no further food until after zero + $4^1/_2$ hours

(2) *Zero + $2^1/_2$ Hours* —The bladder is emptied The prepared radioactive vitamin B_{12} is given in 100 ml of water by mouth All urine is now collected for twenty-four hours, avoiding fæcal contamination

(3) *Zero + $4^1/_2$ Hours* —1000 µg of ordinary vitamin B_{12} is given intramuscularly to ensure a high level in the serum and maximum excretion

10 ml of the twenty-four hour urine collection is assayed on an 'Ekco N550' scintillation counter, and the counting-rate is compared with that given by 10 ml of the standard, due correction being made for background and dead-time Since the quantity of radioactive material actually given to the patient is equal to that contained in 1 litre of the standard, the fraction excreted is computed as follows

$$\text{Percentage of tracer excreted} = \frac{\text{Count-rate of urine} \times \text{vol (litres)} \times 100}{\text{Count rate of standard}}$$

If defective absorption is demonstrated the test is repeated, but this time 100 mg of intrinsic factor is mixed with the radioactive vitamin B_{12} If the patient still fails to excrete the radioactive material at the normal levels, the primary abnormality is not defective production of intrinsic factor and the condition is not subacute combined degeneration

Results

Normal Subjects —Schilling et al (1955) found that the normal range of excretion using this technique was 7–22% of the ingested dose To establish our own standards we tested 5 normal subjects The range of excretion in this series was 4 0–7 1%, and we feel that the figures obtained are satisfactorily free from experimental error It is possible that our lower figures may be due to the age of the subjects studied, for none was under 45 years of age

Patients with Subacute Combined Degeneration —10 patients with classical subacute combined degeneration were subjected to the test They had already been followed for periods of two to seventeen years and had responded to liver or vitamin B_{12} The excretion-range in these cases was 0 3–1 0% (average 0 6%) Thus there is a clear difference between these figures and those for the normals In 4 patients the test was repeated seven days later with the addition of 100 mg of intrinsic factor to the dose of radioactive vitamin B_{12} The excretion-range rose to levels of 4 1–6 0% (average 5 2%) (see table)

Patients with Doubtful Diagnosis of Subacute Combined Degeneration —These comprised the following groups

(a) Subacute myeloneuropathy with achlorhydria (6 patients)

(b) Syndromes similar to (a), with a partial therapeutic response to either vitamin B_{12} or liver extract (4 patients)

(c) A clinical story suggesting subacute combined degeneration of the cord, free acid in gastric juice (3 patients)

(d) Diabetes and neurological manifestations (2 patients)

RESULTS OF EXCRETION TESTS IN 10 CASES OF SUBACUTE COMBINED DEGENERATION WITH HISTAMINE FAST ACHLORHYDRIA

Case no	Age (yr)	Sex	Hb (%)	R B C (in millions per c mm)	Colour index	Marrow	B_{12} excretion (%)	B_{12} excretion after administration of intrinsic factor (%)
1	47	F	72	3 11	1 16	Normal (partly treated)	0 45	4 45
2	[illegible]	M	78	3 14	1 23	Megaloblastic	1 0	—
3	52	M	64	2 24	1 36	Megaloblastic	0 6	—
4	55	M	110	4 27	1 27	Not done	1 0	—
5	60	M	74	3 48	1 13	Megaloblastic	0 3	—
6	48	M	82	3 66	1 12	Megaloblastic	0 9	—
7	56	M	77	2 9	1 32	Not done	0 3	4 1
8	60	M	70	2 96	1 23	Megaloblastic	1 0	5 5
9	52	F	94	5 21	0 91	Normal (treated)	0 9	—
10	66	F	80	3 92	1 02	Megaloblastic	0 7	5 1

Illustrative Case-records

MYELONEUROPATHY WITH ACHLORHYDRIA

Case 11 —A man, aged 52, developed pins and needles in the feet in January, 1956 This symptom became worse and spread to the hands He was admitted to the Manchester Royal Infirmary in July with diminished tendon reflexes, equivocal plantar responses, impaired superficial sensation to the mid calf in both legs, and impaired position sense, in the toes Vibration sense was normal

Blood count, marrow, and liver function tests normal Pyruvate tolerance curve fasting 1 9 mg per 100 ml at 1 hr 2 3 mg per 100 ml, at 2 hr 2 2 mg per 100 ml Histamine fast achlorhydria

Clinically, there was a clear indication of a combined cord and peripheral nerve lesion This, together with a history of chronic alcoholism, and the abnormal pyruvate tolerance, led us to believe that the most probable diagnosis was peripheral neuropathy, possibly due to aneurine (vitamin B_1) deficiency The vitamin-B_{12} excretion test showed that his urinary excretion was 5 3% of the ingested dose in twenty-four hours This ruled out absolutely the alternative diagnosis of subacute combined degeneration The disorder responded to aneurine

MYELONEUROPATHY WITH ACHLORHYDRIA PARTIAL RESPONSE TO VITAMIN B_{12}

Case 12 —In 1951 a man, aged 43, noticed vague discomfort in the left leg which became worse A year later his knee jerks were diminished and ankle jerks absent, plantar responses flexor, and sensation normal In July, 1954, he had extensor plantar responses and the knee jerks were absent, sensation was still normal

Wassermann reactions (W R) of blood and cerebrospinal fluid (C S F) negative C S F normal Radiographs of dorso-lumbar spine, normal Histamine fast achlorhydria Peripheral blood count normal, marrow not examined

The patient was given vitamin B_{12} 100 µg daily for three weeks After three or four days his symptoms cleared up completely, but although the vitamin B_{12} was continued fortnightly, his symptoms recurred with aching pains in the legs The vitamin B_{12}-excretion test in May, 1956, showed that 6 4% of the dose was excreted This, we concluded, ruled out subacute combined degeneration

MYELONEUROPATHY WITH ACHLORHYDRIA PARTIAL RESPONSE TO VITAMIN B_{12}

Case 13 —In 1946 a man, aged 48, began to have an unsteady gait, heaviness of the legs, and tingling in his feet He had extensor plantar responses, impaired deep sensation in the toes, and diminished ankle and knee jerks

Blood count, marrow, C S F all normal, histamine fast achlorhydria W R negative in blood and C S F

From 1949 onwards he was treated with 'Anahæmin' or vitamin B_{12} After six months he was symptomatically improved, but clinical findings were unchanged In September, 1950, his left foot dragged, and he gradually deteriorated In November, 1953, spastic paresis necessitated a mechanically propelled chair In a vitamin B_{12} excretion test in September, 1956 4 4% of the ingested dose was excreted indicating that he had not subacute combined degeneration, but the spinal form of disseminated sclerosis

DIABETES WITH NEUROLOGICAL COMPLICATIONS

Case 14 —In 1950 a man, aged 60, was *found* to have diabetes, which was controlled well with insulin and restricted diet In May, 1956, during an upper respiratory infection, his diabetes became uncontrolled and he was admitted to hospital He had had no neurological symptoms, but was found to have diminished knee jerks, absent ankle jerks, extensor plantar responses and impaired superficial sensation to mid calf, his vibration sense was lost, and his position sense was good

His diabetes was treated in the routine fashion but his neurological signs did *not* change Blood count and chest X ray normal, W R negative

It was felt that his neurological signs were probably due to diabetic myeloneuropathy In a vitamin B_{12} excretion test 7 0% of the dose was excreted in twenty four hours Subacute combined degeneration was thus excluded

It is not, however, certain that the anti allergic properties of these drugs are necessarily responsible for the " cures ", or indeed that the improvement was not due to spontaneous remission Thus in case 4 an exacerbation occurred while cortisone treatment was continuing The subsequent improvement followed the simultaneous administration of penicillin and corticotrophin, and it is impossible to give credit to one rather than to the other

Hence the cause of this syndrome is still obscure The hypothesis of drug allergy has not been supported by any convincing proof—and indeed it is shown that this mechanism is very difficult to prove The apparently satisfactory responses to antibiotics and to cortisone and corticotrophin are also suspect in a disorder which is usually self-limiting, and is liable to apparently spontaneous remissions and relapses

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Five cases of Stevens Johnson syndrome are described Two were fatal, and one showed unusual post mortem changes

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The most satisfactory way of establishing the diagnosis is to demonstrate that the patient cannot absorb vitamin B_{12} This vitamin contains cobalt and can conveniently be labelled with its radio isotopes, ^{60}Co or ^{58}Co, and there are four possible techniques which may be used

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We have applied this last technique to the investigation of neurological disorders, using vitamin B_{12} labelled with ^{58}Co, which has a half-life of seventy two days and is virtually free from risk In our series no patient under 45 was tested and the dose was of the order of 0 5 μC

Methods

Because of the relatively long half-life of ^{58}Co the tracer doses for use over a month or two can be dispensed in a single batch The radioactive vitamin B_{12} is diluted to give 0 5 μC per ml, and inactive B_{12} is added to bring the concentration to 3 μg per ml Accurate 1 ml quantities of the solution are transferred to glass ampoules, which are then sealed off At the same time a 1 in 1000 dilution of this solution is prepared as a standard for the estimation of the radioactivity in urine when the test is performed The preparation is carried out with sterile glassware, and the ampoules are boiled for ten minutes after sealing as a further precaution against contamination with micro organisms that might metabolise the vitamin B_{12} The standard is also made up in *N*/10 hydrochloric acid to preserve sterility, and sufficient cobalt chloride is added to it to impart a definite pink colour to the solution This makes it easily recognisable, and may also reduce the liability to adsorption on to the glass The standard solution is divided into several portions, which are kept in well stoppered bottles until needed One bottle will serve for several tests, but fresh bottles should be used from time to time to avoid the possible accumulation of errors due to evaporation and contamination, and it is wise, on opening a fresh bottle, to check the old standard against the new

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(2) *Zero + $2^1/_2$ Hours.*—The bladder is emptied. The prepared radioactive vitamin B_{12} is given in 100 ml. of water by mouth. All urine is now collected for twenty-four hours, avoiding fæcal contamination.

(3) *Zero + $4^1/_2$ Hours.*—1000 µg. of ordinary vitamin B_{12} is given intramuscularly to ensure a high level in the serum and maximum excretion.

10 ml. of the twenty-four hour urine collection is assayed on an 'Ekco N550' scintillation counter, and the counting-rate is compared with that given by 10 ml. of the standard, due correction being made for background and dead-time. Since the quantity of radioactive material actually given to the patient is equal to that contained in 1 litre of the standard, the fraction excreted is computed as follows:

$$\text{Percentage of tracer excreted} = \frac{\text{Count rate of urine} \times \text{vol. (litres)} \times 100}{\text{Count rate of standard}}$$

If defective absorption is demonstrated the test is repeated, but this time 100 mg. of intrinsic factor is mixed with the radioactive vitamin B_{12}. If the patient still fails to excrete the radioactive material at the normal levels, the primary abnormality is not defective production of intrinsic factor and the condition is not subacute combined degeneration.

Results

Normal Subjects.—Schilling et al. (1955) found that the normal range of excretion using this technique was 7–22% of the ingested dose. To establish our own standards we tested 5 normal subjects. The range of excretion in this series was 4.0–7.1%, and we feel that the figures obtained are satisfactorily free from experimental error. It is possible that our lower figures may be due to the age of the subjects studied, for none was under 45 years of age.

Patients with Subacute Combined Degeneration.—10 patients with classical subacute combined degeneration were subjected to the test. They had already been followed for periods of two to seventeen years and had responded to liver or vitamin B_{12}. The excretion-range in these cases was 0.3–1.0% (average 0.6%). Thus there is a clear difference between these figures and those for the normals. In 4 patients the test was repeated seven days later with the addition of 100 mg. of intrinsic factor to the dose of radioactive vitamin B_{12}. The excretion-range rose to levels of 4.1–6.0% (average 5.2%) (see table).

Patients with Doubtful Diagnosis of Subacute Combined Degeneration.—These comprised the following groups:

(*a*) Subacute myeloneuropathy with achlorhydria (6 patients).

(*b*) Syndromes similar to (*a*), with a partial therapeutic response to either vitamin B_{12} or liver extract (4 patients).

(*c*) A clinical story suggesting subacute combined degeneration of the cord, free acid in gastric juice (3 patients).

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RESULTS OF EXCRETION TESTS IN 10 CASES OF SUBACUTE COMBINED DEGENERATION WITH HISTAMINE-FAST ACHLORHYDRIA

Case no.	Age (yr.)	Sex	Hb (%)	R.B.C. (m. per c.mm.)	Colour index	Marrow	B_{12} excretion (%)	B_{12} excretion after administration of intrinsic factor (%)
1	47	F	72	3.11	1.16	Normal (partly treated)	0.45	4.45
2	57	M	78	3.14	1.23	Megaloblastic	1.0	—
3	52	M	64	2.34	1.36	Megaloblastic	0.6	—
4	55	M	110	4.27	1.27	Not done	1.0	—
5	60	M	34	1.45	1.13	Megaloblastic	0.3	—
6	48	M	82	3.66	1.12	Megaloblastic	0.9	—
7	56	M	77	2.9	1.32	Not done	0.3	4.1
8	60	M	70	2.86	1.23	Megaloblastic	1.0	5.5
9	52	F	94	5.21	0.91	Normal (treated)	0.9	—
10	66	F	80	3.92	1.02	Megaloblastic	0.7	5.1

Illustrative Case-records

MYELONEUROPATHY WITH ACHLORHYDRIA

Case 11.—A man, aged 52, developed pins and needles in the feet in January, 1956. This symptom became worse and spread to the hands. He was admitted to the Manchester Royal Infirmary in July with diminished tendon reflexes, equivocal plantar responses, impaired superficial sensation to the mid calf in both legs, and impaired position sense in the toes. Vibration sense was normal.

Blood count, marrow, and liver function tests normal. Pyruvate tolerance curve: fasting 1.9 mg. per 100 ml., at 1 hr. 2.3 mg. per 100 ml., at 2 hr. 2.2 mg. per 100 ml. Histamine-fast achlorhydria.

Clinically, there was a clear indication of a combined cord and peripheral-nerve lesion. This, together with a history of chronic alcoholism, and the abnormal pyruvate tolerance, led us to believe that the most probable diagnosis was peripheral neuropathy, possibly due to aneurine (vitamin B_1) deficiency. The vitamin-B_{12} excretion test showed that his urinary excretion was 5.3% of the ingested dose in twenty-four hours. This ruled out absolutely the alternative diagnosis of subacute combined degeneration. The disorder responded to aneurine.

MYELONEUROPATHY WITH ACHLORHYDRIA: PARTIAL RESPONSE TO VITAMIN B_{12}

Case 12.—In 1951 a man, aged 43, noticed vague discomfort in the left leg which became worse. A year later his knee-jerks were diminished and ankle-jerks absent, plantar responses flexor, and sensation normal. In July, 1954, he had extensor plantar responses and the knee-jerks were absent; sensation was still normal.

Wassermann reactions (W.R.) of blood and cerebrospinal fluid (C.S.F.) negative. C.S.F. normal. Radiographs of dorsolumbar spine, normal. Histamine-fast achlorhydria. Peripheral blood count normal; marrow not examined.

The patient was given vitamin B_{12} 100 µg. daily for three weeks. After three or four days his symptoms cleared up completely, but although the vitamin B_{12} was continued fortnightly, his symptoms recurred with aching pains in the legs. The vitamin B_{12} excretion test in May, 1956, showed that 6.4% of the dose was excreted. This, we concluded, ruled out subacute combined degeneration.

MYELONEUROPATHY WITH ACHLORHYDRIA: PARTIAL RESPONSE TO VITAMIN B_{12}

Case 13.—In 1946 a man, aged 48, began to have an unsteady gait, heaviness of the legs, and tingling in his feet. He had extensor plantar responses, impaired deep sensation in the toes, and diminished ankle and knee jerks.

Blood count, marrow, C.S.F. all normal; histamine-fast achlorhydria. W.R. negative in blood and C.S.F.

From 1949 onwards he was treated with 'Anahæmin' or vitamin B_{12}. After six months he was symptomatically improved, but clinical findings were unchanged. In September, 1950, his left foot dragged, and he gradually deteriorated. In November, 1953, spastic paresis necessitated a mechanically propelled chair. In a vitamin B_{12} excretion test in September, 1956, 4.4% of the ingested dose was excreted, indicating that he had not subacute combined degeneration, but the spinal form of disseminated sclerosis.

DIABETES WITH NEUROLOGICAL COMPLICATIONS

Case 14.—In 1950 a man, aged 60, was found to have diabetes, which was controlled well with insulin and restricted diet. In May, 1956, during an upper respiratory infection, his diabetes became uncontrolled and he was admitted to hospital. He had had no neurological symptoms, but was found to have diminished knee-jerks, absent ankle-jerks, extensor plantar responses and impaired superficial sensation to mid calf; his vibration sense was lost, and his position sense was good.

His diabetes was treated in the routine fashion but his neurological signs did not change. Blood count and chest X ray normal; W.R. negative.

It was felt that his neurological signs were probably due to diabetic myeloneuropathy. In a vitamin-B_{12} excretion test 7.0% of the dose was excreted in twenty-four hours. Subacute combined degeneration was thus excluded.

This case may be contrasted with the following

DIABETES WITH NEUROLOGICAL MANIFESTATIONS DUE TO SUBACUTE COMBINED DEGENERATION

Case 15 —In 1938 a man, aged 51, began to have classical symptoms of diabetes (blood sugar 281 mg per 100 ml) He was treated with diet and insulin but control was not satisfactory In 1952 he had weakness of the right hand of sudden onset which recovered to some extent, leaving the hand tingling In 1953 his tongue was sore and he was given vitamin B complex Shortly after this he had the first of eight or nine attacks of loss of consciousness, which were felt to be due to cerebral arteriopathy Later his left foot became numb and heavy and his fingers tingled In 1954 he had intermittent claudication In August, 1955, he had superficial glossitis and no pulses were palpable in either leg Examination otherwise was normal

His blood sugar was 246 mg per 100 ml , red cells 3,910,000 per c mm , hæmoglobin 84%, colour-index 1 07 In December, 1955, he complained of definite loss of sensation in both feet

On Nov 3, 1956, he had another blackout Though his tendon reflexes were normal, the plantar responses were doubtful and he had a glove and stocking type of sensory loss to pin-prick and cotton wool Blood red cells 2,970,000 per c mm , hæmoglobin 70%, colour index 1 19 Sternal marrow increased activity of the red-cell series with intermediate megaloblasts and some pro erythroblasts Histamine fast achlorhydria Air encephalogram slight ventricular dilatation Electro encephalogram some slowing of the resting rhythms, suggesting cerebral arteriosclerosis

In a vitamin-B_{12} excretion test only 0 3% of the ingested dose was excreted When, ten days later, the test was repeated with 100 mg of intrinsic factor, the excretion rose to 4 1% Accordingly, subacute combined degeneration was diagnosed independently of the diabetes, and he was given vitamin B_{12} regularly Three months later his neurological symptoms had cleared, and his general condition had improved considerably, his hæmoglobin was 92%

MYELONEUROPATHY WITH FREE ACID IN STOMACH PARTIAL RESPONSE TO VITAMIN B_{12}

Case 16 —In 1952 a man, aged 56, noticed tingling in both hands and both legs, and found that he could not distinguish objects by touch He was liable to stumble, and his legs felt heavy In February, 1954, he had brisk tendon reflexes , extensor plantar responses , impaired superficial sensation in both lower limbs to the mid thigh, and in the upper limbs to the mid forearm , absent vibration sense , position sense slightly impaired

Radiographic examination of the cervical spine showed advanced osteo arthritis Blood and cerebrospinal fluid normal Free acid in the gastric juice W R negative in blood and C S F Marrow not examined

The patient was treated with vitamin B_{12} 100 µg daily for three weeks, and then twice weekly Later in 1954 he considered himself almost back to normal save for numbness in the hands, but in June, 1956, his plantar responses were still abnormal, and sensory changes still present in arms and legs In a vitamin-B_{12} excretion test 11 7% of the ingested dose was excreted in twenty-four hours The correct diagnosis is probably cervical spondylosis.

Discussion

In these doubtful cases the excretion test gave figures from 3% to 12%—well above the range for the proven cases of subacute combined degeneration In case 15 the coexistence of diabetes and subacute combined degeneration was established by the abnormally low excretion of vitamin B_{12} We feel that clinical use of this test in investigating neurological disorders is well justified The technique is safe and relatively easy to apply, and the experimental error is negligible

So far we have applied the tests to only 3 cases of so-called " subacute combined degeneration of the spinal cord " in which there was free acid in the stomach , and in each of these cases vitamin B_{12} was absorbed normally We are anxious to investigate further such cases It seems likely that the controversy over the diagnostic value of achlorhydria in subacute combined degeneration will be resolved by the vitamin-B_{12} excretion test, which will also render the fractional test meal outmoded as the ultimate diagnostic investigation in this condition

Investigation of the myeloneuropathies is often complicated by the fact that the patients have received injections of liver or vitamin B_{12}, when marrow examination and serum-vitamin-B_{12} levels are misleading, but the excretion test remains unaffected Thus in doubtful cases treatment with vitamin B_{12} may be begun before the excretion test It is possible, therefore, to accumulate a series of cases while a batch of radioactive material is being prepared, and yet lose no time in beginning vitamin-B_{12} therapy, which may or may not be continued after the test

In future, patients may be found with excretion figures on the lowest level of the normal range In them the diagnosis may be doubtful It will be reasonable to prescribe vitamin B_{12} and repeat the test later, to see whether absorption has further diminished In this way an incipient neural lesion will have been corrected at the earliest opportunity

Summary

Confirmation of the diagnosis in uncertain cases of subacute combined degeneration of the spinal cord depends on demonstrating incapacity to absorb vitamin B_{12}

Results of an excretion test with radioactive vitamin B_{12} in normal subjects, in classical cases of subacute combined degeneration of the cord, and in a series of patients in whom the diagnosis was in doubt showed that this test confirms or excludes the diagnosis with reasonable certainty

The vitamin B_{12} labelled with ^{56}Co was supplied to us through the kind offices of Dr E Lester Smith, of Glaxo Laboratories Ltd , and the intrinsic factor by Lederle Ltd We are especially grateful to Dr F R Ferguson and Dr G E Smyth for permission to study the cases under their care, and to Prof Robert Platt and Dr Ferguson for helpful criticism and advice

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REVIEW OF
910 CASES OF BRONCHIAL CARCINOMA
WITH RESULTS OF TREATMENT

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There is no need to emphasise the appalling frequency of bronchial carcinoma, for unfortunately it is too obvious But, though several large series of cases have been reviewed recently, it seemed to us opportune to add another series from Manchester The patients in this series of 910 consecutive investigated cases of proved bronchial carcinoma were seen and treated by two of us (A G B and W F N) at the Manchester Royal Infirmary during the seven years 1948–54 inclusive They do not include a number of obviously inoperable patients whom we saw during this period but did not investigate and assess for operative treatment

Clinical Features

Symptoms.—The most common symptom is cough, but it is so usual in the industrial area from which the patients were largely drawn, that many patients accept it as being of no importance. A gradual change in its character, especially to a hard intractable unproductive cough, may serve as a warning. Chest pain, recurrent bronchial obstruction with infection and fever, hæmoptysis, and increasing breathlessness will usually cause a patient to go to his doctor. Hoarseness, dysphagia, pain down the arm, venous obstruction, and severe loss of weight are late symptoms. There were several cases with pulmonary osteo arthropathy—all were inoperable, though in some more recent cases we have resected the tumour.

Duration of Symptoms.—This was deplorably long. On the average, after the onset of warning symptoms, six months elapsed before the patients attended our clinic. The lengths of histories were remarkably constant over the seven years (table I), though increasing prominence was being given to the subject.

TABLE I—AVERAGE DURATION OF SYMPTOMS BEFORE DIAGNOSIS

Year	Duration of symptoms (months)	Year	Duration of symptoms (months)
1948	6·9	1952	6·6
1949	6·3	1953	5·5
1950	6·9	1954	6·6
1951	6·8		

That this interval, during which the illness is progressing, is important for prognosis, is not only obvious, but is well exemplified in our series by those patients who were picked up by miniature or other routine radiography. Of 15 whose disease was thus discovered, 8 were able to have radical resections and 3 (a fifth of those seen) were well after three years. This is a small number, but encouraging when compared with the total results.

The duration of symptoms before diagnosis in the series of Overholt and Schmidt (1949) was eleven months in 1932–42 and ten months in 1947–48. The interval was found to be four and a half months by Taylor and Waterhouse (1950) and only three and a half months by Oswald (1956). In our cases the average duration of symptoms remained remarkably constant, though histories were taken by a variety of observers.

Morbid Anatomy

The two lungs were involved about equally commonly, the order of frequency according to lobes being left upper lobe, right upper lobe, right lower lobe, left lower lobe, left main bronchus, right main bronchus, right middle lobe, and least commonly the lingula (fig 1).

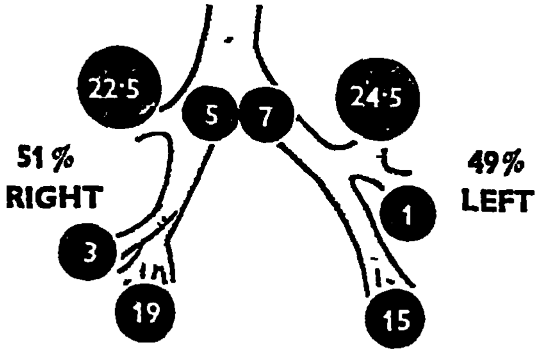

Fig 1—Incidence of tumours in various sites

TABLE II—PROGNOSIS IN DIFFERENT TUMOURS (414 CASES WITH HISTOLOGICAL DETAILS AVAILABLE)

Histological group	Squamous cell carcinoma	Adenocarcinoma	Oat cell carcinoma	Anaplastic carcinoma	Mixed salivary and transitional cell carcinoma	Sarcoma
Number (% of total series)	56	6	21	16	0·8	0·3
Resectable tumours (% of total resected)	69	8	12	8		
Three year survivors (% of total survivors)	85	10	2	2		

Any pathological description clearly applies only to the piece of tissue examined. This may not necessarily be representative. Only by serial sections of the whole tumour and its metastases can an exact histological diagnosis be made. The diagnosis in these cases was determined either by biopsy of a small fragment of tumour or by ordinary histological examination of the resected specimen.

In 414 cases, histological evidence of tumour was obtained. Of these, 56% were squamous cell carcinomas, 6% adenocarcinomas, and 21% oat-cell carcinomas. The rest consisted of spheroidal-cell (8%), anaplastic (8%), and mixed salivary and transitional cell (0·8%) carcinomas, and sarcoma (0·3%). These figures approximate to those of Kreyberg (1952). Reingold et al (1950) and Willis (1952) found several types of cell in a high proportion of the bronchial tumours they examined. In our series also, variations in histological pattern in the same tumour were seen, mainly as areas of differentiated cells in the anaplastic and spheroidal cell tumours. Where this differentiation was recognisable on histological examination, the tumour was labelled according to the differentiated part, without any attempt at grading.

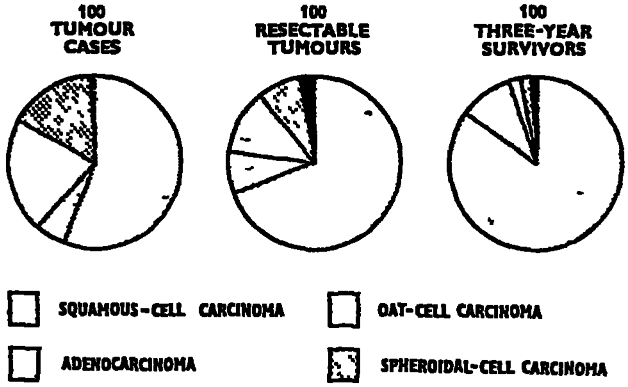

Fig 2—Cases classified according to histological type—operability and survival rates

The creation of separate groups of spheroidal cell and anaplastic carcinoma is fallacious. It results from varying custom in terminology among the pathologists concerned in our series. Most of the anaplastic carcinomas have almost certainly been of the spheroidal cell type. These two groups have therefore been united and termed spheroidal cell carcinomas.

Prognosis

Histology.—The operability-rate and expectation of life after resection were a great deal better for squamous cell carcinoma and adenocarcinoma than for other types of tumour. Oat cell and spheroidal cell neoplasms had an almost hopeless prognosis. This is shown in table II, and graphically illustrated in fig 2, in which the increased proportions of adenocarcinoma and squamous cell car-

TABLE III—EFFECT OF POSITION ON THREE-YEAR SURVIVAL RATE

Site (right)	Survivors (%)	Site (left)	Survivors (%)
Upper lobe	2 5	Upper lobe	4 5
Middle lobe	3 5	Lingula	37
Lower lobe	7	Lower lobe	6
Main bronchus	2	Main bronchus	1 5
All right lung	4 1	All left lung	5 2

cinoma are seen in those patients who had a resection, and still more notably in those who survive three years

Site—In Bignall and Moon's (1955) and Borrie's (1952) cases, prognosis was better when the growth was in the upper rather than in the lower lobes The reverse appears in our cases (table III) Prognosis was a little better with a growth in the left than in the right lung The three year survival-rate was highest in the 8 patients seen with lesions in the lingular bronchus (3 surviving) Tumours arising in the lower-lobe bronchi were found to have a better outlook than those arising anywhere else in the lung (except the lingula)

Sex—There were 70 women amongst the 910 patients, making the proportion of men to women 13 to 1 (a lower proportion of women than in other series) The prognosis was worse in women There were only 5 (7%) in whom resection was possible with any hope of cure, compared with 21% in the combined series Of the 53 women seen between 1948 and 1952, only 2 survived for three years (1 9% in contrast with 6 1% for the series as a whole) Factors which could be responsible for this were investigated The women did not have their symptoms longer than the men the average time between onset of symptoms and arrival at the chest clinic was six and a half months Their average age was 53, against 55 for the whole series The difference does not seem *significant*, and in any case, the average age in patients surviving three years was a little lower than the average for the series The distribution of the tumours in the various regions of the two lungs showed no significant difference from that in the series as a whole There was, however, a definite difference in the histological appearance of the tumours there were considerably fewer of the squamous-cell and many more oat-cell neoplasms, which on the whole give an almost hopeless prognosis This is shown in table IV and fig 3

TABLE IV—INCIDENCE OF EACH HISTOLOGICAL TYPE

Type	Women (%)	Whole series (%)
Squamous cell carcinoma	32	56
Adenocarcinoma	8	6
Oat cell carcinoma	44	21
Spheroidal cell carcinoma	14	16

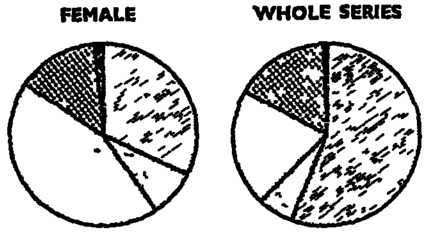

Fig 3—Cases classified according to histological type in each sex

General—There were 44 three year survivors among 720 cases seen between 1948 and 1952 These results correspond roughly to others published recently—Price Thomas (1955), Holmes Sellors (1955), and Bignall and Moon (1955) The number of cases was smaller, but the results were a little brighter They were considerably brighter than those of Taylor and Waterhouse (1950), this may well reflect the combination of improvement of technique and changing criteria of selection

The results cannot be judged as completely representative of all cases of lung carcinoma They come from a thoracic unit, where a certain amount of preselection has taken place before patients are referred Many obviously inoperable cases are thus excluded

Of 910 patients seen, 340 (37%) had thoracotomies, this proportion did not change appreciably in the years between 1948 and 1954 The resectability-rate, however, did change Of the 340 who had thoracotomies, 191 (56%) had radical operations with a hope of cure In the first five years, 52% of the thoracotomies led to a radical operation, this improved to 69% in the last two years of the series This was perhaps achieved by better selection of cases for operation It was not because the diagnosis was made earlier, but there has been some tendency for the operations to become more radical The opinion was held, at one time, that if a patient survived more than two years after operation he had a good chance of being cured This period has been found too short Holmes Sellors has shown that, for a feeling of security, three years must elapse In the years 1948 to 1952, of 720 patients seen, 255 (35%) had thoracotomies, of the latter, 132 (42%) came to radical operation and 44 survived three years—i e, 33 3% of the patients operated on with a hope of cure, and 6% of all patients seen during that period Of the patients seen from 1948 to 1950, 25 are still alive—i e, have survived five years or more (this is 28% of patients undergoing radical operation and 5 5% of all seen) The vast majority of the remainder are known to have died of a recurrence of the condition

Summary and Conclusions

910 cases of bronchogenic neoplasm were studied Only 6% survived for three years

On the average, patients were not seen till six months after the appearance of warning symptoms We must strive to persuade the public to recognise and take heed of these symptoms early, and not to neglect them for six months It is true that in those who died, the duration of symptoms was about the same as in those who survived three years—but the latter were fortunate, most having slowly growing squamous cell carcinomas or adenocarcinomas Those picked up early at routine radiography showed the best prognosis (3 of 15 survived for three years) The prognosis was best for squamous cell carcinoma, and almost hopeless for spheroidal cell, oat cell and *anaplastic tumours*

The best results in our series were obtained when the tumour was situated in the lingula (though the number was small and cannot be considered significant statistically) Of the rest, the results were better in the lower lobes than anywhere else in the bronchial tree

Prognosis in the women was considerably worse than in the men, probably because they had a larger proportion of oat cell and a smaller proportion of squamous cell neoplasms than did the men

The proportion of men to women with this disease was 13 to 1 The average age of all cases was 55 years, that of women 53 years, and that of three year survivors 53 years

It is a pleasure to thank Prof A C Campbell and Dr Raymond Whitehead for their help in the preparation of this paper, for much of it is based on work done in their department of pathology To Dr R G W Ollerenshaw we are grateful for the illustrations, and to Miss M Howarth for help with the records

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ALCOHOL-INDUCED PAIN DUE TO CARCINOMA

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SEVERAL workers have reported the occurrence of pain after the taking of alcohol in some patients with Hodgkin's disease Of all patients with this disease, only a small proportion have been found to have the symptom, even when it is regularly sought Bichel and Bastrup-Madsen (1953) found it in 9 out of 62 cases No other difference has been found between those patients who do have it and those who do not The *British Medical Journal* (1956) states that "it does not seem to occur in other types of malignant lymphomata or other neoplastic conditions"

We describe here 2 patients with alcohol induced pain due, not to Hodgkin's disease, but to carcinoma; though the primary site was in slight doubt in both cases, it was almost certainly in the thymus in one and in the pancreas in the other

Case-reports

Case 1 —A married woman, then aged 47, was first seen in October, 1954, complaining that three weeks previously her left arm had become swollen It had remained so for ten days before returning to its normal size When asked whether she had had pain in the chest, she described attacks of pain behind the upper sternum after taking alcohol The first had been at Christmas, 1952, about five minutes after drinking three quarters of a glass of port After a minute or two the pain had become very severe and had been felt round the root of the neck to the back and down both arms, it had waned during about twenty minutes, but soreness persisted until the next day

Between that occasion and her attendance at hospital in October, 1954, she had taken alcohol five times gin twice, sherry once, a very small amount of stout once, and once a teaspoonful of spirits of sal volatile (70% alcohol) Each drink caused an attack of pain identical with the first She remembered having taken sal volatile in April, 1952, when it did not cause pain. Apart from these attacks and the transient swelling of the arm she had been well except that she had lost a few pounds in weight

Examination and Investigations

The patient looked well, the left external jugular vein was prominent and appeared to be thrombosed. There were no clinical signs of a mediastinal tumour no lymph-nodes were palpable, and the liver and spleen were not enlarged.

Radiographs of the chest (fig 1) showed a round poorly defined opacity about 2 cm in diameter in the antero superior mediastinum, tomography did not define it more exactly Blood hæmoglobin 10 6 g per 100 ml (73%), total and differential white cell counts normal, erythrocyte sedimentation rate (Wintrobe) 38 mm in first hour

Administration of alcohol by gastric tube or by vein produced attacks of the pain of which she complained 5 ml of absolute alcohol in 10% solution was given by vein in six minutes Pain started coincidentally with the end of the infusion, and reached a maximum within three minutes It was very severe, and after twenty minutes 100 mg of pethidine was given. On another occasion 5 ml of alcohol in 10% solution was given by gastric tube pain started six minutes after the end of the instillation and lasted for twenty minutes In both of these observations saline solution was given as a control and the patient did not know when alcohol was being administered

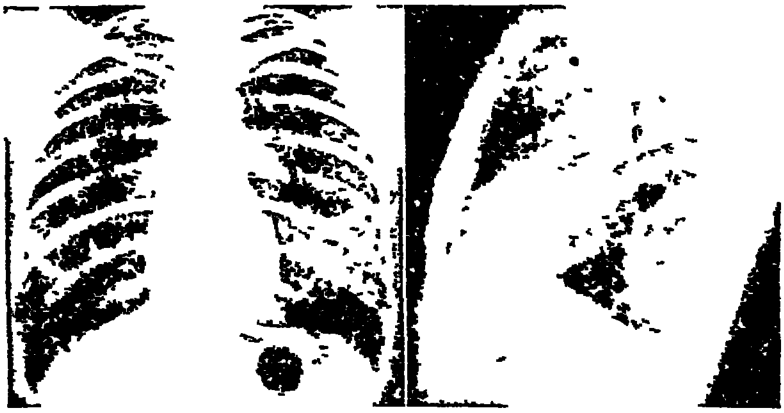

Fig 2—Case 1 Radiographs of chest, May, 1956

Progress

It was decided not to explore the mediastinum because the tumour was presumed to be a manifestation of Hodgkin's disease The patient was therefore advised to avoid alcohol and was discharged from hospital

In February, 1955, having a cold she bought some "cold and influenza mixture" The single dose of this which she took produced an attack of pain like the previous ones except that it was less severe From the composition of this mixture the dose was calculated to have contained about 1 5 ml of absolute alcohol

Apart from this, she remained well In March 1956, a radiograph of the chest showed the tumour to be larger and better defined She was admitted to hospital in May 1956 There was now some dullness behind the upper end of the sternum but no other physical signs Radiography showed bilateral widening of the superior mediastinum, the lateral view showed that the shadow measured 6 4 cm and had an irregular outline, suggesting infiltration (fig 2) Much to our surprise, giving alcohol now caused no pain Under the same controlled conditions as before 20 ml was given by gastric tube The patient had slight discomfort but a similar sensation was sometimes felt after control instillations, she felt no pain then nor did she on another occasion after drinking 80 ml of gin

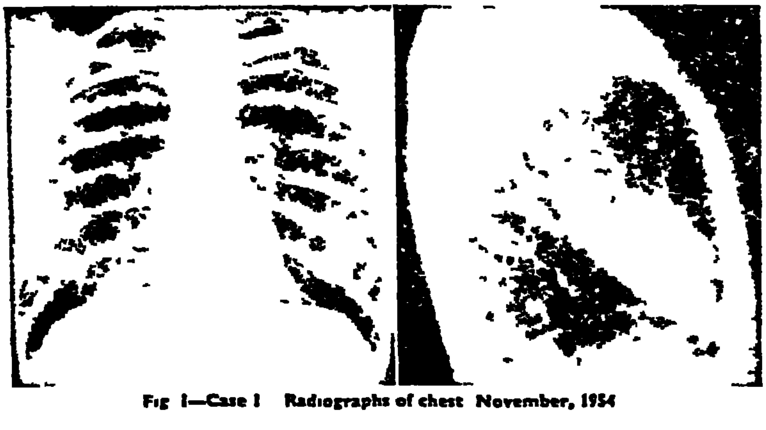

Fig 1—Case 1 Radiographs of chest November, 1954

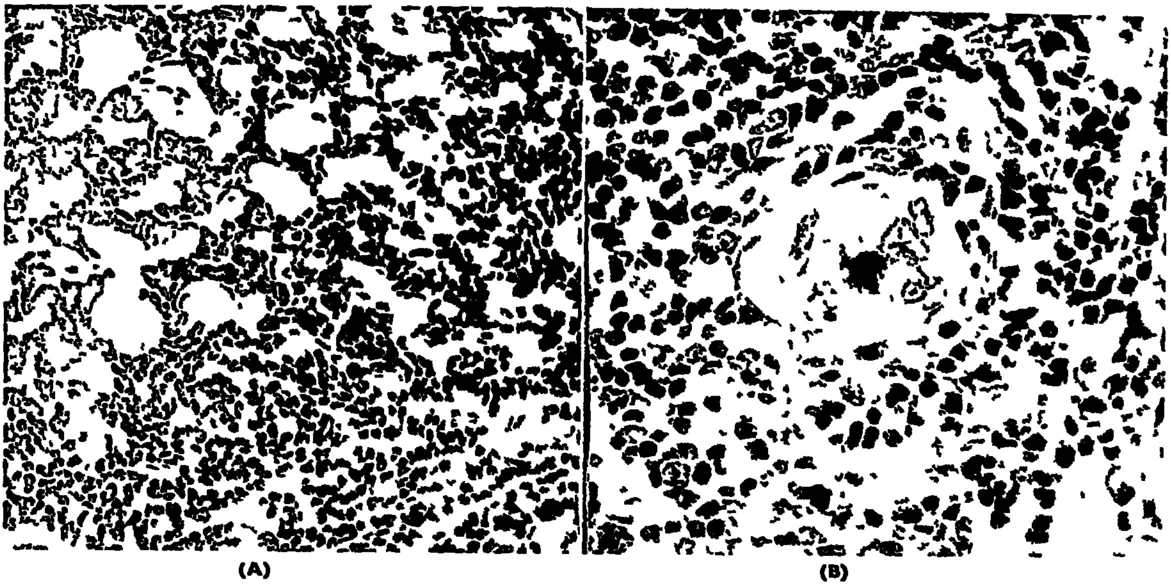

Fig 3—Case 1 Photomicrographs of the tumour A, area showing cribriform pattern with mucoid stroma (Hæmatoxylin and eosin, × 250) B, below abortive Hassall's corpuscle (Hæmatoxylin and eosin × 500)

Operation and Further Progress

It was now decided that the uncertainty about the nature of the tumour justified exploration On May 30, 1956, the sternum was split down to the fourth costal cartilage A hard unencapsulated mass was found infiltrating the front of the pericardium, over an area 2–3 cm in diameter in the region of the roots of the great vessels, as well as the superior mediastinal structures behind the manubrium A globular extension of this mass on each side was invading the anterior margins of the two lungs, more on the right than the left The remaining portions of the lungs, including their hilar regions, were normal When the pericardium was opened a turbid yellow effusion was revealed, and the tumour was seen invading the wall of the pulmonary artery at its junction with the right ventricle The extension of the tumour which had invaded the right lung was resected for histological examination, but the mediastinal part of the mass could not be removed

After her recovery from the operation the patient was given deep X ray therapy to the mediastinum When last seen in October, 1956, she was free of symptoms she has not taken alcohol again

The Tumour

The histological appearances of the tumour varied greatly in the sections examined The tumour consisted in some areas of solid epithelial cords and clusters, and in others exhibited a cribriform pattern composed of slightly elongated ovoid epithelial cells, resembling a bronchial carcinoma (fig 3A), the mucoid stroma in the latter areas gave a positive reaction with the periodic acid/Schiff reagent, whereas staining for amyloid was negative In other areas the tumour was much more pleomorphic, almost mimicking Hodgkin tissue Elsewhere, however, follicular collections of small round cells with abortive Hassall s corpuscles were found (fig 3B) This suggested strongly that the tumour was of thymic origin, as did the appearances at operation

CASE 2 —A married woman, aged 57, was admitted to hospital on Sept 25, 1956 She had felt quite well until eight weeks previously when she noticed aching across the front of her chest, gradually extending to her back, shoulders and upper arms, her whole chest feeling 'stiff and taut" These symptoms persisted and became steadily worse For six weeks she had had a dry cough, there were no other spontaneous complaints, but she admitted a loss of weight of 2 stone in a year

She was a moderate smoker, and had been a moderate drinker until this illness About two weeks after her pain started she noticed that alcohol, which she took in the form of beer, stout, or wine, increased the severity of the pain For four weeks she had preferred to abstain rather than experience the acute exacerbation of pain which alcohol always caused The pain got worse a few minutes after taking the first mouthful, and then gradually diminished, finally disappearing about half an hour later, even though she continued to drink

Examination, Investigations, and Course

The patient was weak, she had evidently lost weight, and she coughed frequently She complained repeatedly of the pain described No abnormal physical signs were detected in any system

She was given 60 ml of 5% alcohol by mouth, in two or three minutes the pain, which before the drink was only slight, became much worse, returning to its original intensity after a quarter of an hour

Radiography of the chest showed a rounded opacity in the left lower lobe, just above the diaphragm, tomography showed this to be lobulated (fig 4) No acid fast bacilli or malignant cells were found in the sputum, and a blood count and a barium meal were normal

Bronchoscopy revealed narrowing of the left main bronchus, which was also rigid, so that the bronchoscope could not be passed more than about 1 cm beyond the carina Several

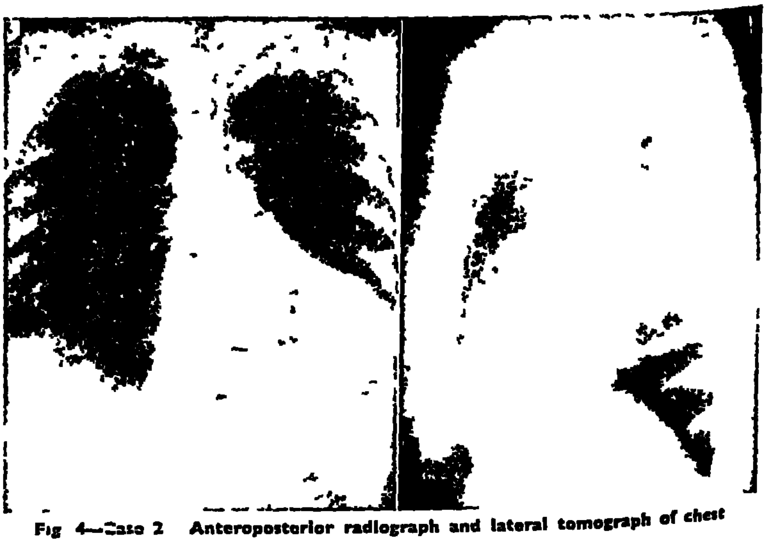

Fig 4—Case 2 Anteroposterior radiograph and lateral tomograph of chest

pedunculated masses were seen, and a specimen was taken for biopsy This was described (Dr R Seal) as showing "a partly necrotic poorly differentiated neoplasm"

The patient's condition deteriorated, and she died thirteen days after admission

Necropsy

At necropsy (Dr B J Stephens) there was a moderate amount of pericardial fluid, and tumour was infiltrating the outer layer of the pericardial sac The left main bronchus was much narrowed by growth infiltrating it from the surrounding tissues, the right main bronchus was narrowed by compression There were several areas of growth in the left lower lobe The pancreas contained a few small areas of growth, and the tail was undergoing necrosis

Microscopy showed, in the pancreas, numerous small areas of pancreatic adenocarcinoma, fairly well differentiated Similar growth was present in the lung, the bronchial mucosa was replaced by a membrane composed of fibrin and partly necrotic carcinoma There was a small deposit of adenocarcinoma in one kidney

Discussion

In case 1 we observed a feature which, so far as we know, has not been described—the spontaneous disappearance of the liability to alcohol-induced pain, at a time when the patient had not had any treatment and the tumour was enlarging There was an interval of just over a year between the last time she had the pain (due to alcohol in influenza mixture) and the finding that pain could no longer be produced We therefore do not know whether the disappearance, which we cannot explain, was sudden or gradual

Before concluding that this rare symptom may very occasionally be produced by any type of malignant tissue, we make two reservations

In case 1 the tumour was probably of thymic origin Thomson (1955) has suggested that Hodgkin's disease is a disseminated carcinoma of which the primary growth is in the thymus, alcohol-induced pain in a patient with a thymic carcinoma might be held to support this hypothesis

The second patient had an adenocarcinoma, probably of pancreatic origin Alcoholism is among the recognised causes of acute pancreatitis, but as a rule the association between drinking and pain is much more remote in time than it was in the patients we have described But in two patients in the series described by Joske (1955) the pain was immediate, and was compared by him to the alcohol induced pain of Hodgkin's disease The mechanism by which alcohol causes such pain in pancreatitis is unknown, but it will be remembered that necrosis was found in the tail of the pancreas in our case 2, and that much of the growth in the chest was necrotic

In neither of our cases was there any evidence of involvement of bone Alcohol-induced pain has been described in two patients with suppurative lesions of bone (Alexander 1953), and one of us has had this symptom at the site of chronic osteomyelitis Infiltration of bone is not essential to the production of alcohol-induced pain in Hodgkin's disease, in several of the reported cases, the patient had such pain at the site of soft-tissue lesions

With these reservations, our experiences suggest that alcohol induced pain is not specific to Hodgkin's disease but that it may occur in other malignant conditions, and that it may be the first indication of their presence Had we known this, case 1 might have been explored while the tumour was still removable Until more is known about this odd symptom it should be systematically inquired for (since it is not always mentioned spontaneously), and it should not be assumed to be diagnostic of Hodgkin's disease

Summary

Two cases of alcohol-induced pain associated with carcinoma, probably of thymus and pancreas, are reported

In one the symptom disappeared spontaneously although the tumour was enlarging

We thank Dr M I Jackson for referring case 2, colleagues named in the text for their help, and Prof Harold Scarborough and Dr Paul Fourman for constructive criticism

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ACUTE PORPHYRIA IN PREGNANCY

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THE manifestations of acute porphyria are widely known, and hundreds of cases have been published, but few reports have appeared of acute porphyria associated with pregnancy, and the conclusions reached in these reports on the influence of porphyria on pregnancy and on the effects of pregnancy on established cases of porphyria are in some ways contradictory The case described here introduces some problems in the management of acute porphyria during pregnancy

Case-report

A housewife, aged 19, was admitted on June 13, 1955, with two days' history of hypogastric pain and early morning vomiting She had been married three months, and her last menstrual period was on March 26, 1955, but she had slight vaginal bleeding five weeks before admission She had been admitted to hospital in November, 1953, with hypogastric pain and diagnosed as having primary dysmenorrhœa, and in March, 1955, with anorexia, colicky lower abdominal pain, and vomiting after meals Her parents were not related, and there was no history of porphyria in the family

On admission she presented no abnormal physical signs, and her general condition was good

Treatment and Progress

For the next week she complained of severe backache and pains in the legs, and during this time she received pentobarbitone sodium ('Nembutal') gr. 1½ on five occasions Slight conjunctival icterus was noted and infective hepatitis suspected She was miserable and uncoöperative and had diffuse abdominal tenderness but no rigidity On June 21, 1955, her urine was of the classical "port-wine" colour Her abdomen was tender on palpation Her limb muscles were tender, but her reflexes were present, and she had no sensory loss Acute porphyria was diagnosed, and the diagnosis was confirmed by finding 127 mg of porphobilinogen per litre of urine Barbiturates were forbidden from then on

The generalised pain and muscle tenderness continued So treatment was begun with subcutaneous neostigmine 0 5 mg six-hourly initially, the dosage being increased daily until a maximum of 4 mg six hourly was reached Pethidine was used to relieve pain with good effect The polyneuritis however, did not remit, and by July 1, 1955, there were obvious abnormal physical signs in the central nervous system weakness of the arms and legs with wasting, especially in the biceps and triceps, quadriceps, and calf muscles, impairment of sensation to pinprick over the front of the thighs and legs lack of tendon reflexes in the arms, right knee jerk and abdominal reflexes, flexor plantar responses, and narrowed calibre of the retinal arteries

After two weeks administration neostigmine was withheld because of signs of intolerance, particularly diarrhœa and sweating Neostigmine did not appear to influence the illness Treatment with tolazoline hydrochloride ('Priscol') 25 mg t d s was started but stopped because of persistent vomiting

Weakness of the intercostal muscles and difficulty in swallowing were evident on July 12, 1955 and the patient was nursed from then on in a ward reserved for cases of bulbar poliomyelitis and providing facilities for suction and intermittent positive pressure respiration Feeding by intragastric drip was necessary partly because of the dysphagia and partly because of the total lack of cooperation by the patient, who remained miserable and depressed Generalised pains were constant and were relieved only by frequent doses of pethidine So subcutaneous pentolinium tartrate ('Ansolysen') 1 mg twelve hourly was given initially, the dosage being increased until 12 5 mg eight hourly was being given, the blood-pressure was measured frequently During this treatment the patient had severe constipation and retention of urine, which were relieved by oral neostigmine 15 mg t d s

Movement of the legs improved by July 14, 1955, and swallowing became easier, but the *patient's mental attitude* remained the same, and she vomited frequently Her blood-pressure fluctuated considerably, there being a tendency to hypertension, the pressure ranged from 120/80 to 150/110 mm Hg according to the dosage of pentolinium

In August, 1955, it became obvious that the patient was pregnant, she still tended to vomit and complained of pains in her back and limbs, whose movements improved a little The pregnancy progressed favourably, but often the presence of severe hypogastric pain suggested premature labour Frequent use of pethidine and amidone effectively relieved the pain After neostigmine was withheld on Oct 6, 1955, there was no more retention of urine Improvement continued until early December, 1955, when the severe pain recurred and the mental attitude deteriorated badly

Delivery and Death

On Dec 13, 1955, labour came on rather suddenly, and a live female infant, only mildly asphyxiated, was born There was a hæmorrhage of about 15 oz during the third stage of labour Injection of ergometrine 0 5 mg and massage of the fundus controlled bleeding After delivery the patient's blood-pressure was 130/115 mm Hg and pulse rate 160 The patient's mental attitude changed profoundly depression gave way to extraordinary cheerfulness Her general condition was poor, she was dehydrated, and her high pulse rate suggested that intravenous fluids and blood were necessary She was vomiting small quantities of brown watery fluid After the blood transfusion was started her pulse rate rose to 186 and blood pressure began to fall She became pulseless and died seven and a half hours after the birth of the infant The infant died a few hours after delivery

Investigations

Examination of the *blood* revealed toxic granules in the polymorphs but no other abnormality *Liver function tests* on June 22, 1955, serum bilirubin 0 2 mg per 100 ml (direct 0, indirect 0 2 mg per 100 ml) and thymol turbidity 3 units, on July 13, 1935, serum proteins 7 g per 100 ml, serum alkaline phosphatase 6 units (King), thymol turbidity 4 units, and thymol flocculation 14 units The *urine* occasionally contained traces of albumin, leucocytes, and erythrocytes It fluoresced under ultraviolet irradiation On June 24, 1955, it contained porphobilinogen 127 mg per litre, and on Sept 13, 1955, 80 mg per litre *Electrocardiograms* were normal The *skin* did not fluoresce under ultraviolet irradiation The patient said that, for as long as she could remember, she had blistered very easily in sunlight, but there was no evidence of scarring as a result of this

Necropsy Findings

Permission was obtained for only a limited necropsy The thoracic and abdominal organs appeared normal on both macroscopical and microscopical examination No abnormality was found in the baby

Effects of Drugs

Pethidine was used frequently and with good effect in the relief of pain in the dosage of 100 mg intramuscularly every four to six hours

Neostigmine was given intramuscularly from June 24, 1955, to July 7, 1955, 0 5 mg six hourly initially and increased to 4 mg six-hourly It was withheld because of diarrhœa, sweating, and dryness of the throat

Given orally in the dosage of 7 5 mg t d s from July 18, 1933, to Oct 6, 1955, it relieved constipation and retention of urine (possibly caused or aggravated by pentolinium) but did not influence the pain or the peripheral neuritis After neostigmine was withheld on Oct 6, 1935, bowel and bladder function were normal

Tolazoline given orally from July 7 to 12, 1955, in the dosage of 25–50 mg t d s was not well tolerated and did not appear to influence the course of the disease It produced persistent vomiting

Pentolinium tartrate—'Ansolysen Retard' was given subcutaneously from July 12, 1955, to Aug 19, 1955, in the dosage of 1 mg eight hourly initially and increasing gradually to 12 5 mg eight hourly The dosage was frequently adjusted to control the rise in blood pressure It did not appear to alleviate the pain, and we were not impressed by its effect

Vitamin B_{12} ('*Cytamen*') was given intramuscularly in dosages of 100–1000 µg daily from Aug 12, 1955, to Sept 20, 1955 Its administration coincided with slight subjective improvement and disappearance of muscle tenderness

Chlorpromazine given orally in the dosage of 25 mg t d s from Aug 22 to Aug 29, 1955, produced no effect

Vitamin B concentrate, vitamin A, and *vitamin D* were also given in full dosages as a routine

Discussion

This case illustrates most of the classical features of acute porphyria This attack appears to have begun in early pregnancy Although there was some improvement in the later months, severe deterioration took place a few days before labour, and the patient died in a state of shock seven and a half hours after the delivery and after having half a pint of blood transfused

Influence of Pregnancy

The influence of pregnancy on acute and chronic porphyria has been commented on in a few published reports

Dean (1953) stated that during pregnancy the patient was usually much worse, and suggested that this might be due to sedatives In the present case the porphyria had presumably developed before admission to hospital, after which barbiturates were given on four occasions before the diagnosis was established

O'Dwyer (1955) suggests that pregnancy may benefit patients with porphyria by stimulating the endocrine system and reports a twin pregnancy in which the patient improved after delivery The improvement, however, did not take place before the end of the pregnancy, so one might argue that his patient benefited more from the return to the non pregnant state

Rawlings (1950) noted improvement during pregnancy Coleman (1948) reported a case in which pregnancy was well tolerated and delivery was by cæsarean section

The case described by Freedman et al (1952) was of great severity and of particular interest because the patient became pregnant in a remission of her ten months' illness Her porphyria was exacerbated in the first trimester but subsequently improved It seems that the pregnancy precipitated a further attack of porphyria

In the present case the pregnancy seemed to precipitate the first major attack of porphyria, but the previous episodes of "primary dysmenorrhœa" and "pelvic congestion" were probably minor episodes of porphyria The number of cases published is too small to show with certainty the effect of pregnancy on acute porphyria but is, I think, sufficient to advise caution in permitting pregnancy in women known to have porphyria It seems clear, however, that pregnancy can proceed normally in cases of acute porphyria, in spite of the clinical deterioration of the patient

Blood transfusion

The fact that the patient died shortly after a blood transfusion may be significant There was nothing to suggest an incompatible transfusion, and one wonders whether transfusion of blood in such a profound metabolic disturbance is advisable Coleman (1948) reported a case in which a blood transfusion was given without untoward reaction, and Freedman et al (1952) noted improvement after a blood-transfusion Possibly in the present case the serious deterioration after the blood transfusion was coincidental

Ergometrine

The use of ergometrine after delivery of the placenta may have been a factor causing the early postnatal deterioration The manifestations of acute porphyria are thought to be due to vasospasm causing foci of ischæmic necrosis, porphyrins being vasoconstrictors It is probably unwise to potentiate this action by using drugs such as ergometrine

A change in mental attitude after delivery has been noted by Freedman et al (1952), whose patient underwent complete change of personality

Summary

A case of acute porphyria in pregnancy is described

Blood-transfusion and ergometrine are suggested as factors that may have caused death

I wish to thank Dr P R C Evans for advice and encouragement in the preparation of this report, and Prof C Rimington for help in investigating the case

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FATAL AGRANULOCYTOSIS DURING CARBIMAZOLE THERAPY

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CARBIMAZOLE appears to be one of the least toxic of anti thyroid drugs In a review of published reports Burrell et al (1956) found an incidence of major toxic effects of 0 5% By "major toxic" effects they meant either serious depression of the marrow or drug fever (with or without enlargement of lymph glands), or arthralgia They found that agranulocytosis had been reported in only 4 cases in the United Kingdom and the United States The toxic symptoms came on within two months of the start of treatment with carbimazole and developed only with a dosage of more than 20 mg daily

Burrell (1956) lists 6 published cases of serious depression of the marrow and adds 1 further case, which was fatal Of the 6 cases 1 was fatal (Richardson et al 1954)

Of the 21 cases I have treated with carbimazole, 2 have shown depression of the polymorphs in the peripheral blood, necessitating a change to other treatment (perchlorate) A third patient developed complete agranulocytosis and died In view of the widespread use of carbimazole and its apparent low toxicity, I record this last case

Case-report

A man, aged 66, was admitted to hospital on April 30, 1956 He stated that he had been well until about a fortnight previously, when he developed what was probably an infection of his upper respiratory tract When he got better from this he did not recover his usual energy and he became short of breath on walking This dyspnœa soon became persistent being greatly aggravated by any attempt to lie down Palpitations began to trouble him Swelling of the feet and ankles appeared about a week after admission to hospital

His previous health had been good, apart from a recurrent cough each winter and a "large neck" for very many years The family history was not relevant

Examination —On admission he was dyspnœic and had engorged neck veins and moderate œdema of his feet and legs The isthmus and the right lobe of his thyroid gland were enlarged and the right lobe was nodular His pulse rate was 150, the pulse being irregular in rhythm and force His heart was enlarged to the left with the apex beat $^1/_2$ in outside the left mid clavicular line At the apex was heard a harsh systolic bruit which was not propagated in any particular direction His blood pressure was 180/80 mm Hg His prostate gland was enlarged

He was regarded as having left ventricular failure with atrial fibrillation due to hyperthyroidism from a nodular goitre

Investigations —Radiography showed an enlarged heart with pulmonary congestion and small bilateral pleural effusions The hæmoglobin was 84% and the white cell count 6000 per c mm (neutrophils 66%, eosinophils 1%, basophils 2%, lymphocytes 21%, monocytes 10%) The blood-cholesterol was 90 mg per 100 ml The urine was infected with coliform bacilli sensitive to chlortetracycline (aureomycin)

Treatment was begun with chlortetracycline 250 mg six-hourly for eight days and digoxin 1 0 mg initially, followed by 0 5 mg six-hourly till digitalised, followed by a maintenance dose A test dose of 0 5 ml of intramuscular mersalyl was given, after which the patient collapsed and his pulse rate rose alarmingly This was regarded as a toxic reaction to mersalyl, and no more was given Carbimazole 10 mg three times a day was administered from the start

Progress —The patient's urinary-tract infection persisted, and culture on May 14 grew coagulase positive *Staphylococcus aureus* sensitive to nitrofurantoin ('Furadantin') During this period the white cell counts showed a neutrophil leucocytosis of 21,650 per c mm on May 11 to 15,000 per c mm on May 19 With nitrofurantoin therapy the urine became sterile on May 24 On May 29 the white cell count was 15,000 per c mm (neutrophil polymorphs 8000 per c mm) By this time the patient was much improved as regards urinary symptoms, cardiac failure, and hyperthyroidism, but on June 7 the white cell count was 7000 per c mm (neutrophils 4550 per c mm) On the 19th his temperature rose suddenly, and he looked ill His throat was healthy Carbimazole was stopped immediately A white cell count showed 300 per c mm (neutrophils 6 per c mm) The hæmoglobin was 62% Treatment with penicillin and blood-transfusion was started, but the patient deteriorated rapidly and died on June 22 Before death his urine again contained coagulase positive *Staph aureus*

Necropsy revealed an enlarged prostate cystitis, and a nodular goitre The heart was considerably enlarged

Comment

This patient developed fatal agranulocytosis while on carbimazole 30 mg daily So far as I am aware, no depression of the marrow has been reported to follow use of treatment with nitrofurantoin, so it seems clear that the carbimazole was responsible The patient developed what was probably a reaction to mersalyl, and this suggests that he may have been predisposed to drug reactions, although he gave no previous history of allergy Most cases of neutropenia recover when the offending drug is withheld, as in the two previous cases, in which, however, the neutropenia was never severe and the patients were never ill These 2 cases were detected by routine white cell counts, which most authorities today regard as of little value Though agranulocytosis usually comes on with dramatic suddenness, occasionally there is a more gradual depression of neutrophils This suggests that the routine white-cell count is not altogether valueless during the first two months of therapy

Summary

A case of fatal agranulocytosis in a man, aged 66, treated with carbimazole is described

This appears to be the eighth recorded case of severe hæmatological reaction to carbimazole, and the third fatal case

Two other cases of neutropenia detected by routine white cell counts are mentioned

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repeated renal circulatory damage was additive in its effects on kidney function Oliguria and anuria due to polyarteritis nodosa or acute glomerulonephritis was of more serious prognosis than the more usual cases of acute tubular necrosis and did not appear to be benefited by cortisone

Of tubular lesions, acute tubular necrosis due to renal ischæmia and proximal tubular necrosis due to nephrotoxic drugs had a more favourable prognosis than renal cortical necrosis with simultaneous glomerular damage and renal papillary necrosis affecting the renal papillæ and collecting tubules Obstructive lesions of the ureters should be treated surgically but were important to the physician since they could mimic medical varieties of anuria Conservative treatment was essential in all cases of acute renal failure, but dialysis with the artificial kidney was useful in cases showing uncontrolled hyperkalæmia or acidosis

Dr A M JOEKES described some illustrative cases of oliguric renal failure complicating medical conditions One cause of acute tubular necrosis which had not often been recognised was the profound circulatory collapse after a major pulmonary embolism Hepatic disease with jaundice seemed to predispose to acute renal failure Dr Joekes described 4 cases associated with biliary cirrhosis and acute hepatitis, all 4 recovering from the episode of renal failure The rôle of hæmoglobinuria in the production of acute tubular necrosis was still undefined While renal damage was common after incompatible blood-transfusion and in blackwater fever, it was rare in acute hæmolytic anæmia An additional element of circulatory shock seemed to be an essential factor in causing renal damage

Percutaneous renal biopsy was sometimes of great value in assessing whether recovery was possible, and therefore in guiding therapy In a case of scleroderma with severe renal damage, prolonged conservative therapy had been deemed undesirable in view of the gross and irreversible renal damage found at biopsy

Dr E M DARMADY described the changes in acute tubular necrosis as shown by microdissection of nephrons and histological preparations Immediately after the onset stage the glomeruli were engorged with blood, and this was followed by a focal loss of translucency of the tubules, mostly confined to the proximal segment In the early stage of anuria or oliguria, transparent casts were seen in the lower end of the proximal tubule and loops of Henle, there was scattered tubular epithelial disarrangement and focal necrosis In the middle of the anuric phase there were tubular ruptures in all parts of the nephron, at the same time there were prominent casts in the distal and collecting tubules In the diuretic phase there was evidence of epithelial regeneration in the previously damaged portion of the nephron Dr Darmady considered that interstitial œdema with increase of intrarenal pressure was not the cause of the oliguria Since many of the tubules were not sufficiently damaged to prevent urinary secretion it was thought the glomeruli must be the operative factor in causing the anuria or oliguria Possibly the engorgement of the glomeruli in the early stages was similar to the anuria occurring in homotransplanted kidneys in dogs, for, although there was damage to the juxtaglomerular portion of the nephron which could be partly prevented by cortisone, injection of indian ink into the renal circulation at the time of anuria showed that the glomeruli were overfilled with blood, suggesting lack of tone of the capillary tuft with a sluggish circulation

In the recovery phase of oliguria there might be considerable excess urinary potassium loss In these cases the tubular cells showed the typical " vacuolar nephropathy " of potassium depletion—a change which Dr Darmady had also found in kidneys from cases of primary aldosteronism

Reviews of Books

Pediatrics

Edited by DONALD PATERSON, M D , formerly clinical professor, department of pædiatrics, University of British Columbia , JOHN FERGUSON McCREARY, M D , professor and head, department of pædiatrics, University of British Columbia Montreal J B Lippincott, London Pitman Medical Publishing 1956 Pp 654 £3 10s

THIS new Canadian textbook is edited by Dr Paterson, whose books on infant feeding and diseases of children became well known in this country when he practised in London, and by Dr McCreary, who crossed the American continent a few years ago from Toronto to become professor of pædiatrics in the new medical school at Vancouver Of the 36 contributors, 21 belong to that school and 7 to Toronto, while 7 other Canadian medical schools are represented

Canadian practitioners felt the need for a book of medium size such as this, with a practical approach and emphasis on diagnosis and treatment and the common problems of pædiatric practice Rarities are mentioned briefly, thus ensuring a well-balanced comprehensive picture The work includes chapters on *accidents* and sudden death , diseases of the ear, nose, and throat, eyes, skin, and bones and joints , disturbances of adolescence , and pædiatric gynæcology It is well arranged and concisely written and the illustrations are good, though more than 102 would have been welcome in such a good volume

Chemosurgery in Cancer, Gangrene and Infections

FREDERIC E MOHS, B SC , M D , associate professor of chemosurgery, department of surgery, University of Wisconsin Medical School Springfield Charles C Thomas, Oxford Blackwell Scientific Publications 1956 Pp 305 102*s* 6*d*

Too little thought has been given to the possibility of destroying surface growths by chemical means Dr Mohs has devised a system whereby such lesions may be eliminated by using zinc chloride, which penetrates and " fixes " the mass After one application the fixed mass is removed and examined histologically , should malignant cells be seen on the deep surface, zinc-chloride paste is again applied to the area , several applications may be necessary Surgical excision can be undertaken initially and followed by chemical treatment The method calls for experienced histological control , the five-year-survival figures indicate that in Dr Mohs's hands chemosurgery compares well with other methods

An Introduction to Electrocardiography

L SCHAMROTH, M R C P E , F R F P S , University of Witwatersrand and General Hospital, Johannesburg Cape Town and Johannesburg Juta 1956 Pp 60 21*s*

IN this short book the essential principles of electrocardiography are clearly explained on a basis of simplified electrophysiology The text is illustrated by diagrams which are mostly helpful , but the value of this introduction would have been enhanced by the inclusion of some typical electrocardiograms diagrams, however good, are indifferent substitutes As it is, the book should be a most useful supplement to larger textbooks of electrocardiography

Traité des urgences en chirurgie

Vols 1 and 2 P BROCQ, F POILLEUX, R CHABBUT Paris Masson 1956 Pp 1301 Fr 8000

THIS comprehensive work on emergency surgery is designed to cover all contingencies which might be encountered by an isolated surgeon working in a remote area , fractures are therefore very properly included It is an instructional work with a didactic flavour Though in some respects practice differs from that in this country, there is a general concurrence of view

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Child Development (London Tavistock Publications 1956 Vol 2 Pp 271 28*s*)—The proceedings of the second meeting of the World Health Organisation study group on the psychobiological development of the child, held in London in 1954, have been published under the editorship of Dr J M Tanner and Prof Barbel Inhelder

THE LANCET

LONDON SATURDAY, FEB 9, 1957

Cancer of the Œsophagus

TWENTY years ago the œsophagus was a surgical no man's land separating the laryngologist from the abdominal surgeon—and both approached it with trepidation The results of surgery for malignant disease of the œsophagus were very poor, and the best that could be said for radiotherapy was that it often precipitated the end by causing a perforation of the œsophagus The picture has changed The opportunities offered by advances in anæsthesia, by the new antibiotics, and by a more physiological approach to postoperative care have been seized with enthusiasm by the surgeon[1], and super-voltage machines have enormously increased the power and range of radiotherapy So impressive are these new methods of treatment, and so many are the alternatives suggested for different types of growth and patient, that, if steady progress is to be achieved, their relative merits must now be carefully weighed SMITHERS[2] rightly insists that, restricted though its use may be to a few centres, modern radiotherapy (like modern surgery) should be judged by the best it can offer, and, reviewing 314 cases of cancer of the œsophagus, seen at the Royal Marsden Hospital between 1936 and 1951, he is in an excellent position to form such a judgment 65 patients in this carefully analysed series are grouped as "untreated", but they include those who had such minor palliative procedures as the passage of Souttar's tubes, gastrostomy, or jejunostomy None survived for two years, and 95% were dead within six months These dismal figures closely agree with the recently published findings of MUSTARD and IBBERSON[3] from the Toronto General Hospital and they confirm the low opinion in which gastrostomy and jejunostomy are generally held Both operations shorten rather than prolong life inflict rather than alleviate suffering This is the grim background against which all the bolder forms of treatment must be evaluated

In the Royal Marsden Hospital series 20 of the 314 patients had the growth resected 5 of them survived for two years and 1 of them is still alive after eight years In the Toronto series (381 cases seen by various members of the General Hospital staff in the years 1947–53) the tumour was operated on in 133 patients and resection was possible in 100 Of these 133, 48 died before they left hospital but 7 survived for five years or more SMITHERS also describes the results in 229 patients treated by radiotherapy 20 survived for two years and 7 for five years (Of these 7 patients 4 eventually died of unrelated intercurrent disease but 2 succumbed to late recurrence of cancer) The Canadian results in 55 irradiated patients show 10 two-year survivals and 1 five-year survival Such figures are, of course meaningless, if not actually misleading, unless note is taken of the many things which influence the selection of patients and, indeed, a consideration of these is in some ways more illuminating than a contemplation of the numerical end-results The most notorious variable in internal selection is the anatomical definition of the œsophagus, and its bearing on statistical findings, especially those relating to cancer, is well illustrated by the Canadian series This group includes among tumours of the upper third of the œsophagus, cancers of the laryngo-pharynx, a type of growth which differs from more distal growths in its age and sex incidence (it predominantly affects middle-aged women), as well as in its accessibility and response to treatment Perhaps because of the "almost infinitely repeated trauma of the food bolus squeezing through the crico-pharyngeal sphincter,"[3] malignant disease is very common in this short segment of the alimentary tract, and no less than 27% of all "œsophageal" tumours in the Toronto series started in this region At the lower end of the gullet it was impossible to exclude with complete certainty all cancers arising from the stomach, and though every effort was made to do so, it is perhaps significant that both the long survivors with lesions of the abdominal œsophagus had adenocarcinomas Other variables, such as standards of skill, differences in the personal experience of the surgeon or radiotherapist, and the closeness of the coöperation between them, make it hard to compare results from different sources Nevertheless, such comparisons are one of the few sources of guidance for the future, true results are, after all, only beginnings

It is often said that by and large, modern radiotherapy and surgery achieve similar results in carcinoma of the œsophagus Such remarks reveal a tendency to stray prematurely to the foot of the column marked "total" rather than examine the data in full, for all surgical series contain a preponderance of lower-third tumours, accounting sometimes for as many as 50% or 60%,[4 5] and disproportionately few upper-third cancers In groups of patients treated by radiotherapy, though results for all sites may be inferior, the growths are usually more evenly distributed[2 6 7] At least one reason is not far to seek surgery is undoubtedly at its best in the lower reaches of the œsophagus, and least successful near the upper end Radiotherapy, on the other hand, has proved most effective in the upper œsophagus (whence metastases to subdiaphragmatic lymph-nodes are late and uncommon)

There is even less justification for saying that today's five-year survivals reflect only the natural history of the disease Gloomy as the prognosis of œsophageal cancer still is treatment has certainly restored health to a few patients, prolonged life in some, and made existence tolerable for many Surgery can do much in the way of palliation and it could do more if surgeons were less reluctant to admit that the chances of absolute cure—even in the best

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[1] See leading article *Lancet* 19[illegible] ii 6 3
[2] Smithers D W *Ann R Coll Surg Engl* 1957 20 36
[3] Mustard R A Ibberson O *Ann Surg* 1956 144 927
[4] Sweet R H *J Amer med Ass* 1954 155 422
[5] Franklin R H Shipman J J *Brit med J* 1952 i 947
[6] Köhler I *Acta radiol Stockh* 1951 35 207
[7] Nielsen J *Ibid* 1945 26 361

hands—are still remote, and that the best radical operations are not always the best palliative ones Now that a sound palliative operation can ensure several months, or even years, of comparative comfort, it is self-deception to say after an unsatisfactory resection and anastomosis (often a patched-up affair at the end of a gruelling three-hour session) that it will at least relieve the patient of his discomfort Should the patient survive (and his chance is hardly better than even) he would have been better served with no resection, and, what is more disturbing, nine times out of ten this has been plain from the beginning "On passe souvent de l'amour à l'ambition, mais on ne passe guère de l'ambition à l'amour"[8] it is a sad paradox that the number of different radical operations recommended (and presumably practised) today almost certainly exceeds their total number of survivors Even those that look sound on paper should be judged with at least one eye on the mortality figures—which are sobering **Humphreys** and **Moore**[9] report from the Presbyterian Hospital in New York that of all patients seen there with primary œsophageal cancer (162 cases in ten years) there was not 1 five-year survivor At the New Haven Hospital, during a similar period, the only 3 survivors had adenocarcinomas, probably originating in the stomach[10] **Parker** and **Jenkins**[11] could find only 1 five-year cure at the Roper Hospital, Charleston, in a review of 210 cases, and **Ravitch**,[12] though he does not give the total number of patients that were seen, could find none at the Johns Hopkins Hospital There may be scope for improvements in operative technique, but neither its present imperfections nor delay in diagnosis can take much blame for these results In contrast to radical operations, **Mustard** and **Ibberson** are convinced that palliative by-pass operations have real merit and that they are usually feasible "The ability to swallow is promptly restored and maintained regardless of whether or not the primary lesion can subsequently be successfully dealt with"[3] At present **Mustard** and **Ibberson** perform an anterior mediastinal by-pass, using a jejunal Roux loop[13] or a colonic segment, in all "good-risk" patients with malignant obstruction As an alternative, a palliative intubation[14] has the merit of simplicity, and it can be used for growths at all levels

An understandable distaste for compromise may partly explain why radiotherapy (by tradition, if not in fact, palliation par excellence) still rarely gets the consideration it deserves Despite a cure-rate of 7% for tumours of the upper third, **Aird**[15] feels that deep therapy has little to offer for œsophageal carcinoma and though "in the middle œsophagus a fairly effective tumour dose can be obtained by rotating the patient in the beam results are not satisfactory, and in the lower part of the œsophagus this form of treatment is entirely useless" No one will dispute these statements but will they not encourage the less experienced to discard a method which has proved useful, within its limitations, in favour of one which is more spectacular but more lethal? As an alternative to survival-rates of less than 1% after radical surgery in the mid œsophagus (and an almost prohibitive operative mortality), radiotherapy can usually restore the patient's ability to swallow, "with a minimum of discomfort, with a stay in hospital of a few weeks and with virtually no treatment mortality the majority of those patients swallow well until their death"[3] There may or may not be a place for combined therapy —either by preoperative irradiation or the use of radioactive-gold-grain implants[16]—but there is certainly a place for combined efforts in selecting cases for whichever form of treatment holds out most promise **Smithers** believes that "both methods are likely to improve still further in the next few years and they have their individual sites of maximum advantage, but competition to the patient's disadvantage instead of cooperation to produce the best results is still far too common" In the treatment of cancer of the œsophagus, no less than elsewhere, isolated surgical successes, however Homeric in their dash and brilliance, do not justify the Homeric afterthought that "the rest were vulgar death unknown to fame"[17]

New Drugs, Old Dangers

Among the many new drugs that have lately been introduced, the most prominently displayed are the organic chemicals for the relief of pain and insomnia, and the so-called "tranquillisers" The chemical structure of many of these drugs raises suspicion that they may damage the blood-forming tissues and the blood-vessels, and evidence is accumulating to show that this suspicion is justified The chances that a given drug will harm a particular patient are probably very small, and the mounting record of blood disorders may be largely a reflection of the great number of patients who are now being given these drugs, rather than a sign of serious toxicity Nevertheless, there is good reason to emphasise again that many of these substances can kill and that others may yet turn out to be potentially lethal We review below some of the examples of drug-induced blood disorders that have come to notice in the past two or three years

Phenylbutazone ('Butazolidine') was introduced for the treatment of rheumatoid arthritis and other painful joint conditions **Leonard**,[18] who reviewed the literature in 1953, collected 356 instances of toxic reactions among 1526 treated patients, and these included 11 cases of agranulocytosis He himself recorded 1 patient who had fatal aplastic anæmia and 1 who had granulocytopenia but recovered. This second patient had been treated for six weeks when sore throat and fever began, the white cell count was 1600 per c mm with 34% polymorphs, he was treated with penicillin and recovered **Dilling**[19] also described a fatal agranulocytosis due to sensitivity to phenylbutazone This patient had 600 mg daily for five days, but when œdema developed the drug was stopped, after seven days treatment was resumed and 450 mg was given daily Three days later she had severe symptoms, the white-cell count was 2000 per c mm, no polymorphs were found, and the patient died three

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8 LaRochefoucauld F Maximes no 490, 1652
9 Humphreys, G H, Moore, R L *Surg Clin N Amer* 1953, 33 389
10 Shedd D P Crowley, L G Lindskog G E *Surg Gynec Obstet* 1955 101 53
11 Parker E F, Jenkins L B *J thorac Surg* 1955 29 373
12 Ravitch M M, Bahnson, H T, Johns, T N P *Ibid* 1952 24 256
13 Robertson, R, Sarjeant, T R *Ibid*, 1950, 20, 689
14 Coyas A *Lancet*, 1955 ii, 647
15 Aird, I Companion in Surgical Studies Edinburgh 1957
16 Fleming, J A C, Barrett, N R *In* British Practice in Radiotherapy London 1955
17 Homer's Iliad Book ii, line 394
18 Leonard, J C *Brit med J* 1953, i, 1311
19 Dilling, N V *Lancet* 1953, i, 1230

days later Another fatal agranulocytosis[20] was the outcome of the patient's insistence on "the new treatment" for her rather vague arthritis After 200 mg daily for four weeks she had sore throat and pyrexia Her white cells numbered 1000 per c mm, with 2% polymorphs, but her marrow still contained 43% myelocytes The white count recovered with treatment, but the patient died, and at the post-mortem examination there were multiple abscesses in the lungs and a few in the liver

Chlorpromazine ('Largactil') is enjoying some popularity as a short-term sedative, and psychiatrists are giving it for longer periods In 1955, Tasker[21] described fatal agranulocytosis in a woman who was being treated for hysteria It is interesting that warning signs appeared when the treatment was begun—pyrexia, slight jaundice, and an irritant rash—but they settled down and treatment was continued for forty-one days to a total of 5 5 g of chlorpromazine Typical acute agranulocytosis, with ulcerative stomatitis then followed, the white count was only 900 per c mm, with 10% polymorphs, and the patient died eight days later Adams et al[22] saw agranulocytosis in a patient in an anxiety state who had been given 12 g of chlorpromazine in eight weeks The onset was sudden with severe pharyngitis and a temperature of 102°F The white cells were down to 800 per c mm, all lymphocytes, and the bone-marrow was almost completely devoid of granulocytes, though erythroblasts and megakaryocytes were present in normal numbers Cortisone and antibiotics were given, and he recovered in a week Another patient was detected at the granulocytopenia stage when she had 1200 white cells per c mm and 34% polymorphs, and she recovered quickly when the chlorpromazine was stopped Schick and Virks[23] have lately collected 21 published cases of agranulocytosis due to chlorpromazine, 8 of them fatal Their own patient had had 100 mg daily for six weeks when the signs and symptoms of acute agranulocytosis appeared, there were 800 white cells per c mm and no polymorphs, the marrow contained only 0 5% myelocytes and no other granulocytes, but normoblasts were plentiful With blood-transfusion, penicillin, and ascorbic acid, the patient recovered in four days

One of the tranquillisers, *meprobamate* ('Miltown,' 'Equanil') has been blamed for purpuric reactions Carmel and Dannenberg[24] saw 3 patients in whom non-thrombocytopenic purpura developed after relatively small doses For example, a woman of 42 was given meprobamate after a minor operation, after 3 tablets of 400 mg purpura appeared over the thigh, trunk, abdomen, and arms, she also had anorexia and fever The platelet-count and other blood examinations were normal, but capillary fragility was increased The purpura subsided in a week Similar purpuric rashes have been reported[25 26] after small doses of meprobamate So far no case of agranulocytosis has been attributed to meprobamate, but 'Pacatal,' another tranquilliser, has been associated with this syndrome Acute agranulocytosis developed after six weeks' treatment with pacatal for depression[27] After 5 5 g had been given, the white count was 3000 per c mm with 53% polymorphs, but nine days later the patient had a sore throat and fever, and the white count fell to 850, polymorphs being completely absent Treated with sodium pentosenucleotide, penicillin, and streptomycin, she recovered in a few days

Another sedative that can cause trouble is *carbromal* It is on sale to the public without restriction and is contained in various proprietary sedatives, such as 'Adalin,' 'Persomnin,' 'Dormiprin,' and 'Somnitil' Borrie[28] described 6 cases of widespread non-thrombocytopenic purpura in patients who had had this drug

Many doctors may be surprised to know that some sedative mixtures still contain the first drug to be implicated as a cause of agranulocytosis, *amidopyrine*, or its derivatives, 'Novalgin' is an example, and it is still causing agranulocytosis from time to time[29 30] There is no virtue (and some danger) in amidopyrine combinations and their use should cease

A quite different drug that is now coming in for criticism is *carbimazole* ('Neo-mercazole'), used in the treatment of hyperthyroidism A patient had typical acute agranulocytosis after six weeks' treatment with doses of 15–30 mg daily[31] The white count was reduced to 150 per c mm, with no polymorphs The patient recovered after blood-transfusion, penicillin, and pyridoxine In another case,[32] a fatal aplastic anæmia supervened after five months' treatment with carbimazole, the hæmoglobin level was 7 6 g per 100 ml, white cells 1500 per c mm (7% polymorphs), and platelets only 2000 per c mm The patient died from a cerebral hæmorrhage In his article on p 303 Dr Tait describes a fatal agranulocytosis in a man who had had carbimazole, this is apparently the third recorded death to be associated with this drug

These serious toxic reactions are admittedly rare, but when they do appear they strike suddenly and quick action is imperative The cases to which we have referred illustrate how these reactions may develop either early, as in the treatment of patients who are sensitive to the drug, or after a long course It cannot be said too forcibly that the drug must be stopped at the very first sign of a reaction, one patient who died had continued taking the drug for three weeks after the first purpuric rash had appeared[32] In treatment, blood-transfusion and penicillin are always advisable, for the rest, the progress of patients with agranulocytosis suggests that sodium pentosenucleotide pyridoxine, or vitamin-B complex make little difference to the outcome A bone-marrow examination is always useful because it is a good guide to prognosis[33] If recovery is going to take place, polymorphs return to the blood within two or three days

Since these drugs, and others like them, can do such damage, they must always be used with caution, and it might reasonably be asked whether some of them should be given at all On the other hand, as incidence of toxic changes is small, large and lengthy trials would be needed to prove that a new drug was invariably safe, and naturally, manufacturers are anxious to bring forward their more promising new products without delay Many manufacturers take great pains to secure evidence of freedom from toxicity, others have less exacting standards But whatever may or may not have been done before a drug is offered for general use, the surest safeguard is to look on every newcomer as potentially dangerous, and to be sceptical of confident statements to the contrary—for the first five years at any rate If a new drug is used only when there is a clear indication for it, and when hospital trial has firmly established its superiority over its more familiar predecessors, then the occasional reaction is a risk that is justified—and one that is taken every day when sulphonamides, chloramphenicol, or phenobarbitone are prescribed And the risk will be reduced still further if, at the first sign of sore throat, purpura or unexplained pyrexia, the patient is sent at once to hospital with a statement of the drugs he has had, in what dose, and for how long

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[20] Wood I H *Brit med J* 1954 i 802
[21] Tasker J R *Ibid* 1955 i 950
[22] Adams J C L, Cortl K D F Hobson, Q J G *Ibid*, 1956 i 1088
[23] Schick G Virks J *New Engl J Med* 1956 255 798
[24] Carmel W J Dannenberg T *Ibid* p 770
[25] Feldman H T Marmelzat W G *J Amer med Ass* 1956 162 62[illegible]
[26] Gottlieb F I *Ibid* 1956 161 96
[27] Gore C P Blezard A *Lancet*, 1956 ii 1081
[28] Borrie P *Brit med J* 1955, i 615
[29] Patuck D *Ibid* 1954 i, 919
[30] Hutchison H F Conway, H *Ibid* 1955 i 208
[31] Harrison A R *Lancet* 1954 i, 396
[32] Burrell C D *Brit med J* 1956 i, 1456
[33] Israëls M C G Atlas of Bone Marrow Pathology London, 1956, p 39

Annotations

AN INCOME-TAX ANOMALY

We can hardly expect that our laws shall always be applied equally, for their application depends on people, and people, as we know, are various On the other hand we are entitled to demand that our statutes shall not discriminate against any group A small but important instance of such discrimination is the inequitable income-tax law which is at present applied to doctors engaged whole-time in the National Health Service

The law is clear Doctors who derive a substantial part of their income from private patients may, under Schedule D, offset against their income the cost of professional journals and books, and of attending scientific meetings The whole timers (under Schedule E) cannot do so—unless perhaps their contracts demand that they shall incur these expenses The discrimination does not end there For instance, the part timer can claim for relief from income tax the cost of professional motor car expenses not covered by the official allowance the full-timer cannot The part-timer can likewise claim for some of the cost of entertaining overseas doctors who are visiting hospitals or attending conferences in this country the whole-timer cannot

Besides whole-time consultants, other doctors and other professional groups are victims of this anomaly, which is not new but is felt more acutely than ever before because high rates of tax begin at lower real incomes Rationally the discrepancy is indefensible This was recognised by the Royal Commission on Taxation of Profits and Income in its declaration that "there is no good reason for treating Schedule E expenses less generously than Schedule D expenses, except to the limited extent that some difference of treatment is inherent in the nature of the two kinds of income" The Royal Commission concluded that the Schedule-E rule governing deductible expenses should be amended to permit the allowance of expenditure "reasonably incurred for the appropriate performance" of the duties of the office or employment

Owing to the rapid progress in diagnostic methods and in therapy, it is quite impossible for doctors to keep up a high standard without having books and journals *at their disposal and without attending meetings of* scientific societies These expenses are an unfairly heavy toll on those who, unlike their colleagues, cannot set them against income We earnestly hope that the Chancellor of the Exchequer will find it possible in the coming Budget to end this inequity

DIABETICS AND DRIVING

The judgment described on p 319 arose out of charges brought against a diabetic driver under the Road Traffic Act The Lord Chief Justice said "this section (of the Act [1]) was designed for the protection of the public, and if people were in a condition of health which rendered them subject to comas, or the remedies for which might send them into comas, they ought not to drive because of the danger which resulted to the rest of Her Majesty's subjects"[2] *Quite so the relevant section* of the Act says that "any person who when driving or attempting to drive or when in charge of a motor vehicle on a road or other public place is under the influence of drink or a drug to such an extent as to be incapable of having proper control of the vehicle shall be liable ", and there can be no serious contention that Lord Goddard's decision is anything but right in law The widespread interest that his ruling has aroused serves not only to waken public concern over diabetic drivers but also to illuminate a rather unsatisfactory section of an Act which daily increases in importance

How dangerous *is* the diabetic in charge of a motor vehicle ? It is clear from the small number of cases that come before the courts that few diabetics are, in fact a serious menace to their fellows On the other hand, a potential hazard does exist, and it remains to assess its dimensions In the first place, only those diabetics who require and receive insulin by injection are concerned Despite learned counsel's contentions, diabetic coma is always of slow onset, and most drivers would have time to relinquish charge of a vehicle in the several hours that pass before consciousness is lost And insulin requiring diabetics make up no more than 20–25% of the total diabetic population Diabetics who do not need insulin may be given it in error, but they are notoriously resistant to its action, and rarely suffer from hypoglycæmia Next, the great majority of insulin-requiring diabetics are well controlled, and, provided that they take their meals regularly and they do not engage in unusual physical exertion, they are not subject to attacks of coma It must be remembered that it is no crime to be in charge of a motor vehicle while under the influence of a drug it becomes a crime only when the drug's action prevents the driver from having proper control of the vehicle

There are five different types of insulin available, one in three forms, and all in three strengths Although dispensing errors are very uncommon, wrongly measured doses are by no means rare, and they account for most reactions in otherwise well-stabilised patients Rarely, reactions occur for no detectable reason, and they are usually attributed to sporadic endogenous production of insulin There remains a very small group of patients, chiefly young people, in whom control is difficult and who often suffer from hypoglycæmia and its consequences It is to these patients that Lord Goddard's remarks seem justly to apply

Diabetics are not alone in their liability to abrupt loss of consciousness Epileptics, for example, are similarly afflicted And since heart-attacks may recur, and often do, at moments of stress, should a patient who has had a coronary thrombosis likewise be excluded from driving ? What is the position of a patient who has *spontaneous* hypoglycæmic attacks ? Manifestly, the law needs some interpretation on this point, and de jure recognition of this is given earlier in the Act,[3] where provision is made *for the licensing of* handicapped drivers in certain circumstances—circumstances which would include all but a handful of diabetics Moreover, it receives much wider de-facto recognition from *most* licensing authorities by the issue of licences to known epileptics, provided that they are reputably certified as having been free from attacks for at least three years and are otherwise suitable persons to hold such licences

Clearly there can be no generalisations about diabetics, even insulin requiring diabetics, each case must be considered on its own, and *although* there are certainly some diabetics who would be a danger to Her Majesty's subjects when in charge of a motor vehicle, their number is undoubtedly small As the British Diabetic Association points out, one of the essentials for safety is that the driver should be able to recognise early the symptoms of hypoglycæmia, and those few who cannot do so should take medical advice before applying for a driving licence In fact, the small number to whom Lord Goddard's warning applies are usually the first to wish to be protected, and to protect the public, by not driving There remains, *however, the isolated* instance of the usually well controlled diabetic who has a hypoglycæmic attack at the wheel Provided it can be shown that the attack was unusual, unexpected, and in no known way attributable to the patient's negligence, he should not be held responsible for its consequences, and the Act should be amended accordingly

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[1] Road Traffic Act (1930) section 15 (2)

[2] *Times*, Jan. 31, 1957

[3] Road Traffic Act (1930) section 5 (2b)

ARTERIAL PUNCTURE

Arterial puncture is being increasingly used in the course of diagnosis and treatment, and it is usually free from complications Even when the needle is of small calibre and of sound design, there is bound to be some trauma to the vessel along the track, and Crawford[1] has lately examined the way in which such wounds in arteries heal His material, mainly carotid arteries, was obtained at necropsy from patients who had been investigated by carotid angiography 4 hours to 240 days beforehand His findings suggest that the track, temporarily blocked with fibrin, is infiltrated with endothelial cells from the lumen of the artery in modified spindle cell and macrophage forms These cells form an avascular plug and derive their oxygen and nutrition by diffusion The surface is completely endothelialised in 6 to 8 days This avascularity of the endothelial plug is to be expected, since thin-walled capillaries would be unable to withstand the transmitted compressing force of the arterial blood-pressure near the intimal surface This type of organisation is comparable to that in a mural thrombosis on a vessel wall From the adventitial end of the track a more classical picture of repair proceeds, with fibroblasts and capillary loops As the scar matures further, collagen fibres thicken, and in four specimens with tracts 44 days or more old, smooth muscle cells were seen lying irregularly among the collagen fibres in the medial end of the scar the muscle coat was not, however, truly reconstructed.

This orderly repair of the damaged artery is very efficient, and few late complications of arterial puncture have been reported When trouble arises, it is usually because a large-bore needle has been introduced into a diseased artery in order to inject a radio-opaque solution rapidly and under high pressure Atheromatous plaques or mural thrombi may be loosened or, more disastrously, if the needle point is accidentally inserted into a branch of the aorta, the whole volume of irritant material may cause sudden thrombosis of the renal, cœliac, or mesenteric arteries and consequent organ infarction If the needle lies in the media of the aorta, the even more dramatic complication of dissecting aortic aneurysm may ensue Gaylis and Laws[2] believe that this is not uncommon and that it may account for many of the complications of aortography previously attributed to the irritating or toxic action of the contrast media Their patients recovered without serious sequelæ, though instances of paraplegia and death have been recorded The greatest care may not always avoid such complications, for Lindgren[3] showed that even when a trial injection confirms that the needle is in the lumen some of the medium may enter the wall during the main injection Aortic pulsation or respiratory movement may produce a small but vital shift in the position of the needle, and during forcible injection the needle may be pulled backwards or the chemical qualities of the injected medium may cause the artery to contract Intramural injections may well account for some of the femoral, carotid, or brachial thromboses which follow peripheral arteriography Moreover, it is known that in the occasional patient the brachial artery responds to trauma by a segmental spasm There can be little doubt too that the toxicity of sodium iodide or high concentrations of the organic iodides may cause endothelial or even parenchymatous damage Though arteries have a great capacity to withstand needling, high-pressure injection of irritant or bland solutions can be dangerous, and, on all counts, the reasons for advising a patient to undergo arteriography should invariably be scrutinised with care

"THE HURT MIND"

The fear of mental illness derives as much from misunderstanding and magical preconceptions as from simple ignorance The series of B B C television programmes, which ended on Jan 29, was designed both to counter old beliefs and to reveal new truths It is perhaps the most comprehensive attack yet made on the public's attitude to a medical problem, and it is to be welcomed as a sensible attempt to dissipate prejudice by information In introducing the series Mr Christopher Mayhew, M P, gave some idea of the size of the problem by pointing out that 1 person in 20 of the population of this country spends some time of his or her life as a patient in a mental hospital

The first programme introduced the theme that it is unjustifiable to look on mental disease as something very different from physical disease To collect material for the series Mr Mayhew was voluntarily admitted to a mental hospital for a few nights, and his excellent interviews with his fellow patients, the nurses, and the doctors helped to dispel the idea that mental patients are uncontrollable A modernised mental hospital, with its quiet, orderly wards and free access to the neighbourhood was contrasted with the old-fashioned institution—of which, unfortunately, there are still examples—with its high walls, locked doors, and patients pacing the airing-courts like captives Many people believe that mental patients must go into a mental hospital for treatment, but the programme showed that general hospitals now give outpatient treatment for mental as well as physical disabilities

The second programme was the least effective of the series It successfully gave an idea of the complexity of the brain by representing the number of its cells by the grains of salt in a specified number of cartons, but the definitions, couched in psychiatric phraseology, were unlikely to be helpful to many viewers The third programme described social and psychotherapeutic methods of treatment It showed that the first step in the reablement of the patient is to restore his sense of belonging to the community The fourth programme showed physical methods such as modified electroconvulsion, insulin shock therapy, and an ether abreaction a neurosurgeon described the operation of prefrontal leucotomy and its effects Patients then recounted their symptoms before treatment and after recovery The wife of a leucotomised patient gave a relative's point of view This was probably the most successful programme of the series and brought out clearly the similarity with physical disease and the improving prospects of recovery

Viewers were asked to send in questions and some 2000 did so In the last programme a panel of experts answered a selection dealing with overcrowding in mental hospitals, unsympathetic general practitioners the possibility of wrongful detention, and reablement, and Sir Geoffrey Vickers added a few words on the future of mental research Summing up, Mr Mayhew suggested that, though the social problem is vast and not yet generally recognised, the future looks hopeful

From the technical standpoint, the quality of production improved throughout the series In the earlier parts there was a tendency to suggest mystery by a haunting opening sequence and close ups of tapping feet and twisting fingers, but later the presentation was straightforward and more in keeping with the aim of the series In refraining from showing the faces of patients the producers—inevitably perhaps—were compromising with the very attitude they were attacking, for when the cameras recently visited a general hospital no such restriction was thought necessary

An associated series of six weekly mental health broadcasts will begin in the B B C Home Service on April 17

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1 Crawford T J Path Bact 1956, 72 547
2 Gaylis, H Laws J W Brit med J 1956 i 1141
3 Lindgren L Acta radiol Stockh 1953 39 205

An introductory leaflet may be had by sending a *2d* stamped addressed envelope to B B C Publications (Mental Health), 35, Marylebone High Street, London, W 1

PREDNISONE AND PREDNISOLONE

ON Feb 1 prednisone and prednisolone were "released" for prescription on form E C 10, and practitioners were reminded of this by a flurry of literature from manufacturers of these steroids A confusing new family of proprietary names should not be allowed to submerge the official titles Prednisone and prednisolone are derived respectively from cortisone and hydrocortisone by the introduction of a double bond between carbon atoms 1 and 2 Pharmacologically, no important difference has been demonstrated between the two derivatives Hitherto they have been restricted to hospitals, but it seems unlikely that there will now be any very striking increase in their use General practitioners in this country were cautious towards cortisone when it became generally available and they will probably feel the same about prednisone and prednisolone They should certainly resist the reported efforts of one manufacturer to persuade them to give a combination of prednisolone and aspirin "for the mild to moderate rheumatic conditions encountered in general practice"

The scope and limitations of these two steroids can perhaps be best assessed by answering certain questions Are there any conditions in which they are the best form of treatment ? In what circumstances are they preferable to cortisone or hydrocortisone ? What are the indications for their use in rheumatoid arthritis and other chronic but generally non-fatal diseases ? What are their undesirable effects and what precautions should be taken to avoid them ?

When a steroid is the only drug which can benefit, even temporarily, a patient with a dangerous illness, or when such treatment is likely to prevent or reduce damage to important structures (especially in self-limiting conditions), the risk of serious side-effects must be accepted Such diseases are likely to be treated initially in hospital, and they include systemic lupus erythematosus, leukæmia, pemphigus, hæmolytic disease, thrombocytopenic purpura, certain ophthalmic conditions, and nephrosis Large doses are often needed in some of these diseases, and prednisone or prednisolone are preferable to cortisone because they are so much less likely to induce retention of sodium and water—a point which makes them particularly appropriate in nephrosis or in incipient heart-failure On the other hand, cortisone retains an advantage in the management of adrenal insufficiency In rheumatic fever cortisone is often used in preference to salicylate when the disease is particularly severe or when carditis is a prominent feature—though there is no proof that damage to the heart is reduced or prevented thereby For those who favour this policy, prednisone and prednisolone are attractive alternatives to cortisone

Except for disturbances of electrolyte metabolism, undesirable side-effects are about as common with prednisone or prednisolone as with cortisone in therapeutically comparable doses Peptic ulceration (which may be caused by a direct local action on the mucosa [1]) has been suspected to occur more often when the newer derivatives are used If the anti-inflammatory potency of prednisone or prednisolone is taken to be four times that of cortisone, treatment with the prednisone or prednisolone is about 40% more expensive

Rather more than a year ago we suggested [2] that experience with cortisone in the treatment of rheumatoid arthritis would make clinicians wary in the use of prednisone or prednisolone in that disease Little more can be added until the results of the controlled clinical trials now in progress have been made known The short-term benefit, albeit often dramatic, is unimportant unless it can, in large measure and with safety, be maintained indefinitely In a comparison of patients treated for six months [3] prednisolone proved slightly superior to hydrocortisone in some respects—but the differences were not statistically significant Certainly few clinicians would choose to use cortisone or its derivatives in early rheumatoid arthritis—when the chances of a natural remission within the next few months are good—or in patients over 60, in whom the dangers of osteoporosis and vertebral collapse are very real If prednisone or prednisolone is given in rheumatoid arthritis, it is sound practice to use the smallest effective dose (which can sometimes be timed so as to reduce the morning exacerbation) and to supplement this with aspirin The combination of prednisolone and aspirin in one tablet cannot, however, be justified, for it deprives the clinician of his freedom to regulate the dose of each component separately Treatment of asthma poses rather similar problems, but the limitations of continuous treatment can be set against the efficacy of short courses for acute seasonal episodes in patients who are resistant to other treatment and in patients with severe status asthmaticus [4]

The contra indications to cortisone and the precautions to be taken during its use apply equally to prednisone and prednisolone—except that the newer steroids may be used with less fear of fluid retention Treatment may reactivate a quiescent tuberculous focus, and a preliminary chest radiograph is a wise precaution An existing peptic ulcer is likely to become worse and may bleed or perforate, and unless the drug has to be used to save life, a history of peptic ulcer is a contra indication A case can be made for giving aluminium hydroxide to prevent peptic ulcer the efficacy of this precaution has not been tested, though Bollet et al [5] recorded two cases in which peptic ulcers which had developed during the administration of prednisone showed signs of healing after treatment with diet and aluminium hydroxide, despite the fact that the patients were still on prednisone Caution is also needed in patients with a history of mental disorder or with signs of mental instability Relative contra indications include diabetes mellitus and hypertension, though an increase in blood pressure is not common during treatment with prednisone or prednisolone Patients suffering from renal disease with nitrogen retention do not do well The precautions that should be taken during treatment include periodical checks of blood pressure, tests for glycosuria, and inquiry for symptoms of dyspepsia There is no simple method for detecting the development of a dangerous degree of osteoporosis, and the difficult task of appraising prophylaxis with testosterone and œstrogens remains to be accomplished

Like cortisone, prednisone and prednisolone suppress endogenous adrenocortical activity, and this effect, which may continue for some months after a long course of treatment, may be dangerous if the patient has a major illness or requires a surgical operation The adrenocortical insufficiency then calls urgently for an increased dose or temporary resumption of steroid therapy, and it is important that a hospital admitting such a patient should know that he is taking, or has recently taken, cortisone or one of its derivatives Surgeons need not fear that normal doses of these drugs will interfere with the healing of wounds

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DR D R MACCALMAN, professor of psychiatry in the University of Leeds, died on Jan 31 at the age of 53

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[1] West H F *Lancet* 1956, ii 1162

[2] *Ibid* 1955 ii 1019

[3] Fisher M *Ibid*, 1956, ii, 18

[4] *Ibid*, p 825

[5] Bollet A J Black, R Bunim J J *J Amer med Ass* 1955, 158, 459

Special Articles

A LONDON TRIAL OF HOME CARE FOR SICK CHILDREN

R Lightwood
M D Lond, F.R C P, D P H

F S W Brimblecombe
M D Lond, M.R C P, D C H

J D L Reinhold
M A, B M Oxfd M R C P, D C H

E D Burnard
M B Otago, M R C P, M R A C P

J A Davis
M B Lond, M R C P

From the Pædiatric Unit, St Mary's Hospital Medical School, and St Mary's Hospital, London

THE transformation of medicine from an art into a complicated science and technology has altered the functions and increased the status of hospitals Founded originally as the medieval refuge for oppressed or destitute persons, they have now become centres for the diagnosis and treatment of disease in all classes of the population The gain from concentrating medical resources is clear, there are, nevertheless, penalties in the overuse of hospitals, especially for children "Few will dispute," says a recent World Health Organisation report, "that the best place to care for a child is in his own home among familiar surroundings, where the people who normally give him security and affection can tend to his needs" (Capes 1955)

Quite apart from humanitarian considerations, there are concrete dangers in admitting young children to hospital on the one hand, cross-infection (Allison et al 1946, Watkins and Lewis Faning 1949), on the other, isolation, which distorts emotional development, can hinder recovery (Bakwin 1942), and is often followed by symptoms of emotional disturbance (Bowlby 1951)

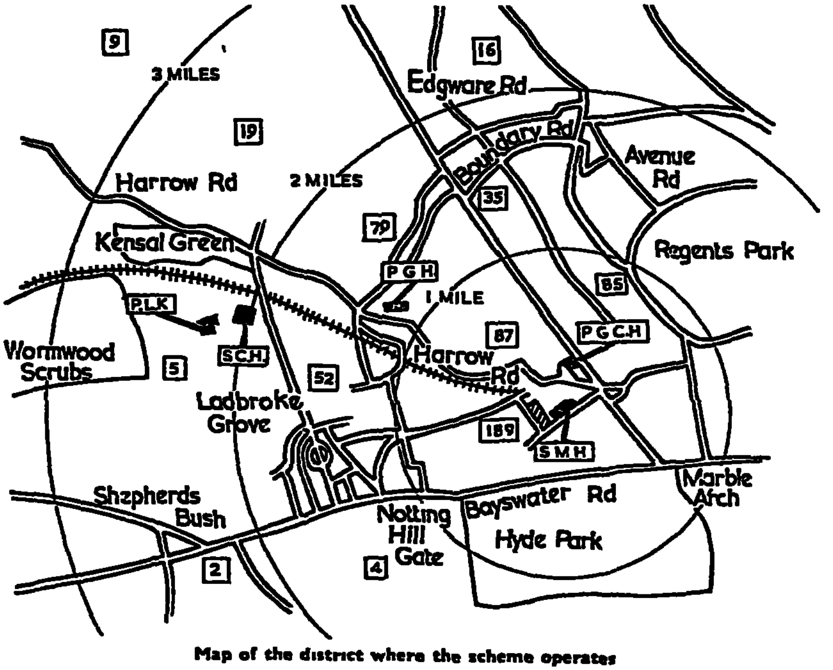
Another disadvantage is the resulting break in the continuity of medical care Responsibility for the patient passes into the hands of the hospital staff, and decisions that could affect the child's whole future may be taken without reference to the family doctor, normally the person best able to relate an illness to its social context Such a reduction in the influence and responsibility of the family doctor is not in the patient's interests, especially in pediatrics where symptoms are often pointers to a strain involving the whole family Moreover, lack of common experience between the general practitioner and the staff of a teaching hospital often means that students are being taught more about "specialist" medicine and less about the everyday problems of family practice—a weakness of modern teaching hospitals not peculiar to pediatrics

Yet another disadvantage of inpatient treatment is its high and mounting cost This in itself demands that a recommendation for admission should be fully justified on the grounds of medical need

Organised Home Care

Domiciliary medicine is the province of the family doctor, but in recent years a number of hospital home care projects have been started which provide special medical and nursing services on a domiciliary basis Hospital home care probably grew out of the old dispensaries founded as charities in 18th-century England It has developed somewhat differently on the two sides of the Atlantic—in America (Bluestone 1954) providing a substitute for private practice, and in Britain supplementing general practice In England, trials have been made of two different patterns of home care for sick children (Lightwood 1956)

The first pattern consists in a home nursing service in which visiting nurses carry out the instructions of the general practitioners Thus, if the doctor requires professional assistance he obtains it by means of a domiciliary consultation, and should his patient need to go into hospital he surrenders his charge for the time being Already in England there are two such schemes for children One is a home nursing unit set up in Rotherham in 1948 (Gillet 1954), and the other a somewhat similar scheme started in Birmingham in October, 1954 (Smellie 1956), in Rotherham there is no direct connection with the hospital services, but in Birmingham newly appointed visiting nurses are welcomed at the children's hospital for a brief refresher period In these two schemes the public-health committee provides a service of visiting nurses, as any comparable health authority has the power to do—the degree to which it is done depending on local keenness in the matter Provided suitable staff can be obtained, a home nursing service is easily organised



Map of the district where the scheme operates

The figures in squares refer to the number of cases dealt with in the areas bounded circumferentially by the 1 2, and 3 mile limits and radially by the Harrow, Edgware, and Bayswater Roads, St Mary's Hospital being the centre of the circles

The local hospitals with children's beds are shown as follows

S M H	St Mary's Hospital
P G C H	Paddington Green Children's Hospital
P L K	Princess Louise (Kensington) Hospital for Children
P G H	Paddington General Hospital
S C H	St Charles Hospital

The first three belong to St Mary's Hospital group *and simple to work, many admissions to hospital* can be prevented, and valuable educational work is carried out by the nurses

The second pattern of pædiatric home care represents the extension of hospital work into the patient's home at the request of and in cooperation with the family doctor (Lightwood, Brimblecombe, and Davis 1956) A project of this type was started in April, 1954, at St Mary's Hospital, London, to redress what we believed to be a faulty balance between hospital and domiciliary practice, for we had found that nearly a quarter of the children in hospital during a review period were admitted *for conditions which could have been managed at home* if the doctors had possessed the facilities and experience required, and that there were other children whose stay in hospital could have been shortened These considerations led the board of governors of St Mary's Hospital, having first consulted the local health authorities, the local medical committee for the County of London, and the Paddington and St Marylebone District Nursing Association, to authorise, and finance from endowment funds, a trial of home care with the following programme

(1) To discover how far, and in what conditions, sick children who would otherwise be in hospital can be nursed at home under the care of general practitioners supported by a mobile hospital team

(2) To determine whether the liaison between the pædiatric staff of the hospital and the general practitioners is thereby improved

(3) To compare the cost of inpatient treatment with the cost to the hospital of such home care arrangements

CHOICE OF DISTRICT

The district chosen for the trial included most of the borough of Paddington and a part of the borough of Marylebone—an area with a population of more than 75,000 (see map) The boundary was drawn after consultation with the local medical committee of the County of London and the London County Council in such a way that journeys would seldom exceed two miles, but as flexibility is essential in a home care scheme the team has not hesitated to go outside the boundary when circumstances have warranted The district has a high proportion of poor and overcrowded houses and a shifting and partly immigrant population, also many Paddington families have been in the habit of taking their children when sick direct to the hospital, rather than calling in a general practitioner For these reasons the locality chosen was by no means favourable for the trial of a home-care project

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A mobile team, fully trained in pædiatric work, has been established to answer calls from family doctors It consists of two pædiatricians, a sister, two nurses, and a part time physiotherapist One of the pædiatricians, giving part time service, devotes himself primarily to consultations, the other, an experienced senior registrar, is responsible for records and liaison, the carrying out of technical procedures, and the day to day supervision of treatment The sister and nurses, who have both general and sick children's nursing certificates, carry out treatment, assist with technical procedures, instruct the mothers in bedside nursing and infant feeding, and keep the usual nursing records They are available for night duty, which is reassuring for the parents, though they are seldom required

A car for morning and evening rounds is provided by the London County Council Full ancillary services, including those of the almoner, the laboratory, diagnostic radiology, use of outpatient operating-theatre and other technical assistance, are available The cost of salaries, equipment, transport, office, and telephone is borne by the endowment funds of St Mary's Hospital

A summary of this expenditure is given in table I, some of the items being estimated The service was paid for entirely out of endowment funds and claims were not made on the National Health Service in respect of *domiciliary consultations*

TABLE I—EXPENDITURE FOR THE FIRST TWO YEARS OF THE HOME CARE SCHEME

—	1954–55	1955–56
	£ s d	£ s d
Salaries and wages		
Medical	1700 15 0	1784 0 0
Nursing	1622 13 11	1709 0 0
Others	162 5 6	[illegible]
Accommodation	100 0 0	160 [illegible] 3
Use of L C C car and other transport	948 9 8	1094 12 3
X ray and pathological services	335 0 0	635 0 0
Other expenditure	174 13 0	378 5 9
—	£5103 17 1	£6116 18 3

MODE OF OPERATION

When a general practitioner needs the help of the team, he telephones the hospital If possible a bedside consultation is arranged, but in some cases it is more convenient to discuss the situation over the telephone If the case proves suitable for home care, the agreed diagnostic and therapeutic measures are undertaken straight away, thereafter the nurses and registrar keep records and notes as in hospital Liaison is maintained by further meetings, by telephone, or by letter, as circumstances dictate, changes in the régime being reported and discussed The patient remains the responsibility of the family doctor throughout No canon of working is applicable to all circumstances, so in each case the general practitioner and the team need to agree at the start on their respective roles

With the cooperation of the various departments, all the diagnostic and therapeutic resources of the hospital can be deployed in the patient's home as required On completion of treatment, the health visitor is told about young children who have been dealt with by the team.

The following example gives an illustration of the kind of work performed

A male infant, aged 12 weeks, had been fretful and feverish with otitis media for three days, and there had been no response to penicillin The family doctor then asked for the assistance of the home care team Bacterial meningitis was diagnosed and confirmed by immediate lumbar puncture Treatment was instituted and a nurse stayed with the child for the night Next day he was well enough to be left in the care of his mother, and within forty eight hours he was almost himself again There was no interruption of breast feeding and little disturbance of the home routine Swabs were taken from the other members of the family, and when the infection was found to be meningococcal each received prophylactic sulphonamide Supervision by the team continued for ten days and when, some months later, the infant was re examined, he showed no sequelæ of the illness

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During the first two years of the project, the home care team cooperated in the management of 582 patients,

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	1st year	2nd year	1st year	2nd year	1st year	2nd year	1st year	2nd year
April	4	23	1	229	2	16	52	477
May	8	25	12	251	4	22	124	694
June	8	25	20	279	5	23	170	729
July	16	31	36	310	10	28	328	896
August	14	17	50	327	10	24	337	751
September	10	22	60	349	14	23	432	696
October	5	34	65	383	11	23	342	712
November	23	34	88	417	12	26	374	784
December	22	42	110	459	19	31	589	940
January	29	41	130	500	16	27	619	437
February	27	41	166	541	19	31	512	906
March	40	41	206	582	21	30	610	915

including cases of nearly all the medical diseases normally encountered in a children's ward Inevitably this has influenced the type of case admitted to our wards, in particular there has been an increase in the proportion of surgical and accident cases, and the medical cases admitted have tended to be more urgent and severe (except for medical patients living outside the home care district) Comparison of home-care cases with current ward admissions shows a bias towards the less urgent conditions, nevertheless serious medical cases are often accepted for home care, including some incurable conditions

Of 3 patients who died while under supervision by the team, 2 were children with severe congenital defects whose deaths were inevitable and expected, the third was an infant who was convalescing from a respiratory infection and approaching the end of a course of chemotherapy When seen at home a few hours before his sudden death, his condition gave no cause for anxiety and there seemed to be no indications for admission to hospital A *post mortem* examination was made and this showed only an early bronchopneumonia

Table II shows the accumulation of the 582 patients who were referred for home care during the first two years

Of these, 460 were nursed at home throughout their illness, 31 were admitted to hospital for part of their treatment, 16, after a domiciliary consultation, were considered not to need the services of the team, and 75 were transferred from hospital to complete their treatment

Origin of Cases—Table III shows the origin of the cases The majority were undertaken after an initial request from general practitioners, a smaller number came on the recommendation of outpatient or casualty department staff, or as early discharges from hospital, the family doctor being asked for his approval

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From outpatient and casualty departments	22	41	50	60
Transferred from wards	22	7	27	19

It will be seen that the number and proportion of patients directly referred by family doctors increased as the scheme got into its stride Of one hundred and fourteen family doctors whose patients have been dealt with under the scheme, thirty-seven first used it on their own initiative and seventy seven as a result of a case being referred from hospital, of the latter twenty-three subsequently called in the team to help with another case Among the sixty doctors who chose to use the scheme five used it in more than 20 cases, thirteen in from 10 to 20 cases, ten in from 5 to 10 cases and thirty-two in from 1 to 5 cases

Age distribution—33% of the patients were infants and 30% were toddlers (1–4 years old)—the two groups that most pædiatricians feel are best kept out of hospital if possible

Housing

Full records were kept of the home conditions under which the patients were nursed This information is not easy to classify, on the whole, the quality of a home is more a reflection of the parents' way of life than of their housing 20 cases were rejected because the home was poor or overcrowded in 6 cases nursed at home the parents said they thought that their housing had been inadequate for home care, and in a further 15, experience was such that the team would not agree to look after a sick child in that home again

PROCEDURES

Experience has shown that the following procedures can be carried out efficiently and safely, even in poor homes

Diagnostic

- Test feeding
- Catheterisation
- Venepuncture
- Lumbar puncture
- Pleural aspiration
- Duodenal intubation
- Estimation of basal metabolic rate and respiratory quotient
- Fat balance
- Subdural tapping

Therapeutic

- Surgical dressings
- Removal of stitches
- Removal of plasters
- Ephedrine replacements
- Setting up steam tent
- Administration of oxygen (by mask)
- Administration of intravenous fluids, including blood
- Continuous limb traction
- Physiotherapy

RELATIONS WITH FAMILY DOCTORS AND PARENTS

In practice, contact with the family doctor, while always sufficient to ensure proper treatment of the patients, was sometimes not close enough to realise fully the main object of the scheme—a closer rapport between hospital and family doctors Experience soon showed that it was difficult for a busy family doctor to keep in close enough touch with the nurses in a serious case, and that the best arrangement was for the registrar to undertake supervision of such patients on his behalf In less urgent cases, some family doctors delegated their authority to the medical members of the team, retaining only a watching brief, while others preferred to manage the case independently after an initial consultation With a third group, mostly doctors with a high proportion of children amongst their patients, relations were close and satisfactory, and these doctors soon came to use the scheme regularly In no case was home care abandoned because of difficulties between the team and the practitioner concerned, and only once did a doctor decide against using the scheme when invited by the hospital to do so

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The presence of the parents often makes it harder to examine a child and to carry out special procedures, but it has the advantage of making the examiner temper his thoroughness with a sense of proportion It is essential for the doctor to be thoroughly trained, for an unsuccessful lumbar puncture or venepuncture at home would be a minor disaster leading to loss of confidence all round

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Accommodation	160	0	0	160	[illegible]	[illegible]
Use of L C C car and other transport	948	9	8	1094	1[illegible]	[illegible]
X ray and pathological services	335	0	0	635	0	[illegible]
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Estimation of basal metabolic rate and respiratory quotient
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Surgical dressings
Removal of stitches
Removal of plasters
Ephedrine replacements
Setting up steam tent
Administration of oxygen (by mask)
Administration of intravenous fluids including blood
Continuous limb traction
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The nursing team make about twenty-five visits a day, fifteen in the morning "round" and ten in the evening In cases of anxiety, one of the nurses stays on till the danger is over in less serious cases one to three visits daily are necessary in convalescence three visits a week commonly suffice Usually the nurses spend about ten minutes with each patient, but sometimes, when the household are agitated or some special procedure has to be done, they will have to remain for an hour or more Most families are satisfied with an approximate indication of the time of the next visit and this makes for a flexible time table, especially when the telephone is available The time spent in travelling from case to case averages about five minutes, and each visiting round lasts about four hours

Discussion

The practicability of home care for any given patient depends on whether the treatment involves the use of fixed hospital equipment, on the nature of the living accommodation, and on the willingness of those concerned (the family, the family doctor, and the leader of the hospital team) to accept the added responsibility entailed Thus it is not possible to say which diseases are suitable for home care except in a broad way Patients with nearly all the acute and chronic diseases commonly met with in the wards of children's hospitals have been treated without serious difficulty, including 3 who died, yet there are many cases in which hospital admission is the best solution, as when the mother is overburdened, unable to accept the added responsibility, or not sufficiently intelligent to fill a nurse's rôle, or when there is a risk of a dangerous situation arising in the absence of those able to deal with it

Home care has a special place in the following cases

(1) In the treatment of infants with medical conditions (*such as feeding difficulties and gastro enteritis*) where also there are many opportunities of giving education in preventive measures

(2) In children under 5 years of age, for a severe illness *may lose much of its misery when they can stay at home*

(3) In older children with chronic or incurable illness, since a long stay in hospital would deprive them of joining in family life at home Moreover, in a long term illness a great saving of hospital beds is possible

Some of the practitioners have said that the diagnostic facilities of our home care service are particularly helpful A consultation on a sick child is much more useful to a hard-pressed *doctor* when *all necessary investigations* can be carried out on the spot and the results reported back promptly for discussion Without these facilities it had previously often been necessary to arrange admission for investigations now shown to be feasible at home

Although the structure of the National Health Service provides a background *favourable for organised* home care, success of a home-care project will turn on whether it is wanted by the public and the *family doctors* Therefore it will be asked whether the project at St Mary's Hospital offers more to our patients and their doctors than services already available—i e, domiciliary consultations, visits by *district* nurses and health visitors, and X-ray and laboratory diagnostic facilities The doctors who have used the project find that, through it, these services can be deployed more promptly and efficiently for the benefit of sick children whom in the past they would have been forced to send into hospital, and they are given an opportunity of sharing responsibility without surrendering it, and of keeping in touch with the hospital staff and scientific progress

TABLE IV

—	Cost per patient per week	Cost per case
	£ s d	£ s d
Home care scheme	4 1 0	16 5 4
Princess Louise (Kensington) Hospital for Children	29 19 8	52 0 0
Paddington Green Children's Hospital	25 15 3	32 15 1

COMPARISON OF COST

It is impossible to make a direct comparison between the cost of home care and that of hospital care This is because the cases are differently selected, the criteria for admission and discharge are dissimilar, and the home care project depends on the parent hospital A comparison depending on the relative cost per week is less reliable than one based on cost per case (table IV) because the duration of home care supervision is influenced by the fact that "discharge" is less urgent than with hospital care The comparative costs for the second year of the scheme given in table IV show that with home care organised on these lines the cost per home care patient (incurred by the hospital) was considerably less than the cost per patient in hospital

EDUCATIONAL VALUE OF HOME CARE

Home care has great educational value Some mothers, especially younger ones, seem to gain in character by nursing their children through an illness, others come to realise that the treatment of illness, even by the most modern methods, is all in the day's work and not a mysterious rite *practised* only by initiates in hospital surroundings This realisation may help them to trust their own common sense in minor illness and to rely on their family doctor rather than taking the child directly to hospital In addition, home care helps many parents to realise why their child has become ill and how to prevent a recurrence, whereas if he had gone into hospital he might have returned to the same unsatisfactory conditions which caused his illness

Of those engaged professionally, it would be difficult to say which party has profited most from experience shared by all The nurses, previously trained in hospital, were doing home nursing for the first time and gaining an insight into human character and maternal problems which could hardly have been learnt in hospital The medical members of the team have certainly gained immeasurably by their contacts with the practitioners and by their experience in domiciliary pædiatrics Such experience can be a real asset in teaching students, either directly as when the students accompany members of the team on domiciliary visits, or indirectly through the influence which the work can have on the teacher's clinical outlook, also enabling him to appreciate better what general practitioners need when they refer a patient for consultation, and providing him with a more real understanding of social medicine

Summary

There are disadvantages in removing sick children to hospital for treatment A high proportion of pædiatric cases can be nursed safely and efficiently at home when the family doctor is given the support of a *mobile* hospital team

Home care is less expensive than hospital care, and has an educational value Both hospital personnel and general practitioners can benefit from cooperating directly in the care of a patient

Home care requires the exercise of tact, sympathy, and a high standard of medical etiquette in *order to prevent* misunderstandings and overcome difficulties

Throughout the planning and operation of the scheme, we have had the coöperation of the local medical committee of the County of London, the Paddington and St Marylebone district nursing association, the London County Council, the local medical officers of health, and the constituent hospitals of the St Mary's Hospital group Our grateful thanks are due to the members of these bodies

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MOTHER AND CHILD

ON Jan 30 Dr MARGARET MEAD delivered the 8th Ernest Jones lecture of the British Psycho-Analytical Society Dr Mead's contributions to psycho analytical understanding through her study of social anthropology, and her use of psycho analytical concepts in her field-work, are well known In this lecture on changing patterns of parent relations in an urban world, she was enlarging on the way in which observation of mother-child relationships in more primitive societies could throw light on what those who live in an urban society wanted to achieve in this sphere and on the difficulties they encountered

A film of the care of a newly delivered baby in New Guinea showed the very close physical contact between mother and baby, from a few minutes after birth In New Guinea there was not even clothing to intervene between mother and baby The baby was introduced to the world by a breast feed from a lactating neighbour, a few minutes after he had been born Within a day he was suckled by his mother, who cared for him with calm assurance Dr Mead showed how this type of mother-infant relationship threw into relief some of the present-day problems of mothers and babies Perhaps most interesting was Dr Mead's thesis that in a primitive society weak babies did not survive and were not expected to A puny infant who did not suck well provoked anxiety in his mother by failing to thrive, and her anxiety diminished her capacity to produce the milk essential for the baby's survival In this way babies who failed to achieve a satisfactory relationship with the mother, whether for physical or psychological reasons, actually died

In modern society all babies are expected to grow up and nearly all of them in fact do so But the responsibility for their survival is thrown on the mother, there is a tendency to speak of "good" and "bad" mothers rather than "good" and "bad" babies The cost in maternal guilt can hardly be measured and must play a profound part in the current uncertainty of aim in child-rearing Actually the morally tinged words "good" and "bad" should not be applied to either mothers or babies in this context It is how the particular mother and baby respond to each other, within their social setting which is of importance for the future emotional development of the child Both psycho analysts and anthropologists have separate, yet overlapping, parts to play in developing an understanding of these responses and their results

It was fitting that this tribute to Dr Ernest Jones, who contributed so much to the study of psycho analysis in Britain, should have been made by an anthropologist whose field work has so often confirmed what analysts have deduced from their study of individual patients

Medical Education

REFLECTIONS

D A K BLACK
M D, B Sc St And, F.R C P
READER IN MEDICINE, UNIVERSITY OF MANCHESTER

TEN years in the practice of medical teaching in a large and active school have left me little leisure in which to systematise whatever impressions I may have acquired However, a recent short visit to the United States has allowed me the luxury of calm reflection and has even stimulated me to make some comparisons which I hope may not prove too odious In this self-appointed and otiose task I draw both strength and responsibility from the monitory words of R L Stevenson, who wrote

> "Perhaps there is no subject on which a man should speak so gravely, as that industry, whatever it may be, which is the occupation or delight of his life, which is his tool to earn or serve with, and which, if it be unworthy, stamps itself as a mere incubus of dumb and greedy bowels on the shoulders of labouring humanity"

In my submission, the general aims of a medical school are to find good students, to impart to them a system of technique, a body of knowledge, and also an outlook on medicine which will leave them with both the desire and the capacity to accept the changes and accretions in knowledge which will surely come, to do all this in such a way that their time will not be wasted, their enthusiasm damped, and their maturity postponed by an enforced submission to evanescent authority, and finally to set them, not ungrateful, on the narrow way between brittle self-confidence and unhelpful hesitancy For aims such as these, good teaching is a necessary, but not a sufficient, condition, there must also be examples of clinical care, of scientific critique, and of the advancement of learning Just as many philosophers have thought that happiness comes as a by-product of the pursuit of other ends, so I would boldly say that an excessive preoccupation with pedagogy, and in particular with its mechanical aids, may be an actual hindrance, in that it diverts enthusiasm and time from clinical and investigative work, which supply the true content of medical teaching Interest and clarity should stem directly from content, and not be conscious additions to pedestrian material

Before discussing the various means which are available to us in the pursuit of these aims, I would direct attention to two distinctions which are commonly made in discussions on medical education, but which seem to me prolific sources of verbiage and confusion, in that each of them is based on an outlook which is false, or at best incomplete I refer to the distinction between science and art in medicine, and to that between an academic and a practical education

Taking the distinction between science and art, it seems to me that in the practice of medicine we use our minds in a number of ways, which include the deliberate use of experiment, whether laboratory or clinical, the simple observation of Nature, either at first or at second hand, and the making of practical decisions, often in circumstances where our action will be the beginning rather than the conclusion of an experiment, and where we may have little guidance from our own experience or that of others. (Each new therapeutic agent poses this kind of problem) Now, a narrow definition of science (as experimental testing of hypotheses) would include only the first of these, a wider definition of science, based on the fact-finding which should precede hypothesis, would include the second *mode of thought* as well, but the third type of mental activity, which embraces the practical application of the first two, would scarcely be included in any reasonable definition of science Moreover, the planning of scientific observations and experiments is itself an art These various activities of the mind may require isolation for purposes of discussion, but this is an artificial process, and an education based exclusively on one of these types of mental activity would be grossly incomplete

Again, the distinction between a "practical" and an "academic" education means very little, at least to me I may not be understanding the issues involved, but "know-how" is scarcely of value unless attended by "know-why" and "know-when" It is a witless task to ascribe priority as between theoretical knowledge and practical skill, for the one cannot get along without the other *At times, the right action may be inaction* (fortunately, it was an American who composed the guileful epigram—"Don't just *do* something, John *stand* there") If medical practice were made up of eternally valid stereotypes of procedure, it could be taught by rule of-thumb methods, but we all know that in medicine, as in life, the problems encountered are infinitely various, providing the truthful component of that veteran cliché "Each case must be judged on its merits" It seems plain that a medical training must inculcate both knowledge of currently accepted practical routines, and an ability to depart from or modify them in new situations

SELECTION OF STUDENTS

At the age when most students in this country apply for entry to medical school, they are in practice, if not in theory, selected largely on the basis of their showing in General Certificate of Education (advanced level) Reports from headmasters would often be of great value (positive or negative) if the headmaster himself were the applicant, but in assessing the students, with honourable exceptions, *they are less helpful* The *10–15* minutes' interview gives a few applicants an opportunity for self-elimination, and others give evidence of great promise, which may even be fulfilled, but the findings at interview rarely deviate from those predictable on examination results More elaborate selection procedures have been described, but there is no solid evidence that their results justify the added load on teaching staff The main defect of selection by G C E results is the admission of the occasional student who can reproduce the input of intensive coaching, but who cannot learn for himself in a university (I am not being cynical about this in the long run, we must be able to teach ourselves, and to criticise what others teach us, and if a university encourages us to do this, it is doing its job) The American medical schools seem to me to have an advantage here, in that their applicants have already had their chance to prove themselves under university-type conditions for three years, so that the selecting school has more to go on, and there may be less compunction in rejecting people who at least have a modest college degree than in excluding people who have done badly in anatomy and physiology If the "premedical subjects" are used as a screen, we run the risk of excluding otherwise adequate students who have had no satisfactory schooling in science, and are merely slow in coming to terms *with it*

CONTENT OF THE MEDICAL CURRICULUM

The present medical curriculum is a sort of Christmas tree, in which a conventional basic structure (common to *all* schools, *stereotyped* by regulation, and scarcely altered since 1900) has been decorated with tinsel and fairy lights (varying from school to school, and reflecting the localised enthusiasms of teaching staff) There has been much criticism, and this has very properly been based on the burden which such a curriculum lays on the medical student The outstanding student can take it, but his less *gifted* colleague, even if he scrapes through all the examinations, becomes dispirited by the mass of factual information I am *quite unashamedly* with the pruners rather than with the decorators, and three changes in the past year or two seem to me to enhance the case for vigorous pruning

The first two are the compulsory postgraduate year and the increasing recognition that "general practice" needs some measure of postgraduate training as much as any "specialty" These two things seem to me to legitimise something which has in any case come about from the pressure of events—that the student no longer leaves us fully armed against all medical contingencies (did he ever do this?), and that we on our part need not lie awake at nights if he should slip through our meshes *ignorant* of the insertions of certain muscles, the posology of each of the *British Pharmacopœia* preparations of mercury, or even of the factors governing sodium reabsorption in the renal tubule

Thirdly, in the past year, the curriculum committee of the General Medical Council has made recommendations which are permissive, and no longer restrictive If these are accepted by the council, the individual schools will have the responsibility and opportunity of planning a course which may allow students to think and do more, and sit and suffer less

The task of refining the content of the medical course will be long, and the result will itself require revision as the years speed past Sectional interests will impede the process, and the ultimate beneficiaries, the students, will probably have too little voice in what is done Nevertheless, the prospects for radical changes in the medical course are more hopeful than they have ever been I hope that the systematic lecture course of 80–100 lectures will disappear, and that the time gained will be mainly used to give the students more time with their patients, from whom I believe they will in the long run learn more than from their teachers

This does not mean a smaller teaching load on staff, but a diversion of their time from formal lecturing to giving clinical *tutorials* and *supervising* the work of students in the wards Trial could be made of mixed firms of 4 senior and 4 junior medical and surgical clerks, in which the seniors would be responsible for note taking and would go on staff rounds, while the juniors would be coached in physical signs and in history taking, both by staff and by the senior students Students are much better deployed in small responsible groups than in *masses* of passive listeners

THE SPIRIT OF A MEDICAL SCHOOL

There is general agreement, though with some variation in emphasis, that we have to provide both an education and a technical training In the first of these, *the emphasis is on drawing out* the student's own latent processes of thought and expression, in the second on handing on to him those practical courses of action which are appropriate *to our* present understanding of patients and their diseases Because of human frailty, the time devoted to technical training—a relatively simple matter—tends always to encroach on the time available for education In the last result, the student probably has to educate himself by discussion with his colleagues and teachers, by hearing his teachers discuss patients, by his own observations on patients, and by reading outside the student textbooks Such activities are refractory to planning, although something can be done by arranging discussion classes, sometimes with members of different departments, at which attendance is voluntary More important, however, is the provision of time for those activities which *cannot* be planned from above Negatively, this means *that* we must not fill up the student's days, weeks, and *months* with organised programmes Positively, it means that teachers must always be willing to respond to inquiries which may be ill phrased or based on ignorance, it is far too easy to get a cheap laugh from the rest of the class, and so ensure that that student will never ask you a question again Teachers must be willing to discuss diagnosis and treatment with their colleagues in the presence of students, without the short-cut of authoritarian pronouncements In Manchester, our curriculum has been modified to allow students at least one summer vacation in their clinical years, how they use this time is ultimately at their own discretion, though the dean of clinical studies gives advice and help on clinical opportunities in non-teaching hospitals

In so far as we liberate the curriculum in such ways, we are taking a chance on the initiative and self-discipline of our students For the man who demands passive instruction, the free time which we provide will be given over to textbooks, or even wasted On the other hand, the man with initiative will be able to spend more time in the wards, to see what goes on in other hospitals or in general practice, or even to take part in investigation, if his interests lie that way This is the kind of activity which goes on in the best American schools It would be foolish to extrapolate from the leaven to the lump, but I was tremendously impressed by the way in which students were an integral part of the hospital service and able to discuss things freely with the staff This is partly a matter of the staff being very numerous, so that each of them had far less "routine" clinical work than would be usual over here, but the general spirit of inquiry and discussion was obvious, nor was this achieved at the expense of careful clinical work I would agree with almost all the points made by Bauer,[1] describing the American system from the inside; my chief reservation would be that the "on and off service" arrangement is not compatible with our present ideas of a continuing relationship between a physician and his patient While the alternation of teachers may benefit the students, the alternation of physicians is less closely in the patient's interests, unless of course it is made at his own or his doctor's request

"FINALLY"

It has not escaped me that these reflections do not contain any definite plan for a medical curriculum While I am bold enough to have opinions on the general principles of curricular reform, my audacity stops short of describing the syllabus for a medical course in my private utopia Rather, I have drawn attention in no very original way to problems which will be discussed in the next year or two by medical teachers in the different schools, their formal solution is a task for medical faculties, acting in such concert as they may achieve To colleagues on my own faculty I owe a debt which cannot be assessed, let alone repaid, but they have no responsibility for these reflections, and I doubt if any of them would agree with all the opinions I have voiced I have a more clearly defined obligation to the Wellcome Trust, who made it possible for me to visit the medical schools at Johns Hopkins, Columbia and Harvard, and to the teachers in these schools who so willingly explained their beliefs and practices

Finally, I should emphasise that my criticisms of present institutions are not to be construed as support for a radical re shuffling of the medical course, such as has been in progress at Cleveland, I have not witnessed this far-reaching experiment, but have heard reports that the pressure of formal teaching, although it is cast in a different pattern is as heavy on the student there as elsewhere, and more so on the staff, so that they have less time for original work Moreover, I am not maintaining that in this country we have any need to feel ashamed of our general standard of medical practice or teaching, by comparison with other countries I have little patience with bitter statements that medicine "has been ruined as a career," and that we have "lost our professional freedom", I know of no other qualification which opens the door to so many different and interesting ways of spending one's life as a degree in medicine

Medicine and the Law

Under the Influence of Insulin

THE Divisional Court of the Queen's Bench Division allowed this appeal from a decision by justices dismissing charges under the Road Traffic Act, 1930, brought against a diabetic driver

A pharmaceutical chemist who had had diabetes for 12 years was charged before the justices with unlawfully driving a motor car (1) when under the influence of a drug to such an extent as to be incapable of having proper control of the vehicle, contrary to section 15 (1) of the Road Traffic Act 1930, (2) without due care and attention, and (3) without reasonable consideration for other persons using the road, contrary to section 12 of the same Act The justices found that on Aug 13, 1956, after taking by injection his usual and prescribed quantity of 18 units of soluble insulin B D and consuming a regulated meal, the defendant drove his motor-car to a cinema, arriving at 6 40 P M At about 9 P M he left the cinema, unaccompanied, and remembered no more than walking down the entrance steps In fact he got into his car and drove it along a road for about four miles, when the car left the road, went through a hedge into a field, and stopped in gear He was discovered at about 10 15 P M sitting rigidly at the wheel but in a semicomatose state He was taken to hospital and found to be in a hypoglycæmic coma due to the over action of the insulin injection taken earlier

It was contended for him that on the medical evidence before the justices the taking of insulin was not the taking of a drug but the replacement of an essential hormone which his body mechanism was unable to secrete, and of which it was therefore totally deficient, and that he was not therefore under the influence of a drug within the meaning or contemplation of section 15 (1) of the Act of 1930, and that being totally unaware that he was driving a motor car he could not be guilty of the offences with which he was charged under section 12 The justices dismissed the charges The prosecution appealed to the Divisional Court of the Queen's Bench Division

The LORD CHIEF JUSTICE said that insulin was clearly a drug for the purposes of the Act of 1930 He thought that a drug meant a medicine or medicament given to cure or alleviate or assist an ailing body No doubt a person taking insulin was taking a drug in the sense of a medicine, but this was a clear case which should go back to the magistrates, who should remember that section 15 was designed for the protection of the public, and if people were in a condition of health which either of itself rendered them liable to go into a coma, or the remedies for which might send them into a coma, they must not drive, because of the danger that would result to the rest of Her Majesty's subjects

Mr Justice CASSELS, agreeing said that he would define "drug" as a substance used as a medicine It would be no consolation to anybody who might unfortunately be injured by a person when driving under the influence of a drug to be told "It was not my fault because I was under the influence of a drug"

Mr Justice LYNSKEY, also concurring, said that under section 15, if it were proved that (*a*) the person accused was driving or attempting to drive a motor vehicle on a public road and (*b*) that he was under the influence of a drug to such an extent as to be incapable of controlling the vehicle, the justices were compelled to convict On the ordinary definition his Lordship thought that insulin was, and was to be treated as, a drug mode of thought as well, but the third type of mental activity, which embraces the practical application of the first two, would scarcely be included in any reasonable definition of science Moreover, the planning of scientific observations and experiments is itself an art These various activities of the mind may require isolation for purposes of discussion, but this is an artificial process, and an education based exclusively on one of these types of mental activity would be grossly incomplete

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[1] Bauer, W *Brit med J* 1956 ii 1443

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A pharmaceutical chemist who had had diabetes for 12 years was charged before the justices with unlawfully driving a motor car (1) when under the influence of a drug to such an extent as to be incapable of having proper control of the vehicle, contrary to section 15 (1) of the Road Traffic Act 1930, (2) without due care and attention, and (3) without reasonable consideration for other persons using the road, contrary to section 12 of the same Act The justices found that on Aug 13, 1956, after taking by injection his usual and prescribed quantity of 18 units of soluble insulin B D and consuming a regulated meal, the defendant drove his motor-car to a cinema, arriving at 6 40 P.M At about 9 P.M he left the cinema, unaccompanied, and remembered no more than walking down the entrance steps In fact he got into his car and drove it along a road for about four miles, when the car left the road, went through a hedge into a field, and stopped in gear He was discovered at about 10 15 P M sitting rigidly at the wheel but in a semicomatose state He was taken to hospital and found to be in a hypoglycæmic coma due to the over action of the insulin injection taken earlier

It was contended for him that on the medical evidence before the justices the taking of insulin was not the taking of a drug but the replacement of an essential hormone which his body mechanism was unable to secrete, and of which it was therefore totally deficient, and that he was not therefore under the influence of a drug within the meaning or contemplation of section 15 (1) of the Act of 1930, and that being totally unaware that he was driving a motor car he could not be guilty of the offences with which he was charged under section 12 The justices dismissed the charges The prosecution appealed to the Divisional Court of the Queen's Bench Division

The LORD CHIEF JUSTICE said that insulin was clearly a drug for the purposes of the Act of 1930 He thought that a drug meant a medicine or medicament given to cure or alleviate or assist an ailing body No doubt a person taking insulin was taking a drug in the sense of a medicine, but this was a clear case which should go back to the magistrates, who should remember that section 15 was designed for the protection of the public, and if people were in a condition of health which either of itself rendered them liable to go into a coma, or the remedies for which might send them into a coma, they must not drive, because of the danger that would result to the rest of Her Majesty's subjects

Mr Justice CASSELS, agreeing said that he would define "drug" as a substance used as a medicine It would be no consolation to anybody who might unfortunately be injured by a person when driving under the influence of a drug to be told "It was not my fault because I was under the influence of a drug"

Mr Justice LYNSKEY, also concurring, said that under section 15, if it were proved that (*a*) the person accused was driving or attempting to drive a motor vehicle on a public road and (*b*) that he was under the influence of a drug to such an extent as to be incapable of controlling the vehicle, the justices were compelled to convict. On the ordinary definition his Lordship thought that insulin was, and was to be treated as, a drug

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[1] Bauer, W *Brit med J* 1956 ii 1443

The Court allowed the appeal and sent the case back to the justices with an intimation that they should convict

Armstrong *v* Clark—*Queen's Bench Divisional Court* (Lord Goddard, *C J* Cassels and Lynskey *JJ*) Jan 30, 1957 R J Parker and Patrick Neill (Gregory Rowcliffe & Co for Hugh Carswell, Chester), Geoffrey Howard, Q C, and J W Da Cunha (Charles Russell & Co for Skelton and Co Manchester)

M M HILL
Barrister at Law

The Hospital Doctor's Unprotected Belongings

A doctor was employed by a hospital management committee at a remuneration of £425 a year with a deduction of £125 "in respect of board, lodging and other services provided" He lived in a hostel near the hospital, and came back one night to his room to find that a number of personal effects had been stolen He brought an action in the county court for the loss, claiming against the management committee that they owed him a duty that they would take reasonable care of his bedroom, personal effects, and the keys to the doors, or alternatively that there was an implied term in his contract of employment that they were under the same duty By their defence the committee denied that they owed any duty of care to him The county court judge held that the committee was not under any duty of care The doctor appealed, his counsel stating that the case was supported by the Medical Defence Union and was a test case in the sense that this was one of three similar thefts

Lord Justice HODSON said that from one point of view the house officer's salary was £425 and from another was £300 plus board and lodging valued at £125 The county court judge had accepted the committee's general proposition of law that there was no duty on the occupier of premises to safeguard against theft the chattels of an invitee by a third person who came on to the premises There were exceptions to that general rule in the case of guest houses or boarding-houses which people carried on as a business for gain, they had to take some care of the goods of their guests But the duties of boarding-house keepers could not possibly be said to arise in the present case The management committee was not carrying on a boarding-house but keeping this hostel for the benefit of the staff, just as if the staff were resident in the hospital building itself and getting their food and lodging free This was simply a case of master and servant where the master paid the servant partly in cash and partly by giving him food and lodging The house-officer did not make any separate payment for what was provided It was simply deducted from his pay and he received the net sum in the same way as would a domestic servant who lived in and got her keep In Deyong *v* Shenburn [1946] 1 K B 227, Lord Justice du Parcq had said that there was no decision and no authority for the proposition that a master must, merely because of the relationship of master and servant, take reasonable care for the safety of his servant's belongings in the sense that he must take steps to ensure that no wicked person should have an opportunity of stealing the servant's goods Those words applied directly to the present case and were not confined to what were called "domestic servants" If that was right, this claim must fail

The only way in which the house-officer could succeed in his claim would be if he could show that such a term must be implied in the contract of employment On the facts as found and pleaded there was here no room for such an implication It would be going a long way if it were held that the intervention of a wicked person such as a thief should be insured against by masters employing servants in any capacity, and there would have to be a specific term in the contract or circumstances from which such a term must necessarily be implied before such a result could be reached

Lord Justice MORRIS, concurring, said that it would be quite unreal to say that the management committee were in any sense lodging-house keepers The house officer was presumably resident in order to be available at nearly all times at short notice The position was thus simply that of master and servant, with an obligation on the servant to live in the hospital That did not mean that somebody in the position of this doctor must be called a domestic servant, but merely that he had to live in the hostel just as a domestic servant would live in

Lord Justice SELLERS delivered a concurring judgment The appeal was dismissed

Edwards *v* West Hertfordshire Group Hospital Management Committee *Court of Appeal* (Hodson Morris, and Sellers *LJJ*). Jan 31, 1957 Neville Faulks (Hempsons), J P Widgery (Sedgwick, Turner, Sworder, and Wilson, Watford)

M M HILL
Barrister at Law

Public Health

Poliomyelitis Vaccine

IT is hoped that distribution of anti-poliomyelitis vaccine will begin again throughout England and Wales about the middle of this month

Supplies had been expected during January, but the vaccine has to satisfy stringent standards of purity and potency, and one large batch was rejected because there was evidence of slight contamination, though no live virus was found In another batch, one test must be re-done, and this will take about a fortnight

Sir John Charles, chief medical officer of the Ministry of Health, has explained the position in a letter to medical officers of health The next few issues of vaccine should, he said, be large enough to provide two injections each for about 200,000 further children aged 2–9 from those who registered last year for vaccination

The Midwifery Service

In his report for 1955 Dr William Sharpe, medical officer to no 16 division of Lancashire, *observes* that of the 1588 births in the division during the year 81% occurred in hospital Most mothers, he says, obviously prefer not to have their babies at home, but why this should be so is not easily ascertained

> "Is it that we are not sufficiently persuasive in pointing out the advantages of making the birth of a child a real family affair which it can be only at home? Or is the economic disincentive applied to home confinement too great? It seems that if this latter factor is the main one it might be offset a little by offering free, or at reduced rates, home helps during the lying in period This concession, though a little more costly to the Local Health Authority, would, if it had the effect of decreasing hospital admissions, be a considerable national saving for the health service"

Infectious Diseases in England and Wales

Disease	Week ended January			
	5	12	19	26*
Diphtheria	2	0	4	1
Dysentery	535	530	477	635
Encephalitis				
Infective	6	3	3	5
Post infectious	2	1	3	
Food poisoning	143	162	148	165
Measles excluding rubella	10,971	9281	8202	[illegible]
Meningococcal infection	31	35	30	[illegible]
Ophthalmia neonatorum	32	25	25	[illegible]
Paratyphoid fever	3	4	2	
Pneumonia primary or influenzal	644	648	516	[illegible]
Poliomyelitis				
Paralytic	44	47	30	21
Non paralytic	19	25	11	6
Puerperal pyrexia	190	224	210	211
Scarlet fever	572	528	693	[illegible]
Smallpox				
Tuberculosis				
Respiratory	537	543	612	636
Meninges and C N S	7	10	9	7
Other	53	74	64	[illegible]
Typhoid fever	2	1	5	1
Whooping cough	2111	2486	2664	3243

* Not including late returns

In England Now

A Running Commentary by Peripatetic Correspondents

LAST Sunday, soon after the night nurses came on duty, the patient at the far end of the ward developed more pain and the house-physician was summoned Five minutes later, nineteen pairs of eyes watched curiously as he made his way down the length of the ward and back. He thought the patient too ill to have an operation and he telephoned his chief Twenty minutes later, all eyes turned as the physician, accompanied by his house-physician and the nurse, marched briskly to the far end of the ward He thought that an operation, although indicated, carried considerable risk and called in the surgeon To the inhabitants of a medical ward, the appearance of a surgeon is always regarded with grave misgivings, and all eyes were agog when the procession of four set out on the journey to the end of the ward some twenty minutes later In the opinion of the surgeon, the operative risk was negligible compared to the risk of the anæsthetic, and the anæsthetist was invited to express an opinion Soon after, a wakeful ward watched a quintet of specialists and auxiliaries on their pilgrimage to the last bed

Now anæsthetists, like spectators at a football match, are often inspired to a plan of action not readily apparent to the principal combatants Thus the anæsthetist opined that the risk of the operation depended on the result of a blood-test, and the pathologist was summoned. Twenty minutes later, he too ran the gauntlet of curious gazes as he negotiated the length of the ward Few pathologists, called in to help with a difficult case, can resist suggesting a further investigation The first blood-test was normal, but the result of the second made an immediate X-ray examination imperative

By this time, the area before the hospital main entrance was enough to set every National Health Service heart beating with pride In an imposing row stood the parked cars of as many members of the staff as could be seen on any weekday The physician's old Ford rubbed noses with the pathologist's A70, while the anæsthetist's Velox stood alone some distance away, because it was brand new And when the brilliant headlights of the radiologist's Jaguar swept through the drive, hospital history was made

The procession that entered the ward on its final journey brought a gasp of admiration from the two rows of figures sitting bolt upright in their beds With bulging eyes, the nineteen heads swivelled slowly through a full semicircle Gloriously, majestically, past went the consultants and specialists, the residents and nurses, and, bringing up a triumphant rear, the crane-like apparatus of the portable X ray, propelled by two porters

It took all of us exactly four-and-a-quarter hours to decide to do nothing that night

* * *

Our R S O has just got his fellowship Hearing himself called Doctor used to give him a bitter-sweet extrasystole in memory of all the examination hazards safely and astonishingly negotiated Now he feels the same lift of the emotions when addressed once more as Mister and regards the reassumption of a title common to most of his fellow men as a rare and delightful distinction He feels hurt when it is forgotten Perhaps the rules are a little difficult to grasp in our hospital Many of our patients think that all specialists should be Mister and whenever Doctor slips out it is corrected to Mister I mean A visiting American surgeon expected Doctor and we had been carefully coached in the fact that the qualifying examination "over there" is the M D One of our own surgeons has his M D , and one of our physicians, for some reason, has not At the same time as our R S O was promoted from Doctor to Mister, our biochemist, a science graduate, who has always been careful to inform newcomers that he is not a doctor, got his PH D

* * *

To the public at least, the significance of the surgeon s CH M , or M CHIR , or M S is little known Perhaps they would be better informed if it were used more conspicuously with "Master of Surgery' after it in parenthesis Two things then might happen Probably some people would regard the surgeon as being addressed as Mister by virtue of being a Mister of Surgery , but others would address him by his true title of Master This innovation would be agreeable Now that Master is less used in the nursery, few surgeons should greatly object to sharing the title with the head of Balliol College or some of the elder sons of the Scottish peerage

* * *

Full fathom five lay the father of all pike in England's loveliest lake Not that he was a serious competitor to the sportsmen flicking their trout-flies from the shallows, it was much more serious than that He was cruising over my favourite larder, the dark layers of ice-cold water between 50 and 70 feet, where waiting for our delectation are those arctic lovelies the char

If the name of char or *Salvelinus willoughbyi* means nothing to you, indeed the loss is yours Some fine spring day you should come and see for yourself that the polar ice-cap has receded from Cumbria Otherwise you may pass to dust without being tranquillised by the soothing vortices gliding away from your oars as you row slowly between wooded slopes, the tinkle of the bell on your trolling tackles, and the call to action You may be denied the breathtaking sight of a spawning char, vivid red belly and emerald green back glistening with the brilliance of enamel for the few fleeting moments ere corruption starts before your eyes The frailties of human flesh may keep you and me off the water, but we can still solace ourselves on the fishmonger's slab The pink delicacy of char lies somewhere between salmon and trout, and not nearly so dear to buy , it has the vicarious piquancy of lamp and gaff without the risks

That was why the char and I took a very dim view of the pike down there Maybe a little self-centred in our outlook, we each made out plans for survival, limited in the chars' case vis-a-vis the pike They retired to the basement while the local experts set some large-mesh nets Both parties waited with interest for a couple of weeks before patience was rewarded At twenty-six pounds our pike tipped the scale, and there were a couple of fine char inside him Justice was satisfied by converting his mighty bulk into cookable steaks When it comes to stuffing specimens, around our way we believe that charity begins at home—an elementary rule of survival which gives us the strength to catch some more

* * *

After watching a television programme last night I was so irritated that I sat down and wrote myself this letter

Dear Doctor,

Please sign my family s cards as I want to change my doctor like Christopher Mayhew said I should on the television All that happens when I see you is we talk and talk about my nerves and you do nothing for me I want to go to the hospital for proper treatment and I won't have to do anything about getting better myself Perhaps they will give me a bottle of nerve tonic too like I said I needed

Truly yours,

N E PATIENT

* * *

We were visiting one of those admirable hospitals which have grown up by unplanned accretion from a cottage hospital and now carry the load of a population of 100,000 or more Matron asked if we would like to see the nurses' home It was not on our programme but she was so charming that, noses dripping, we hurried across the windswept plateau to the usual mid-Victorian ex-rectory designed by Nature to be the nurses' home of those admirable hospitals which have grown up by unplanned &c , &c As we opened the door of a small sitting-room, two young and pretty probationers sprang to their feet in some confusion, one of them dropping the book she was reading My companion said as he picked it up—rashly I thought—"Well, nurse what have you been reading ? " "And what do you think it was ? ' I asked the friend to whom I was telling the story "Oh Plato's *Republic*, I expect," he answered It was

* * *

A patient from H B - "Yes, they ve done three autopsies on me so far"

Letters to the Editor

"DOCTOR"

Sir,—May I congratulate Doctor George Graham on his delightful article last week? How kindly he refers to the inverted snobbery which makes many surgeons insist on being called Mister—a proper title for the mate of a sailing ship, but to a surgeon, a reminder of a humbler origin than his brother physician In Dublin it is interesting to read on the plates on doors in Fitzwilliam Square and elsewhere where consultants practise, Surgeon So and so How very sensible!

Dr Graham correctly says that the curious practice does not exist in other countries except in those Dominions of the British Commonwealth which follow the practice of the Royal College of Surgeons But even in those countries the custom is by no means universal thus in Australia while there are some surgeons in some States who like to be called Mister, many prefer Doctor

May Dr Graham's hope be realised and in time this curious survival, reminiscent of the barber surgeons, cease Surely we should be proud to belong to the profession of doctors Please call *me* Doctor

Surgical Unit,
Cardiff Royal Infirmary

LAMBERT ROGERS

Sir,—Dr Graham wonders why fellows of the Royal Colleges of Surgeons prefer to be called Mister He might be interested in an explanation which I read or heard, I know not where, some little time ago

Most of the universities conferring the degree of doctor of medicine also confer a parallel degree of master of surgery, M S, or CH M The proper form of address for the holder of such a degree is surely Master, or the popular form, Mister Is it perhaps the wish to draw a parallel between this degree and the fellowship of the Royal Colleges that prompts the fellows to adopt the appellation Mister?

Aberdeen University
Hall of Residence,
Foresterhill, Aberdeen

GEORGE L CHALMERS

TOWARDS PREVENTING SUICIDE

Sir,—Well might the Rev Edward Young exclaim in the year 1742 "O Britain infamous for suicide!" (Jan 26, p 203) Up to 1823 it was legal (and it was done in June of that year) to bury suicides at crossroads with a stake through their bodies, and up to 1870 the Crown had the right (though latterly it was not exercised) to confiscate the personal estate of a person dying by his own hand

DEATHS FROM SUICIDE, ROAD ACCIDENTS, AND HOMICIDE
(1948–51)

Country	Death rate (per 100 000 persons)			
	Suicide	Road accidents	Homicide	Suicide + road accidents + homicide
Switzerland	23 5	12 7	1 0	37 2
Denmark	23 3	7 8	1 3	32 4
Austria	22 7	5 5	1 4	29 6
Western Germany	18 2	15 4	1 0	34 6
Japan	17 5	2 2	2 1	21 8
France	15 2	2 5	0 6	18 3
Sweden	14 9	7 0	0 6	23 4
Belgium	13 6	10 1	1 3	25 0
U S A	11 2	22 1	5 8	39 1
South Africa	11 1	15 2	2 9	29 2
England and Wales	11 0	8 4	0 5	19 9
Australia	9 3	21 6	1 0	31 9
New Zealand	9 2	11 8	1 1	22 1
Canada	7 7	16 8	1 3	25 8
Norway	7 4	3 7	0 4	11 5
Israel	7 1	6 5	0 9	14 5
Italy	6 8	9 6	1 5	17 9
Holland	6 2	7 4	0 3	13 9
Scotland	5 7	9 0	0 3	15 0
Spain	5 4	1 3	0 8	7 5
Chile	4 8	1 2	10 2	16 2
Northern Ireland	4 2	9 7	0 2	14 1
Eire	2 7	4 8	0 2	7 7
Columbia	1 3	5 7	28 7	35 7

I doubt, however, whether the reverend gentleman would wish to reproach us over the present (1948–49) suicide-rates, the table shows that, of the 24 countries, England and Wales ranks 11th, with Scotland, Northern Ireland, and Eire ranking 19th, 22nd, and 23rd

Since you, Sir, called attention to the fact that prevention of fatal road accidents attracts more public attention with us than prevention of the (latterly) more numerous suicides (Jan 26, p 206), I have given rates for these, and, for the benefit of students of the polar character of suicide and homicide, those for homicide[1]

The aggregate mortality-rates for suicide plus road deaths plus homicide are highest in the United States and Switzerland, and lowest in Spain and Eire

Isleworth, Middlesex

H PULLAR STRECKER

Sir,—The article by Dr Parnell and Dr Skottowe (Jan 26) deserves the closest attention, but I think it is unfortunate that they give the impression that suicide can only be prevented, and depression treated, by admission to a mental hospital A large number of depressed patients is now being successfully treated by means of electroconvulsive treatment, modified by relaxants, in outpatient clinics of general hospitals Most of the mental hospitals, at least in the London area, are overcrowded, often there is a considerable delay, amounting in some cases to several weeks, before a bed can be obtained The patient may well commit suicide during this waiting period Outpatient treatment, on the other hand, can usually be arranged immediately and with the willing cooperation of the patient—which is not always so readily forthcoming when admission is proposed

There are, of course, cases where the suicidal risk is too great to permit the patient to remain at home, but the clinical judgment of an experienced psychiatrist can usually be relied on to decide which method of treatment should be adopted There is much to be said in favour of keeping patients at home,-apart from the shortage of mental hospital beds and mental nurses, and the cost of inpatient treatment

London W 1

J C SAWLE THOMAS

Sir,—It is good to see Dr Parnell and Dr Skottowe ventilating the subject of suicide, particularly among students in universities, and one is grateful to them for emphasising the importance of direct questioning of depressed or anxious patients on this matter I have more than once established a sound relationship with such a person and produced relief by anticipating the student's confession and expecting the temptation to suicide to be present I am therefore the more surprised to see these physicians so strenuously recommending the admission of patients to hospital on this sign alone I wonder whether I have misunderstood them, but I was once similarly surprised by the attitude of a consultant psychiatrist who, after seeing and talking in a friendly way with a depressed patient of mine about the suicidal situation that he was in, said to me, "Did you see how that man talked to me as though we two understood one another in this matter? He is dangerously suicidal and should be in hospital" I can see that for therapists with hospital beds readily available, admission may offer the best solution, but surely for the general practitioner the need for admission recedes in proportion to the increase of understanding of the position achieved between patient and therapist

I was visited early one summer morning by a distraught young man who, in an exaggerated manner, was working through an early pattern of panic at examinations He had had no sleep at all that night In the course of half an hour I heard a good deal of hatred poured out upon both his parents, whom he felt to be pushing him along a path he could not take Then suddenly he blurted out "At one o'clock in the night I mixed myself a glass of thirty aspirin tablets I had it beside me on the table" I reacted with, 'That would have 'taken it out' of the people you hate so much, I suppose," and he said quickly, "Yes, I thought it would serve them jolly well right" He was aware of a powerful suicide deterrent in his loving a girl who loved him, but I think he had been less aware before our talk of the hate motive which had been tempting him to suicide and I hope that the conscious emphasising of it by both of us will stand him in good stead if the situation ever recurs, particularly if there should be less help from the girl

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[1] United Nations, Demographic Yearbook. New York, 1953, table 12

It is sometimes necessary to explain to a confused and careless student that his apparently unaccountable behaviour springs from suicidal urges of which he has been unaware I am thinking of absent-minded people who expose themselves to traffic dangers, and foolhardy folk who take inordinate risks in their adventures with the elements, on mountains, in caves, or over the sea A proper wariness of his own weakness on this score can greatly help a person to avoid damage Where one cannot find acceptance of the inner threat, as in a patient who assured me repeatedly that she took eighteen carbromal tablets all at once simply to get a good night's sleep, one is safer to assume serious, if not psychotic, disturbance, but it is very hard to persuade such a person to be admitted voluntarily

I doubt whether any depressed person has no suicidal inclinations, and young men and women suffering their first attacks of this torturesome complaint need very careful attention, if only to support them until they have learned to manage their own condition A bond of real affection can work miracles, but it is difficult to forge

The older person, particularly the physician, needs to take herself or himself to task lest anxieties with regard to patients are in too great part projected from inside the observer Which of us has not, in our fantasies, done rather more than just to long for release from difficulty, for oblivion, for perpetual sleep, for death itself? It is not given to all of us all the time to see life as ever lasting challenge We must therefore be afraid of suicide in others as in ourselves Let us sustain one another, face risks together, and pray that we be kept from panic

Students' Health Service,
University of Bristol
AGNES WILKINSON

SIR,—The article by Dr Parnell and Dr Skottowe is most valuable and will cause most of us general practitioners deep and helpful searching of heart The important omission, however, to my mind, is the lack of any mention of the relationship of alcoholism to suicide Often this connection is not made public at inquests, just as often the true state of affairs is not realised by the family or even by the family doctor

When will we come seriously to grips with this vital and tragic problem?

Bewdley Worcs
G S LAWRENCE

THE REMUNERATION CLAIM

SIR,—Last week I attended a meeting held under the auspices of the local branch of the B M A at which the remuneration dispute was discussed

I was amazed and shocked by the views expressed by the convener of the meeting and by many members of the audience What the association advocates, if the claim fails, really amounts to strike action, although some prefer to call it resignation from the service Whether called "strike" or "resignation" it is really nothing but shameless blackmail, since, as one member of the B M A pointed out such action would cause a crisis A special point was made of the Government's moral obligation towards the profession, but it seems hardly right for doctors to insist on the moral aspect if they intend to follow trade-union tactics and add yet another crisis to the long series of miserable strikes, and thus forfeit what little is left of public sympathy for the medical profession

Brighton
NOEL ALDER

POST-GASTRECTOMY BILIOUS VOMITING

SIR,—There is no doubt that the method of investigation of bilious vomiting presented by Mr Scott and Dr Whiteside (Dec 29) is extremely valuable Bilious vomiting is an annoying and at times a disabling condition, and it is hoped that many cases will be investigated by this method in the future, so that a true conclusion can be reached

One of us (G R A) started using this technique in 1954, and since then we have used it in over 50 cases to demonstrate the afferent loop in these post-gastrectomy disorders The afferent loop is shown best, whether there is stasis or not, *before* the gall-bladder is caused to contract A film taken two hours after injection of 'Biligrafin' and while the patient is still fasting is optimal After food has been taken and the gall bladder has contracted, the fine contrast pattern of the normal afferent loop is lost The films should always be taken with the patient erect, as the effects of afferent loop stasis are shown to the best advantage in this position The afferent loop tends to empty (in the absence of physical obstruction) in the supine position

Our observations suggest that distension of the gall bladder is not a factor in bilious vomiting In nearly all cases of 70% gastrectomy, the vagal fibres to the gall bladder are divided, and the gall bladder function thereafter follows the features so clearly described by Johnson and Boyden.[1] They showed that complete severance of vagal fibres results in progressive enlargement of the gall-bladder Under no other conditions does such a rapid increase in size occur Vagotomy, however, does not affect the rate of evacuation of the gall bladder after a fatty meal They suggest that the vagi control the tone of the gall bladder while the evacuating mechanism is probably under hormonal influences It may be that the interdigestive size of the gall-bladder is a good test to see whether the vagal fibres have been divided Certainly in nearly all, if not all, the cases of gastrectomy we have reviewed, the gall bladder is distended in this way As only a few of these patients had bilious vomiting, it is unlikely that gall bladder distension per se is a factor In a patient seen this week who had a Polya gastrectomy ten years ago, severe and intractable bilious vomiting has recently started, even though his gall bladder was removed five years ago Sometimes the gall bladder is shown grossly distended after gastrectomy even when it contains gall stones, in one case where the gall bladder was removed for such stones, the bilious vomiting persisted Our findings in these cases suggest that the bile pools, either in the gastric remnant or in the efferent loop We have some doubts, therefore, whether anastomosis of the gall bladder to the efferent loop will really cure the condition. We agree, however, that distension of, or stasis in, the afferent loop does not appear to be a necessary accompaniment of bilious vomiting

Unfortunately, the clinical manifestations of this condition do not suggest an easy answer Some patients vomit the bile after food and some before In some cases it appears immediately after the gastrectomy and clears up within a year, in others it does not come on for two, three, or even ten years after operation, and can then be very severe Some cases vomit bile every day, and others have attacks lasting two or three days, after which the condition will remit for a week or more In many cases, lying down will clear the condition, this fits in with the observation that the biligrafin-loaded bile which pools in the efferent loop will pass on when the supine position is adopted T J Butler (personal communication 1951) made the interesting observation that the condition was twice as common in the right to left as in the left-to-right anastomosis We have been unable to find figures of other observers on this point

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[1] Johnson F E Boyden E A *Surgery* 1952 32 591

To us it appears that the afferent loop in these cases is usually normal as shown by this technique, why the biliary fluid is held up in the gastric remnant or efferent loop in some cases, and not in others, remains an unsolved problem

Southmead Hospital,
Bristol

W M CAPPER
G R AIRTH

SIR,—We have read with great interest the article by Mr Scott and Mr Whiteside, for we, too, have investigated gall bladder function after gastrectomy[1] Nine patients were studied, before and after gastrectomy, by intravenous cholecystography and duodenal drainage The following results were obtained

1 In four patients who had had Polya gastrectomy, gall bladder function was normal

2 In three patients who had had total gastrectomy and œsophago jejunostomy the gall bladder was enlarged and insufficiently contracted after the test meal

3 In two patients who had had total gastrectomy and œsophago duodenostomy or œsophago jejunostomy, visualisation of the gall bladder was impossible despite repeated examination

Duodenal drainage revealed continuous bile-flow, and detection of the A, B, and C fractions of the bile was absolutely impossible in all this group of patients

It is our impression that all types of gastrectomy alter the function of the gall-bladder In the Polya type gastrectomies, these changes are rather slight, but in total gastrectomy the functions of the gall-bladder are much altered

Istanbul

K I GURKAN
IMRAN HATIBOĞLU
NASUT ÖZGE

RETURN TO PLANNING

SIR,—May I commend your leading articles on Psychotherapy in General Practice (Dec 29) and on Return to Planning (Jan 5) and Dr Hopkins's highly relevant letter (Jan 5)?

Dr Hopkins's plea for some special fee for psychotherapeutic sessions, such as is already provided for obstetrics under the National Health Service, might be extended to other lengthy procedures, thus encouraging general practitioners to lift some of the load off hospital staffs and add variety to their repertoire

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Saskatoon,
Saskatchewan, Canada

A G RICHARDS

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In my experience, injection of the appropriate stellate ganglion is the treatment of choice for an acute attack Having seen the effect of an immediate block in six patients, with dramatic improvement in their symptoms I am convinced that this measure is of great value If successful, it should be followed up by regular vasodilator drug therapy until the patient is fit enough for thorough investigation and decision as to the future means of treatment

Immediate stellate block is also imperative in those not uncommon cases of sudden perceptive loss of hearing in one or both ears, usually in young healthy adults Injection must be very early in these cases, or the cochlear damage becomes irreversible, if, however one is fortunate in seeing the patient soon enough quite remarkable rises in hearing level can be obtained by this means Sudden deafness, especially of perceptive type, should therefore be considered an emergency and treated accordingly

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SIR,—Your valuable leading article includes the statement "psychological disturbances are common and this is not surprising in patients who are ever expecting further attacks of disabling giddiness"

I entirely agree with this statement and should like to underline it In my experience cases of Ménière's disease are not infrequently referred to the psychiatrist in the first instance in the mistaken belief that the symptoms are wholly psychogenic This is especially likely to happen if the deafness and tinnitus are less severe than the vertigo In these cases the patient's principal complaint may be that he is frightened to go out alone in case he falls over, and this may be thought to be a phobic manifestation in an anxiety state

It is clear that to most people a severe attack of vertigo is a frightening thing and that the fear of subsequent attacks gives rise to a considerable sense of insecurity It is, however, most important to be sure whether or not true vertigo is present, for the treatment of Ménière's disease is quite different from that of agoraphobia

London, W 1

ANTHONY STORR

DANGEROUS CONTAMINANTS IN STORED BLOOD

SIR,—Dr Discombe (Feb 2) concludes *Experientia docebit*, yet he states "Dr Marsh's (Jan 12) criteria for deciding whether death was due to bacterial contamination are not valid" Surely, experience should have taught him better! Even better—perhaps—if he had read what Dr Marsh actually wrote

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[1] 14th Turkish National Medical Congress Izmir, 1956

Epping, Essex FRANK MARSH

A NEW CLINICAL ENTITY?

SIR,—The letter of Professor Nihoul and Dr Quersin-Thiry in your last issue was of great interest to me From some of the 100 cases in this hospital which I have recently surveyed [1] a virus akin to ECHO-9 has been isolated [2] Other cases of aseptic meningitis in the U S.A, from which ECHO-6 virus was isolated, have recently been described [3]

One of the patients whom I studied developed aseptic meningitis five days after his return from holidays in the Netherlands

Leicester Isolation Hospital and Chest Unit CHAVA E ROTEM

UNMARRIED PARENTHOOD

SIR,—Dr Comfort (Jan 26) makes a very good point, which, as he says, is wilfully ignored by responsible bodies from Parliament downwards

In my maternity unit, just over 100 illegitimate babies are born every year Some years ago I questioned every unmarried mother as to whether contraception was practised History of exposure-rate being notoriously inaccurate, I classified them on vaginal examination as habituated to coitus or not, and also made an arbitrary attempt to assess their intelligence A sample of married women (including only 4 primigravidæ) admitting to unwanted pregnancies showed slightly better education The results were as follows

Marital status	*No of women*	*Intelligent*	*Habituated to coitus*	*Contraception*				
				Condom	*Pessary*	*Diaphragm*	*Combined*	*Nil*
Unmarried	121	87	103	6	10			105
Married	48	34		2	13	2	4	27

As far as I can ascertain, so called sex education seems to be limited to the processes associated with pregnancy and delivery, while the equally natural but often socially less desirable processes leading up to conception are left in an idyllic cloud

Prevention is said to be better than cure, and certainly it is better than abandoning the victim to her fate

London W 1 GILBERT DALLEY

SIR,—Dr Comfort's plea for dissemination of contraceptive knowledge as a first step in preventing unwanted pregnancies deserves support

The social attitudes to the problem of unmarried motherhood vary widely from one individual to another, but the general community attitude is ostrich like because we fail to recognise that, in spite of moral teachings and social pressure sexual union will occur and because we fail to prevent the consequences of coition by active steps to teach the use, and to ease the supply, of contraceptive materials Hence the miseries of unwanted pregnancies and children

As 20% of the first children born in 1953 were conceived out of wedlock (i e 8 months or less after marriage) the problem cannot be said to be small Mr Greenland also shows (Jan 19) that among mothers aged 16–19 65–69% of first children are conceived out of wedlock This would suggest that the logical place to teach the rudiments of contraception is in the schools

Fawley, Hampshire A WARD GARDNER

THE FUTURE OF NURSING

SIR,—I cannot this time complain that the response to my letter (Jan 5) has been disappointing! It may be that one could have wished for more discussion of the subject by doctors, but at least the subject is live —indeed lively

Your own leading article (Jan 26) contains, as one would expect, a great deal of wisdom Nevertheless, although your opening paragraph stresses the need for a resolution of the differences if hospitals are to continue giving of their best, one is a little frightened that some may regard your wisdom as in line with the paternal pat on the back which endeavours to reconcile a quarrelsome pair of children My purpose in writing is to draw attention to what has been made abundantly plain by at least one of the letters—namely, that there are some members of the nursing profession who seem almost to have reached the "point of no return" in regard to discussion of this subject with doctors Such nurses see people like Dr Ritchie Russell and myself as reactionary types who are standing in the way of a fuller development of the nursing service Our sole purpose I am sure is to voice alarm at the danger of making still more elaborate arrangements for the higher training of nurses when the existing structure at the lower level is faulty

May I suggest that one of our dangers in discussing the subject is the present-day fashion for loose analogies and the formation of fine sounding phrases which may mean little? For example, it is common to speak of the nurse's place in the "health team" The word "team" here is a little dangerous, for most teams are made up of persons of completely equal status Now although I am the first to agree with the importance of bringing the trained nurse fully into discussions—and indeed I welcome and often accept her suggestions—the fact needs to be emphasised that under few circumstances is the trained nurse in Great Britain permitted to make decisions of herself regarding the patient's treatment There are, of course, many areas in the world where the absence of a sufficiency of doctors means that highly trained and dedicated nurses accept a much greater measure of responsibility But, although I would hope that Britain will still produce some of these, I do not consider that training should be focused primarily to that end I suggest that the "team" analogy has a nice "matey" sound but may mean very little

I observe, too, from a leading article in the *Nursing Times* (Jan 11) that the degree course in nursing "would be one way of bringing into the profession those with trained minds and a broad outlook and making the nurse's preparation more attractive to those who now find it intellectually unsatisfying" Does nursing sick people bring intellectual satisfaction? I would doubt it very much Surely such people should be advised to get out of nursing and adopt some other form of service This and such a phrase as caring for "the patient as a whole person" are examples of high falutin' phraseology which make me feel that we have passed very far away from the patient's bedside

British nursing has always taken a very proper pride in its emphasis on bedside nursing Some of us believe that before taking steps to build a superstructure for those who find bedside nursing intellectually unsatisfying there is a need to ensure that there is some thought expended upon the needs of hospital patients and sick people generally In my own view this will involve an appreciation that the present emphasis on "science" should give way to a greater emphasis on "nursing" left-to-right anastomosis We have been unable to find figures of other observers on this point

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[1] Rotem C E In publication.

[2] Boissard G P B Stokes L J Macrae A D MacCallum F O In publication

[3] Karzon D T Barron A L Winkelstein W jun, Cohen S J Amer med Ass 1956 162 1298

To us it appears that the afferent loop in these cases is usually normal as shown by this technique, why the biliary fluid is held up in the gastric remnant or efferent loop in some cases, and not in others, remains an unsolved problem

Southmead Hospital,
Bristol

W M CAPPER
G R AIRTH

SIR,—We have read with great interest the article by Mr Scott and Mr Whiteside, for we, too, have investigated gall bladder function after gastrectomy[1] Nine patients were studied, before and after gastrectomy, by intravenous cholecystography and duodenal drainage The following results were obtained

1 In four patients who had had Polya gastrectomy, gall-bladder function was normal
2 In three patients who had had total gastrectomy and œsophago jejunostomy the gall bladder was enlarged and insufficiently contracted after the test meal
3 In two patients who had had total gastrectomy and œsophago duodenostomy or œsophago jejunostomy, visualisation of the gall bladder was impossible despite repeated examination

Duodenal drainage revealed continuous bile flow, and detection of the A, B, and C fractions of the bile was absolutely impossible in all this group of patients

It is our impression that all types of gastrectomy alter the function of the gall-bladder In the Polya type gastrectomies, these changes are rather slight, but in total gastrectomy the functions of the gall-bladder are much altered

K I GURKAN
IMRAN HATIBOĞLU
NASUT ÖZGE

Istanbul

RETURN TO PLANNING

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Immediate stellate block is also imperative in those not uncommon cases of sudden perceptive loss of hearing in one or both ears, usually in young healthy adult Injection must be very early in these cases, or the cochlear damage becomes irreversible, if, however one is fortunate in seeing the patient soon enough quite remarkable rises in hearing level can be obtained by this means Sudden deafness, especially of perceptive type, should therefore be considered an emergency and treated accordingly

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inquest reports you quote illustrate only too well—and on the other hand it gathers in nearly three times as many as do need it This wastes their time as well as ours, and this is often forgotten

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May I repeat, Sir, that we would welcome help ?

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SIR,—With reference to Dr Brafield's question last week, I have noted this occurrence about a dozen times in the past six years Some of the cases have been of poliomyelitis, others of lymphocytic meningitis of undetermined ætiology and others of encephalitis The sugar levels have mostly been about 140 mg per 100 ml, but I can remember two in which it was 180 mg per 100 ml In all these the blood sugar was normal This finding is described by Purves Stewart[1] as occurring in epidemic encephalitis (Incidentally he does state that it forms a diagnostic point in contrast with poliomyelitis, which in the light of Dr Brafield's and my experiences is incorrect) The older neurologists did not, however, have the facilities for virus examinations that we have today Dementia præcox and cerebellar abscess are also cited as causes

The mechanism is, I believe, irritation of the medullary sympathetic centre

It is also stated that diabetes mellitus is not likely to be confused with encephalitis That this is untrue is illustrated by the tragic case of an 8 year-old boy admitted to a fever hospital with vomiting, drowsiness, and abdominal pain Acute gastritis or encephalitis were suspected The C S F sugar was 800 mg per 100 ml shortly before death The blood-sugar could not be estimated, but I think there is no doubt that he was in diabetic coma

Western General Hospital
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NEONATAL COLD INJURY

SIR,—Last week's paper by Dr Mann and Dr Elliott is of great importance to all those concerned with the care of infants It may be of interest to recount briefly our experience in Bristol, as it differs in some respects from that of Dr Mann

We have records of 13 instances of cold injury with 3 deaths from 1953 to 1956 An analysis of these cases shows

Sex distribution males, 12, females, 1 Delivery home, 11, hospital, 2 (symptoms developing several days after discharge) Age on admission less than 24 hours, 1, 1–7 days, 7, 8–21 days, 5 Lowest temperature 82–85°F, 3, 86–90°F, 4, very cold but temperature unrecorded, 6 Pre existing conditions cerebral birth injury, 2, immaturity 5, infection, 4 blue asphyxia at birth with development of symptoms within 24 hours, 1, ? hiatus hernia, 1

The clinical features of the disease followed the description of Dr Mann and Dr Elliott, and we agree entirely with their views on management We noted especially that rhinorrhœa and nasal obstruction together with adventitious sounds in the chest often developed after rewarming and did not necessarily indicate infection Apnœic attacks and convulsions also tended to occur after rewarming

The male preponderance in our series is intriguing, and it would be of interest to know if this is general We have not seen cold injury occur in a healthy, full term infant, and in this we are at variance with Dr Mann and Dr Elliott Of our 3 fatal cases, 2 had post-mortem evidence of cerebral birth-injury, 1 with a tentorial tear, the other with generalised cerebral œdema, pulmonary hæmorrhage, and patchy atelectasis, following a prolonged labour and forceps delivery The 3rd infant showed immaturity and necropsy evidence of generalised asphyxial hæmorrhages, with pulmonary hyaline membrane and resorption atelectasis

Of the non-fatal cases, on admission 4 had infections which we feel preceded the hypothermia 3 infants had purulent rhinitis, in 2 cases due to a penicillin-sensitive, coagulase positive *Staphylococcus aureus*, and 1 due to pneumococcal infection The 3rd had bilateral purulent conjunctivitis, purulent rhinitis, umbilical sepsis, and consolidation of the right middle lobe

In addition to the preventive measures suggested by Dr Mann and Dr Elliott, we would like to stress the greatly increased importance of adequate warmth in those infants whose natural vitality is lowered by any degree of immaturity, trauma, or infection

Department of Child Health,
University of Bristol

THOMAS E OPPÉ
KENNETH SIMPSON

TREATMENT OF SORE THROAT

SIR,—What has become Fry *versus* Wheatley in the treatment of sore throats (Jan 19 and 26) resolves, for those of us who can neither rise to the challenge of a nomogram nor sacrifice our patients' bottoms to our high principles, into the search for a happy medium Something between Dr Wheatley's intractable prophylactic enthusiasm and Dr Fry's fashionable eschewal of oral penicillin is the goal for the likes of us

Just to judge each case, giving the benefit of the doubt in favour of antibiotics, unbedevilled by rigid theories or authoritarian attitudes, is lovely for patient and doctor In any case there are perhaps at least three sorts of tonsillitis which do different things

1 With big red shiny tonsils with or without pyrexia This sort hangs about in children and worries the mother conditioned by welfare clinics It subsides in about 24 hours with penicillin, usually orally but sometimes intramuscularly This type in adults does just as well on aspirin gargle

2 With big red dull tonsils exuding pus This does well with penicillin, oral in children, intramuscular in adults

3 With small very angry looking red tonsils, and a wide spread, rather granular, intensely red pharyngitis, very painful, only seen in adults Penicillin does not seem to touch it When it does not settle on simple measures, it needs four days of tetracycline

Some of the fun of general practice is in using one's own quirks, based on one's own unsystematic, constantly changing, cumulative impressions (is that what's called experience ?), not in obeying others' theoretical or moral mandates

And, whilst, unprotesting, we eat pigs fed on penicillin and include penicillin in poliomyelitis vaccine, where is the logic in railing against the possibility of its inducing resistant strains in inadequate doses ?

London, S W 7 BENJAMIN LEE

SIR,—Like Dr Brumfitt and Dr Slater (Jan 5) subsequent correspondents sensibly discourage the indiscriminate use of antibiotics But the danger of uncontrolled infection by hæmolytic streptococci of group A (especially of type 12) and by diphtheria bacilli, though much diminished in this country, is real, and such other infections as thrush and Vincent's angina are best curtailed by specific treatment

" Sore throat " is not a diagnosis and, for that reason in all severe cases the throat should be swabbed before treatment This preliminary swabbing should be regarded as a rule where there is visible exudate, adenitis, or fever of 100°F or more The laboratory report will often,

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[1] Purves Stewart, J The Diagnosis of Nervous Diseases London 1945 p 730

I end this letter as I did my last Is this not a subject which demands some kind of formal inquiry? If another *Lancet* Commission is not the answer, is it inappropriate to suggest that the matter is important enough to require consideration at Ministry level?

Department of Infectious Diseases,
University of Glasgow

THOMAS ANDERSON

SIR,—This correspondence has brought to light the great shortage of trained nurses in the hospital service, but no concrete suggestions have so far been made to remedy the position

Undoubtedly the initial trouble is economic

With an ageing population, many nurses today have family commitments which in the days when staff nurses earned £50–60 per annum were unheard of, many old people on small pensions now must have financial help from their children

Male nurses are much in the picture again, and obviously family obligations must be considered sensibly A man cannot support a wife and family, at present living costs, on a staff nurse's salary which at minimum is £425 per annum, taking seven years to reach a maximum of £530 per annum and from which deductions are made for National Insurance, superannuation, meals on duty, uniform, and laundry

Duty covering twenty four hours a day and seven days a week must entail work at all hours, and, while undoubtedly all hospitals would if possible adopt straight shift duties, at present staffing levels this is seldom possible so hospitals have the eternal problem of split duties With families to consider, staff are more and more reluctant to take night and weekend duties, and with no monetary incentive these periods become increasingly difficult to cover

With so many vacancies in hospitals, obvious from the many pages of advertisements in the nursing journals, staff nurses are seldom content to remain in that grade, and very quickly on completion of training take positions at higher salary levels

Today, postgraduate courses are multiplying rapidly, not only in specialist hospitals but in training schools At one time added certificates were useful in obtaining promotion and, to a limited extent, they still are, but no matter how many postgraduate certificates a nurse holds, except in a very few types of work there is no extra salary on completion of the course, or in subsequent employment.

The next factor is the changing function of nursing

A leader in the *Nursing Times* of Jan 11 states that there is a much wider definition than is given in the Nurses' Act, which says "a nurse means a nurse for the sick and nursing shall be construed accordingly" I agree that nurses must share in membership of the health team, but it does seem that the hot house nurturing of the healthy against something which may not happen has been grossly overdone, to the detriment of care of the sick, and, because most preventive health organisations can be conducted on Mondays to Fridays between 9 A M and 5 P M, of course large numbers take such posts In these days of well guarded machinery is it really necessary to have such an exodus of trained nurses from the hospitals to the factories, and are these nurses really more competent in dealing with accidents than the well trained first aid team?

Then back to the question of nurse training

The large majority of men and women taking up this work enter their training with a clear cut picture of nursing the sick, and in the past that ambition was fostered and encouraged, with the ultimate result of well trained nurses prepared to do every duty in the care and comfort of their patients Now it would seem that nurse training is educating the nurse beyond that level to an unhappy state wherein she is neither nurse nor doctor, and wherein, on completion of training, it is no longer her duty to do the intimate treatments like bathing, feeding, bed panning, care of pressure points, and making beds—all things which to a sick person mean far more than non touch technique, and during which duties a nurse really gets to know her patient's anxieties, fears, symptoms, and needs These duties are now passed on to the assistant nurse or to the completely untrained nursing auxiliary

It is no wonder that many medical men are now saying that the assistant nurse should be made the nurse and the S R N be called something else

Of course there are far too few assistant nurses—the further dilution of the profession in 1955 has militated against recruitment Can any sensible person really think it is worth while to take a secondary grade of nurse training, when the completely untrained can earn practically the same salary and do much the same work, and when on completion of training the assistant nurse is limited in what she can do except under supervision—the classic example being hypodermic injections—and cannot hope ever to gain promotion?

A new approach is needed—a basic training for nurses at a three-year minimum, the potential S R N and S E A N not segregated from each other but working together with exactly the same practical training. Those who do not wish to do theoretical examinations should be examined in practical subjects only, entitling them to the hospital certificate of practical efficiency, which in turn should permit them to be entered on a register known possibly as the "Qualified Nurses' Register," and those wishing to take the whole State examination still being classified as State-registered nurse

I would like to see some organisation like the British Nurses' Association upholding a sane and balanced view of what nursing really means This association, formed in 1887, included liberal-minded leaders of the medical and nursing professions, and could be the agency whereby the nursing profession would once more get its feet firmly planted on the ground

G G GOODCHILD
Matron

A RAPID BLOOD-SUGAR SCREENING METHOD

SIR,—We were interested to read the letter by Dr Kohn (Jan 26) We have found that satisfactory results can be obtained with plasma or serum from capillary blood—about 0 5 ml of blood can easily be collected from an ear or finger prick into a small tube, and after about 20 minutes enough plasma or serum will separate to do the test by dipping the tape

A 'Tes Tape' reading of "0" always means a blood sugar of less than about 60 mg per 100 ml It is usually possible to equate a tes-tape reading of "+" with a blood sugar of 60–150 mg, of "++" with a blood sugar of 150–250 mg, of "+++" with a blood sugar of 250–400 mg leading to "++++" with a blood sugar above 500 mg Absolutely reliable readings were obtained at either end of the scale

We should like to thank Messrs Eli Lilly for supplying 'Tes Tape'

D N BARON
CELIA M OAKLEY

Royal Free Hospital, London

HEAD INJURIES

SIR,—Mr Alexander (Jan 26) advises me to consult my neurosurgeon by telephone in difficult cases of head injury, and implies that in such cases a neurosurgeon at the end of a wire is wiser than I am by the side of my patient I do so consult my neurosurgeon, and I willingly confess that the implication is correct But should this be so? My neurosurgeon happens to be one who has thought deeply and given some advice on this problem[1] I myself[2] have made an attempt to define conditions upon which transfer should be considered But I am by no means satisfied with my own attempts, and I am sure my neurosurgeon will agree that there is still much to be done before we can be satisfied—even with his!

We have long observed the criterion Mr Alexander advises for local admissions—that anyone with a history of unconsciousness, however transitory, should be admitted Nevertheless on the one hand this does not gather in all the cases needing surgical care—as the

inquest reports you quote illustrate only too well—and on the other hand it gathers in nearly three times as many as do need it This wastes their time as well as ours, and this is often forgotten

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[1] Rowbotham, G F Acute Injuries of the Head. Edinburgh 3rd Ed p 107 et seq

[2] Lowdon, T G The Casualty Department. Edinburgh 1955 p 227

Finally, two or three days in a general surgical ward is, so far as I can see, no prophylactic against some of the worst sequelæ of head injuries—headaches, dizziness, inability to concentrate, depression, and all the other manifestations of the post-concussional syndrome

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In addition to the preventive measures suggested by Dr Mann and Dr Elliott, we would like to stress the greatly increased importance of adequate warmth in those infants whose natural vitality is lowered by any degree of immaturity, trauma, or infection

Department of Child Health
University of Bristol

THOMAS E OPPÉ
KENNETH SIMPSON

TREATMENT OF SORE THROAT

SIR,—What has become Fry *versus* Wheatley in the treatment of sore throats (Jan 19 and 26) resolves, for those of us who can neither rise to the challenge of a nomogram nor sacrifice our patients' bottoms to our high principles, into the search for a happy medium Something between Dr Wheatley's intractable prophylactic enthusiasm and Dr Fry's fashionable eschewal of oral penicillin is the goal for the likes of us

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Some of the fun of general practice is in using one's own quirks, based on one's own unsystematic, constantly changing, cumulative impressions (is that what's called experience ?), not in obeying others' theoretical or moral mandates

And, whilst, unprotesting, we eat pigs fed on penicillin and include penicillin in poliomyelitis vaccine, where is the logic in ruling against the possibility of its inducing resistant strains in inadequate doses ?

London, S W 7 BENJAMIN LEE

SIR,—Like Dr Brumfitt and Dr Slater (Jan 5) subsequent correspondents sensibly discourage the indiscriminate use of antibiotics But the danger of uncontrolled infection by hæmolytic streptococci of group A (especially of type 12) and by diphtheria bacilli, though much diminished in this country, is real, and such other infections as thrush and Vincent's angina are best curtailed by specific treatment

" Sore throat " is not a diagnosis and, for that reason, in all severe cases the throat should be swabbed before treatment This preliminary swabbing should be regarded as a rule where there is visible exudate, adenitis, or fever of 100°F or more The laboratory report will often,

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[1] Purves Stewart J The Diagnosis of Nervous Diseases London 1945 p 730

I end this letter as I did my last Is this not a subject which demands some kind of formal inquiry? If another *Lancet* Commission is not the answer, is it inappropriate to suggest that the matter is important enough to require consideration at Ministry level?

Department of Infectious Diseases,
University of Glasgow — **Thomas Anderson**

SIR,—This correspondence has brought to light the great shortage of trained nurses in the hospital service, but no concrete suggestions have so far been made to remedy the position

Undoubtedly the initial trouble is economic

With an ageing population, many nurses today have family commitments which in the days when staff nurses earned £50–60 per annum were unheard of, many old people on small pensions now must have financial help from their children

Male nurses are much in the picture again, and obviously family obligations must be considered sensibly A man cannot support a wife and family, at present living costs, on a staff nurse's salary which at minimum is £425 per annum, taking seven years to reach a maximum of £530 per annum and from which deductions are made for National Insurance, superannuation, meals on duty, uniform, and laundry

Duty covering twenty four hours a day and seven days a week must entail work at all hours, and, while undoubtedly all hospitals would if possible adopt straight shift duties, at present staffing levels this is seldom possible so hospitals have the eternal problem of split duties With families to consider, staff are more and more reluctant to take night and weekend duties, and with no monetary incentive these periods become increasingly difficult to cover

With so many vacancies in hospitals, obvious from the many pages of advertisements in the nursing journals, staff nurses are seldom content to remain in that grade, and very quickly on completion of training take positions at higher salary levels

Today, postgraduate courses are multiplying rapidly, not only in specialist hospitals but in training schools At one time added certificates were useful in obtaining promotion and, to a limited extent, they still are, but no matter how many postgraduate certificates a nurse holds, except in a very few types of work there is no extra salary on completion of the course, or in subsequent employment.

The next factor is the changing function of nursing

A leader in the *Nursing Times* of Jan 11 states that there is a much wider definition than is given in the Nurses' Act, which says "a nurse means a nurse for the sick and nursing shall be construed accordingly" I agree that nurses must share in membership of the health team, but it does seem that the hot house nurturing of the healthy against something which may not happen has been grossly overdone, to the detriment of care of the sick, and, because most preventive health organisations can be conducted on Mondays to Fridays between 9 A M and 5 P M, of course large numbers take such posts In these days of well guarded machinery is it really necessary to have such an exodus of trained nurses from the hospitals to the factories, and are these nurses really more competent in dealing with accidents than the well trained first aid team?

Then back to the question of nurse training

The large majority of men and women taking up this work enter their training with a clear cut picture of nursing the sick, and in the past that ambition was fostered and encouraged, with the ultimate result of well trained nurses prepared to do every duty in the care and comfort of their patients Now it would seem that nurse training is educating the nurse beyond that level to an unhappy state wherein she is neither nurse nor doctor, and wherein, on completion of training it is no longer her duty to do the intimate treatments like bathing, feeding bed panning, care of pressure points, and making beds—all things which to a sick person mean far more than non touch technique, and during which duties a nurse really gets to know her patient's anxieties, fears, symptoms, and needs These duties are now passed on to the assistant nurse or to the completely untrained nursing auxiliary

It is no wonder that many medical men are now saying that the assistant nurse should be made the nurse and the S R N be called something else

Of course there are far too few assistant nurses—the further dilution of the profession in 1955 has militated against recruitment Can any sensible person really think it is worth while to take a secondary grade of nurse training, when the completely untrained can earn practically *the same salary and do much* the same work, and when on completion of training the assistant nurse is limited in what she can do except under supervision—the classic example being hypodermic injections—and cannot hope ever to gain promotion?

A new approach is needed—a basic training for nurses at a three year minimum, the potential S R N and S E A N not segregated from each other but working together with exactly the same practical training Those who do not wish to do theoretical examinations should be examined in practical subjects only, entitling them to the hospital certificate of practical efficiency, which in turn should permit them to be entered on a register known possibly as the "Qualified Nurses' Register," and those wishing to take the whole State examination still being classified as State-registered nurse

I would like to see some organisation like the British Nurses' *Association upholding a sane and balanced view* of what nursing really means This association, formed in 1887, included liberal minded leaders of the medical and nursing professions, and could be the agency whereby the nursing profession would once more get its feet firmly planted on the ground

G G Goodchild
Matron.

A RAPID BLOOD-SUGAR SCREENING METHOD

SIR,—We were interested to read the letter by Dr Kohn (Jan 26) We have found that satisfactory results can be obtained with plasma or serum from capillary blood—about 0 5 ml of blood can easily be collected from an ear *or finger prick into* a small tube, and after about 20 minutes enough plasma or serum will separate to do the test by dipping the tape

A 'Tes-Tape' reading of "0" always means a blood sugar of less than about 60 mg per 100 ml It is usually possible to equate a tes tape reading of "+" with a blood-sugar of 60–150 mg, of "++" with a blood sugar of 150–250 mg, of "+++" with a blood sugar of 250–400 mg leading to "++++" with a blood sugar above 500 mg Absolutely reliable readings were obtained at either end of the scale

We should like to thank Messrs Eli Lilly for supplying 'Tes Tape'

D N Baron
Celia M Oakley
Royal Free Hospital, London

HEAD INJURIES

SIR,—Mr Alexander (Jan 26) advises me to consult my neurosurgeon by telephone in difficult cases of head injury, and implies that in such cases a neurosurgeon at the end of a wire is wiser than I am by the side of my patient *I do so consult my neurosurgeon, and I* willingly confess that the implication is correct But should this be so? My neurosurgeon happens to be one who has thought deeply and given some advice on this problem[1] I myself[2] have made an attempt to define conditions upon which transfer should be considered But I am by no means satisfied with my own attempts, and I am sure my neurosurgeon will agree that there is still much to be done before we can be satisfied—even with his!

We have long observed the criterion Mr Alexander advises for local admissions—*that* anyone with a history of unconsciousness, however transitory, *should* be admitted Nevertheless on the one hand this does not gather in all the cases needing surgical care—as the

inquest reports you quote illustrate only too well—and on the other hand it gathers in nearly three times as many as do need it This wastes their time as well as ours, and this is often forgotten

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[1] Rowbotham, G F Acute Injuries of the Head Edinburgh 3rd Ed p 107 et seq
[2] Lowdon, T G The Casualty Department Edinburgh, 1955 p 227

Finally, two or three days in a general surgical ward is, so far as I can see, no prophylactic against some of the worst sequelæ of head injuries—headaches, dizziness, inability to concentrate, depression, and all the other manifestations of the post-concussional syndrome

May I repeat, Sir, that we would welcome help ?

Sunderland   T G LOWDEN

RAISED C S F -SUGAR LEVELS

SIR,—With reference to Dr Brafield's question last week, I have noted this occurrence about a dozen times in the past six years Some of the cases have been of poliomyelitis, others of lymphocytic meningitis of undetermined ætiology and others of encephalitis The sugar levels have mostly been about 140 mg per 100 ml, but I can remember two in which it was 180 mg per 100 ml In all these the blood-sugar was normal This finding is described by Purves-Stewart[1] as occurring in epidemic encephalitis (Incidentally he does state that it forms a diagnostic point in contrast with poliomyelitis, which in the light of Dr Brafield's and my experiences is incorrect) The older neurologists did not, however, have the facilities for virus examinations that we have today Dementia præcox and cerebellar abscess are also cited as causes

The mechanism is, I believe, irritation of the medullary sympathetic centre

It is also stated that diabetes mellitus is not likely to be confused with encephalitis That this is untrue is illustrated by the tragic case of an 8-year-old boy admitted to a fever hospital with vomiting, drowsiness, and abdominal pain Acute gastritis or encephalitis were suspected The C S F -sugar was 800 mg per 100 ml shortly before death The blood sugar could not be estimated, but I think there is no doubt that he was in diabetic coma

Western General Hospital
Hull   J G ALEXANDER

NEONATAL COLD INJURY

SIR,—Last week's paper by Dr Mann and Dr Elliott is of great importance to all those concerned with the care of infants It may be of interest to recount briefly our experience in Bristol, as it differs in some respects from that of Dr Mann

We have records of 13 instances of cold injury with 3 deaths from 1953 to 1956 An analysis of these cases shows

Sex-distribution males, 12, females, 1 Delivery home 11, hospital, 2 (symptoms developing several days after discharge) Age on admission less than 24 hours, 1, 1–7 days, 7, 8–21 days, 5 Lowest temperature 82–85°F, 3, 86–90°F, 4, very cold but temperature unrecorded, 6 Pre-existing conditions cerebral birth injury, 2, immaturity 5, infection, 4, blue asphyxia at birth with development of symptoms within 24 hours, 1, ? hiatus hernia, 1

The clinical features of the disease followed the description of Dr Mann and Dr Elliott, and we agree entirely with their views on management We noted especially that rhinorrhœa and nasal obstruction together with adventitious sounds in the chest often developed after rewarming and did not necessarily indicate infection Apnœic attacks and convulsions also tended to occur after rewarming

The male preponderance in our series is intriguing, and it would be of interest to know if this is general We have not seen cold injury occur in a healthy, full term infant, and in this we are at variance with Dr Mann and Dr Elliott Of our 3 fatal cases, 2 had post-mortem evidence of cerebral birth-injury, 1 with a tentorial tear, the other with generalised cerebral œdema, pulmonary hæmorrhage, and patchy atelectasis, following a prolonged labour and forceps delivery The 3rd infant showed immaturity and necropsy evidence of generalised asphyxial hæmorrhages, with pulmonary hyaline membrane and resorption atelectasis

Of the non-fatal cases, on admission 4 had infections which we feel preceded the hypothermia 3 infants had purulent rhinitis, in 2 cases due to a penicillin-sensitive, coagulase positive *Staphylococcus aureus*, and 1 due to pneumococcal infection The 3rd had bilateral purulent conjunctivitis, purulent rhinitis, umbilical sepsis, and consolidation of the right middle lobe

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Department of Child Health,
University of Bristol   THOMAS E OPPE
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Just to judge each case, giving the benefit of the doubt in favour of antibiotics, unbedevilled by rigid theories or authoritarian attitudes, is lovely for patient and doctor In any case there are perhaps at least three sorts of tonsillitis which do different things

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And, whilst, unprotesting, we eat pigs fed on penicillin and include penicillin in poliomyelitis vaccine, where is the logic in railing against the possibility of its inducing resistant strains in inadequate doses ?

London, S W 7   BENJAMIN LEE

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"Sore throat" is not a diagnosis and, for that reason, in all severe cases the throat should be swabbed before treatment This preliminary swabbing should be regarded as a rule where there is visible exudate, adenitis, or fever of 100°F or more The laboratory report will often, though not always, provide useful information, and allow the initial therapy of the case to be pursued or *modified* for clear reasons

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[1] Purves-Stewart J The Diagnosis of Nervous Diseases London 1945 p 730

London, N W 11 **MAIR THOMAS**

Parliament

QUESTION TIME

Group Practices

Dr BARNETT STROSS asked the Minister of Health how many group practices now existed, whether he was satisfied that sufficient *loan capital was still* available for them, and what amount of increase over the annual sum of £100,000 was contemplated —Mr DENNIS VOSPER replied The total number is not known, but loans to about 100 such practices have been approved in England and Wales and the money involved is about £450,000, the fund is now increasing by over £100,000 a year and I think this should be sufficient

Health Centres

Mr W J PROCTOR asked the Minister what areas were now provided with a health centre under the National Health Service, and what proposals he had for extending the health centres provisions of the National Health Service Act —Mr J K VAUGHAN-MORGAN, parliamentary secretary to the Ministry *of* Health, replied The *following centres* have been provided

Berkshire County Council	Faringdon Health Centre
Bristol County Borough	William Budd Health Centre
London County Council	Woodberry *Down* Health Centre
Nottingham County Borough	John Ryle Health Centre
Essex County *Council*	*Harold Hill*
Gloucestershire County Council	Hesters Way Estate
Sunderland County Borough	Alderman Jack Cohen Health Centre

In addition, premises were taken over in July, 1948, by 6 *local authorities* so that general *medical or dental services could be continued there Current restrictions on capital* expenditure rule out further provision for the time being

Dr STROSS asked the Minister how many *local* authorities had applied during 1956 for permission to build health centres, the average estimated cost, and how many medical-practitioner suites were to be made available —Mr VAUGHAN MORGAN replied 4 authorities applied for approval for schemes where building was ready *to* start The average estimated building cost was £25,000 and a total of *15* medical practitioner suites was included In the case of 4 other authorities, approval in principle was sought or consideration of proposals was continued during the year Dr STROSS Would the Minister agree that it is important to press forward with all types of health centres so that we *may* find out which are best ? Will he accept that £25,000 seems a much more reasonable figure than the fantastic sum spent on Woodberry Down, which I hope we shall never see repeated ?—Mr VAUGHAN MORGAN I am sure that the Minister would be in agreement with the imputation in the last part of the question We should do well to remember the approach of the Guillebaud Committee in this matter It was in favour of pursuing an *experimental approach towards development*

Cancer Research

Mr R R HARRIS asked the Minister, as representing the Lord President of the Council, what information his department *now had on the connection* between diesel engine fumes and the increase in cancer —Mr VOSPER The investigations being made under the auspices of the Medical Research Council into the nature and effects of the exhaust products of diesel engines have provided no evidence to support the suggestion *that these fumes are a cause of cancer*

Mr G D N NABARRO Is it not a fact that diesel oil fumes in congested urban areas are a direct contributory factor to smog ? As smog has detrimental effects upon everybody's lungs, is it not reasonable to suppose that diesel *oil fumes have an important* bearing upon the incidence of lung cancer ?—Mr VOSPER I dare say that that is so Investigations are continuing But the direct association between diesel fumes and cancer has not been proved

Mr MARCUS LIPTON asked the Minister how much was being spent from public funds on research into the connection between smoking and lung cancer —Mr VOSPER In the current financial year the Medical Research Council is spending about £29,000 on research on this subject Most of this sum comes from the lung cancer research fund put at the disposal of the council by a group of British tobacco manufacturers Mr LIPTON Is it *not quite deplorable that the Government* are making no contribution at all towards research in this matter ? Is the fact that the Government are making no contribution to be explained by the policy announced by the Chancellor of the Exchequer recently that the Treasury does *not* want *too many* people to stop smoking ? Is that not an immoral and infamous attitude ?—Mr VOSPER It is not of course, true that the Government are *making no contribution* They are making *some contribution towards* this particular piece of research, and the Medical Research Council this year spent £327,000 from public funds on cancer research as a whole, but the mere expenditure of money will not necessarily provide the answer *to this problem* Mr *LIPTON In view of* the proved connection between smoking and lung cancer, has the Minister any comment to make *on* what apparently is the policy of the Treasury, that the Treasury does not want too many people to stop smoking ?—Mr VOSPER I am anxious *to* find the solution *to* this problem, and I would not be influenced by any views of the hon Member

A Pep Drug

Mr MAURICE EDELMAN asked the Minister whether he had studied the claims contained in the advertisement of a proprietary drug, particulars of which had been sent to him, what was its composition, whether it was to be included in *Prescriber's Notes*, what equivalent preparation of a non proprietary nature was already included in *Prescriber's Notes*, and at what cost —Mr VOSPER 50 milligrammes of caffeine per tablet The preparation has been noted for inclusion in the list of preparations advertised to the public which doctors have been asked not to prescribe A standard drug of similar therapeutic effect is included in the *British Pharmaceutical Codex*, retail price 11½*d* for 25 tablets, and I am advised that its clinical use is small and diminishing Mr EDELMAN Is the Minister *aware that this so called* pep up *drug is retailing at 2s 6d per* phial ? Is it not undesirable that this drug should be available indiscriminately, even to children, without prescription ? Are there not certain *social*—quite apart from physical—dangers arising from the promiscuous use *of* this drug ?—Mr VOSPER I understand that the drug *is* not harmful and that in fact the the effect of one tablet is about equivalent to that of a cup of tea or coffee I agree that on social grounds it is undesirable, and for that reason it has been included in the list of drugs which should not be prescribed

Jobs for Tuberculous People

Mrs SLATER asked the Minister of Labour what advice or help was given to encourage employment *of* people suffering from tuberculosis —Mr ROBERT CARR, parliamentary secretary to the Ministry of Labour *and National* Service replied My officers do all they can, in coöperation with chest physicians, to help the tuberculous to obtain employment For this purpose, all the services provided under the Disabled Persons (Employment) Act, including industrial rehabilitation and training, are available to the tuberculous *as they* are to other disabled people Special *facilities for* training and employment under sheltered conditions are provided by Remploy, and by some voluntary bodies and local authorities

Mr WILFRED PALING Is the Minister aware that Government departments do not make matters too easy *for people* who have had tuberculosis ? Is he aware that, if a man *applies for any unestablished* post in a department, he has to state specifically whether he has ever suffered from tuberculosis or not, and that, when most applicants read that, they are likely to jump to the conclusion that their case has been damned even before it is considered ?—Mr CARR *I do not* think the *right hon* Gentleman's conclusion is necessarily justified *It probably is right* that employers should get this information We must, of course, while providing opportunities for the tuberculous, protect the health of other people as well

Industrial Health Services

Mr F T WILLEY asked the Minister of Labour when he expected to be able to make a statement on industrial health services and organisation as envisaged in the report on the Staffing and Organisation of the Factory Inspectorate —Mr IAIN MACLEOD replied *I am not able to say* when I shall be in a position to make such a statement I think that it is more *important* that we *got* the right answer than that we come to a conclusion quickly In particular, I am sure *that* we want *the result of the important* survey going on in Stoke-on *Trent into the pottery industry,* which will not be available *until the end of the year*

Mr WILLEY asked the Minister the present strength and grades of the medical inspectorate of his department, and to what extent he was proposing to increase the numbers in any grade during 1957 —Mr MACLEOD replied There are at present on the strength of the medical inspectorate 1 senior medical inspector, 3 deputy senior medical inspectors, and 11 medical inspectors I hope to increase the strength by 3 medical inspectors during 1957, to fill existing vacancies —Mr WILLEY While I appreciate that the increase this year is encouraging, would not the Minister recognise that this service appears to be inadequate, and that that is another reason for our hoping to get a reply earlier than he has indicated in his reply to a previous question ?—Mr MACLEOD This and the previous question are closely linked The reason why, in part at any rate, no suggestions have been made for increases in the cadre is that it was thought that those changes should await the decisions on policy to which I referred in my earlier answer

Mr A M SKEFFINGTON asked the Minister when it was proposed to announce the successor to the senior medical inspector of his department who was to retire this year —Mr MACLEOD The senior medical inspector of factories will retire at the end of August next I hope to be able to announce his successor well before August Mr SKEFFINGTON Does the Minister realise that many people on both sides of industry regard the work of this inspectorate as of great importance, and want to see it extended, as the Minister has indicated in reply to an earlier question Therefore, in building up an effective department, the name of the gentleman who is to be in charge should be known soon Mr. MACLEOD I recognise that, and I attach the greatest importance to the medical inspectorate

Number of Mental Defectives

The number of mental defectives detained in hospitals and colonies in England and Wales has risen from 4411 in 1916 to 60,457 in 1955 The figure for 1955 includes 6336 patients out on licence from these institutions

Use of Trilene

The use of 'Trilene' by domiciliary midwives is on the increase At the end of 1955 about 236 trilene sets were in use in England and Wales, while the number at the end of 1956 had risen to about 900

Hospital Waiting-lists

The number of patients awaiting admission in England and Wales on Dec 31, 1955, was 454,878 This is a reduction of some 20,000 since the end of 1954 and of 71,000 since the end of 1953

Cost of Prescriptions

The average cost per prescription dispensed in November 1956, was 5*s* 1*d* compared with 4*s* 5 81*d* in November, 1955

Obituary

CHARLES LEONARD GIMBLETT

M D Camb , M R C P , F R C S

Mr Gimblett, late senior surgeon to the Westminster branch of Moorfields, Westminster, and Central Eye Hospital, London, died on Jan 21 at the age of 66

The son of Robert Wheddon Gimblett, he was educated at Clifton College and at Gonville and Caius College, Cambridge, and received his clinical training at St Thomas's Hospital After qualifying, in 1914, he held several house-appointments there, including that of house-surgeon in the ophthalmic department where he came under the influence of Fisher and Hudson During the 1914–18 war he served as surgeon lieutenant in the Royal Navy In 1919 he took the M R C P and in 1922 the F R C S Early in his career he decided to specialise in ophthalmology, and he prepared himself with characteristic thoroughness

He was elected to the honorary staffs of the Royal Westminster Ophthalmic Hospital and the Royal Northern Hospital in 1923 During the late war he was ophthalmic surgeon to the Haymeads E M S Hospital, Bishop's Stortford In 1947 he became senior surgeon at the Royal Westminster Ophthalmic Hospital, shortly before it amalgamated with Moorfields and the Central London Ophthalmic Hospitals, and he retired last August

He was fond of children and for many years was consultant to the Lord Mayor Treloar Orthopædic Hospital, and he was chairman of the medical advisory committee till his death His interest in the problems of squint had been stimulated by the teaching of Claud Worth, and Gimblett was instrumental in forming the orthoptic department at the Royal Westminster Ophthalmic Hospital, of which he was given charge He was largely responsible for developing the training school and getting recognition for orthoptists as medical auxiliaries He was the first chairman of the British Orthoptic Board

P McG M writes

Gimblett was essentially a clinical ophthalmologist of the highest order His early training in general medicine and surgery was of immense value to him He was indefatigable in his work, never sparing himself and in spite of two severe illnesses he continued his hospital work for some time after he had reached retiring age In private life he was interested in mediæval art and on holiday he enjoyed sailing and swimming He was beloved by his patients because of his tact and patience and by his colleagues because of his loyalty and friendship

He married in 1935 Andreen daughter of Duncan McNicol She survives him with two sons

HORACE MINTON SHELLEY

M R C P , F R F P S , D T M & H

Dr H M Shelley was director of medical and health services in Cyprus during the later stages of the campaign which rid the island of the malaria mosquito After he retired in 1952 he made his home there, and he died on Jan 26 at the age of 56 while on a voyage to Greece

He qualified from the University of Sheffield in 1923 and joined the Colonial Medical Service the following year From 1924 to 1939 he served in Nyasaland, at first as a medical officer In 1927 he took the D T M & H and in 1934 he was elected F R F P S The same year he was appointed government pathologist He took the M R C P in 1938, and in 1939 he transferred to Tanganyika as senior medical officer In 1947 he became D M S in Cyprus, and he held this post until his retirement

W M A , who visited Cyprus while Shelley was D M S , writes

I carried away with me the impression of a deeply devoted doctor dedicated to the concept of the best possible medical service He strove consistently for the integration of all communities in Cyprus His ideal was a service in which all worked together, not as Englishman, Greek, or Turk, but as Cypriots It was characteristic of his devotion to this cause that he settled in Cyprus after retirement It must have been an especially deep sorrow to him to see how deeply divided have become the peoples he longed to see live and work in amity The hospitality he and Mrs Shelley gave to all visitors was deeply appreciated

Of his work for the Colonial Medical Service E D P writes

Dr Shelley's devotion to duty, enthusiasm, warm humanity, and consideration for others were qualities which endeared him to many He always retained his interest in clinical medicine and after retirement became consulting physician to the Limassol government hospital in Cyprus His name will long be remembered with gratitude in the countries where he served so devotedly and faithfully

JOHN HOWARD SIMMONS

M D Lond , M R C P

Dr J H Simmons, consulting physician to the Lewisham group of hospitals, died on Jan 17, at the age of 54

He qualified from King s College Hospital in 1925, and after holding house-appointments there he spent some time in general practice In 1930 he took the M R C P and the following year the M D , and soon afterwards he joined the London County Council's hospital service as a junior medical officer Before he was appointed as physician specialist to Lewisham Hospital in 1941 he had held the post of deputy medical superintendent at Mile End Hospital and at St Charles' Hospital

Under the National Health Service he became consultant physician, and he served Lewisham Hospital and St John's Hospital as senior physician He was always interested in hospital administration, he was chairman of the Lewisham Hospital staff committee for a time, and later for three years he served as chairman of the group medical advisory committee His tactful handling of many difficult problems proved a valuable asset in the early stages of the development of the Lewisham hospitals as a group

After the retirement of the former medical superintendent in 1951, Dr Simmons undertook the medical administrative duties of the hospital—with the title of executive medical officer—but he still gave the greater part of his time to his clinical work

A colleague writes

Dr Simmons's opinion was respected and widely sought, and his kindly nature and good advice brought him many friends Much of his time was given to the welfare and medical care of the nursing staff, who held him in great affection He was fond of his garden to which he gave many of his leisure hours He shared his happy family life freely with a large circle of friends, and at Christmas it was the custom for him and his wife to entertain Dominion students

Dr Simmons leaves a widow and daughter

ALFRED CHAD TURNER WOODWARD

Kt, M B Edin, F R C S

Sir Chad Woodward, who died in Birmingham on Feb 2, at the age of 76, was educated at Radley and at Edinburgh University, where he graduated M B in 1904 Returning to the West Midlands he served as resident surgeon in the general hospital, Birmingham, taking his F R C S in 1911 For a time he practised in London, but in 1914 he joined the R A M C in which he continued to serve as an active surgeon until 1919 He succeeded his elder brother, who had been killed in the war, as heir of the Arley Castle estates in Worcestershire—an obligation which necessitated his retirement from medicine Instead he became an authority on forestry, and, like his father before him, was mindful of the public responsibilities of a land-owner

In 1926 he was elected to the Worcestershire County Council He served for many years as chairman of the education committee, vice-chairman of the council, and chairman of the standing joint committee From 1939 to 1943 he served on the Radium Commission In 1942 he was elected chairman of the county council and held office until 1955 He was a governor of the London School of Hygiene and Tropical Medicine and of Birmingham University He was knighted in 1944

A colleague writes

Woodward, who was tall and handsome in appearance but somewhat quiet in manner and reserved, was an able administrator and a gifted chairman—sympathetic but impartial, firm yet courteous, and always with that redeeming light touch at the right moment He was a well read man knowledgeable in many fields, yet he always retained an interest in medicine and enjoyed "talking shop" with a member of his former profession

He married in 1934 Martha Grace, daughter of Canon Rowland Wilson She survives him with three daughters

Appointments

Lyons Joseph M B Leeds, D P H M O H and divisional M O Morley Horbury, Ossett Wakefield, and West Riding of Yorkshire
Meara R H M B Camb M R C P consultant dermatologist, St John's Hospital for Diseases of the Skin, London
Shennan E T M B Aberd, D P H M O H Evesham and district
Strickland Basil M B Lond M R C P F F R D M R T D M R D, D C H assistant radiologist, Westminster Hospital London
Swann G F M B Lond, M R C P D M R D assistant radiologist, Westminster Hospital, London
Vickers H R, M D M B Sheff F R C P part time consultant dermatologist United Oxford Hospitals and the Oxford Regional Hospital Board
Walker P J C M B Birm school M O, South Staffordshire area

East Anglian Regional Hospital Board

Bergin J T M B N U I senior registrar in mental deficiency and child psychiatry Little Plumstead group of hospitals
Butcher A S F M B Camb registrar in obstetrics and gynaecology east Suffolk and Ipswich area hospitals
Das, N B M B Calcutta, T D D medical registrar, Papworth Hospital
Ghoshal, J, M B Calcutta registrar in psychiatry Suffolk mental hospitals

Notes and News

THE PORCUPINE MAN

In a lecture at University College, London, on Jan 31 Prof L S Penrose, F R S, told the story of Edward Lambert, the porcupine man, and his progeny

In the transactions of the Royal Society for 1731, he was described by John Machin as "an uncommon case of distempered skin" Born in Suffolk in 1716, he appeared normal at birth, but, when he was 6 weeks old his skin, except for the palms, became like the bark of a tree, with many spines like those of a hedgehog His parents and siblings were unaffected, and Machin noted that the mother had not been frightened while carrying him

After she died, his father took him to London to be exhibited as a freak His appearance cannot have been utterly repulsive (he was described as well proportioned, with a florid complexion), for in 1744 he married, and begot a son who was similarly affected and who was presented to the public "with other strange animals" Two grandsons (John and Richard) were also affected and toured Continental cities, where they were examined by many eminent scientists and physicians, including Tilesius and Alibert They were said to be intelligent and expert linguists, though their veracity, it seems, could not be entirely relied on John had a son, and apparently the anomaly died with him

It is now thought that these men had familial ichthyosis hystrix, a rare condition which has been seen on both sides of the Atlantic Some of the patients have been women, [illegible] brothers described recently in the United States were similarly affected, and their mother and other relatives had the condition less severely

The genetic interest of the porcupine men lies in the fact that records in the literature seemed to show that all the direct male descendants, and none of the females, were affected It was thought that the disease was a Y borne trait and the putative family tree has appeared often in the literature

But Professor Penrose, and his colleague, Prof C Stern of California, were more critical By examining the parish registers in several Suffolk churches, Penrose disproved some of the imaginative stories of John and Richard (for example, that their grandfather was a scaly American savage brought by sailors from the Davis Strait, and that they had no brothers but seven unaffected sisters) The results of their researches have allowed them to draw a revised pedigree, which shows affected females and unaffected males, and the ichthyosis is now thought to be an autosomal dominant trait They conclude that there is no reliable evidence at present for inheritance by Y-borne genes in man

MIDWIFERY AND DAY-NURSERY COSTS

In his latest report on the civil appropriation accounts[1] Sir Frank Tribe, the auditor general, remarks that the Local Health Statistics for 1954–55 showed that average midwifery costs were £13 3s per maternity case for county boroughs and £16 14s for counties, but the ranges of costs were from £7 7s to £25 6s and from £11 to £58 14s respectively Likewise, the average cost per child in daily attendance at day nurseries was £161 2s per annum for county boroughs and £169 2s for counties, but the ranges of costs were from £86 11s to £424 14s and from £67 16s to £214 14s per annum respectively

CANCER AND PEOPLE

That a carefully planned and conducted educational campaign on the early detection of cancer does not flood doctors' surgeries with hypochrondriacs was shown by Mr John Wakefield, secretary of the Manchester Committee on Cancer, at a conference organised by the Central Council of Health Education on Jan 24 The three other speakers were Mr R W Raven and Dr John Burton, who reviewed the position of cancer and the problems it presented, and Mr Mackenzie editor of the *Sunday Graphic*, who described the results of running a series of articles on cancer, the responses of readers its popularity, and the correspondence evoked

Mr Wakefield told of the programme of instruction introduced into a number of areas, so limited and defined that their experience could be compared with that of their neighbours Large audiences were avoided, in order to encourage informal discussion between the speaker and the group, description

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[1] Civil Appropriation Accounts (Classes I–V) 1955–56 H M Stationery Office Pp 323 13s 6d

Planning for Safety in the Home

Dr C A Boucher will give a lecture on this subject at 8, Hill Street, London, W 1, on Wednesday, Feb 27, at 3 30 P M The meeting has been arranged by the women's group on public welfare of the Council of Scientific Management in the Home

A New International Society

The Société Médicale Internationale de Photo Cinématographie et Télévision Endoscopiques et de Radiocinématographie was inaugurated, with Professor Soulas as president, on Dec 8 The next meeting will be in Paris on March 9 Dr P H Holinger will act as president, and Prof Chevalier L Jackson as hon secretary at the first annual general meeting, which will be held in New York on June 3 and 4 The permanent hon secretary is Dr J M Dubois de Montreynaud, 4, Rue du General Baratier, Reims, France

Scottish Maternity Services Review

The committee set up by the Scottish Health Services Council to review maternity services in Scotland held their first business meeting on Jan 29 They are hearing oral evidence from selected organisations, and they will be prepared to consider written evidence which may be offered in relation to their terms of reference, which are

> To consider through a professional subcommittee in the first place, the range of provision which should be available in the National Health Service in the interests of the mother and child during pregnancy, confinement, and lying in, and to advise how best such provision can be secured within the framework of the service

The chairman of the committee is Prof G L Montgomery The medical secretary is Dr Mabel Mitchell, and the lay secretary Miss L C Watson, both of the Department of Health for Scotland

Austrian Institute

Prof V Frankl, of the University of Vienna, will give a lecture at this institute, 28, Rutland Gate, London, S W, on Thursday, Feb 21, at 8 30 P M He is to speak on collective neuroses of the present day

Increases for Seriously Disabled War Pensioners

At the beginning of February, some 77,000 seriously disabled war pensioners, most of them veterans of the 1914-18 war, began to draw the improved allowances announced by the Minister of Pensions and National Insurance on Nov 19 (*Lancet*, 1956, ii, 1110)

Exports of Drugs and Medicines

In 1956 British exports of drugs and medicines reached a record of £35,943,000 Of this total, antibiotics accounted for nearly £7 million and vitamins for nearly £3 million. Sulphonamide preparations (£1$^1/_2$ million), aspirin and synthetic antimalarial drugs (£1 million each), and barbiturates, insulin and anti-histamine drugs (£$^1/_2$ million each) also contributed to the total Proprietary medicines not covered by specific headings in the Board of Trade returns amounted to ove £10 million

Australia and India were the leading export markets fo British drugs, with purchases around £3 million Next came Nigeria, Pakistan, South Africa, New Zealand, the Republic of Ireland, and Burma, all taking between £1 million and £2 million Sales to the United States of America increased from £660,000 in 1955 to nearly £1 million last year

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A new British Standard (B S 2805 1957) specifies a range of straight artery (hæmostatic) forceps of the Spencer Wells pattern having a screw joint and made of stainless steel Provision is made for 5 in, 6 in, 7 in 8 in, and 9 in sizes Copies of this standard (3*s* 6*d*) may be obtained from the sales branch of the British Standards Institution 2, Park Street London, W 1

Diary of the Week

FEB 10 TO 16

Monday, 11th

Postgraduate Medical School of London, Ducane Road, W 12
3 P M Dr John McClintock (New York) Thyroid Cancer
4 P M Dr Sheila Sherlock Portal Hypertension

Tuesday, 12th

Royal Society of Medicine 1 Wimpole Street, London, W 1
5 30 P M *Experimental Medicine and Therapeutics* Prof C A Keele Chemical Causes of Pain and Itch (Presidential address)
8 P M *Psychiatry* Dr J D W Pearce, Prof E W Anderson, Prof W C W Nixon Psychiatric Indications for the Termination of Pregnancy

British Postgraduate Medical Federation
5 30 P M (London School of Hygiene and Tropical Medicine, Keppel Street, W C 1) Mr H J Seddon Paralytic Poliomyelitis

St Mary's Hospital Medical School, London W 2
5 P M Mr W G Mills Dysmenorrhœa and Pelvic Pain

Royal Army Medical College, Millbank London, S W 1
5 P M Lord Cohen of Birkenhead Concept of Collagen Disease

Institute of Dermatology, Lisle Street, London, W C 2
5 30 P M Dr O L S Scott Genodermatoses

Chelsea Clinical Society
8 30 P M (Rembrandt Hotel, Thurloe Place, S W 7) Dr Alistair Dudgeon, Dr F O MacCallum Prevention and Laboratory Diagnosis of Virus Diseases

Manchester Medical Society
8 P M (Clinical Science Building, York Place, Manchester 13) *Surgery* Mr A G Riddell Surgery in Portal Hypertension

Wednesday, 13th

University of London
5 30 P M (London School of Hygiene and Tropical Medicine) Prof J B Duguid Mechanical Factors in Atherosclerosis

Royal Society of Medicine
4 30 P M *Physical Medicine* Dr A C Boyle Clinical Problems in Physical Medicine (Presidential address)
8 P M *Proctology* Prof E Boyland, Dr P S Macfarlane Mr I S R Sinclair, Mr A N Smith Argentaffinoma

Postgraduate Medical School of London
2 P M Prof C L Oakley Food Poisoning Due to *Clostridium welchii*

Institute of Dermatology
5 30 P M Dr Henry Haber Clefts Vesicles and Bullæ

Institute of Diseases of the Chest Brompton, London S W 3
5 P M Mr Dillwyn Thomas Surgery of Primary Tuberculosis

Eugenics Society
5 P M (26 Portland Place London W 1) Prof Tage Kemp Genetic Hygienic Experiences in Denmark in Recent Years (Galton lecture)

Manchester Medical Society
4 30 P M (Medical School, University of Manchester) *Pathology* Dr M T Parker Versatility of *Staphylococcus aureus* (Presidential address)

Royal College of Surgeons of Edinburgh, Nicolson Street Edinburgh, 8
3 30 P M Mr G E Mavor Administration of Potassium to the Hypothermic Heart (Sir Harold Stiles lecture)

Royal Faculty of Physicians and Surgeons of Glasgow 242, St Vincent Street Glasgow
5 P M Dr E Noble Chamberlain British Contributions to Cardiology (Walker lecture)

Thursday, 14th

Royal College of Surgeons of England, Lincoln's Inn Field London, W C 2
4 P M Sir Ernest Finch Influence of the Hunters on Medical Education (Hunterian oration)

University of London
5 30 P M (Westminster Medical School, Horseferry Road S W 1) Dr E Weston Hurst Approaches to the Chemotherapy of Virus Diseases (First of two lectures)

Royal Society of Medicine
5 P M *Ophthalmology* Dr R E Hoover (Baltimore) Therapeutic Corneal Grafts

British Postgraduate Medical Federation
5 30 P M (London School of Hygiene and Tropical Medicine) Mr W H Whelan, D SC Synthesis and Degradation of Polysaccharides

Institute of Dermatology
5 30 P M Dr S C Gold Bullous Eruptions

Nuffield Orthopædic Centre
8 30 P M (Wingfield Morris Orthopædic Hospital, Oxford) Mr J M Zarek Biomechanical Problems in the Reconstruction of the Femur

St Andrews University
5 P M (Queen's College, Small's Wynd, Dundee) Dr W R Doll Smoking and Lung Cancer

Friday, 15th

University of London
5 30 P M (Westminster Medical School) Dr Weston Hurst Approaches to the Chemotherapy of Virus Disease (Second of two lectures)

Royal Society of Medicine
5 P M *Epidemiology and Preventive Medicine* Dr A M Ramsay Encephalomyelitis Simulating Poliomyelitis in North West London Dr E R Mitchell Nottingham Meningiti
8 15 P M *Radiology* Dr C J Hodson Renal Aortography i Hypertension Dr R L Steiner Renal Phlebography Dr Thomas Philip Aorto arteriography in Obliterative Vascular Disease of the Lower Limbs

Postgraduate Medical School of London
10 A M Prof J B Kinmouth Lymphœdema
4 P M Dr E N Rowlands Symptomatology of Peptic Ulcer

Institute of Laryngology and Otology 330 Gray's Inn Road London, W C 1
3 30 P M Mr K G Rotter Common Diseases of the External Ear

Royal Medico Chirurgical Society of Glasgow
8 30 P M (Royal Faculty of Physicians and Surgeons of Glasgow) Dr J H Cyriax Backache

CHEMICAL CARCINOGENS AND THEIR SIGNIFICANCE*

J W COOK

D Sc, Ph D Lond, F R S, F R I C

VICE CHANCELLOR OF THE UNIVERSITY OF EXETER

THE success achieved by chemotherapy against parasitic organisms gives grounds for hope that chemotherapeutic agents against cancer may eventually be found Hitherto the search has been largely empirical, but, if distinctive differences between normal and malignant tissue were found, the way would be open for a more rational approach Some promising results have recently been reported with modified amino-acids and purines, such as 6-azauracil and 6-mercaptopurine riboside Such substances might be expected to act by displacing some normal components in the synthesis of nucleoproteins

I have been concerned with chemical carcinogens for the past twenty five years, during which time our knowledge of this subject has increased so extensively that I can do no more than touch on some selected aspects

Historical

Sir Ernest Kennaway first showed, in 1930, that cancer could be produced by a pure chemical compound, but this discovery had its origin in observations made by Percivall Pott in the latter part of the eighteenth century Pott described chimney sweep's cancer, which he clearly recognised as an industrial disease and attributed to some peculiar quality of the soot to which the sweeps were exposed This view was vindicated by Passey in 1922, when he showed that skin cancer could be produced in mice by painting them with an ethereal extract of soot The first such experimental production of cancer had been accomplished in 1915 by Yamagiwa, who applied coal tar to the ears of rabbits, and the same agent was shown a few years later by Tsutsui to cause skin tumours in mice This procedure of application to the skin of mice has been used extensively ever since in testing for carcinogenic action

During the 1920s and earlier, other examples of industrial skin cancer became recognised Coal-tar workers were found to be liable to the disease, as also were workers in the Scottish shale oil industry, especially those engaged in handling the paraffin scale A similar liability was found in workers in the Lancashire cotton industry and traced to the action of mineral lubricating oil to which the mule spinners were exposed The question was, therefore, what particular constituents of these materials were responsible for these effects Coal tar, lubricating oil, and shale oil are all complex mixtures, and it became a matter of importance to determine which of their components had these pathological effects The problem was taken up by Kennaway, who tested many of the known constituents of coal tar without result but was able to prepare new forms of carcinogenic tars, the study of which provided valuable clues, especially those arising from the spectroscopic work of Mayneord and Hieger I joined the team at the Cancer Hospital in London in 1929, so that chemical methods could be brought to bear on the problem, and was assisted in these by another young chemist, Hewett

Carcinogenic Hydrocarbons

The efforts of our small team were rapidly crowned with success, and in a relatively short time we had synthesised a considerable range of pure chemical compounds with cancer producing activity, some of them remarkably potent For the most part these were new compounds, prepared for the first time in connection with these studies, and they belong to the class of polycyclic aromatic hydrocarbons The parent compound of the first group of such hydrocarbons found to have this biological action is 1 2-benzanthracene Although in itself it has little or no activity, active compounds arise when substituents are introduced into suitable positions in the molecule By preparing and testing large numbers of compounds we were able to make some rough generalisations about the conditions necessary for carcinogenic activity within this group

Fluorescence spectroscopy of carcinogenic tars provided the clue which led to the discovery of these cancer-producing hydrocarbons They have a fluorescence spectrum similar to that characteristic of the tars The same clue was used by Hieger in the systematic fractionation of coal-tar pitch, which led eventually to the isolation of a very potent carcinogenic hydrocarbon, hitherto unknown, which was shown to be 3 4-benzpyrene This we also synthesised, and the synthetic material was just as active as that isolated from coal tar pitch This hydrocarbon is related in molecular structure to 1 2-benzanthracene It is a fair presumption that 3 4-benzpyrene is responsible, at least in part, for the skin cancer in coal-tar workers Direct proof of this would naturally be difficult to secure

Whether mineral oils have this or similar carcinogenic constituents is still an open question The matter is being investigated under the auspices of the Medical Research Council Chemical separation of pure components of the active fractions of a Kuwait oil is being undertaken by Dr W Carruthers and Mr A G Douglas They have already, in Glasgow, isolated and identified a considerable number of new constituents of the oil, and this work is now being continued in Exeter, in the laboratory of the new M R C Carcinogenic Substances Research Group at the university

The carcinogenic hydrocarbons have very interesting biological properties Applied to the skin of laboratory animals they cause first papillomas and then malignant tumours which have all the usually accepted criteria of carcinomas They show invasion of muscle and they give rise to secondary tumours, usually in the lungs or the axillary glands If the same compounds are applied by subcutaneous injection they cause sarcomas which can be grafted and maintained in successive hosts, apparently indefinitely In fact, with these compounds, cancerous tumours have been obtained in a great variety of tissues and in a number of different species of animal (e g, rats, mice, rabbits, hamsters, guineapigs, and fowls) The tumours also show great variety morphologically, and their nature seems to be determined mainly by the character of the cells in the tissues affected by the carcinogenic agent

Differences between the substances are *quantitative* rather than qualitative Thus, two compounds may vary in the rates at which their application to a given tissue leads to tumour formation, and the relative potencies determined in this way will not necessarily be the same if a different tissue is used as test object To put this last statement in another way, a compound A may give epitheliomas in mice twice as rapidly as a compound B, but in the production of sarcomas in fowls or epitheliomas in rabbits B may prove to give a response three times as rapidly as A

The certainty with which malignant tumours are produced—e g, by painting on mice—with the more potent compounds is very impressive, as also is the smallness of the dose, amounting in the case of the more active compounds to microgramme quantities, with which tumours have been produced If chemical compounds are concerned in the initiation of human cancer in general, as may well be the case, it is important to recognise that we may be dealing with either small amounts of highly active compounds, perhaps acting for a relatively short time, or larger amounts of weakly carcinogenic compounds acting over many years, perhaps the major portion of the normal life span

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* Abridged from a lecture given to the Devon and Exeter Medico Chirurgical Society on Oct 18, 1956

The intensive research on carcinogenic substances which has been undertaken during the past quarter of a century has complicated rather than simplified the problem Many active compounds are known, not only among the various groups of polycyclic hydrocarbons but also with analogous compounds in which one or more of the aromatic rings has either nitrogen or sulphur as part of its make-up There are also carcinogenic compounds of widely different chemical types in which no *common feature can* be *recognised* These include azo dyes and aromatic amines, both of which groups merit comment

A characteristic of the carcinogenic hydrocarbons is that they act locally, at the site of direct application Injection into the subcutaneous tissue gives spindle-cell sarcomas of connective tissue, application to the skin gives squamous cell epitheliomas, tumours have been obtained by direct application to other tissues—e g, liver, spleen, and brain—and insertion of pellets in the femur and tibia has given osteosarcomas and fibro sarcomas

Azo Dyes

The azo dyes, of which the carcinogenic action was first reported by Yoshida and Kinosita, give, on the other hand, only tumours of the liver (hepatoma and cholangioma), irrespective of the route of administration Metabolic studies support the view that the action of the carcinogenic hydrocarbons is a direct action on the cells, but in the case of the azo dyes the action is probably indirect, resulting from the conversion of the dye in the liver into a carcinogenic metabolic product, which may be an aromatic amine A compound of the latter class, β naphthylamine, has been shown to cause bladder cancer in dogs and is probably responsible for the high incidence of cancer of the bladder found among workers in dyestuffs The evidence incriminating β-naphthylamine in this is so strong that the manufacture of this important dyestuffs intermediate has been abandoned in the United Kingdom

The action of azo dyes in producing liver tumours is also of practical importance inasmuch as compounds of this class have been used for colouring food Dietary deficiency, particularly of protein and riboflavine, seems to be a factor in influencing the production of liver tumours, for which massive doses of the dye are required But the possible carcinogenic effects of these dyes has led a Government committee to recommend that only a restricted list of dyes should be used for colouring food

Other types of compounds which have been shown to be carcinogenic are certain epoxides, such as the diepoxide of vinylcyclohexene, some ethyleneimines, and the so called nitrogen mustards These three groups are all highly reactive chemically, in contrast to the polycyclic hydrocarbons, and they act as cytotoxic agents They appear to act directly on the chromosome mechanism of the cells and, in doing so, bring about effects indistinguishable from those of X rays, which also have a carcinogenic action

In spite of much research we still do not know anything of the mechanism by which the polycyclic hydrocarbons transform normal cells into cancer cells, but it may be associated with the fact that at least *one of them* is known to become firmly attached to skin proteins In a similar way the azo dye butter-yellow has been shown to form a complex with liver proteins, and this is formed more slowly in rats given a protective diet containing added riboflavine These and other findings have suggested that the induction of malignant change is attributable to the gradual deletion of key proteins essential for the control of growth Among the experimental observations which require explanation are the findings that the production of tumour by carcinogenic hydrocarbons can be considerably accelerated by co carcinogens (e g, croton oil) and retarded by other agents (e g, mustard oil)

Tobacco and Lung Cancer

Cancer of the lung has increased at least tenfold during the past thirty years and is well on the way to becoming the most common form of cancer in men Lung cancer has not increased in women to anything like this extent In 1954, for example, in England and Wales, six men died from cancer of the lung for every woman There is now an impressive amount of statistical evidence which seems to incriminate cigarette smoking in the increase of lung cancer, but this is clearly not the only factor In England and Wales in 1950 there were 15,000 deaths attributed to cancer of the lung, and in 1955 the figure had risen to 17,270 A fifth of the victims were non smokers, and in these also cancer of the lung is increasing But the statistical data undoubtedly suggest a much enhanced liability to lung cancer among cigarette-smokers and to a lesser extent among smokers of pipes and cigars

If smoking is the cause of this increase of lung cancer, presumably there are carcinogens in the smoke The tarry condensates of the smoke obtained by smoking cigarettes in machines designed to reproduce the conditions of human smoking have indeed been shown to contain small amounts of polycyclic hydrocarbons, among them 3 4 benzpyrene But the amount is exceedingly small, and there is considerable doubt about whether the concentration is high enough to produce carcinogenic action Wynder, in the United States, has obtained malignant tumours of the skin in mice by the application of tobacco tar prepared in this way, but other workers have obtained purely negative results, and it is possible that, in the preparation of his tar, Wynder had used more drastic conditions, especially as regards temperature of combustion, than we have in normal smoking This question of whether there are harmful amounts of carcinogen in tobacco smoke, and, if so, what is the nature of the carcinogen, is one of the two problems to be investigated in the new carcinogenic substances group of the Medical Research Council in Exeter A major difficulty is that we have not yet a satisfactory method of biological test The lung tumours which have been induced in animals with chemical carcinogens are usually adenomas, and tumours analogous to the bronchocarcinoma of man have not so far been induced experimentally in animals

Atmospheric Pollution

The other main factor which may be concerned in the increase of lung cancer is atmospheric pollution associated with urbanisation and industrialisation Town air is at times heavily contaminated with soot, which is known to contain occluded 3 4-benzpyrene, and this soot is deposited in the lungs of town dwellers Also, experiments have shown that 3 4-benzpyrene may be present in the exhausts of petrol engines and diesel engines under conditions of inefficient running, and there is reason to think that other carcinogens may be present in the fumes from petrol engines

It may well be that a summation effect is operative, *and that the combined* effect of soot, engine fumes, and tobacco smoke will produce sufficient concentration of carcinogen to give lung tumours under conditions where none of these alone would be effective A plausible suggestion is that the solvent action of the constituents of tobacco smoke may extract the benzpyrene absorbed in the soot deposited in the lungs with the result that this carcinogen is brought into intimate contact with the tissues. Kotin of Los Angeles who discussed cancer-morbidity data for different countries and different regions, concluded that the main factors influencing the incidence of lung cancer are environmental and associated with the degree of atmospheric pollution, and that tobacco-smoking plays a subsidiary rôle. Conclusive evidence of the importance, both relative and absolute, of these various factors is going to be very difficult to secure. In the meantime the best advice that can be given, especially to young people, is that it would be well to avoid the large cities, particularly in industrial areas, and to give up smoking.

Cholesterol

I began by recording facts; I have moved into the realm of conjecture; and I am going to finish by becoming frankly speculative. What about cancer of the internal organs of man? Is this due to the action of carcinogenic substances? I can answer this question only in a negative way; there is no evidence to show that it is not. In a malignant tumour induced by a polycyclic hydrocarbon there is no longer present the substance which initiated it, and the fact that such carcinogens cannot be detected in spontaneous tumours is no proof that they were not concerned in the origin of the tumours. Although the known powerful carcinogens have not been detected in tissues or body-fluids, it is suggestive that Hieger and others produced sarcomas in mice by injecting unsaponifiable fractions of the fats extracted from livers not only of patients who had died of cancer but also of non-cancer patients. An invariable constituent of such unsaponifiable fractions is cholesterol, which is notoriously difficult to obtain in a state of complete chemical purity. Tumours have also been induced in a small proportion of the treated mice, with cholesterol samples of various degrees of purity as well as with products formed by oxidation of cholesterol.

Cholesterol and the related bile acids are also of interest from another standpoint. Haslewood and I showed about twenty years ago that the hydrocarbon methylcholanthrene, which may be obtained by relatively simple procedures, involving oxidations, reductions, dehydrations, and dehydrogenations, from some of the bile acids—notably deoxycholic acid—is a very powerful carcinogen. It is a member of the 1 2-benzanthracene group and is closely related to other carcinogens of this group. May it not be that, under some conditions not yet defined, natural steroids present in the body undergo similar chemical transformation into either methylcholanthrene or a related carcinogen? There is no evidence to support this other than a suggestive structural relationship; but it is a possibility which should not be too lightly dismissed.

Sunlight

Then there is skin cancer other than the industrial forms which are known now to be due to the action of chemical carcinogenic agents. I have been surprised to find that this has been stated to be the most common form of cancer in the United States; but it is undoubtedly very prevalent in some parts of the world, especially among people who undergo prolonged exposure to strong sunlight, such as farmers in Australia and South Africa. And there is a precancerous skin condition among seamen that has been called seaman's skin. Excessive exposure to strong sunlight is undoubtedly the primary cause of much of this skin cancer, and skin tumours have been produced experimentally in rats by prolonged exposure to sunlight.

The rays of the sun may have a direction action on the cells; but it is at least possible that the action may be indirect and involve a photochemical conversion of some constituent of the skin into a chemical carcinogen. A substance which suggests itself in this connection is provitamin D, which is known to be converted into the vitamin by ultraviolet light. Provitamin D is closely related to cholesterol and is, in fact, cholesterol from the molecule of which two atoms of hydrogen have been abstracted. Recent work has shown that, by some relatively minor variations in the conditions of irradiation, the photochemical transformation of provitamin D may take a different course and give rise, by a modification of the ring system, to a substance known as an anthrasteroid, which has a structure not far removed from that of a carcinogenic hydrocarbon of the benzanthracene group. To the chemical mind there is no difficulty in imagining photochemical conversion of provitamin D to a chemical carcinogen. But again I am being fanciful and am speculating about changes which might well take place but for which there is no direct evidence.

Conclusion

I think, however, that I am on fairly safe ground in suggesting that, for some time to come, the study of chemical carcinogens is likely to prove one of the most profitable forms of cancer research and to give increasing insight into the nature of malignant change. Such lines of investigation will not necessarily point the way to cancer cures; but, if we can achieve a better understanding of the nature and origins of cancer, there is a good chance that, just as with industrial forms of cancer, the way may be open to prevent the onslaught of this great enemy of mankind. The road may be hard and long, but the impressive advances of knowledge of cancer in the past half-century give good grounds for hope that the goal may eventually be reached.

RESPONSE TO ALCOHOL IN CHRONIC ALCOHOLICS WITH LIVER DISEASE*

CLINICAL, PATHOLOGICAL, AND METABOLIC CHANGES

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The clinical association between liver disease, chronic alcoholism, and malnutrition is accepted, but the relationship of any one of these factors to the others remains unresolved.

There is a geographical correlation between the incidence of human malnutrition and cirrhosis; and diets lacking lipotropic substances, particularly choline and methionine, will induce fatty change and fibrosis, similar to those in the human liver, in laboratory animals

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TABLE I—PATIENTS, DIAGNOSIS, AND DETAILS OF DIET

Case no	Age (yr)	Sex	Histological diagnosis	Daily intake of 95% alcohol (ml)	Duration of alcohol treatment (days)	Details of daily diet		
						Calculated protein (g)	Total calories	
							Control period	Including alcohol
1	41	F	Portal cirrhosis and fatty vacuolisation	90	21	65	2770	3350
2	61	M	Portal cirrhosis and fatty vacuolisation	120	32	60	2800	3400
3	67	M	Fatty vacuolisation	120	20	25	2500	2500
4	45	M	Portal cirrhosis	90	10	61	2480	3000
5	58	M	Portal cirrhosis and fatty vacuolisation	120	14	60	2550	2550
6	33	M	Portal cirrhosis and fatty vacuolisation	120	24	25	2300	2300
7	42	M	Portal cirrhosis and fatty vacuolisation	90	21	65	2770	3150

(Himsworth 1950) Attempts to extend these observations to the treatment of liver disease in alcoholics with such agents have been unsuccessful (Phillips and Davidson 1954), although Patek and Post (1941) showed that a diet high in protein, calories, and vitamins, together with rest in bed and abstention from alcohol, produced clinical improvement Later work, however, showed that recovery was also possible with a relatively low intake of protein (Klatskin and Yesner 1949), thus emphasising the importance of abstention from alcohol and of a hospital regimen

An action specific to alcohol and leading to the appearance of fat and fibrosis in the liver has not been established in either man or other animals, but it has been shown that alcohol enhances the toxic effect of certain agents on the liver of laboratory animals (Rosenthal 1930) It has therefore been postulated that hepatic disease results from the combination of excessive alcohol intake and dietary deficiency Results of experiments on animals further indicate that the high caloric content of alcohol may increase the demand for lipotropic substances and thereby lead to pathological changes in the liver despite an otherwise adequate diet (Best et al 1949) Reports on the effect of alcohol in human patients with liver disease are limited to the observations that the addition of alcohol to the diets of 1 inpatient (Volwiler et al 1948) and 4 outpatients (Patek and Post 1941) did not interrupt their satisfactory progress

The characteristic protein malnutrition of the alcoholic has been related to economic factors and pathological changes in appetite, but calories derived from alcohol do not spare nitrogen in animals on low-protein diets (Mitchell and Curzon 1940), and the same action may operate in man

In an attempt to elucidate further the relationship between liver disease, alcoholism, and malnutrition we allowed alcohol to 7 patients already exhibiting these features Their intakes of protein were 25–65 g daily in the presence of adequate calories Some of the patients had calories derived from alcohol added to their diet, but others were maintained on an isocaloric regimen Nitrogen balances were recorded, and the effect on the course of the liver disease was followed by liver biopsy and serial liver-function tests

Material

Observations were made on 7 patients (6 male and 1 female) aged 33–67 (table I)

All the patients had been either unemployed or doing casual work in bars or restaurants, and the 5 married patients were either divorced or living apart from their spouses Their domestic environment was always unsatisfactory, and their nutritional histories revealed that, apart from alcohol, sandwiches were the main source of food during periods of drinking The female patient (case 1) was reluctant to divulge her alcoholic habits, whereas the other patients admitted drinking heavily for 20–40 years Cases 2 and 3 indulged in prolonged sprees, but cases 4–7 were steady drinkers The confessed intake is exemplified by case 7 (10 cans of beer and 7 shots of whisky daily) and case 6, whose preference for wine led to a daily consumption exceeding 5 quarts Except case 1, all the patients gave a history of "shakes," "jitters," "cold sweats," "dry heaves," or other disorders incident to alcoholism, and case 6 admitted previous hospital treatment for delirium tremens and "rum fits"

There was no history suggesting hepatic disorder until the period just before admission to hospital, but every patient had clinical signs of liver disease 4 patients (cases 3, 5, 6, and 7) were icteric, and 3 (cases 2, 4, and 6) had ascites on admission, but alcohol was not given until these complications had improved Liver biopsy revealed portal cirrhosis and fatty infiltration in 5 patients (cases 1, 3, 4, 5, and 7), cirrhosis without fat in case 4, and fatty vacuolisation without fibrosis in case 3

Muscle mass was reduced in all the patients, and in 5 (cases 1, 2, 5, 6, and 7) peripheral neuritis was the cause of admission to hospital, being sufficiently severe either to cause gross abnormality of gait or to prevent walking unaided Case 5 had mild Korsakoff psychosis and stigmata of recent scurvy

Methods

The patients were up and about in the ward of the Thorndike Memorial Laboratory, and their weight, temperature, pulse rate, and output of fæces and urine were recorded daily After a period of equilibration on the prescribed diet the patients were studied during an 8 day control period, during alcohol consumption, and for 8 days after the alcohol had been withheld Biochemical determinations and liver biopsies were done on the last day of the initial control period and when the alcohol was withheld Liver biopsies were made at about the same site in each patient with a Vim Silverman needle The histological interpretation of these specimens was undertaken by an independent observer, Dr D Campagna Pinto, of the Mallory Institute of Pathology, to whom we are most grateful

Diets and Alcohol Consumption

The daily diets contained adequate calories (2800–2285) and multivitamin supplements † The calculated content of protein was 25–65 g daily, and, on analysis, the diets contained 4 0–10 9 g of nitrogen

After the initial control period alcohol was given as 95% ethyl alcohol in fruit juice in divided doses six times daily for 10–32 days The total daily intakes of alcohol were 90–120 ml Alcohol was added to the caloric intake in 3 patients (cases 1, 2, and 4), and 3 patients (cases 3, 5, and 6) were kept on an isocaloric regimen by the deduction of carbohydr m the diet during the treatment with alcohol 7 the carbohydrate equivalent of rather less caloric value of the alcohol v thheld

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† 'V ules' pro tories ork. the of

Nitrogen Balances

Nitrogen balances were studied in every patient except case 1 After the period of equilibration either 2-day or 4 day specimens of urine and of fæces were collected throughout the study and analysed for total nitrogen content

Biochemical Methods

Liver-function tests were made by methods reported earlier (Phillips and Davidson 1954) Blood-alcohol levels were determined by the technique of Conway (1950) and total nitrogen contents of diets, urine, and fæces by standard Kjeldahl procedures Starch tolerance tests were made in 2 patients by the method of Althausen and Uyeyama (1954)

Results

General Observations

The consumption of alcohol appeared to have no adverse effect on the clinical condition of any patient Case 5 developed pyrexia (102°F) with increasing jaundice during treatment with alcohol but recovered during continuation of the regimen, and a similar episode occurred several days after alcohol had been withheld Mild pyrexia (99–100°F), considered to be related to the liver disease, was present in 5 patients during the initial control period In every instance the body-temperature fell gradually towards normal either before or during treatment with alcohol

The effect of alcohol on the appetite was striking At the beginning of the study anorexia was usually severe, and difficulty was experienced in keeping the dietary intake constant at this stage in 4 patients (cases 3, 5, 6, and 7) The addition of alcohol to the diet led to rapid improvement in appetite, regardless of the total caloric intake, in every patient This increased desire for food continued after alcohol had been withheld, by which time the general condition had improved

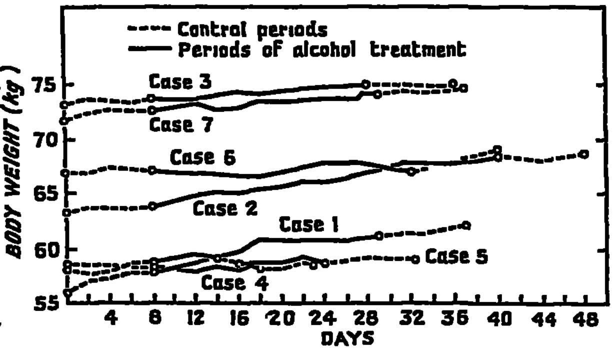

Fig 1—Alterations in body weight in relation to diet and consumption of alcohol

Most of the patients were more alert, euphoric, and cooperative during treatment with alcohol There was no evidence of gross inebriation, but intermittent drowsiness (cases 5 and 6) and unsteadiness of gait (cases 2 and 6) were observed Case 7 exhibited mild withdrawal symptoms—tremor, with disordered speech and behaviour —when the alcohol was withheld

In cases 5 and 7 the size of the liver, assessed by physical examination, became smaller during alcohol consumption and all the patients with peripheral neuritis (cases 1, 2, 5, 6, and 7) steadily improved in muscle power and gait

Body weight and Nitrogen Balance

Alterations in body-weight in relation to the administration of alcohol are shown in fig 1 3 patients were on an isocaloric regimen, receiving either 25 or 60 g of protein daily, and there was no significant change in weight in 2 of them (cases 5 and 6) The 3rd patient (case 3), whose diet contained 25 g of protein daily, gained 1 2 kg during a 21 day course of alcohol, but this was in proportion to his weight gain during the initial control period

TABLE II—BIOCHEMICAL FINDINGS BEFORE AND AFTER TREATMENT WITH ALCOHOL

—		Serum bilirubin (mg per 100 ml)	Serum albumin (g per 100 ml)	Serum globulin (g per 100 ml)	Brom sulphalein retention at 15 mins (%)	Cephalin flocculation (units)	Blood alcohol (mg per 100 ml)
Normal values		<1 0	>4 0	<2 5	<5 0	1 +	6
Case no							
1*	Before alcohol	0 4	3 4	3 3	17 3	0	0
	After alcohol	0 4	3 8	2 4	14 3	0	46 1
2	Before alcohol	1 1	4 3	2 0	30 0	1 +	0
	After alcohol	0 8	4 4	1 9	23 0	0	17 0
3	Before alcohol	0 6	3 6	2 3	11 5	2 +	0
	After alcohol	0 6	3 8	2 2	8 4	1 +	46 5
4	Before alcohol	0 6	2 4	3 9	2 8	0	
	After alcohol	0 5	3 6	2 7	2 3	0	
5	Before alcohol	1 5	4 2	2 6	42 0	3 +	
	During alcohol	(1) 8 5	3 7	2 9		3 +	
		(2) 5 1					
	After alcohol	(1) 1 1	4 1	3 0	19 6	0	
		(2) 7 1				1 +	
6	Before alcohol	0 7	3 7	1 3	20 4	1 +	
	After alcohol	0 5	3 8	1 8	10 8	0	
7*	Before alcohol	0 4	3 2	2 5	10 6	0	0
	After alcohol	0 3	3 3	3 0	5 4	0	17 3

* Starch tolerance tests also made before and after consumption of alcohol

3 patients whose diet contained 60–65 g of protein daily received the calories from alcohol in addition to those derived from the diet Case 2, whose weight was relatively constant before and after treatment with alcohol, gained 3 6 kg during a 32-day course of alcohol Case 1's weight increased rapidly during the initial control period and continued to do so when alcohol was added, but the rate of increase diminished as time progressed and was not clearly related to the alcohol alone In contrast, case 4's weight remained constant before, during, and after alcohol was given

During alcohol consumption case 7's intake was increased by 370 calories, rather less than the equivalent of the alcohol he received, and in the 3 week period he gained only 1 4 kg , an increase similar to that occurring before and after alcohol was allowed

The increases in weight of these patients were most closely related to the total calorie content of their diet (table I) and were greatest in cases 1 and 2, who received 3350 and 3400 calories respectively Except case 4, the patients who gained little or no weight were those on smaller caloric intakes The capacity to gain weight was not related to the severity of liver disease judged by liver-function tests (table II) and histological appearances (table III)

There was no evidence that alcohol consumption had any constant or significant effect on nitrogen balance (table IV) The retention of nitrogen was greatest in patients receiving the larger amounts of protein, and the balance was barely positive in cases 3 and 6, who were given only 25 g of protein daily These findings were comparable in each patient before, during, and after consumption of alcohol The retention of nitrogen was not increased by increasing the caloric intake with alcohol in 3 patients (cases 2, 4, and 7), nor was it greatly altered during alcohol administration in patients maintained on an isocaloric regimen (cases 3, 5, and 6)

Urinary loss of nitrogen was definitely greater in case 5 and smaller in cases 3 and 4 during consumption of alcohol, but little change was observed in the remainder Similarly, the nitrogen content of the fæces was usually

TABLE III—HISTOLOGICAL FINDINGS ON LIVER BIOPSY BEFORE AND AFTER ALCOHOL CONSUMPTION

Case no	—	Derangement of liver pattern	Portal space			Liver lobule				
			Fibrosis	Cellular infiltration	Bile duct proliferation	Fat	Alcoholic hyaline	Polymorph infiltration	Necrosis	Nuclear changes
1	Before alcohol	+ +	+ +	+ Mixed	+	+ + +	0	+	0	-
	After alcohol	+ +	+	+	+ (less)	+ +	0	+	0	-
2	Before alcohol	+ + +	+ + +	+ + Polys	+ +	+	+ + +	+ + +	+ +	+
	After alcohol	+ + +	+ + +	+ Polys	+	0	+	+	0	-
3	Before alcohol	0	0	+ Lymphs	0	+	0	0	0	±
	After alcohol	0	0	+ Lymphs	0	+ (less)	0	0	0	-
4	Before alcohol	+	+	+ Mixed	+	0	0	0	0	-
	After alcohol	+	+ +	+ +	+	0	0	0	0	-
5	Before alcohol	+ +	+ +	+ + Polys	+	+	+ +	+ +	+	-
6	Before alcohol	+	+ +	+ Mixed	+	+	0	+	0	-
	After alcohol	+	+ +	+ Mixed	0	0	0	0	0	-
7	Before alcohol	+	+	+ Polys	0	+ + +	0	+	0	+
	After alcohol	+	+	+ Polys	0	+	0	+	0	+

unaffected by alcohol consumption, but it was smaller in case 5 and larger in case 4

Biochemical Changes in Relation to Alcohol Administration

Liver-function tests were made immediately before and after the course of alcohol in every patient (table II) In no case was there any deterioration, and in most cases clear evidence of improvement was obtained

Serum bilirubin levels either fell or remained unchanged in every patient, but values above 1 0 mg per 100 ml were present initially in only cases 2 and 5 Case 5 developed pyrexia with hepatic enlargement and increasing jaundice (serum-bilirubin level rising from 1 5 to 8 5 mg per 100 ml) 5 days after the administration of alcohol Alcohol was omitted for 2 days, by which time the serum-bilirubin level had fallen to 5 1 mg per 100 ml , and the alcohol was then resumed Clinical improvement continued , and, when alcohol was finally withheld, the serum bilirubin level *had fallen to 1 1 mg* per 100 ml We therefore considered that the deterioration shown by liver function tests was unrelated to the consumption of alcohol, and this was supported by the onset of a second brief episode of pyrexia and jaundice (serum bilirubin level 7 1 mg per 100 ml) 5 days after alcohol had been withheld

Serum albumin levels either rose or remained relatively unchanged in every patient during consumption of alcohol, whereas *serum-globulin* levels fell in 2 patients (cases 1 and 4) and rose in 3 others (cases 5, 6, and 7) *Flocculation tests* were unchanged in 3 cases but were less strongly positive after consumption of alcohol in 4 patients (cases 2, 3, 5, and 6) The retention of bromsulphalein was less after alcohol administration in every patient, strikingly so in 3 patients (cases 5, 6, and 7)

Improvement in *liver-function tests* was greatest in patients in whom they were most grossly abnormal initially (cases 2, 3, 5, and 6) and was unrelated either to the constitution of the diet or to the dosage of, and duration of alcohol administration

Pancreatic function before and after the course of alcohol was assessed in 2 patients (cases 1 and 7) by the starch-tolerance test, and no change was observed Similarly, there was no change in the levels of *sodium potassium, chloride, and non-protein nitrogen in the serum* in relation to the consumption of alcohol in any patient *Blood-alcohol* levels, determined in 4 patients, were 17 0–46 5 mg per 100 ml

Hepatic Histology in Relation to Alcohol Consumption

Histological abnormalities in the liver were present in every patient and, except in case 5, liver biopsy was done both immediately before and after the treatment with alcohol (table III)

The gross abnormality of liver pattern always remained unaltered, and the degree of portal fibrosis and infiltration was usually the same, although both appeared greater in case 4 On the other hand, less portal fibrosis was *observed in the second biopsy in case* 1, and cellular infiltration of the portal space became less obvious in case 2 The proliferation of bile-ducts was less after the course of alcohol in 2 patients (cases 2 and 6) and a less striking decrease was seen in case 1, but it was unaffected in the remainder

Changes in the liver lobule during *alcohol consumption* were more striking Fat was present in 5 of the patients who had biopsies before and after alcohol The amount of fat, judged histologically, was clearly less after alcohol in 4 patients (cases 1, 2, 6, and 7) and appeared to be less in case 3 Alcoholic hyaline (Mallory 1911) was greatly reduced and liver cell necrosis *no longer* evident after alcohol in the patient who presented *these* abnormalities (case 2) Polymorph infiltration was present initially in 4 patients and decreased after alcohol in 2 of them (cases 2 and 6) but remained unchanged in the others (cases 1 and 7) Nuclear abnormalities of the liver-cells were present in every patient, but after alcohol they were less obvious or no longer apparent in 3 patients (cases 3, 6, and 7) and unaffected in the other 3 patients

TABLE IV—NITROGEN BALANCES IN RELATION TO DIET AND CONSUMPTION OF ALCOHOL

Case no	Body weight (kg)		Daily intake of nitrogen (g)	Daily output of nitrogen (g)								
				Before alcohol			During alcohol			After alcohol		
	Before alcohol	After alcohol		Urine	Fæces	Balance	Urine	Fæces	Balance	Urine	Fæces	Balance
2	64 8	68 4	10 9	4 52	1 97	+4 41	4 86	1 61	+4 43	5 40	1 00	+4 50
3*	73 6	74 8	4 0	4 37	0 22	−0 59	2 19	0 39	+1 42	3 70	0 93	−0 63
4	58 2	58 6	7 9	2 48	0 79	+4 63	1 81	1 73	+4 36	2 90	0 56	+4 44
5*	55 4	55 4	9 7	3 12	1 12	+5 46	4 67	0 66	+4 37	5 83	0 67	+3 21
6*	67 0	67 0	4 0	2 70	0 30	+1 00	2 20	0 37	+1 43	1 60	0 28	+2 12
7	72 6	74 0	9 6	4 17	0 69	+4 74	4 17	0 50	+4 93	4 16	0 74	+4 70

* Diet isocaloric throughout study

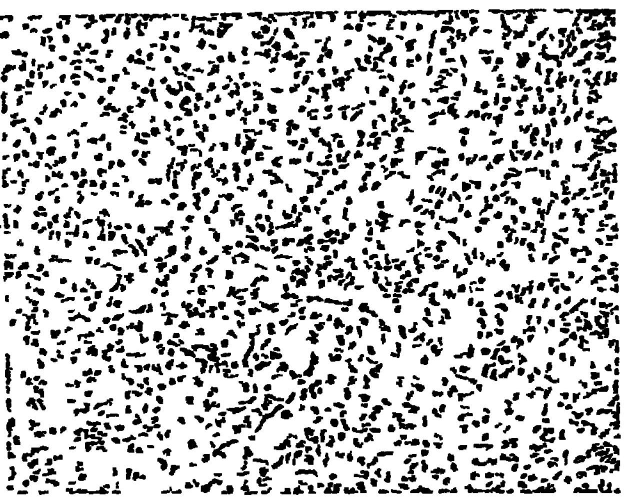

Fig 2—Case 2 liver biopsy before administration of alcohol (× 158)

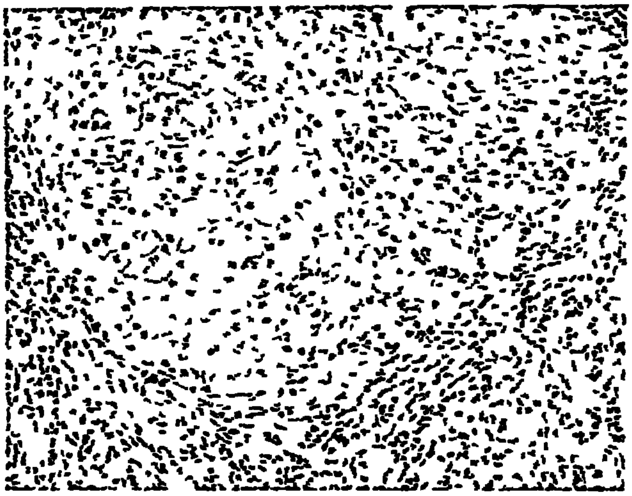

Fig 3—Case 2 liver biopsy after administration of alcohol (× 158)

The best-defined improvements in histological appearances were found either in patients who received the longer courses of alcohol, with consequently a greater interval between the two liver biopsies, or when the initial changes were most severe Case 2 who received the larger daily intake of alcohol for the longest period (32 days) exhibited the greatest degree of improvement (figs 2–5), whereas case 4 had a short course of alcohol with little alteration in histological findings The pathological changes, particularly the fatty infiltration, could not be related either to the caloric intake or to the protein content of the diet

Discussion

In no patient was an adverse metabolic effect attributable to consumption of alcohol Most of the patients improved clinically, with corresponding changes in liver-function tests and histology The rate of recovery in these respects was comparable to that reported by Volwiler et al (1948) in response to diets high in protein and calories together with abstention from alcohol, but the possibility cannot be excluded that improvement may have been delayed by alcohol in our patients in a degree too subtle to be appreciated in the absence of controls

The most striking clinical effects of alcohol were the increased appetite and the euphoria that immediately followed its addition to the regimen These facts suggest that small doses of alcohol should be given therapeutically to alcoholics with liver disease, because the anorexia which often complicates their management may be due to abstention from alcohol Alcohol did not impede the improvement of peripheral neuritis as Strauss (1935) has shown earlier, and the liver became smaller during treatment with alcohol in 2 patients 1 of whom also recovered simultaneously from jaundice The increases in body-weight suggest that the alcoholic with liver disease can use calories from alcohol in the dosage given and possibly in larger dosages (Newman 1949), although they may not be directly available as a source of muscular energy (Mitchell and Curzon 1940)

Nitrogen balance was more clearly related to the protein intake than to the calories consumed or to the severity of the liver disease It was maintained with difficulty if at all on the diet containing only 25 g of protein but these patients made satisfactory progress The addition of alcohol did not influence the nitrogen balance: this fact supports the view that the protein malnutrition of alcoholism is an expression of dietary deficiency alone In particular, there was no evidence of an effect of alcohol on pancreatic function, because the nitrogen content of the fæces remained constant and, in 2 patients thus studied, starch-tolerance tests were unaffected

Derangement of liver function tests and hepatic histology was usually diminished after alcohol administration Although there was a poor relationship between the biochemical and pathological changes the degree of

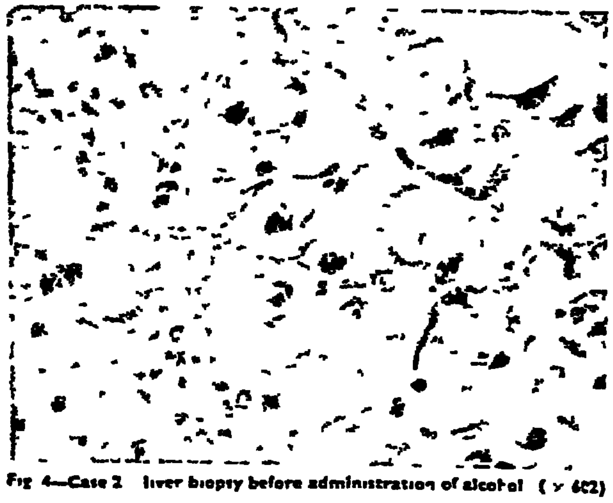

Fig 4—Case 2 liver biopsy before administration of alcohol (× 402)

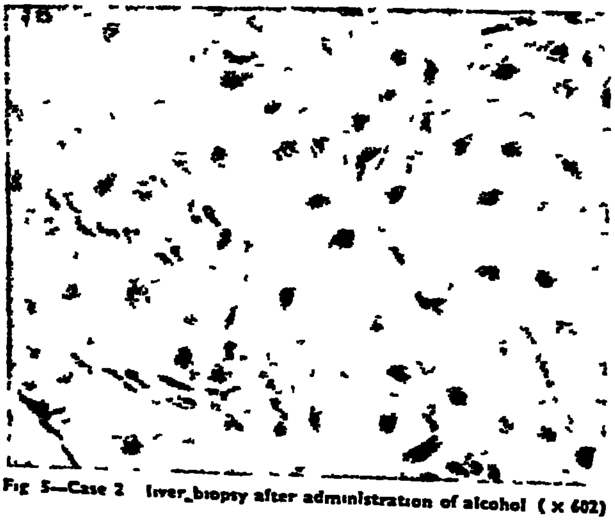

Fig 5—Case 2 liver biopsy after administration of alcohol (× 402)

improvement in both was related more closely to the severity of the initial abnormalities and to the length of time between observations than to the constitution of the diets Thus the lack of alteration in the amount of portal fibrosis during treatment with alcohol was attributable to the short duration of the study, whereas the more acute changes of cellular infiltration, alcoholic hyaline, and either necrosis or nuclear abnormalities of the liver-cells diminished or disappeared Excess fat in the liver decreased after alcohol was given The cause of fatty vacuolisation is uncertain, but the results of experiments on animals relate the presence of fat to a high caloric intake from alcohol or from sucrose in the absence of adequate lipotropic substances (Ashworth 1947, Best et al 1949) Klatskin et al (1954), confirming that alcohol increases the choline requirement, considered that the effect was independent of the caloric intake In our patients fat disappeared from the liver regardless of the total intake of calories or of alcohol and when the diet was marginal in protein content, although not necessarily so in lipotropic factors However, patients on a diet devoid of protein do not show any convincing diminution in liver fat (Phillips et al 1952), and it is therefore possible that the limitation of protein and the intakes of calories and alcohol used in this study were insufficient to delay significantly improvement in hepatic histology

The factors of importance in the genesis of liver disease in the chronic alcoholic consequently remain obscure No clinical or pathological improvement takes place during rest in bed with adequate calories, minerals, and vitamins, and abstention from alcohol (Phillips et al 1952), even when choline is added to the regimen (Phillips and Davidson 1954) Recovery may be initiated, however, by relatively small amounts of protein in the diet (Gabuzda and Davidson 1954), and we confirmed this

The consumption of alcohol may be a determining factor in deterioration of liver function, but we did not find any adverse clinical, pathological, or metabolic effect, even on marginal intakes of protein Interpretation of our results demands recognition of the differences that existed between the hospital regimen and the way of life normally pursued by these patients Although the amount of alcohol given was in most cases equivalent to half a pint of spirits daily and exceeded that prescribed in similar circumstances by earlier workers (Patek and Post 1941, Volwiler et al 1948) it was nevertheless smaller than that to which many such patients have become accustomed Similarly, even the low-protein diets given in hospital were probably more adequate than the food usually taken during periods of drinking On the other hand, the alcohol consumed was more than sufficient to satisfy the criteria of chronic alcoholism in liver disease (Olsen 1950), and nitrogen balance was precarious on the diets containing the least amounts of protein Furthermore, it may be argued that any deleterious effect of alcohol and dietary deficiency should have been rapidly apparent in these patients, because malnutrition and hepatic disease were already established

We therefore conclude that, if a combination of alcohol and dietary deficiency contributes to liver disease in the chronic alcoholic, it is in excess of what can reasonably be reproduced in a study of this nature

Summary

7 chronic alcoholics with liver disease and malnutrition were given 90–120 ml of 95% ethyl alcohol daily

The protein content of the diet varied from 25 g, on which the nitrogen balance was marginal, to 65 g daily The diet of 3 patients was kept isocaloric, but the remaining 4 patients received alcohol in addition to the previous caloric intake

Consumption of alcohol was accompanied by euph
and increased appetite

Increased body-weight showed that calories fr
alcohol could be used by these patients, and nitrog
balances were not changed by alcohol

Liver biopsies and biochemical liver function tests d
not reveal any adverse effect of alcohol

If alcohol alone or in combination with inadeq
protein nutrition contributes to liver disease in th
alcoholic, these factors are greatly in excess of th
reproduced in this study

Alcohol may have a place in the treatment of alcohol
with liver disease

We are grateful to Miss E Antonaros and Mrs M F Bradley for dietetic assistance, to Miss A N Ballou and M E A. Hirshberg for the biochemical determinations, a to Miss L Leavitt for the histological preparations

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ACUTE POLYNEURITIS TREATED WITH CORTISONE

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THE cause of the disease, variously called acute tox febrile, or infectious polyneuritis, or the Landry Guill Barré syndrome, has never been established with a certainty Its frequent occurrence as a sequel to so non specific febrile illness was originally thought t indicate that the peripheral nervous system was dama by some toxic or infective agent, though none h been isolated from pathological material In recent y the concept of the disease as an allergic manifesta has steadily been gaining ground One of the first suggest this was Furtado (1950) He argued that its clinical manifestation as a "second illness" occurr within narrow time limits after a primary infection a the characteristic changes in the protein content of t cerebrospinal fluid (C S F) could best be explained b regarding it as a "peripheral form of neuro allerg He thought, too, that there might be a relation between this illness, secondary to some unknown infection, and those types of polyneuritis complicat known infections, such as diphtheria and glandular fev or the introduction of foreign proteins, such as injecte serum

At the same time fresh histological studies wit modern techniques have shown that the patholog changes in the disease are not those of a primary infla mation Haymaker and Kernohan (1949), in a mo extensive and impressive review of the subject base on the findings of fifty fatal cases, showed that, for th first 3 or 4 days of the illness, the only change was œdema of the nerve roots This was followed by d integration of myelin sheaths and axis cylinders only in the 2nd week of the illness did a cellular reacti evelop. Much the same findings were reported by cheinker (1949), who thought that the œdema of the ots caused paralysis by mechanical constriction of e radicular nerves at their points of penetration of the pinal meninges.

Final proof that polyneuritis can be allergic in origin s provided by the interesting experimental work of aksman and Adams (1955).

They have produced in rabbits, by injecting homologous r heterologous sciatic nerve tissue plus an adjuvant (tubercle acilli), a polyneuritis comparable to the human disease. his condition occurred about 14 days after inoculation, and rogressed rapidly for about 3 days, after which, if the rabbit urvived (as it usually did), a rapid and more or less complete ecovery ensued. As in the Landry-Guillain-Barré syndrome, he polyneuritis was associated, in most cases but not all, ith a rise of protein as the only change in the C.S.F. Pathoogically, lesions were found in spinal roots, ganglia, and erves. Myelin sheaths and axis cylinders degenerated, and here was a cellular infiltration; but which came first, in uch a brief and intense reaction, it was difficult to be certain about.

Waksman and Adams compare this condition to experimental allergic encephalomyelitis produced by the injection of brain or cord tissue with adjuvants and known to be due to an immunological reaction.

Such, then, is the evidence supporting the hypothesis that acute toxic polyneuritis is an allergic disease and providing the rationale for its treatment with cortisone and corticotrophin (A.C.T.H.). First reports of its use were unfavourable. Shy and McEachern (1951) and Merritt (1952) each recorded, without detail, three cases which did not respond. Since 1952, however, cases have been described in which cortisone or corticotrophin halted the disease or even produced dramatic improvement and early cure (Stillman and Ganong 1952, Seltzer et al. 1952, Blood et al. 1953, Newey and Lubin 1953, Drenick and Arol 1953, Senseman and Greenstein 1953, Plum 1953, Vernon 1954, Guiang and Leones Guiang 1954, Luzes 1954, Tupper and Foster 1954, Guichard et al. 1955).

In this country the only recorded case is case 3 of Clarke et al. (1954): cortisone was given to a man apparently in extremis with respiratory paralysis and cardiovascular failure, and he slowly recovered. These workers felt that the use of cortisone merited further investigation, and thought it especially indicated in cases pursuing a relentless course and those with respiratory failure or hypotensive cardiovascular collapse. Yet if allergy is the underlying basis of the disease and structural changes in peripheral nerves follow œdema, it seems more rational to use cortisone at the earliest possible opportunity before severe damage has been done to the nerves. It might then be expected to act rapidly and effectively, whereas, once nerve fibres have been destroyed, no treatment is likely to hasten the normal process of repair. In this paper I attempt to show that such results are usually achieved in practice.

Clinical Study

In the past two years seven patients with acute toxic polyneuritis have been treated with cortisone. One patient (case 2) had two attacks. All showed the usual features of a symmetrical muscular weakness of varying severity associated with loss of tendon-reflexes, an increase of muscle tenderness, and peripheral sensory symptoms with or without objective sensory loss. All except case 2 had an increase of protein as the only abnormal change in the C.S.F. Four (cases 1–4) are regarded as mild cases, and three (cases 5–7) as more severe—though none were exceptionally severe for respiratory failure did not occur. All were given cortisone as soon as the diagnosis was established. The dosage used for cases 1–5 was 100 mg. daily for 2 days, 75 mg. daily for 2 days, and then 50 mg. daily for 10 days. The experience of case 6, however, showed that this schedule was insufficient for severer cases. Case 7 was therefore given 300 mg. daily for 2 days, then 200 mg. for 2 days, and 100 mg. daily thereafter.

Mild Cases

Case 1.—A boy of 14 was admitted to hospital on the 8th day of illness, complaining of progressive weakness of both arms and legs, with tingling in his fingers and feet.

Examination showed moderate generalised weakness of all muscle groups in his legs. He could stand and walk only with difficulty; knee and ankle jerks were absent, and plantar responses were flexor. Tenderness of the calves was increased, but there was no demonstrable loss of superficial or deep sensation. In the arms deltoid, biceps, triceps, and finger extensor muscles were weak. Biceps jerks were sluggish, other arm reflexes were absent. There was slight bilateral facial weakness. The C.S.F. contained protein 400 mg. per 100 ml.

Cortisone was given on the day of admission and continued for 14 days. After 7 days there was no change in his condition and no new symptoms had arisen. In the 2nd week, however, he made a very rapid recovery, and by the 14th day his arms were normal except for fractional weakness of the triceps, and his legs were normally strong except for slight weakness of the toe and ankle extensors. He was then allowed to go home. A month later he had fully recovered.

Case 2.—A woman of 34 was first seen on Oct. 11, 1955, giving 4 weeks' history of shooting pains in her lower legs, with numbness and tingling in her feet, spreading up to her calves. Walking had become difficult, and she felt unsteady.

Examination showed a weakness of hip flexors, ankle dorsiflexors, and toe extensors and flexors in the legs, and of deltoid, biceps, and triceps in the arms. All tendon reflexes were absent. Calf tenderness was increased and vibration sense lost at the ankles, but there was no loss of superficial sensation. The C.S.F. was normal (protein 10 mg. per 100 ml.).

Cortisone was given for 2 weeks. As in case 1, there was no change after 7 days, but improvement was rapid in the 2nd week, and after 14 days muscular power was normal in her limbs and she was symptom free.

She remained well until June, 1956, when her symptoms recurred and slowly progressed until she was seen 6 weeks later. By then her walking was unsteady and she had continuous tingling over the legs below the knees and from the mid forearms distally. In the arms all muscle groups were weak, but there was no sensory loss. In the legs weakness affected the hip flexors and all muscles below the knees. Superficial sensation to pain and touch was diminished almost up to the groins, and muscle tenderness was increased. She was treated at home with cortisone for 2 weeks. By then the only remaining signs were a very slight weakness of triceps and hip flexors and the persistence of increased calf tenderness. These improved spontaneously without further treatment during the next month. Her tendon reflexes remained absent after her first attack.

Case 3.—A woman of 56 was admitted to a surgical ward on Nov. 1, 1955, for treatment of hiatus hernia. During the previous 3 weeks she had had increasing weakness of her arms and legs to a point where she could no longer walk, and also continuous tinglings in her hands and feet.

When I saw her on Nov. 8 she showed a moderately severe weakness of all muscle groups in both arms and legs, though no group was completely paralysed. Tendon jerks were absent in the legs and diminished in the arms; muscle tenderness was increased, and she had hyperalgesia over her soles. The C.S.F. contained protein 100 mg. per 100 ml.

She was transferred to a medical ward, and cortisone treatment was started on Nov. 13—i.e., 5 weeks after the onset of her symptoms. There had been no progression in the week before treatment began. Improvement began within 48 hours and continued rapidly and steadily until, at the end of the 2 weeks' course, no residual weakness or sensory signs were found.

Case 4.—A man of 56 was admitted to hospital on Feb. 25, 1956. 2 weeks previously he had had a transient feverish illness with aches and pains in his limbs and back. He stayed in bed for a day. 5 days later his legs felt weak while he was out walking, and later that day he found he could not use his fingers properly. This limb weakness had increased slightly, but he was still able to walk. There was no tingling or numbness in his extremities.

Examination showed a slight bifacial weakness; in the arms a weakness of biceps, triceps, forearm, and hand muscles;

in the legs weakness of hip flexors and all muscles below the knees The arm reflexes and the ankle jerks were absent, the knee-jerks sluggishly present Calf tenderness was increased There was no sensory loss The C S F contained protein 90 mg per 100 ml

Cortisone treatment was started on Feb 26—i e, 10 days after the onset of his polyneuritis After 3 days improvement in power was obvious, and this continued steadily until, after 2 weeks' treatment, he had completely recovered

Severe Cases

Case 5.—A man of 64 was first seen on May 1, 1956 His illness had started 17 days previously with tingling over the soles of his feet 2 days later his legs became weak and he fell at work Thereafter progress was rapid, and within 10 days of the onset he was unable to walk and had developed paræsthesiæ in his hands

Examination revealed profound weakness of his legs He could raise his right leg two inches off the bed and the left one inch Toe movements were flickers only Tendon jerks were absent, calf tenderness increased, joint sense impaired in the feet, and superficial sensation diminished below the knees In the arms all muscle groups were affected but only moderately, no muscles being completely paralysed Touch and pain sense were impaired below the level of the wrist joints The C S F contained protein 55 mg per 100 ml

Cortisone treatment was started on May 1 After a week his arms were stronger but his legs showed no change After 2 weeks power in his arms was normal save for fractional weakness of the triceps, and sensation had recovered, though he still had tinglings in his fingers He could lift both legs two feet off the bed, but there had been no recovery in muscles below the knees He was then transferred to a hospital nearer his home, where through a misunderstanding cortisone treatment was continued, 50 mg daily, for another month By this time he had no symptoms in his arms, his thigh muscles had recovered fully, but his lower leg muscles were still moderately weak After another 4 weeks—i e, 10 weeks from the onset of treatment—he had completely recovered

Case 6.—A man of 40 was seen on June 2, 1956 A week previously he had been slightly unwell for a day, with headache and pains in the back, which he had put down to a feverish cold On May 30 he complained of stiffness in his legs and tingling in his fingers and toes, and these symptoms became worse

Examination on June 2 showed minimal signs There was just detectable weakness of hand muscles, hip flexors, and toe extensors, tendon reflexes were diminished but not absent, calf tenderness was severe, and there was a little blunting of sensation over his feet His C S F contained protein 450 mg per 100 ml

Cortisone treatment was started on June 3 In the next 3 days his condition deteriorated slightly, weakness becoming slightly more evident in the muscles originally affected and also now involving deltoid, biceps, triceps, and toe flexors on each side, and the facial muscles 2 days later slight improvement was evident in arms and legs, and on this day the dose of cortisone was reduced to 50 mg daily (after 3 days on 100 mg and 3 days on 75 mg daily) 2 days later (June 10) he was much worse, with generalised weakness of face, arms, and legs loss of reflexes, and sensory loss over feet and hands He remained in this state for 10 days before improvement was first noted in arm muscles and face

Cortisone was continued (50 mg daily) for a further 10 days until June 30 By this time his arms and face had improved considerably but his legs less so He was discharged home 2 weeks later (July 14), by which time his face was normal, only weakness of finger muscles remained in the arms and he could stand and walk with assistance, though all groups of leg muscles were still weak A month later he had completely recovered his illness having lasted 10 weeks

This patient was the only one of the series who did not respond to cortisone In retrospect it was felt that dosage had been inadequate and that this was why he rather suddenly deteriorated when it was reduced

Case 7.—A woman of 69 was transferred on Oct 11, 1956, from another hospital, to which she had been admitted 11 weeks previously with a fracture of the neck of the left femur This had been pinned and plated and was healing satisfactorily She had begun to get about on crutches, avoiding weight bearing on the left leg when about 6 weeks before transfer she noticed that walking was becoming difficult Gradually her legs became weaker until she could not move them, her fingers became feeble, and she developed at the same time tingling in fingers and feet

On admission her legs were completely paralysed except for feeble movement of the hip flexors, and the arm muscles were all weak, but the finger flexors and intrinsic hand muscles were much more severely affected than other groups Arm reflexes were diminished, leg reflexes absent Muscle tenderness was increased Joint sense was impaired in the fingers and lost in the toes, but there was no alteration in skin sensation Her C S F contained protein 140 mg per 100 ml

She was given cortisone 300 mg daily for 2 days then 200 mg daily for 2 days, and then 100 mg daily thereafter After a week weakness in the arms was confined to finger flexors and hand muscles In the legs there was still no movement below the knees, but muscles in the thighs were seen contracting After 2 weeks hand and finger muscles were improved but not normal, and there had been a further slight improvement in the legs, with a flicker of contraction in the left toe extensors Cortisone treatment was then stopped (Oct 28) 3 days later slight weakness had recurred in biceps, triceps, and wrist extensors, and there was no contraction in the left toe extensors She was then (Nov 1) given 200 mg daily for 2 days and then 100 mg daily After 4 days power had returned to these arm muscles, and they were normal again

Cortisone was continued for 2 weeks and then stopped (Nov 14) By that time she still had some weakness of the interossei in the hands, but they were much stronger She could lift her legs well in the air, and the quadriceps, hamstrings, and calf muscles were quite strong, but there were only flicker movements of toe and ankle dorsiflexors and no movement in the peroneal group There was no further relapse thereafter, and she slowly improved, though her recovery was not yet complete 7 weeks after the beginning of treatment

DISCUSSION

The severity of these cases has been judged not by the extent of the distribution of muscle weakness but by the degree of paralysis in the muscles worst affected In the mild cases (cases 1–4) no muscles were completely paralysed, though paresis was moderately severe in some muscles in all four limbs The results of treatment in this group are summarised in table I They show that recovery was complete or almost so in all these cases after 2 weeks' treatment with a small dosage of cortisone The more severe cases (cases 5–7), summarised in table II are those in which some muscle groups were paralysed or reduced to flicker movement and others less affected

TABLE I—RESULTS IN MILD CASES

Case no	Sex	Age (yr)	Degree of weakness	Onset before treatment	C S F protein (mg per 100 ml)	After two weeks	Remarks
1	M	17	F + A + L +	10 days	400	F 0 A– + 90% L– + recovery	Improvement began in week
2	F	34	*1st attack October 1955* F 0 A + L +	4 weeks	10	F 0 A 0 L 0	Improvement in 2nd week
			2nd attack June 1956 F 0 A + L +	6 weeks		F 0 A– + 95% L– + recovery	
3	F	36	F 0 A + L +	3 weeks	100	F 0 A 0 L 0	Improvement began in week
4	M	56	F– + A + L +	10 days	90	F 0 A 0 L 0	Improvement after 3 days

F face A arm L leg
+ Diffuse weakness but no muscle group paralysed completely
+ + Diffuse weakness with one muscle group paralysed completely
+ + + Total or almost total limb paralysis

TABLE II—RESULTS IN SEVERE CASES

Case no	Sex	Age (yr)	Degree of weakness	Onset before treatment	C S F protein (mg per 100 ml)	After two weeks	Remarks
5	M	64	F 0 A − L −+−	17 days	55	F 0 A 0 L −	Improvement in 1st week Complete recovery in 10 weeks Cortisone continued for 6 weeks
6	M	40	F 0 A −− L −+	4 days	450	F − A −− L ++	Slight deterioration in first 5 days Much worse 2 days after reduction of cortisone Recovery after 10 weeks
7	F	69	F 0 A ++ L +−−	6 weeks	140	F 0 A + L −+	Improvement in 1st week

This group includes case 6, where deterioration occurred in spite of treatment ; this coincided with a reduction of the daily dose of cortisone, and treatment is thought to have been inadequate The two other cases in this group showed improvement after 2 weeks but of varying extent Muscles affected in these two patients to a similar degree as in the mild cases showed an equally good response and had by then completely recovered More severely affected muscles, however, were still very weak, and some had not begun to recover In case 7 a return of weakness followed within a few days of the cessation of cortisone therapy, but recovery was rapid when cortisone was given again It is clear from tables I and II that recovery is not related to the duration of the illness before treatment begins but only to the severity of the paralysis at this time In some cases improvement was apparent after a few days but in others it was not noticeable until the second week Except in case 6, no deterioration took place once cortisone had been given

It may well be thought that, in a disease whose severity and duration are very variable, these results are no better than chance would allow, especially as most of the patients had mild attacks The disease is so relatively uncommon that a control series would be impossible to obtain in a reasonable time , and therefore comparison has to be made with the reports of others not treated with cortisone The largest series in recent years is that of Crozier and Ainley (1955), who reviewed seventeen cases seen in 8 years Three patients died, and the period of recovery in the survivors varied between 1 and 4 months These figures show that the untreated disease, at best, lasts twice as long as when cortisone is given I have found no published report of any patient having died of the disease after cortisone was given

It seems justifiable, therefore, to conclude from this trial that cortisone is the remedy of choice in acute toxic polyneuritis but must be given as soon as possible and in adequate dosages If treatment is started before paralysis becomes severe, the chances of rapid improvement should be good Beyond this stage it should stop the disease from progressing, but the over-all recovery-time of completely paralysed muscles may not be shortened In view of the pathology of the disease we may suppose that, to be effective, it must be given when œdema of nerve roots is present and before structural changes have taken place For the average case the dosage suggested is 300 mg daily for 2 days 200 mg daily for 2 days, and then 100 mg daily for 10 days If, after withdrawal at this stage, deterioration occurs, further treatment for another week or more may be needed

In fulminating cases of the Landry type intravenous infusions of corticotrophin might well be more effective, but I have not yet had an opportunity to treat such a case

The results of cortisone treatment support the opinion that this disease is an allergic disturbance If further experience confirms this, the term acute allergic polyneuritis would be preferable to any of the various synonyms at present in vogue

Summary

Eight attacks of acute polyneuritis in seven patients were treated with cortisone

In only one case was the disease not promptly arrested and in this case the amounts of cortisone given were probably inadequate

In seven attacks recovery took place quickly within a period of 2 weeks in those muscles not severely affected—i e , mild cases recovered completely, and severe cases improved partially

Improvement is related to the severity of muscle weakness at the onset of treatment Hence very early diagnosis is necessary for successful therapy

I am grateful to Dr Wilfred Brinton for referring cases 5 and 6 to me

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MASSIVE THROMBOPHLEBITIS

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MASSIVE thrombophlebitis (massive venous thrombosis, phlegmasia cærulea dolens) may rapidly kill a patient by immobilising large amounts of fluid and blood in the leg Alternatively it may cause " stagnation " gangrene of the foot—a condition which may be confused with an arterial ischæmic lesion

Massive thrombophlebitis is by no means uncommon, but it is probably often misdiagnosed and wrongly treated I therefore report five cases, and discuss the physiopathology, differential diagnosis, and treatment

Case-reports

Case 1 —A woman, aged 65, complaining of abdominal colic with the passage of blood and mucus per rectum, was admitted to hospital 10 months after the onset of her symptoms There was a large tender mass in the left iliac fossa and left side of the pelvis Shortly after admission she developed a colovesical fistula. A transverse colostomy was performed and some 12 days later she developed a classic white leg " (phlegmasia alba dolens) on the left side The limb was raised initially and mobilised early , no anticoagulants were used

On the 21st postoperative day she suddenly complained of intense pain in her right leg This pain had reached its peak within 30 minutes and completely prohibited any movement, either active or passive

The limb was cyanotic from the inguinal ligament to the toes with abundant petechial hæmorrhages above and below

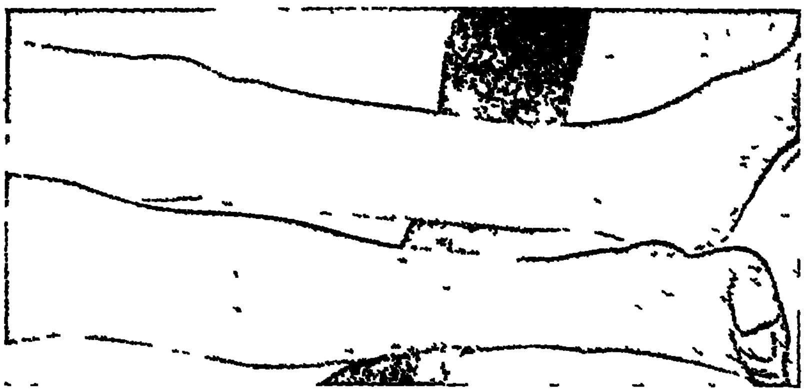

Fig 1—Case 1 three hours after onset of massive thrombophlebitis in right leg Left leg is recovering from iliofemoral thrombophlebitis A group of petechial hæmorrhages is ringed

the knee (fig 1) It felt cool, and no pulse distal to that of the femoral artery at the groin was palpable, the involved skin was grossly hyperæsthetic Intra arterial (femoral) tolazoline ('Priscol') 50 mg had no apparent effect on the condition of the limb Œdema developed rapidly, and the patient became shocked Transfusions of blood and of plasma did not arrest the fall of blood-pressure, and she died 16 hours after the onset of the pain

At restricted necropsy an abscess was found surrounding a carcinoma of the pelvic colon which had eroded into the bladder The left iliac veins were occluded by organising blood clot, the lowest three inches of the inferior vena cava and the right iliac veins were obstructed by recent adherent clot The corresponding arteries were patent

Case 2 —A woman, aged 34, in her 9th month of pregnancy, was admitted to hospital with œdema of the lower legs and hydramnios A stillborn anencephalic child was delivered 24 hours after artificial rupture of the membranes 15 hours after delivery anticoagulant therapy was started because œdema had spread to the inguinal ligaments During the next 3 days œdema persisted, but the circulation of the limbs was not impaired The patient then complained of tingling in the toes of her left foot, which became cold and dark blue œdema of the calf increased Pain in the first and second toes worsened, and within 12 hours they had become virtually black (fig 2)

The patient was then transferred to a vascular unit She was not shocked, there was no evidence of any arterial insufficiency in her feet, and peripheral pulses were present, but her left leg was still œdematous to the groin Anticoagulant therapy was stopped, and lumbar paravertebral block was performed—without benefit The swelling of the limb slowly resolved, and the necrotic areas of the toes were allowed to demarcate before being surgically removed, complete healing was slow The patient has since remained well but has to use elastic support to control the hydrostatic œdema of her left leg

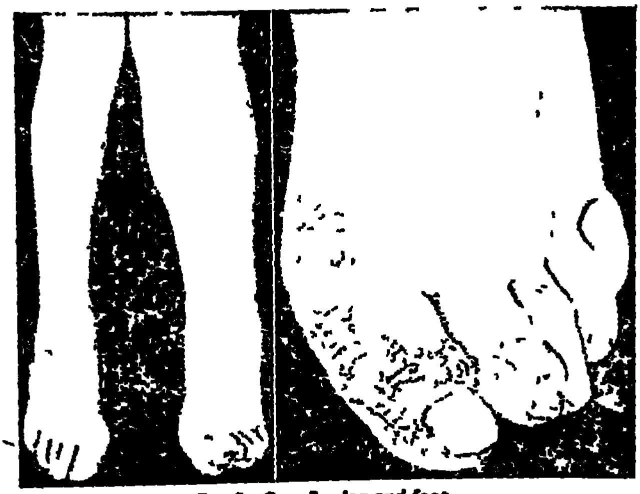

Fig 2—Case 2 leg and foot

Case 3 —A woman, aged 20, and 2 m pregnant, complained that for 4 mont had been passing multiple loose stools occasionally tinged with blood 2 weeks be admission she had had a cramp like pain the left ankle and calf preventing her fr bearing weight on the heel Œdema of t foot followed 4 days later, and the calf pa now bursting in character, was accompan by a deep ache in the thigh She next dev oped a cramp like pain in the right calf 4 days, there was no noticeable œdema the calf felt hard Both legs then began t improve

The patient was admitted to hospital investigation owing to continued diar and ulcerative colitis was diagnosed 3 da after admission severe pain, reaching a max imum in 15 minutes, recurred in the l thigh It spread slowly down the leg, wh felt as though it would burst The li was blue to the groin, showed turgid veins a rapidly swelled Over the next 4 days both the colour a pain of the limb improved 6 days after the onset of th episode she was woken at night by a burning pain in the foot, with severe paræsthesiæ in the toes, which became d cyanosed The foot swelled again, but toe movement was still possible Within 10 minutes the burning sensation began to go, but paræsthesiæ persisted in the second and third toes, which became gangrenous in their distal portions (fig 3)

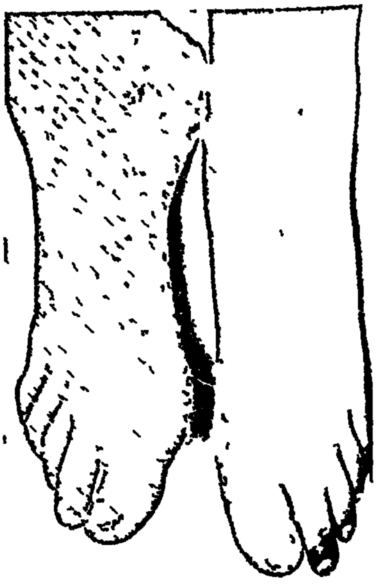

Fig 3—Case 3 staged development of mas thrombophlebitis has given rise to gangren terminal parts of second and third toes

From the time when the left thigh was involved in hospital she was treated with anticoagulants, but in spite of this she had further attacks of phlebitis At no time, however, was she shocked Physiotherapy was begun when swelling had considerably subsided, dilated veins having developed aroun the root of the thigh and on the lower abdomen Th necrotic areas of the toes were allowed to separate spontaneously

Case 4 —A woman, aged 38, was admitted urgently t hospital, where on laparotomy a ruptured cystadenocarcino of the ovary with widespread pelvic metastasis was foun Immediately after the operation her right calf swelled, w pain on dorsiflexion of the foot and tenderness of the ca and the popliteal fossa

12 days after the operation she complained of a sh pain in the right chest and was found to have œdema of th left leg up to the groin Anticoagulant therapy was starte and morphine prescribed She had bloodstained sputum 24 hours later and two further episodes of acute pain in th right chest, after which these symptoms improved 8 day after the initial swelling of the left leg, however, there wa a sudden increase in œdema with severe pain and cyanosis of the whole limb Anticoagulants were continued, and wh she was seen 6 days after this episode, there were hæmorrhag blebs on the dorsum of the foot with gangrene of the secon and third toes (fig 4), ankle pulses were palpable Ant coagulants were stopped, and mobilisation was encouraged

The patient's general condition slowly improved in th next few weeks, before ascites and a rapidly advan

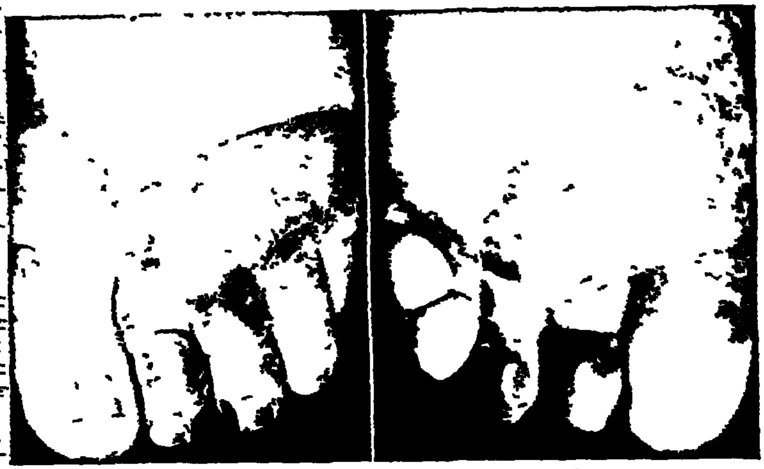
(a) (b)

Fig 4—Case 4 dorsal (a) and plantar (b) aspects of foot involved by massive thrombophlebitis.

achexia became obvious She was allowed home, where she ied of widespread metastatic disease 4 months after aparotomy No necropsy was performed

Case 5 —A man aged 67 had been losing weight and feeling eak for 3 months A recent pneumonia had caused his doctor o suspect carcinoma of the bronchus. On the morning of dmission to hospital the patient awoke to find his right leg wollen (fig 5) It continued to swell felt very heavy and as blue when he was admitted to hospital 7 hours after he first symptoms At no time did he feel any pain

On examination the limb was swollen from the toes to the ower abdomen and deep blue, with multiple petechial hæmorrhages (fig 6), particularly involving the thigh The œdema was hard, but ankle pulses were still palpable The terminal phalanges of the toes were hypoæsthetic The patient was enerally wasted, and several hard glands were palpable in he lower part of his neck 30 minutes after admission his pulse rate was 140 and systolic blood pressure 70 mm Hg An intravenous drip was immediately set up, and within 7 hours he had received two pints of blood and five pints of lucose saline solution Simultaneously vigorous passive exercise of the whole leg which was kept raised, was begun and continued for the first 12 hours in hospital The patient's general improvement was considerable, and the œdema of the leg began to soften.

2 days later his entire left leg became blue and began o swell his pulse rate rose and his blood-pressure again fell Intravenous fluids and elevation and exercise for this limb were started and produced immediate improvement No anticoagulants were used during either episode

Radiography revealed massive secondary deposits in the chest, bloody stools were passed and the patient went steadily downhill to die of cachexia 4 weeks after admission Necropsy showed a primary stenotic carcinoma of the pelvic colon with gross secondary carcinomatosis of his liver and lungs The inferior vena cava below the renal veins and all the pelvic veins were occluded by thrombus as far distally as the metatarsal veins

DISCUSSION

The symptoms of massive thrombophlebitis in a leg result from venous occlusion sufficient to cause nearly complete arrest of capillary blood flow This may occur as a solitary dramatic episode (e g cases 1 and 5) or as a result of a series of attacks of thrombophlebitis over a matter of days or even hours (e g, cases 2–4) The veins involved by the occlusion may be predominantly those carrying blood out of the limb at its root the small radicles at the periphery (Haimovici 1950) or both groups of vessels In whatever way this massive thrombophlebitis develops, the blood-flow through the capillary bed is eventually reduced while the arterial input continues to congest the tissues

Another consequence of the high capillary pressure is a considerable rise of capillary filtration, which leads to rapidly developing œdema The loss of circulating blood volume both in the congested vessels and by œdema fluid may be sufficient to produce fatal oligæmic shock (e g, case 1)

If after massive thrombophlebitis ischæmia lasts long enough gangrene results This is generally moist but occasionally dry (Haimovici 1950), it varies in extent and usually involves the distal part of the foot Gangrene of the thigh, however, has been described (Hershey and Snyder 1953)

The ætiology of massive thrombophlebitis seems to be similar to that of the less extensive form (white leg phlegmasia alba dolens) Massive phlebitis in the leg is often associated with inflammation or neoplastic disease of the pelvis and this was so in all the present cases Nevertheless it has been known to develop in an apparently healthy young man (Halligan et al 1953)

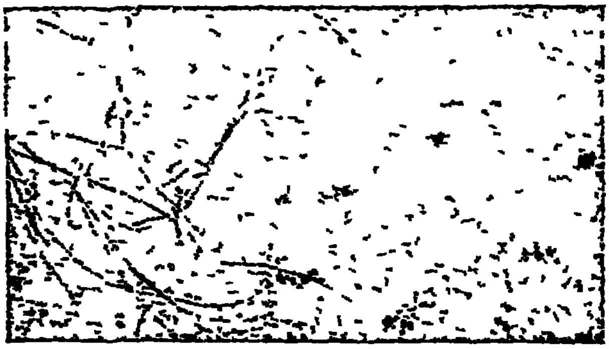
Fig 6—Case 5 petechial hæmorrhages in skin of thigh

The sexes are equally involved, and no age-group seems to be immune

The symptoms resolve as unoccluded venous channels dilate the intense congestion remits, and œdema fluid is slowly absorbed Often masses of small anastomotic veins become visible in the skin of the limb and lower abdomen, depending on the extent of the original occlusion

There is little difficulty in making a correct diagnosis when a clinical history or actual observation has indicated recurring thrombophlebitis Eventually as in case 3, one such episode by further occluding an already impaired venous system, is sufficient to cause tissue ischæmia with its sequelæ of pain and gangrene Further swelling and deep cyanosis are characteristic The area involved is usually well localised often to the end of the limb

It is however the single dramatic episode of massive thrombophlebitis which gives rise to difficulty, acute ischæmia of

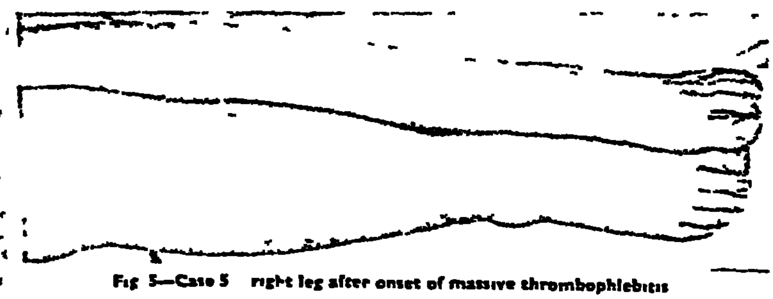
Fig 5—Case 5 right leg after onset of massive thrombophlebitis

DIFFERENTIAL DIAGNOSIS OF ARTERIAL OCCLUSION AND MASSIVE THROMBOPHLEBITIS IN THE LEG

	Arterial Occlusion	*Massive Thrombophlebitis*
1	Little, if any, shock	Severe shock may be present or incipient
2	Involvement of distal part of the limb even with proximal occlusion	Generally whole limb often with the lower abdomen, involved
3	Œdema absent initially and any late development is of minor degree	Œdema develops with dramatic rapidity and usually involves the whole limb
4	Waxy yellow colour or mottled cyanosis paling on elevation	Whole limb to groin dusky purple persisting on elevation
5	Subcutaneous veins poorly filled, “gutter” on elevation	Subcutaneous veins, turgid with blood, do not empty on elevation
6	No skin hæmorrhages	Petechial or more severe hæmorrhages
7	Subpapillary veins do not fill after pressure	Rapid refilling of subpapillary veins after pressure
8	No pulses and no oscillometric evidence of arterial pulsation present below occlusion.	Pulses may be absent Oscillations usually less than in normal limb
9	Pain usually not severe	Pain may be agonising
10	Any loss of movement is due to ischæmia	Any loss of movement is generally due to pain.
11	Hyperæsthesia, hypoæsthesia and anæsthesia may occur	Hyperæsthesia, hypoæsthesia, and anæsthesia may occur

arterial origin often being diagnosed in error (see table) It may therefore be helpful to describe the symptoms and signs of massive thrombophlebitis and later to compare them with those resulting from acute arterial occlusion.

The patient, while in bed or going about his normal activities, develops a severe pain in his leg, beginning in the upper thigh (Haimovici 1950) and rapidly extending downwards to reach agonising proportions within an hour Less often the pain begins in the region of the knee and spreads up and down Initially of an intense burning or paræsthetic nature, it prohibits either active or passive movement Almost coincidentally the limb takes on a dusky cyanotic appearance from the groin distally, petechial hæmorrhages may appear, and swelling begins, sometimes involving the lower abdominal wall As this congestion and œdema progress, compensation for loss of circulating blood volume may fail, with a rise of pulse-rate and fall of blood pressure, locally the skin appears tight and shiny with the changes of *peau d'orange*, and the superficial veins are distended The patient complains of a deep aching or bursting sensation in the limb

On examination the skin may be hyperæsthetic, hypoæsthetic, or patchily anæsthetic, especially in the most deeply cyanotic areas, it blanches only with the firmest pressure and rapidly congests again If subcutaneous veins can be massaged empty, it is only with difficulty—they may be thrombosed Skin-temperature is usually lowered, to a greater extent peripherally, and this is exaggerated by any associated circulatory collapse Raising the limb does not affect the colour or the degree of venous filling Deep muscular tenderness in the foot, calf, and thigh is usual, but for the first 24 hours tenderness over the major veins is rarely elicited, after that time, however, it becomes severe Initially, peripheral pulses may be felt even though they are relatively less than those of the opposite leg, later, œdema and any peripheral vascular collapse make their palpation very difficult Oscillometry usually indicates continued arterial pulsation

The rôle of associated arteriospasm in this condition is disputed Many (e g, Veal et al 1951, Turner 1952, Hershey and Snyder 1953) think that, if arterial spasm occurs—and it is recognised that it may occur reflexly in thrombophlebitis (Ochsner and DeBakey 19[illegible] —the part it plays in causing the symptoms is not cert[illegible] Others (Janes and Hopmans 1953, Martin 1953) re[illegible] arteriospasm as a sinister complication Con[illegible] Burch et al (1939) have shown experimentally that occlusion of the venous return from a limb can reduce oscillometric readings by more than half However, the absence of palpable peripheral pulses in massive thrombophlebitis may be due to previous atherosclerotic occlusive disease, the masking effect of œdema, or associated peripheral circulatory failure quite apart from spasm

Provided the threatened circulatory collapse is sur[illegible] or suitably treated, the dilatation of anastomotic vascular channels during the succeeding days leads to a [illegible] resolution of the œdema, blood flow improves, pain passes, cyanosis fades, petechial hæmorrhages are absorbed, and any resulting necrosis begins to demarcate. Massive gangrene is unusual, and part of the foot or [illegible] the toes may slough Though this sequence is typical, pain is by no means constant and may be absent (see case 5) So far as the development of gangrene is concerned, absence of pain seems to be a good prognostic omen Absence of pain, however, does not preclude the onset of severe, even fatal, circulatory collapse (case 5)

Immediately after the attack of massive thrombophlebitis, phlebitis of the opposite limb is quite possible (cases 1, 3, and 5), particularly when clot fills a common iliac vein There is also the risk of an occult phlebothrombotic process developing with subsequent pulmonary embolism From the small number of previously published cases this certainly seems to be rare

To summarise then, the clinical features of massive thrombophlebitis are those associated with a degree of vascular turgidity sufficient to arrest the circulation they usually overlie some other systemic disorder

Almost the contrary is true for the syndrome of acute arterial occlusion While embolism most commonly results from cardiac disease, and arterial thrombosis from severe atherosclerosis, the ischæmic limb in these conditions presents a picture of severe deprivation of blood Unless there is aortic thrombosis or a dissecting aneurysm (in which cases both legs will be involved) early pain is not a prominent feature, there is no severe shock, and life is not immediately endangered Even when the common iliac artery is occluded, it is rare for the whole limb to show ischæmic change as high as the inguinal ligament Thus, after occlusion of the external iliac artery, ischæmia reaches about mid thigh level, after occlusion of the superficial femoral artery it reaches to just below the knee-joint, and after occlusion of the popliteal artery it reaches to about the ankle joint This contrasts with the extensiveness of the fulminating attack of massive thrombophlebitis

Pain immediately after arterial obstruction is rarely severe and never has a bursting character, but paræsthesiæ and heaviness are not unusual Œdema does not develop immediately, and if it does occur in the “twilight” area of relative ischæmia it is slight As regards skin colour changes, there may be uniform cyanosis of the ischæmic part, a waxy yellow pallor, or a patchy mixture of the two colours, *slight pressure*, however, blanches the skin, which remains pale Petechial hæmorrhages do not occur Raising the limb produces or exaggerates the pallor and “gutters” the veins Areas of hypoæsthesia and anæsthesia are found, a [illegible] involving almost the whole of the ischæmic zone It may be easy to localise the site of arterial obstruction by simple palpation, otherwise oscillometry may be used The slight tenderness of a thrombosed artery developing one or two days after the occlusive episode is considerably less than that of the corresponding venous lesion Active or passive movement is rarely precluded by pain, but necrosis of muscle groups donetimes give rise to tenderness and contracture, rticularly in the calf Loss of movement of the toes d ankle joint rarely occurs from occlusion below the rel of the superficial femoral artery, and any gangrene sulting tends to be more extensive than that following ssive thrombophlebitis

The salient differences between the two conditions erefore lie in the extent of the changes, the colour of e skin, the type and severity of the pain, and the velopment of œdema with its risk of secondary circula- ry collapse Diagnosis should then be clinical, arterio aphy (Moore and Scott 1956) can hardly have a place hen the serious general condition of these patients is nsidered

The changes which develop in phlegmasia alba dolens iofemoral thrombophlebitis, white leg) are altogether ilder but may be precursors of the more extensive sease The upper limb has sometimes been involved y the process (Mills and Bennetts 1955), but not all ablished cases (Pringle 1938) attributed to massive rombophlebitis are altogether convincing, certainly is uncommon in this site

Moser et al (1954) state that gangrene develops in least half the limbs involved by massive thrombo- lebitis, and that a quarter of the patients die This tter figure seems one which should be capable of nsiderable reduction The most important aspect of eatment is the anticipation of circulatory collapse hole blood is lost from the circulatory volume into the mb, and what little escapes from it is hæmoconcentrated y the loss of much œdema fluid A large volume of line solution, plasma or plasma substitute, and blood likely to be required within the first 12 hours of the nset of the condition Delay can be fatal for the patient his, of course, applies to the fulminating attack, e staged development of massive thrombophlebitis, eing much more gradual, does not overtax the circula- ory system, and transfusion is not likely to be necessary

When general resuscitative treatment is under way, reatment of the limb can begin Perhaps the most ational measure is to remove as much clot as possible rom the femoral and iliac vessels This has been done uccessfully by DeBakey and Ochsner (1949), Miles 1951), and Ellis and Windham (1952), but Miles (1951) ttributed his success to associated ligation of the inferior ena cava, a manœuvre which has been reported to itiate the condition (Veal et al 1951) However, many atients with massive thrombophlebitis are in no condi ion for surgical intervention, the results of which are t best likely to be doubtful

The rôle of arteriospasm has been considered above Those who are impressed by the possibility of it advocate he use of sympathetic blocks, spinal anæsthesia, vaso ilators (Haimovici 1950, Halligan et al 1953, Janes and Hopmans 1953), and heavy sedation (Martin 1953) Others (Ebel et al 1952, Turner 1952), finding that none of these treatments affected pain, œdema or ischæmia, egard them as useless

Is it reasonable to induce vasodilation ? If the very doubtful entity of venospasm actually is a factor in the genesis of the condition (Manheimer and Levin 1954) its relaxation is obviously desirable To induce any arterial dilation, however, seems equally undesirable, there is already a surfeit of blood in the affected limb, and to increase this seems likely to make matters worse It is therefore suggested that the initial use of para vertebral blocks and vasodilators is illogical and should be avoided (Ebel et al 1952)

A further question which arises is the indication for anticoagulant therapy It has been pointed out that capillary pressure is not infrequently high enough to give rise to petechial hæmorrhages (DeBakey and Ochsner 1949, Veal et al 1951, Manheimer and Levin 1954) In the acute phase any increase of the clotting-time is obviously liable to worsen this tendency and possibly further to embarrass the circulation by increasing tissue tension In one case (not reported here) where anticoagulant therapy had been energetically pursued the entire skin area below the knee contained extravasated blood Since, therefore, anticoagulant therapy increases the liability to gangrene or its extension in the initial stages of massive thrombophlebitis it should not be used (Veal et al 1951) When, however, venous collaterals have begun to open up and symptoms subside, there may be a place for such therapy because the risk of further intravascular clotting in the same limb or else where remains Even so consideration will have to be given to the risk of hæmorrhage from any other associated pathology

It is obviously desirable to aid drainage of blood from the congested limb, and its elevation is certainly indicated Veal et al (1951) advocated vigorous exercise in an attempt to pump blood out of the limb This advice has been followed satisfactorily by Moser et al (1954) and was applied in case 5, when almost continuous active and passive movement of the leg was kept up for twelve hours This patient never gave any anxiety as to the leg becoming gangrenous, but it is felt that the exercise and vigorous intravenous therapy enabled him to recover from his peripheral circulatory collapse This régime initiated by Veal et al (1951) is therefore recommended in the treatment of massive thrombophlebitis, but in many cases it will have to be given after analgesics have been given to the patient The possibility that such treatment may give rise to pulmonary embolism has been raised (Mills and Bennetts 1955), but there seems to be little risk of this (*Lancet* 1955) The patient should be encouraged to move about in bed to reduce the risk of chest and other complications The heavy sedation which has been advised (Martin 1953) seems to have little to recommend it

Limbs incipiently gangrenous should be kept in an environmental temperature of 20°–25°C (68–77°F) because the tissue demand for oxygen will be reduced without the vasoconstriction due to cold resulting (Catchpole and Jepson 1955)

As soon as swelling has begun to subside and the patient's general condition is satisfactory, he may be allowed up with the limb well supported Although it has been noted (DeBakey and Ochsner 1949), and I have personally observed, that resolution may appear virtually complete, more commonly the typical indurated post-phlebitic leg results Gangrenous tissue should be allowed to separate and any precipitous amputation avoided because necrosis may be no more than skin deep

Whilst awaiting this development, the patient must be investigated to disclose any underlying disease which has predisposed to the attack of phlebitis

Summary

Five cases of massive thrombophlebitis (massive venous thrombosis phlegmasia cærulea dolens) are described

The rarity of the condition has undoubtedly been over-emphasised, with the result that it is often tardily diagnosed and inadequately treated

The pathology of the condition has been briefly outlined and the diagnosis and clinical course discussed

The urgent need for vigorous treatment early in the fulminating type of the disease to prevent or overcome shock and to avert a speedy death is emphasised

Attempts to induce vasodilation are contra indicated, and initial anticoagulant therapy should be avoided

Exercise is advocated to pump blood from the congested tissues, if it is not feasible to remove the offending blood-clot surgically

Any tissue necrosis which results should be treated with conservatism

I should like to thank Dr E G Rhind for permission to examine his patient and publish her case report (case 3) I am grateful to Prof R P Jepson for much encouragement in the study of this disease

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INDUCTION OF LABOUR TO PREVENT RECURRENT STILLBIRTH DUE TO HÆMOLYTIC DISEASE

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WHEN more than 95% of mature liveborn babies with hæmolytic disease can survive (Diamond et al 1950, Walker and Murray 1954) there is little indication for induction of labour before term unless it may prevent stillbirth The over all risk of stillbirth in hæmolytic disease is 15%, but varies from 2% following mild disease in the previous pregnancy to 80% following multiple stillbirths (Walker and Murray 1956)

With the cooperation of colleagues throughout the Newcastle region, we have in the past three years made a trial of premature induction in families with a high risk of stillbirth—i e, those in which a previous stillbirth has been due to hæmolytic disease and in which the father is homozygous D/D

Management

Clinical and radiological assessment was carried out at the 34th week of pregnancy If the fœtus was alive and not hydropic, labour was induced 35 days before the expected date of delivery During the first year of the trial induction was started by rupturing the hind waters with a Drew Smythe catheter, and, if labour did not begin within forty-eight hours, an intravenous oxytocin drip, as described by Theobald et al (1948), was given In the next two years an oxytocin drip for forty-eight hours was given, followed if necessary by rupture of the membranes If labour did not begin within forty eight hours, a second oxytocin drip was given In all cases where the membranes had been ruptured for more than forty eight hours, the patient received streptomycin 1 daily and sulphadimidine 1 g six hourly

TABLE I—RESULTS IN 108 CASES WITH PREVIOUS STILL

			Rh positive cases				
			No	Still births	Hæmolytic disease		
					Severe	Mild	
Not induced	Cause of previous stillbirth unknown		11	3 (31%)	7	4	1
	"Spontaneous"	Father heterozygous	13	9 (69%)	4	Nil	[illegible]
		Missed	6	5 (83%)	1	Nil	[illegible]
Induced			60	37 (62%)	23	Nil	[illegible]
Total			93				[illegible]

Using this induction routine, 21 babies were deliv per vaginam using Wrigley's forceps Another 4 ba were delivered by cæsarean section—1 because of fœ distress before the onset of labour, the others because failure to initiate delivery All 25 were delivered betw thirty five and twenty-five days before the expected da of delivery

Results

During the three years, 102 women were seen, early in pregnancy, who had previously had a stillbirth po attributable to hæmolytic disease 48, however, we not selected for induction—in 27 because the father wa heterozygous D/d, and in 15 because the stillbirth, after careful review of the history, was not regarded as due to hæmolytic disease 6 additional cases were not reco nised until admitted in labour The general result in all 108 cases are shown in table I

Where the previous stillbirth was not due to hæmoly disease the severity of the infant's illness was what w should expect in unselected material (Walker and Murra 1954), and only 1 of the 3 stillbirths was a case of hydrops fœtalis

The Rh-positive babies of heterozygous fathers sho the high proportion of stillbirths expected, and all th born alive were severely affected If we add to this gr the 6 Rh-positive babies detected too late for inducti the incidence of stillbirth in "spontaneous" ca 73% In the cases selected for induction, the incidence stillbirth is only a little less (62%), largely becau of the 37 stillbirths were at less than 35 weeks Howev only 3 of the 19 "spontaneous" cases (against 24 of t 60 "induced" cases) were preceded by more than 1 stillbirth due to hæmolytic disease, and, since multi stillbirths carry a worse prognosis, this would tend t make induction look less valuable than it is Table I

TABLE II—RESULT IN RELATION TO NUMBER OF PREVIO STILLBIRTHS AND STAGE OF GESTATION

Stage of gestation (weeks)	1 previous stillbirth		More than 1 previous stillbirth		Total	
	Still born	Live born	Still born	Live born	Still born	Li
Before 28	3		1		4	
28–32	3		7		10	
33–35	5		8		13	
36–37	5	17	2	6	7	[illegible]
After 37	2				2	
Total	18	17	18	6	36	[illegible]
Not recorded	1				1	
Total	36		24		60	

shows the duration and result of pregnancy in relation to the number of preceding stillbirths

We expected 30% of live births when there had been ne previous stillbirth, but we found 50% , when there ad been multiple stillbirths we expected 20% and found 5% The results were better in the first group, essentially because 68% reached 35 weeks' gestation, whereas in the second group only 35% did so The time of fœtal eath does not necessarily correspond with delivery, and re should mention that, though only 45% of the babies n the trial cases were stillborn by 35 weeks' gestation, 65% were already dead If, however, a pregnancy did reach 35 weeks satisfactorily, the prospect of bringing about a live birth was about the same whether there had been 1 stillbirth or more than 1—i e , 17 24 and 8 respectively

We have, therefore, without subdivision as to number of previous stillbirths, compared the "induced" and "spontaneous" cases which reached 35 weeks' gestation table III)

These findings are significantly in favour of premature induction (P=0 02—0 01), in spite of including 7 in the induced group, and only 3 in the spontaneous group, who were already dead or hydropic at 35 weeks If these cases are excluded a truer evaluation of premature induction can be made (table IV)

TABLE III—RESULTS IN PREGNANCIES REACHING 35 WEEKS' GESTATION

—	Live birth	Stillbirth	Total
Induced	23	9	32
Spontaneous	5	10	15
Total	28	19	47

This difference is highly significant and in favour of premature induction (P=0 004)

We conclude that if there has been a previous stillbirth due to hæmolytic disease, and a subsequent Rh-positive fœtus reaches 35 weeks' gestation, alive and not hydropic on X ray examination, premature induction at this stage gives a better chance of live birth than does spontaneous delivery

The prospect of live birth is high (probably more than 80%), but one must remember that the nearer a pregnancy approaches term successfully, the greater is the chance of spontaneous live birth Therefore the longer premature induction is delayed, the better will the results appear if early stillbirths are ignored

The importance of the Rh genotype of the father was recognised only late in the trial, and retrospectively it was seen that, of the three common genotypes homozygous for D, the prospect of reaching 35 weeks' gestation was poorer if the father was cDE/cDE (R_2R_2) (Murray 1956)

The Severity of Disease in "Induced" Liveborn Babies

Relatively severe disease is to be expected in any liveborn baby if a previous sibling was stillborn with hæmolytic disease In this series all the premature babies were severely affected and 5 out of 23 died In the figure we have shown the distribution of birth weight cord hæmoglobin, and bilirubin values

Birth weights varied from $3^1/_2$ to 7 lb , but 40% were between 5 and 6 lb and this distribution corresponds closely to the expected weight-distribution in babies of any parous women at $35^1/_2$ weeks' gestation (Walker, J 1955)

The average cord-hæmoglobin value was 68% (10 g per 100 ml) this should be compared with an average of 94% (14 g per 100 ml) for all cases of hæmolytic disease, in which only 48% have less than 100% (14 8 g per 100 ml) In 90% of the induced cases the level was below this

TABLE IV—RESULTS IN PREGNANCIES REACHING 35 WEEKS GESTATION WITH A LIVING AND NOT HYDROPIC FŒTUS

—	Live birth	Stillbirth	Total
Induced	23	2	25
Spontaneous	5	7	12
Total	28	9	37

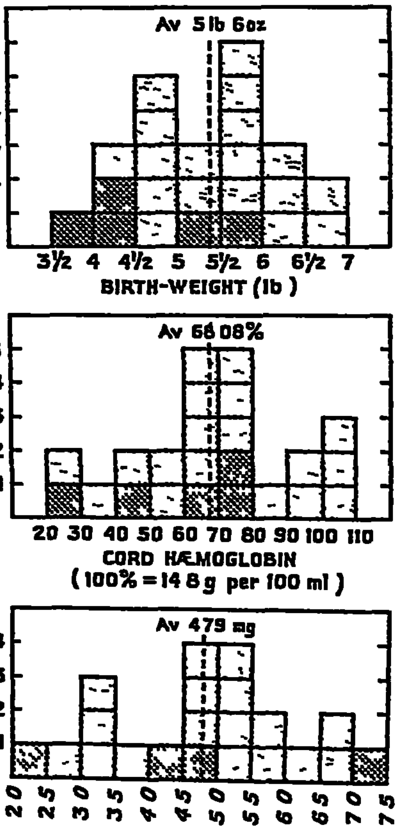
The cord bilirubin values also confirm the severity of the disease in the induced cases Of these nearly 50% had values higher than 5 mg per 100 ml , compared with 20% of the whole series

Treatment and Mortality

Babies were selected for treatment on the basis of cord hæmoglobin and bilirubin values, relying on the criteria we have used since 1951 (Walker 1953) All required early exchange transfusion, and were treated in the way already described (Walker and Neligan 1955) except that, in the light of early experience with "induced" babies, we decided to take into account the baby's cord-hæmoglobin value and were content with transfusion of smaller amounts—as little as 40 ml per lb in one or two very anæmic babies

We have taken as our criterion for repeating exchange transfusion a bilirubin level of 25 mg per 100 ml during the first 6 days of life 9 out of 18 survivors required multiple exchange transfusion compared to 13 (5%) of 255 other infants with hæmolytic disease who were treated by exchange transfusion during the same period None of the "spontaneous" group became so deeply jaundiced as to require repeated exchange transfusion There was no absolute correlation between the need for repeating exchange transfusion and birth-weight, cord hæmoglobin or bilirubin levels or the age at which the first exchange transfusion was performed

The other major difference between the "induced and "spontaneous" cases is in regard to mortality All 5 spontaneous liveborn babies survived, despite severe disease In contrast 5 of 23 "induced" babies died 4 died in the course of exchange transfusion—an event which is extremely rare, even in very severely affected babies, if they are born near term These deaths which are not fully explained took place without warning but after an appreciable amount of



Babies born alive after premature induction blood had been exchanged The baby, often well and improving since the start of transfusion, became cyanosed, the venous pressure was suddenly raised, respiration became gasping and irregular, the heart had already stopped, and resuscitation was impossible Necropsy supplied no direct explanation, though in all cases important contributory features associated with prematurity or premature induction were found—e g, 2 babies had severe pneumonia, and 3 had pronounced cardiomegaly, while tentorial tears, hyaline membranes, or pulmonary hypoplasia were present in some cases Recently in 2 cases not included in this report, labour was induced before term for obstetrical reasons Neither baby was very severely affected, yet both died during exchange transfusion

Discussion

Stillbirth remains the outstanding problem of hæmolytic disease The stillbirth rate in our material is 16%, which corresponds with other recent estimates (Davies et al 1953, Allen et al 1954), but the risk in a family is higher when there has been a previous stillbirth from this cause (Allen et al 1954, Walker and Murray 1956)

In considering a policy of induction before term, one must set the greater risk of neonatal death against the greater chance of live birth (Mollison and Walker 1952, Armitage and Mollison 1953, Allen et al. 1954) Kelsall and Vos (1955) recommended induction at 36 weeks' gestation for most cases of Rh isoimmunisation, but we do not think their figures justify the claim that nearly all stillbirths could thereby be prevented Dundon et al (1952) similarly estimated that there would be very few stillbirths if all babies alive at 36 weeks' gestation were delivered then, but other workers have been less optimistic Obviously the efficacy of induction depends on the time at which it is done and the time at which intra-uterine death occurs Davies et al (1953) held that induction at 35 weeks would prevent 75% of stillbirths, but Allen et al (1954) concluded that only 28% would be avoided by delivery at $36^1/_2$ weeks Our experience is more in line with this latter view, but in addition we have found that the chance of successfully reaching an advanced stage of gestation can be related to the family history We calculate that induction at 35 weeks can possibly prevent 50% of all hæmolytic stillbirths, but the proportion falls below 30% if hæmolytic disease has caused more than one previous stillbirth The stage of gestation reached in an earlier pregnancy is not an accurate guide to what may be expected in the present one, nor, in our experience, is it satisfactory to be guided by fœtal activity

On the evidence presented, we believe that premature induction is indicated in families where there has been a preceding stillbirth due to hæmolytic disease, and should be considered where there has been a previous "very severely affected" baby Induction at 35 weeks carries a good chance of initiating prompt delivery, and the degree of prematurity does not in itself carry a bad prognosis In families where two or more previous babies have been stillborn or very severely affected, one should consider delivery at 32 weeks—at which time elective cæsarean section will probably be indicated

If induction is performed because of a bad obstetrical history, severe disease in a premature baby must be expected and arrangements must be made for prompt (and in many cases repeated) exchange transfusion Some premature babies tolerate exchange transfusion badly, and we have found it expedient to do this in two stages, each taking half an hour with an interval of half to one hour between In deciding the volume of blood to be transfused we take account of the relative hæmoglobin values of baby and donor

Absolute rules cannot be laid down satisfactorily for the conduct of all cases.

Summary

Between July, 1952, and July, 1955, induction of labour at 35 weeks' gestation was considered in families in which a previous stillbirth had been attrib to hæmolytic disease

60 were selected for induction because the preced stillbirth was undoubtedly due to hæmolytic disea because the father was homozygous D/D

Only 25 of the 60 reached 35 weeks with a living fœt apparently normal on X-ray examination, all we induced at this stage

23 liveborn babies resulted, and, though all w severely affected by hæmolytic disease, 18 survived

Attention is drawn to the fact that many stillb from hæmolytic disease occur early in pregnanc that the premature baby with hæmolytic disease pre a difficult problem of treatment

Again we are indebted to our colleagues in obstetrics pæd trics and pathology throughout the Newcastle region and the staff of the Newcastle Maternity Units and National Bl Transfusion Service We thank especially Dr George And and Dr T D Davies for their help and interest

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THE CORRELATION BETWEEN URINARY ŒSTROGEN AND VAGINAL CYTOLOGY

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IT is very desirable that the treatment of metastati breast cancer by the administration of hormones or by ablation of endocrine organs should be controlled and rationalised by repeated assessment of the hormonal status of the patient For this purpose the first essential is to investigate the formation and utilisation of the œstrogenic steroid hormones, with the object of gaining knowledge of ovarian and adrenal cortical function In this connection it would be of inestimable value if it were possible to determine the œstrogen content of the circulating blood Until a reliable method applicable to the human cancer patient becomes available, we must be content with the chemical estimation of the œstrogens and their excretion products in the urine, together with a determination of the presence or absence of œstrogen stimulation of the secondary sex organs, judged by cytological examination of the vaginal fluid

A reasonably accurate biochemical method elaborated in the Medical Research Council's endocrinological unit in the University of Edinburgh (Brown 1955) measure the urinary output of œstrogens in three fraction— œstrone, œstradiol 17β, and œstriol The method is too elaborate and costly for routine clinical use, but its accuracy recommends it as a research method, and nce it has been standardised in a well equipped laboratory, many estimations can be undertaken by a trained technical staff

Unless supported by significant biological correlation, the chemical estimation of excreted œstrogens gives no precise information about the production and utilisation of œstrogens in the body We report here an attempt to determine the correlation between the level of œstrogens in the urine and the degree of œstrogen stimulation of the vaginal mucosa, as judged by vaginal cytology The observations were made in 53 premenopausal and postmenopausal women, whose ages ranged from 26 to 80 years the majority were postmenopausal, and some of them had mammary cancer

Methods

Vaginal Cytology

Vaginal fluid was taken from the posterior fornix, 75 specimens being obtained from the 53 women

Several methods have been proposed for recording the cellular pattern of the vaginal fluid Except in the technique proposed by Mack, a fixed film of the stained fluid is graded according to the intensity of the œstrogenic stimulation, judged by the predominant cell type The fluid from an unstimulated mucosa shows "deep" cells only, if the mucosa is moderately stimulated, "intermediate" cells predominate, and if it is powerfully stimulated most of the cells are "superficial" and many are cornified The grading may be assessed by simple inspection (Graham 1950) or by estimating glycogen-containing cells, for this purpose the glycogen may be stained by iodine vapour (Mack 1943) or by other methods such as Best's carmine after wet fixation in alcohol ether A differential count may be made, we have done this by counting 500 cells in each preparation, each group of 100 cells being taken from a different area of the film a chess-board graticule was used in one eyepiece and a measuring graticule in the other The frequency of five cell types was recorded

By the differential count three indices were calculated

(1) *Deep index* (percentage of deep cells)

(2) *Pyknotic index* (percentage of superficial cells, both cornified and uncornified)

(3) *Cornified index* (percentage of cornified superficial and intermediate)

Again by the differential count smears were assigned to the following groups or grades cited by Kasdon (1953)

Grade 0 —No œstrogen effect deep cells only.

Grade I —Very slight œstrogen effect, 25% deep cells with 75% intermediate cells

Grade II —Slight œstrogen effect, almost all cells intermediate

Grade III —Moderate œstrogen effect, 75% intermediate, superficial cells approaching 25%

Grade IV —Considerable œstrogen effect, 75% or more superficial

Our routine technique was to collect the vaginal specimen on the same day that a 24 hour specimen of urine was being obtained Several films of each vaginal fluid were prepared on slides immediately after collection These were appropriately fixed and stained, and the vaginal fluid from each patient was cytologically graded according to the following criteria

(1) Into one of five grades by simple inspection (Graham 1950)

(2) Into one of four grades from glycogen index by iodine staining (Mack 1943)

(3) Into one of four grades from glycogen index by carmine staining

(4) By differential cell count and calculation of deep index

(5) By differential cell count and calculation of the pyknotic index

(6) By differential cell count and calculation of the cornified index

(7) Into one of five grades from the differential count (Kasdon 1953)

Chemical Method

Œstrone, œstradiol-17β, and œstriol were estimated separately in 200-ml aliquots from the daily specimens of urine by the method of Brown (1955) The amounts of the three œstrogens excreted daily were calculated from the mean of the two estimations and the volume of the 24-hour urine In outline the method depends on the partial purification and separation of the three œstrogens and their colorimetric measurement, a spectrophotometric correction being applied for non-œstrogenic chromogens

Usually the smallest amount of each œstrogen calculated to be significantly different from zero is about 1 2 µg per 24 hours At this the lowest level of detection, there is an error of about ±50%—i e, if a result of 1 2 µg œstrone per 24 hours is obtained, the true figure may lie between, but not beyond, 0 6 and 1 8 µg per 24 hours The percentage error decreases rapidly as increasing amounts of œstrogen are measured, and at 2 5 µg per 24 hours of each œstrogen the error amounts to about ±20%

Values for the individual œstrogens in the 75 urine specimens taken were about equally divided between the ranges of 0–1 2 µg, 1 2–4 0 µg, and over 4 µg daily

Results

Correlation

Most of the films examined were random samples The remainder formed groups taken serially from each of three patients The large majority of the stained films prepared from 75 specimens of vaginal fluid were graded according to each of the seven cytological methods described For each of the resulting large number of graded films we had the corresponding 24-hour output of œstrogens on the day of collection of the specimen From these data the correlation coefficient (r) was calculated The number of comparisons made is indicated by n, and p is the probability

The results are seen in table I, which shows that

(1) The urinary output of œstriol correlates with grading by all methods of assessing œstrogenic stimulation of the vagina

(2) The total urinary output of œstrogen correlates with grading by all cytological methods except the glycogen index

TABLE I—RESULTS

Method of grading	Œstrogen excreted in urine (log µg in 24 hr)			
	Œstrone	Œstradiol	Œstriol	Total œstrogen
Simple inspection				
r	0 40	0 22	0 57	0 44
p	< 0 001	> 0 05	< 0 001	< 0 001
n	75	66	74	73
Glycogen index (iodine staining)				
r	Not significant	Not significant	0 42	0 37
p			< 0 001	< 0 01
n			70	66
Glycogen index (carmine staining)				
r	Not significant	Not significant	0 41	0 26
p			< 0 01	> 0 05
n			56	53
Deep index				
r	0 21	Not significant	0 31	Not significant
p	> 0 05		< 0 01	
n	67		67	
Pyknotic index				
r	0 22	Not significant	0 53	0 38
p	> 0 05		< 0 001	< 0 01
n	67		67	67
Cornified index				
r	Not significant	Not significant	0 39	0 33
p			< 0 01	< 0 02
n			66	53
Differential count				
r	0 44	Not significant	0 53	0 42
p	< 0 001		0 001	< 0 01
n	74		71	74

TABLE II—MEANS OF OUTPUTS OF ŒSTRIOL

gen by lo tion	Arithmetic means of œstriol values	Standard deviations	Arithmetic means of logarithms of œstriol values	Standard deviation of logarithm of œstriol values	n
	1 4	2 049	0 757	0 68	19
	2 8	3 268	0 943	0 793	8
	4 05	4 468	1 332	0 627	26
	10 38	9 116	1 784	0 547	21

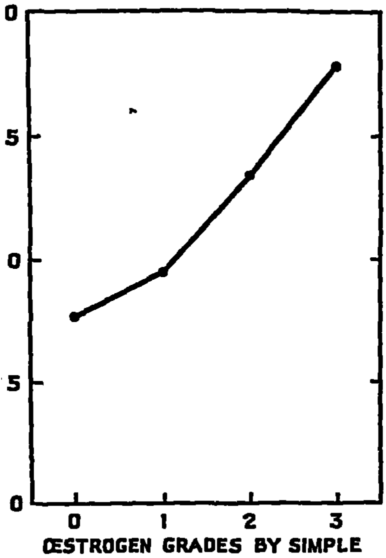
armine stained preparations and the deep index by ntial cell count

The output of œstrone correlates with grading by inspection and with the assignment of films into one of ades by a differential cell count

The output of œstradiol correlates with none of the methods used for the assessment of vaginal stimulation

The comparison between the output of œstriol and the nent of films to one of five grades by simple inspection it enumeration of cells gives the best correlation of any table

alculating r, instead of using the number of µg of estrogen excreted in 24 hours, we used the logarithm s figure because an almost linear relationship was to exist when the logarithms of these values were plotted against the degree of œstrogen stimulation determined by cytological grading



·Relation of means of log œstriol excretion s to œstrogen grades estimated by simple ction

In table II the arithmetic means of the outputs of œstriol and the arithmetic means of the logarithms of the outputs of œstriol are given against each of the œstrogen grades obtained by simple inspection The respective standard deviations are also given

neans derived from the log œstriol excretion figures otted against the œstrogen grade in fig 1 Although elationship is not exactly linear, the result is highly cant statistically

Estimations

results of serial estimations on specimens of urine erial vaginal films from a menopausal woman aged shown in fig 2 The pyknotic index follows the n shown by œstriol and the total output of œstrogen ugh not included in the graph, œstrone has a r correlation At low œstrogen levels the deep shows a clear inverse relationship to both œstrogens chemical and cytological methods show an initial ollowed by a gradual fall in both the urinary gen and the intensity of œstrogenic stimulation of ginal mucosa Œstradiol was excreted at a fairly nt rate 1 5 µg per 24 hours A particularly clear onship is present in this case between the pyknotic and output of œstriol, and maximum cornification place two days after the output of œstrogens was st

Two other short series also gave good correlation between vaginal cytology and urinary output of œstrogen

Accuracy of Œstrogen Estimations

Since the œstriol values show a high degree of correlation with the assessment of the vaginal reaction by all methods of grading, whereas the œstrone values correlate with the grade determined by one method only, the question arises whether this particular lack of correlation is due to inaccurate chemical estimation at very low levels of excretion Table III shows the percentage of estimations of urinary œstrogens grouped according to whether they fell below our lower limit of sensitivity or below that given by Brown (1955) Over two thirds of the estimations were below 4 0 µg per 24 hours

Nevertheless the œstrone and œstriol values have almost identical distributions The failure of œstrone to correlate cannot therefore be regarded as due to inaccurate estimations of very low amounts Œstradiol has a preponderance of low values, and this may explain the absence of any correlation

TABLE III—DISTRIBUTION OF ESTIMATIONS OF ŒSTROGENS

Percentage estimations	Œstrone	Œstradiol	Œstriol
From 0 0 to lower limit	27	48	26
From lower limit to 4 µg	42	42	43
More than 4 µg	31	10	31

Discussion

Some measure of agreement between the biological and chemical results was to be expected Brown (1956) has shown a close correspondence between physiological events and the output of œstrogen, while Rubenstein and Duncan (1941) have demonstrated correlation between vaginal cytology and urinary œstrogen measured by bio assay

Our work shows that there is a correlation between vaginal cytology and urinary output of œstrogen measured chemically, even when the latter is very low, and such a relationship implies that each method gives a result proportional to the amount of hormone or precursor in the circulation

The best correlation is that given by œstriol At first sight this is surprising in view of the alleged biological

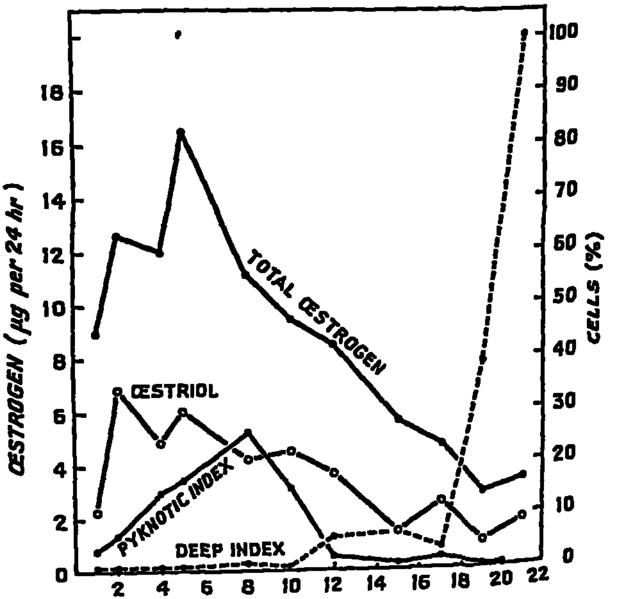


Fig 2—Serial estimations of urine and vaginal films from menopausal woman aged 56

inactivity of this steroid It may be that when œstradiol and œstrone act on their target organs they are metabolised to œstriol On this supposition the quantity of œstriol excreted would become proportional to the biological effect, and our results support such a thesis

Close correlation between the cytological and chemical findings is given by the œstrogen grading obtained by simple inspection and by differential counts At high œstrogen levels the pyknotic index, and at low œstrogen levels the deep index, both give good correlation The last three methods, however, require the performance of a differential count, which is unnecessary if the same result can be obtained without one

The value of the correlation appears to be statistical rather than practical In each œstrogen group the standard deviation is wide and there is considerable overlap in output of œstrogen from one group to another From the examination of vaginal fluid from different patients taken at random we do not think it possible to predict the urinary level of œstrogens with much accuracy We believe however, that in individual cases serial vaginal films can provide a good estimate of urinary œstrogen excretion , or, conversely, that urinary output of œstrogen is an accurate reflection of œstrogen effect on the patient

Summary

Vaginal cytology and urinary output of œstrogen have been compared on over 70 occasions, and a statistically good correlation has been found between them

We are indebted to Dr Clive Spicer for advice on the statistical methods used

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PREGNANCY IN THE DIABETIC MOTHER WITH NEPHRITIS

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The number of juvenile diabetics reaching the child-bearing years with already established renal complications is small, but probably diabetes lasting ten or more years becomes complicated by nephropathy in about 20% of cases (Forsythe and Payne 1956) Many such women wish to bear children and little is known about the outcome of pregnancy in these conditions Some clinics either discourage or terminate pregnancy, but no precise information has been published about the risk to the fœtus We have analysed a series of these cases and report our findings here

Material

In 1940-56 767 diabetic women attending the Joslin Clinic had pregnancies which attained viability (28 weeks) Of these, 31 (4%) were in White's (1949) class F, and 10 other women in class F became pregnant but had their pregnancies terminated naturally or artificially before 28 weeks Class-F pregnancies are uncommon, even in a clinic dealing with large numbers of diabetics A woman was classified as belonging to class F if, when her pregnancy became known, she had chronic renal disease in addition to diabetes The presence of other complications of diabetes—e g , calcified vessels and retinitis proliferans—were ignored for classification purposes All these women had diabetes of long duration, all had retention of nitrogen, and some had hypertension and diminished renal function Albuminuria was constant, but it is not uncommon in all diabetic pregnancies Many women had other vascular complications of diabetes Unfortunately the renal lesions of diabetes are not yet susceptible to precise clinical classification Moreover, although all these women probably had intercapillary glomerulosclerosis, it is uncertain how many had chronic pyelonephritis also

Methods

The pregnancies were managed according to the régime of Nelson et al (1953), which includes close supervision of diet and insulin requirements, together with early antenatal admission to hospital Some of the women also received large doses of sex hormones Hydramnios was almost constant, and most mothers had toxæmia in addition to the preceding renal disease Because of either this or diminished vitality of the fœtus delivery was by cæsarean section in all but 6 cases

One of the two pædiatricians (S S G and D Y-Y H) was present at each delivery and supervised personally the resuscitation and aftercare of the infant No matter what their birth-weight was, the infants were managed according to the routine practice for immature infants All were treated in incubators and given oxygen Fluids were withheld for the first forty-eight hours, and glucose was not given Respiratory distress was treated with oxygen and, in some cases, supersaturation of the atmosphere with water vapour Investigations and treatment were instituted when necessary for specific complications

Outcome of Pregnancy

Of the 41 class F mothers 15 were primigravidæ, 19 had had one previous pregnancy, and 7 were undergoing their third or later pregnancy Altogether the results of 83 pregnancies were known There were no maternal deaths, but therapeutic abortion was induced in 8 cases because of either increasing renal disease or advancing retinitis proliferans It was considered justifiable to sum the total pregnancy experience (table I) to give some idea of the over-all hazard to the fœtus, although we realise that, at the time of the previous pregnancies, not all the women had progressed to nephropathy or received the same obstetric care The 61% survival rate of the 31 viable fœtuses of the present series of pregnancies may be compared with the experience of 736 viable pregnancies in women with diabetes but without nephro-

TABLE I—OUTCOME OF PREGNANCIES

Outcome	Pregnancies		
	Present (41)	Past (42)	Total (83)
Miscarriage	2	26	28
Therapeutic abortion	8	0	8
Stillbirth	4	2	6 (8%)
Neonatal death	8	5	13 (16%)
Total loss	22 (54%)	33 (79%)	[illegible] (66%)
Survival of child			
Actual no	19	9	28
% of pregnancies	46	21	34
% of viable fœtuses	61	56	60

pathy who attended the same clinic and were managed in the same way (Gellis and Hsia, unpublished data)

Stillbirths	53 (7%)
Neonatal deaths	84 (11%)
Survivors	599 (82%)

The class-F pregnancies were associated with a greater mortality both from stillbirths and neonatal deaths, but there are insufficient data for us to draw conclusions about the abortion-rate The number of pre-viable fœtal deaths appears large in the class-F pregnancies, but without precise knowledge of the abortion-rate among other diabetic or non diabetic pregnancies it is impossible to speculate on the cause Some women appeared to have a tendency to repeated miscarriages, but such a history did not always preclude an eventually successful pregnancy

Intra-uterine Deaths

The intra-uterine deaths in the present series took place at 29, 31, 32, and 33 weeks, which fact suggests that the combination of diabetes and renal disease may prove lethal to the fœtus at an earlier stage than is usual in uncomplicated diabetes However, it was the practice of the clinic to forestall intra uterine death by early admission of the mother to hospital and rapid delivery at the first signs of diminished fœtal vitality This procedure may well have prevented intra uterine deaths at later gestational ages

Of the 27 live born infants 17 developed, in the neonatal period, respiratory distress characterised by tachypnœa and grunting respirations shortly after birth, followed by obstructive dyspnœa with retraction of the chest wall and attacks of cyanosis 8 of them died, and in 6 of these necropsy revealed hyaline membrane and resorption atelectasis These infants had been delivered by cæsarean section and died 1–96 hours after birth One other baby died 30 minutes after birth, having failed to establish effective pulmonary ventilation, necropsy revealed intra-uterine asphyxia and aspiration of cellular debris into the lungs The eighth neonatal death was ascribed to bronchopneumonia No important congenital abnormalities were observed

Birth weights

Many of these infants, unlike the characteristic infant of the diabetic mother, were small A comparison of birth-weights with those of 157 infants of diabetic mothers (classes A–E) by gestational age confirms this impression (table II)

TABLE II—BIRTH WEIGHTS OF INFANTS OF DIABETIC MOTHERS

Birth-weight (lb)	Gestational age (weeks)					
	< 33		33–35		35–37	
	Class F	Classes A–E	Class F	Classes A–E	Class F	Classes A–E
< 4	2	4	1	1	2	0
4–5	1	3	1	4	2	3
5–6	1	1	6	18	4	19
6–7	—	0	3	10	5	37
7–8	—	0	—	15	0	35
> 8	—	0	—	1	0	6

Discussion

The results of this study confirm the high fœtal mortality in pregnancy where maternal diabetes is complicated by nephritis (Pedersen and Brandstrup 1956) but does not indicate any special cause for this other than what might be suspected from the additive effects of the lesions That the intra-uterine environment is unfavourable is shown by the tendency to early intra-uterine death of the fœtus and by the latter's relatively small size After delivery the infant shows a tendency to hyaline membrane, which is known to be an almost constant feature of early neonatal death in the infants of diabetic mothers (Winter and Gellis 1954) Whether this susceptibility is a specific result of maternal diabetes or merely underlines the immaturity of these babies cannot be answered yet (Miller 1956)

The outcome of pregnancy reported here, unsatisfactory though it is, probably represents the maximum that can be achieved by the application of existing knowledge It therefore seems reasonable to offer the diabetic woman with nephritis an approximately 50% chance of bearing a surviving child under conditions of expert diabetic and obstetric management Such a risk may well be thought unjustifiable when the dangers of such pregnancies to the health of the mother are also considered

Summary

41 class F diabetic pregnancies are reviewed The fœtal wastage was 55%

The infants were smaller than infants of diabetic mothers usually are, but showed the same tendency to hyaline membrane as a cause of neonatal death

Our thanks are due to Dr Priscilla White for making available her records and to Dr Phillip Le Compte and Dr Kurt Benirschke for pathological material

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NEPHROTIC SYNDROME

PREDNISONE THERAPY WITH TWO DEATHS FROM CELLULITIS

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In some cases of the nephrotic syndrome treatment with corticotrophin or cortisone is of value (Roscoe 1956) The special risks entailed in this form of therapy have often been emphasised and are well summarised by Luetscher et al (1953) We record here two deaths, due to rapidly spreading cellulitis, during a trial of prednisone in the nephrotic syndrome

Case-reports

Case 1 —A man, aged 66 In February, 1956, an exacerbation of his chronic bronchitis and emphysema resulted in congestive heart failure, which was successfully treated with rest, digitalis, and mersalyl His urine was then repeatedly protein free The last weekly dose of mersalyl was given in April and acetazolamide (' Diamox ') was substituted

In August his legs swelled On examination he had moderate œdema, *normal* blood pressure, a daily urinary protein loss up to 28 5 g, plasma proteins 5 2 g per 100 ml (albumin 1 5 g, globulin 3 7 g), and blood urea 36 mg per 100 ml There were no signs of heart failure Renal biopsy showed changes compatible with early type II nephritis After 2½ weeks' rest with high protein low salt diet there was no improvement

Prednisone 20 mg b d for 6 days was then followed by 10 mg b d On the 7th day of this treatment, when there was still moderate œdema of the legs and back, the right lower part of the abdomen became hot, red, tender and œdematous This cellulitis rapidly spread over the abdomen back thighs legs, and chest The rectal temperature reached 101 5°F, and the patient s general condition rapidly deteriorated In spite of intramuscular penicillin 1 mega unit b d he died within 48 hours Necropsy was not performed

Case 2 —A man, aged 35, in February, 1956, developed œdema and was found to have heavy proteinuria and a low plasma protein level In June he had slight œdema, blood-pressure 150/100 mm Hg, a daily urinary protein loss up to 27 g plasma proteins 5 9 g per 100 ml (albumin 2 9 g, globulin 3 0 g), and blood urea 45 mg per 100 ml Renal biopsy showed changes compatible with early type II nephritis In spite of 3½ weeks' rest with a high-protein low salt diet the plasma protein had fallen to 4 7 g per 100 ml

Treatment with prednisone 20 mg b d was started on July 3 After 3 weeks the patient had a massive diuresis and improved, and the dosage of prednisone was reduced to 10 mg b d In September, on the same dosage, the œdema returned, proteinuria increased, and the plasma protein level fell to 4 3 g per 100 ml On Sept 8 the dosage of prednisone was reduced to 5 mg b d 2 weeks later when he still had moderate œdema up to the lower thoracic region, he developed pain in the back and pyrexia to 103°F, his lumbar region being hot, red, tender, and indurated This cellulitis rapidly spread over his back, abdomen, thighs, legs, chest and arms He was given corticotrophin 50 units instead of prednisone, intramuscular penicillin 1 mega unit b d and two days later aureomycin 250 mg q d s 2 days before death his plasma-sodium and plasma potassium levels were normal and his blood urea level 45 mg per 100 ml He deteriorated and died within 4 days of the onset of the cellulitis Immediate post-mortem culture of the subcutaneous fluid from the arms and leg grew *Escherichia coli*

Comments

The incidence and gravity of intercurrent infections in œdematous patients have been reduced by antibiotic therapy Both these patients were treated with prednisone and during treatment developed a spreading cellulitis which was rapidly fatal, the source of the infection is unknown Neither patient was grossly œdematous, and cellulitis would not normally have been considered a serious risk We think the fulminating nature of the infection was related to the use of prednisone, which is known to have an anti-inflammatory effect These two fatal cases have impressed on us the necessity for early recognition of cellulitis and for its immediate vigorous treatment

We wish to thank Sir Horace Evans for permission to publish

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A GIANT DIVERTICULUM OF THE BLADDER

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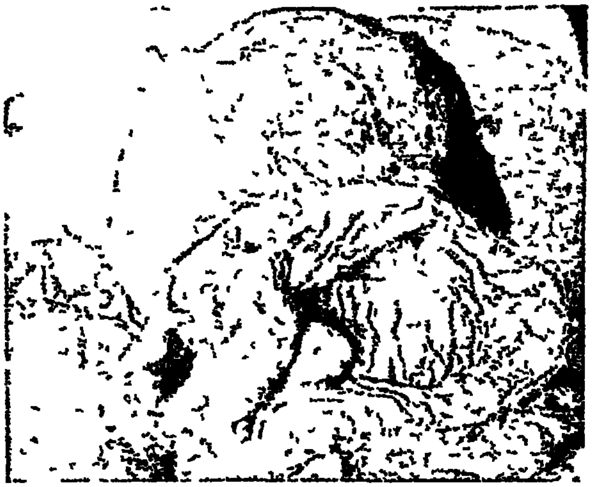
A MAN, aged 70, referred by Dr D Gullick, was admitted to hospital on Aug 30 1955, having had severe abdominal colicky pain for five days He had not vomited but he had lost his appetite and had had no bowel action since the onset of pain an enema given the previous day had been returned clear He had had no trouble with passing urine, there had been no increased frequency and no nocturia On admission he passed 10 oz of urine, which, except for a trace of albumin, was normal on routine examination Apart from attacks of bronchitis and an operation for varicose veins there was no previous history of importance In fact he had regarded himself as a fit man for his age

Examination —It was obvious that he was ill, for he was pale and sweating and his tongue was furred His abdomen was distended and tense and somewhat tender but there was no rebound tenderness Bowel sounds were scanty Hæmoglobin was 111%, and the blood urea level was 122 mg per 100 ml Straight radiographs of the abdomen showed coils of dilated gut suggesting obstruction It was difficult to be sure if there was free gas under the diaphragm



Giant diverticulum of urinary bladder lying posteriorly The bladder has been opened, showing the enlarged middle lobe of the prostate

Operation Findings —At laparotomy three hours after admission, gas escaped when the peritoneal cavity was opened, and a considerable amount of free purulent fluid was found An enormous cystic mass resembling a huge ovarian cyst was seen rising out of the pelvis Needle aspiration of this mass produced fluid like urine, and so a catheter was passed per urethram As urine was evacuated, the mass gradually subsided When 8½ pints of urine had been drawn off, a more or less normal bladder with a huge diverticulum was revealed

Further exploration showed a perforation of the first part of the duodenum This was closed by suture over a plug of omentum Purulent fluid was sucked out of the peritoneal cavity, and the abdomen was closed, a drainage tube being inserted The bladder was then opened by a separate suprapubic incision and an enlarged middle lobe of prostate was found acting as a ball valve obstruction of the internal meatus A De Pezzer catheter was inserted for drainage

Postoperative Course —During the next few days the patient was treated by gastric aspiration and intravenous drip, and his condition remained fairly satisfactory except that his urinary output fell very low (though it later improved) The ominous feature was that the blood urea (122 mg per 100 ml on admission) rose to 240 mg Ten days after the laparotomy (on Sept 9, 1955) the patient had a sudden hæmatemesis followed by melæna Despite blood transfusion he died next day

Necropsy Findings —The heart was a little dilated, and there were some degenerative changes in its muscle wall The lungs showed some basal congestion, but the remainder of the respiratory tract showed no abnormality The peritoneal cavity was dry except for a layer of thick pus around the spleen The stomach and intestines contained a considerable amount of blood and were dilated The hæmorrhage had come from two acute gastric ulcers There was a large duodenal ulcer, the perforation of which was noted to be firmly closed by sutures The liver showed pallor and fatty changes The spleen was engorged, the gall bladder and bile ducts were normal

The kidneys and ureters were normal, as were the pancreas and adrenal glands The bladder was hypertrophied (wall 1 cm thick), and its mucosa was congested showing patchy hæmorrhages The diverticulum on the posterior upper wall had an opening 3 cm in diameter and a capacity of about 3 litres The prostate showed slight uniform hyperplasia and a pedunculated middle lobe about 3 cm in diameter

Dr K A Mische photographed the specimen after stuffing the diverticulum with cotton waste Unfortunately, as it had been treated with solution of formaldehyde it had shrunk somewhat, and so the original huge distension seen at operation could not be fully reproduced Nevertheless the accompanying figure depicts the immense diverticulum along with the obstructing lobe of the prostate

Comments

The particular points of interest are -

(1) The absence of any previous history of disturbance of micturition (despite further postoperative questioning of the patient) and the fact that he passed urine in a normal quantity after admission to hospital

(2) The enormous size of the diverticulum It held nearly 8 pints at operation, and 5 pints post mortem after treatment with solution of formaldehyde Winsbury-White (1948), Ainsworth-Davis (1950), and Badenoch (1953) say that bladder diverticula may be larger than the bladder but do not suggest that any are nearly so large as the one reported here A search through the literature has not revealed any comparable case, but Pfau (1952) reported a diverticular calculus which weighed 610 g It fitted the diverticulum snugly, and radiologically this appeared to be nearly as large as a child's head, and so considerably smaller than the one described above

(3) Though theoretically it was probably unwise to remove so much urine rapidly, it was necessary to do so in order to gain access to the duodenal perforation

(4) Death was due to gastric ulceration and hæmorrhage and not, apparently, to uræmia (though this no doubt was a factor), because necropsy revealed normal kidneys

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Reviews of Books

Pulmonary Emphysema

Editors ALVAN L BARACH, M D, clinical professor of medicine, Columbia University College of Physicians and Surgeons, HYLAN A BICKERMAN, M D, assistant clinical professor of medicine, Columbia University College of Physicians and Surgeons Baltimore Williams & Wilkins London Baillière, Tindall, & Cox 1956 Pp 545 80*s*

THIS book will be welcomed by those who are looking for a comprehensive, authoritative account of pulmonary emphysema

Different aspects of the subject are discussed by eighteen well known American experts In the opening chapters Barach, Bickerman, and G J Beck discuss methods of therapy employed at New York Presbyterian Hospital In later sections there are interesting appraisals of fairly new forms of treatment—continuous and intermittent positive pressure breathing, bronchial exsufflation, steroid therapy, and graduated exercise in an oxygen enriched atmosphere—but the most valuable feature of the book is the insistence on examining problems in the light of fundamental work on respiratory physiology The disturbance of pulmonary function in emphysema, and its effect on blood gas exchange and on the pulmonary circulation, are analysed in detail, and there is a chapter on lung function tests of value in clinical practice It is unfortunate that in so useful a book the writing does not always match the material some contributions could be described as treatises on the shortwinded by the longwinded

The Microscopic Diagnosis of Human Malaria

Part II *A Morphological Study of the Erythrocytic Parasites* JOHN W FIELD, C M G, M D, director, Institute for Medical Research, Federation of Malaya, P G SHUTE, M B E, assistant director, Malaria Reference Laboratory, Medical Research Council Kuala Lumpur Government Press 1936 Pp 251

THIS is the sequel to an earlier volume, *A Short Descriptive Atlas of Thick-Film Diagnosis*, published in 1918

The present volume begins with a short history of the microscopic diagnosis of malaria in man, and goes on to describe the parasites and their relations with the host red cells The terms applied to the various stages of the parasites are defined and the changes which take place in the cells are described The question whether the parasites are in or on the cells is left undecided

There are separate chapters for *Plasmodium falciparum*, *P vivax P malariæ*, and *P ovale*, and the authors have adopted a uniform scheme (with appropriate variations) for them all, though *P falciparum* receives most space These chapters contain much more than observations on microscopic diagnosis, and the book is, in fact, full of valuable information not always easy to find elsewhere, on a very wide range of subjects connected with the parasites and even the diseases they cause The pre erythrocytic and exo erythrocytic stages are referred to, but are not described at length since they do not come within the scope of the book

Methods of examination for malaria parasites—during life and after death—are dealt with, and technical details are given in a full chapter, but perhaps the most notable feature of the book is the extensive set of 59 full page plates, 24 in colour and the rest in monochrome, illustrating parasites at all stages as seen in thin and thick blood films The illustrations of the Malayan parasites are all new, being made by Yap Loy Fong at the microscope in the course of day to day work They are beautiful The hundreds of monochrome drawings depict the parasites in, one would say, all the shapes they could assume There are also coloured plates of spores, pollen grains, and other cells of vegetable origin, and other objects which might confuse a diagnosis

This book is a masterpiece which should be available in all laboratories in which the diagnosis of malaria is undertaken, and in all institutions where the subject is taught

Diagnostic différentiel radiologique des ulcerations gastriques

GEORGES CANDARDJIS Paris Masson 1956 Pp 188 Fr 1500

THIS book is based on an analysis of clinical records and radiographic examinations of some 133 patients submitted to gastrectomy between January, 1950, and December, 1954 The radiological signs are described, and the value of each is discussed in detail It is a comprehensive and good review of a difficult subject

Progress Report on Birth Control

LELLA SECOR FLORENCE, chairman of the Birmingham Family Planning Association London Heinemann Medical Books 1956 Pp 260 21*s*

THE title of this book might lead readers to expect a complacent account of grateful patients attending at expanding family-planning clinics Instead it recognises frankly that there is still much progress to be desired

The book deals mainly with a survey carried out by the Birmingham Family Planning Association on patients attending their clinic during 1948, with a careful follow up of a large number (about half) who failed to return This survey disclosed that to many couples methods of contraception advised at clinics are far from fully acceptable or reliable, and the author urges the need for examination, not only of the work of clinics, but of the general approach of the medical profession to this urgent problem Sterilisation and therapeutic abortion are discussed with forthright courage

All workers, medical and lay, in family-planning clinics should read this book, but it will also be useful to other doctors, nurses, and social workers

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Sequeira's Diseases of the Skin (6th ed London J & A Churchill 1957 Pp 843 £3 5*s*)—The new edition of this book, appearing ten years after the last, is most welcome The editors, Dr J T Ingram and Dr R T Brain, have ensured that it remains well written, balanced, and comprehensive without being tiresomely encyclopædic Theory and practice are equally well represented, and bibliography is limited to a helpful minimum Omission of some of the reproductions of drawings might dispel the slight aroma of mothballs that may unreasonably discourage the use of a book which otherwise has an up to date freshness

International Review of Cytology (Vol V New York and London Academic Books 1956 Pp 570 92*s*)—The latest issue of this well established annual series, edited by G H Bourne and J F Danielli, includes a comprehensive and magnificently illustrated survey of the achievements of electron microscopy, written by F S Sjostrand of Stockholm Other articles cover such subjects as enzymic adaptation, the subcellular organelles of muscle, and the measurement of intracellular pH, while medical readers may be particularly attracted by T A J Prankerd's paper on transport across the erythrocyte membrane and A H Coons's review of the histochemical applications of labelled antibodies

THE LANCET
LONDON SATURDAY, FEB 16, 1957

Clinical Picture of Sickle-cell Disease

The sickle cell diseases have been the subject of intensive research ever since the demonstration by Pauling and by Perutz that the extraordinary shapes seen in the red blood-cells were due to the presence of an abnormal type of hæmoglobin which showed curious biophysical changes when exposed to relatively low concentrations of oxygen Harris and his colleagues,[1] in a recent survey, summarise the biophysical change as follows ' in hæmoglobin solutions of concentrations comparable to intracellular conditions, the abnormal hæmoglobin S molecules undergo alignment and parallel aggregation following deoxygenation to form birefringent hæmoglobin tactoids Consequently, the conclusion was reached that in all probability the birefringent sickled cell is a membrane covered hæmoglobin tactoid " (A tactoid is a spindle-shaped liquid crystal mass) We now know that in sickle-cell anæmia the red cells contain 75–100% of this unusual hæmoglobin (hæmoglobin S), with 0–25% of the normal hæmoglobin A In the sickle cell trait the red-cell hæmoglobin is a mixture of 25–45% hæmoglobin S with 55–75% hæmoglobin A Three other sickle cell diseases have been identified in sickle-cell/hæmoglobin-C disease the proportions are about 50% hæmoglobin S and 50% hæmoglobin C , in sickle-cell/thalassæmia disease, 67–82% of the hæmoglobin is the sickle cell form and up to 20% is fœtal hæmoglobin, the small remainder being hæmoglobin A , the third form (sickle cell/hæmoglobin-D disease) is so far less well-known (a case was described in our columns by Stewart and MacIver[2]) In all these varieties the oxygen tension at which tactoid formation and sickling can be induced is roughly correlated with the proportion of hæmoglobin S in the red cells of a particular patient

But patients with sickle-cell anæmia vary considerably in the clinical severity of their disease They can carry on for long periods in a precarious state of equilibrium between mild hæmolysis and red-cell regeneration, and then suddenly a hæmolytic crisis causes severe anæmia and grave illness People with sickle-cell trait or with the other varieties of sickle cell disease rarely suffer any disability and their abnormality is discovered only if their blood is examined because they have some illness, or because a relative has sickle cell anæmia But instances have lately been recorded of people who suffered a splenic infarction during an aeroplane flight, and who were found to have sickle cell trait or one of the other related conditions Rotter and his colleagues[3] described 6 such incidents in 3 the patients had sickle cell trait, in 2 they had sickle-cell hæmoglobin-C disease, and the sixth had sickle-cell thalassæmia , 5 were American Negroes and 1 was a Puerto Rican Griggs and Harris[4] studied the levels of oxygen tension at which the bio physical changes of sickling appeared in the various syndromes in sickle-cell disease, sickling will occur at an oxygen partial pressure of 60 mm Hg, a tension corresponding to that of mixed venous blood , the patients with 50–80% of hæmoglobin S, such as is found in sickle-cell/hæmoglobin-C and sickle-cell/thalassæmia diseases, must have a lower oxygen tension of about 40 mm before sickling appears , and in sickle-cell trait the oxygen partial pressure must be reduced below physiological levels (to 10 mm) before the cells will sickle Even though the patients who had splenic infarction were travelling in unpressurised planes, it is not certain that the oxygen partial pressure in their mixed venous blood fell as low as 10 mm , and it is noteworthy that symptoms did not come on until the patient had been some time in the air All this suggests that some factor in addition to low oxygen tension is concerned in the production of the *clinical* manifestations of the sickle-cell diseases Allison[5] suggests that this additional factor is time—the time of exposure of abnormal red cells to low oxygen tension -

What Allison has done is to repeat some older experiments in which blood from patients with sickle-cell disease is equilibrated with gas mixtures under conditions corresponding to mixed venous blood , such a gas mixture has an oxygen partial pressure of 40–45 mm , and when blood from a patient with sickle-cell disease is equilibrated at 37°C for four hours 10–20% of the red cells become sickled But if venous blood from an antecubital vein of such a patient is fixed by formalin immediately after withdrawal, sickle cells number less than 2% The reason for this is that a period of some *minutes'* exposure to low oxygen tension must elapse before the maximum sickling develops , thus, Allison shows that after two minutes' partial deoxygenation the proportion of sickled red cells is about 5% but after six minutes it has risen, in various samples, to between 12% and 18%, most of the increase taking place between two and four minutes From estimations of circulation-time, it seems likely that under physiological conditions most red cells are deoxygenated for ten to twelve seconds, and only a few for longer than fifteen seconds Thus, though most tissues are sufficiently low in oxygen to induce some sickling of red cells in persons with sickle cell disease, the fact that the red cells are exposed for only fifteen seconds or so means that most cells will be re-oxygenated before they can become sickled But if anything holds up the flow of cells through the tissues, the proportion of sickled cells will rise rapidly , any form of vasoconstriction or inflammation for example, could in that way increase sickling, and since the sickled cells themselves are likely to intensify the hold-up by blocking blood-vessels, it is easy to see how a " crisis " can be built up Allison observes that restoration of sickled cells by re-oxygenation takes just as long as the process of sickling, so that when sickled cells escape into the general circulation they will not stay long enough in well oxygenated parts to allow them to revert to a discoid shape As Harris et al[1] point out sickled cells are mechanically fragile and rapidly destroyed so that once sickling begins on any sizeable scale, a hæmolytic phase soon appears Allison also notes that sickling takes place more readily in the spleen than in other organs, and in the spleen stasis of blood is physiological

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[1] Harris, J W Brewster H H Ham T H Castle W B *Arch intern Med* 1956 97 14

[2] Stewart J W MacIver J E *Lancet* 1956, i 23

[3] Rotter R Luttgens W F Peterson W L Stock A E Motulsky A G *Ann intern Med* 1956 44 257

[4] Griggs R C Harris J W *Arch intern Med* 1956 97 315

[5] Allison A C *Clin Sci* 1956, 15, 497

As we have already seen, in patients with sickle cell variants, sickling occurs only when the oxygen tension is reduced to between 15 and 40 mm , and in people with sickle-cell trait, oxygen pressure must be even lower The only conditions in which such low pressures are commonly found are in aeroplanes ROTTER et al[3] think that persons with sickle-cell trait may be in danger of sickling and splenic infarction only when flying at 10,000–15,000 feet in unpressurised aircraft , but persons with sickle-cell/hæmoglobin-C or sickle-cell/thalassæmia disease may have sufficient abnormal hæmoglobin for sickling to develop at 4000–6000 feet, and many commercial airlines operate at such heights They think the problem sufficiently important to warrant the screening, by paper electrophoresis, of Negro and Puerto Rican military personnel to detect those who have any abnormal hæmoglobin Sickle-cell diseases are also common in the West Indies (HERRICK's original case, described in 1910, was a West Indian from Grenada), so the same problem may arise there In fact, the diseases produced by abnormal hæmoglobins may become of increasing significance in many ways because they are common in countries where much has lately been done to check malnutrition and the infectious diseases, which were prolific causes of death and which made the hæmoglobin disorders seem relatively trivial LEHMANN[6] remarks how the hæmoglobin abnormalities may thus assume increasing importance in many parts of the world , the change is already apparent, he points out, in the Lake Kopias area of Greece, where sickling and thalassæmia are common but where the once formidable malaria has been eradicated, and where the hæmoglobinopathies are now the most pressing medical problem

Keratinous Cysts in the C.N.S

KERATINISING squamous epithelium in the wrong place behaves with great uniformity, wherever that place may be (and most parts of the body may be involved) and by whatever mechanism of displacement, maldevelopment, metaplasia, or even benign neoplasia it may get there It rounds off into a cyst, and the gradual accumulation of keratin leads to the growth of the cyst, a growth measured often in decades rather than years Breakdown of the keratin results in the accumulation of that ultimate indigestible fragment of most protein complexes, cholesterol The cyst contents are in fact highly irritating and excite a violent granulomatous reaction if the protecting layer of squamous epithelium breaks down In the body generally it is easy to recognise this constant pattern in "sebaceous" cysts, in implantation dermoids, in the cysts which complicate buried whole-skin grafts and the healing of epithelialised sinuses, in ureteric stumps, in line-of-closure dermoids (of which branchial cyst is the type), and in benign teratomatous cysts like the ovarian dermoid The presence of sebaceous glands and hair follicles in the lining of the teratomatous cysts (and sometimes in the line-of-closure dermoids, and rarely in the other types) makes remarkably little difference to the behaviour of these cysts, though it alters the appearance of the contents For this reason, little care has been taken to distinguish in ordinary speech between the terms "dermoid" and "epidermoid" cysts

Keratinous cysts in and about the central nervous system are usually described (often under the name of "pearly tumours") as though they were a separate entity, and had an element of unexpectedness denied to similar cysts elsewhere In fact they differ little in diversity of origin and uniformity of behaviour from those found elsewhere in the body They are not very rare, forming as much as 1% of reported series of cerebral "tumours" Series as large as 23 cases[1] have been described in the past, and TYTUS and PENNYBACKER,[2] in Oxford, have lately recorded 43 cases Their work illustrates the many different sites in which these lesions may arise 2 were pericranial, 6 orbital, 6 petrous, 2 diploic, 2 suprasellar, 7 intracerebral, 3 cerebello-pontine, 8 midline subtentorial, and 7 spinal A few of these can be extracted as special groups 3 of the midline subtentorial and 2 of the spinal cysts had associated dermal sinuses, which could clearly be responsible for the complication of septic meningitis , and, perhaps for that reason, this variety often causes symptoms early in life These midline cysts are obviously due to imperfect closure of the neural canal, a simple and obvious type of congenital lesion The suprasellar ones are perhaps related to Rathke cysts The petrous lesions include some at least of the "cholesteatomas" of the otologists it is interesting to find that it is by no means certain that these are the chronic infective granulomas that they are generally assumed to be, but may be primary keratinous cysts of the petrous bone infected secondarily from the middle ear Teratomatous cysts of the pineal body or elsewhere in the median plane must also be included, though they are rare and usually malignant[3] Benign forms do occur, however, and it is not clear whether TYTUS and PENNYBACKER saw no such lesions or have deliberately excluded them The remaining cysts seem to be scattered almost at random through the brain, the meninges, and the adjoining bone They are not confined to the midline, and malocclusions of the neural canal will not account for them It can only be supposed that, since the brain is ectodermal in origin, and the meninges and a surprisingly large part of the cranium arise from the neural crest[4] which is also ectodermal, we are witnessing the occasional anomalous appearance (presumably congenital) of the most characteristic end-product of the ectoderm, squamous epithelium, at these unlikely sites

The symptoms to which these cysts give rise are those of any benign space occupying lesion of very slow growth The absence of protein changes in the cerebrospinal fluid may be of help in diagnosis Treatment should clearly be excision as early as possible Even when involvement of vital structures makes complete excision of the lining epithelium impossible, the slow rate of growth fully justifies partial removal , but escape of the irritant contents into the C S F is a complication to be avoided if possible

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[6] Lehmann H *Practitioner*, 1957 178 198

[1] Rand, C W Reeves D L *Arch Surg* 1943 46 350
[2] Tytus, J S Pennybacker J *J Neurol Psychiat* 1956 19 241
[3] Russell D S *J Path Bact* 1944 56, 145
[4] Hörstadius S The Neural Crest Oxford 1950 chapter 3.

The analogy between these cysts and those appearing elsewhere in the body has recently been completed by CHOREMIS et al,[5] who demonstrated that implantation dermoids can arise in the spinal canal, and described 6 examples after recovery from tuberculous meningitis CHOREMIS et al justifiably assumed that these cysts arose from squamous epithelium carried into the canal during one of the many spinal punctures involved in the treatment of tuberculous meningitis It is curious that this sequel has not been observed before, for examination of drill biopsies shows how often an ordinary needle carries a little disc of skin in with it CHOREMIS et al used a spinal needle without a stilette, and it may well be that the general use of a stiletted needle for spinal puncture has had the unforeseen but fortunate result of preventing this unpleasant complication

"Doctor"

IF names are important—and they are—the descriptions and titles given to different kinds of doctor in this country should be reconsidered before they become any more chaotic In the first place, is it allowable to use the word "doctor," in this way, to denote members of our own profession, implicitly excluding anyone without a medical qualification? In his article a fortnight ago Dr GEORGE GRAHAM explained how last century the holders of medical licences managed to capture for themselves a title which, in its primary meaning, belonged only to holders of university doctorates Whether or not this act of aggression was justifiable, it has certainly been successful—so successful that the secondary meaning of the word is now dominant, and when people say 'He s a doctor" or "Is there a doctor in the house?' there is no thought in their minds of higher degrees or of any faculty but medicine Of course everybody knows that there are other kinds of doctor—in law, divinity, science, music, philosophy, and so on—but the assumption is that anyone called Doctor is medical unless stated to be otherwise In any medical context or environment there is particular reason to suppose that the title has a medical connotation and this week we publish a letter showing how much difficulty and annoyance can arise, in consequence, where doctors whose degrees are not medical are associated with our profession in their work In this journal, to prevent any misunderstanding, we have long made a practice of referring to non medical doctors on their first mention as "Miss A B Dash, PH D, or "Mr A B Blank, D SC"—after which explanation we naturally accord them their proper title To many this has seemed tiresome and invidious, but it is at least better than the custom by which some hospital nurses and others refuse to call anyone Doctor unless he is on the Medical Register No doubt, as the Medical Act of 1858 says "it is expedient that persons requiring medical aid should be enabled to distinguish qualified from unqualified practitioners', but it is paradoxical, to say the least, that titles which are incontestable because conferred by a university, should thus be set aside in favour of one which is conferred only by courtesy and custom Now that some of the best work in medicine is done by science graduates who do not happen to have a medical qualification, most hospital workers should surely have become accustomed to the presence of more than one kind of doctor in the Greater Medical Profession[1], and politeness if nothing more suggests that doctors of science or philosophy should be addressed in hospital as they would be outside Has not the time come, indeed, when our emphasis could be less on distinctions and more on the common effort?

The next anomaly is that, though our entire profession have acquired a *de facto* right to call themselves Doctor, this title is spurned by many of those who hold it *de jure* as university doctors of medicine If we ask why surgeons should have cherished their lesser title of Mister, and why obstetricians and gynæcologists adopted it, the answer may be that they liked the prestige of difference, or that they loved tradition, or merely that the public were known to associate Misters with rather higher fees These reasons may be respected, or at any rate understood but is it really still necessary or desirable to lay so much stress on the unlikeness of the surgeon to other doctors? Times have changed since WOODALL in 1639 could epitomise the characteristics of the two branches of the profession by saying that "the more learned sort are justly stiled by the title of Physicians, and the more experienced sort are called Chirurgions or Surgeons"[2] Today not only are surgeons learned and physicians experienced, but the former sharp division between their functions is breaking down With physicians using operative techniques, and surgeons practising electrolytic augury, the everyday work of many specialties shows an increasing reintegration of medicine and surgery, and we are already seeing the emergence of neurologists and thoracologists who are professionally ambidextrous—limited, perhaps, by the region or system with which they are concerned, but paying no attention to the limits formerly denoted by "surgical" and "medical" For our part we deplore the persisting separation of surgeons, not only because it discourages a natural evolution in the specialties but also because it is bad for the profession The functional union which was officially achieved in 1858 with the creation of a Medical Register has never been completed except on paper, but it would be brought a stage nearer reality if surgeons and gynæcologists would hearken to the words of Dr GRAHAM, and of Dr LAMBERT ROGERS last week—if they would curb their separatist tendencies, and accept the same honourable title as all the other exponents of our science and art

If specialists in surgery are to be asked to sacrifice, for the general good, their title of Mister, specialists in medicine may equally be asked to abandon their lien on the designation of physician, which ought to be once more at the disposal of any member of the profession In the old days the family doctor put on his plate Physician and Surgeon, and only comparatively recently has the idea arisen that these names are the exclusive property of consultants *who confine* themselves to one or other of the branches If the fellows or members of the Royal Colleges of Physicians react to our suggestion by claiming a *monopoly* we shall remind them of Henry VIII's remarks

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[5] Choremis C Economos D Papadatos C Gargoulas A *Lancet* 1956 ii 437

[1] See *Lancet* 1956 ii 779

[2] See New English Dictionary, vol vii p 807

> “ Forasmuche as the science of phisicke dothe comprehend the knowledge of surgery as a speciall membre and parte of the same, therefore be it enacted that anny of the said company or felawshipp of Phisitions may exercise the said science of Phisick in all and every his membres and partes ” [2]

The practice of surgery, then, does not prevent a person being a physician—a principle indeed inherent in the present constitution of the London college, which since Lord DAWSON’s time has conferred its fellowship on people in almost every department of medicine, including a number who are known elsewhere as surgeons. If “ physician ” could be restored as applicable to anyone with a medical qualification, ‘ family physician,” or even “ general physician,” could take the place of “ general practitioner ”—a term without ancestry or international currency, conceived (we believe) in desperation and a Government office. It could be used, too, in describing any post held by a doctor as such—e g , physician biochemist to St. A’s Hospital, or physician administrator to St. B’s.

Which brings us to a neologism that really does matter—“ medical officer ”. To many people, of course, this seems no more than a harmless synonym for doctor ; but that is either because they are insensitive to its implications or because they are no longer interested in professional freedom. In its military sense, “ officer ” implies a person occupying some position in a chain of command ; and in clinical medicine there should be no chain of command. In administration, “ officer ” means a person holding office under government ; and in this sense it is wholly inapplicable to hospital doctors or general practitioners in the National Health Service, who work under contract with a non-governmental board or committee and are definitely not Civil Servants. As everybody well knows, patients attending a hospital or surgery want the help of a doctor, not of an official ; and it would be salutary to emphasise the correct personal relationship of doctors with their patients by eradicating from medicine all use of the bureaucratic term ‘ officer ”. The professional equivalent is “ physician ” or “ surgeon ” ; and in hospital the present casualty officers and resident medical officers could properly be called casualty house surgeons (or assistant casualty surgeons) *and resident assistant physicians*. In industry there is the same need for the doctor not to let himself be represented as an official ; and, instead of industrial medical officer, he should be called industrial physician. For the M O H and his staff ‘ medical officer ” is partly accurate ; for, besides advising his authority, the M O H is an executive officer, charged with enforcing the law ; but, even so, it is preferable to think of him primarily as physician (or health physician) to his borough or county. Again, in the Civil Service, though technically doctors are officers of the Crown, they exert their influence almost entirely as advisers, and it would be better if SIR JOHN CHARLES were *called chief physician to his* Ministries. Our terminology should be such as to show that, wherever a doctor is working, he is there as a member of his profession ; and, *in* small things as *in* great, we should use the names and words that belong to our profession rather than those that belong to government. Thus for doctors to say (as so many now do) that they are going “ on leave ” is in 1957 no longer excusable as a nostalgic echo of the war. In the N H S at any rate, the doctor is not a subordinate who applies for leave but a physician who takes a holiday or vacation when he is satisfied that his patients’ needs can be temporarily met by someone else. Too many members of our profession have shown themselves readily addictable to bureaucratic language, and this addiction is more perilous than anything that administrators could do to the profession from outside. If doctors continue long enough to think of themselves as no more than medical officers in what so many of them persistently miscall a State service, *that is what they will infallibly become*. For as a man “ thinketh in his heart, so is he ”.

Annotations

TRAINING THE ASSISTANT

IN 1954 the General Medical Services Committee of the British Medical Association appointed a subcommittee to examine the scheme for training assistants in general practice. Their report [1] is a clear endorsement of the scheme, which has fully justified itself and should remain a permanent feature of the National Health Service. The report makes constructive suggestions which would increase the value of the scheme still further, and it proposes that an advisory body be set up. This body would keep the future evolution of the scheme under review, and it would include two members of the council of the College of General Practitioners. This collaboration with the college at the centre might be extended to the periphery, and the selection boards of local medical committees, who interview applicants for appointment as teachers, might well seek the help of the postgraduate education committee of the college faculty.

The trainee assistants scheme could usefully be expanded as more family doctors prove that they can teach others to attain the high standards of work they have themselves achieved. *The selection of teachers* must be strict, but the proposed advisory body would have promising material to develop ; and teachers, potential and actual, would be encouraged to attend courses, such as those offered by the British Postgraduate Medical Federation.

Perhaps the most important line of future development is indicated by the report’s remark that the advantages of the scheme should not necessarily be restricted to those intending to make a permanent career in general practice. Although the present arrangements were devised for general practitioners, a number of registrars take advantage of a year’s training in general practice. A full year’s work with a general practitioner might restore to the future consultant something which he is in danger of losing—the ability to see beyond the limits of an ever narrowing specialty. Some senior hospital appointments are now being filled by doctors whose outlook is entirely confined to hospital medicine, and the help they can give to the family doctor must be restricted because their advice can be framed only in terms of experience gained in institutions. With the help of the Postgraduate Federation, the universities, and the College of General Practitioners, general practitioner teachers may, within *the next few years, be able to offer a year’s training in* breadth to all those on their way up the rungs of the hospital ladder. And it may even be that a trainee assistantship in general practice may become an essential for the higher university and hospital clinical appointments.

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[1] Report of Trainee General Practitioners Subcommittee British Medical Association. Circulated to Executive Councils by the Ministry of Health (E C L 5/57)

CANCER AND ATHEROSCLEROSIS

FROM time to time pathologists have pointed out that patients dying of malignant disease have less atherosclerosis than those who die of other causes. The most obvious superficial explanation of this difference is that those with malignant disease may have lost more weight than the others, and Wilens[1] showed that at necropsy coronary atheroma was less severe in patients who had lost weight than in those who had not. The most evident difference between the two groups lay in the amount of lipoid infiltration, though there was also some difference in the amount of hyaline change and calcification.

Recent work has suggested that the obvious answer may not be the correct one. Elkeles[2] has approached the problem radiologically. Having previously found that patients with cancer of the stomach had much less calcification in their abdominal aortas than patients with gastric ulcer, he has gone on to consider the frequency of aortic calcification in patients with cancer elsewhere. 700 control cases were compared with 416 patients in the same age groups with proven malignant disease, and the amount of calcification was roughly graded by eye. In view of the possible dangers of observer error in such a subjective assessment, it might have been better to use a "blind" method of scrutiny. Nevertheless, the results seem quite clear. Calcification of the aorta was seen in just under 19% of the cancer group and in rather more than 35% of the control group. The difference was greatest in the patients aged 71–80, where 28% of the cancer group showed calcification, compared with 72% in the control group. Elkeles remarks that his results do not support the view that wasting is responsible for the reduced frequency of calcification in patients with cancer, but he gives no direct evidence to support this statement. The most interesting indication that wasting is not the true explanation comes from a comparison of the frequency of calcification in patients whose cancers arose from different primary sites. Calcification was seldom seen when the primary tumour was in the stomach, breast, or prostate, but when the primary site was in the respiratory tract, calcification was as common as it was in the control population. In general, this finding agrees with the results of Creed et al.,[3] who investigated the incidence and severity of aortic atheroma in a series of 1223 necropsies. They themselves examined only 167 of these specimens, the rest were evaluated from post-mortem records. Nevertheless, they felt confident enough to undertake a statistical assessment of the results. They found that patients who had died of bronchial carcinoma had the same degree of atherosclerosis as patients with hypertension, and significantly more than the control population. The severity of atherosclerosis was significantly less in patients who had died of leukæmia or malignant lymphoma. Surprisingly, patients who had lost weight rapidly before death showed more atherosclerosis than patients who had not lost weight, or who had lost weight slowly.

It is hard to draw any definite conclusions from these studies. Though some of the evidence is conflicting and insecure, it is clear that atherosclerosis and malignant disease are related in some peculiar way. It may well be that a better understanding of this relationship will lead to big advances in our knowledge of both types of disease, so that inquiries of this kind are of great importance. Because of the distribution of carcinoma of the stomach between the different blood groups[4] and the familial distribution of hypertension,[5] it is tempting to consider a genetic basis for the relationship, but a great deal of careful work is required before this idea can be seriously entertained. In the circumstances the anomalous position of bronchial carcinoma in relation to atherosclerosis might be attributed to extraneous carcinogens.

PROGRESS IN MICROSCOPY

POSSIBLY no single instrument has done more for medical and biological research than the microscope. After Zernike's development of the phase contrast microscope (a contribution recognised by the award of a Nobel prize in 1953) microscopy went through a stage of remarkable progress. The pace of discovery now seems to be slackening and it is possible to take stock. One way of doing so is to consult a useful series of thirteen articles, originally published in *Research*, which have now been reprinted as a small book.[1]

Electron microscopy, discussed by V E Cosslett, has been transformed by the development of methods for cutting sections of the order of one-fiftieth of a micron in thickness. This has led to such important advances in cell micromorphology that the electron microscope should become part of the routine equipment of every medical school. The chief use of reflecting microscopes, the subject of two contributions by K P Norris and E M F Roe, is in ultraviolet and infra-red microspectroscopy, from which valuable chemical information can often be derived about microscopic objects. Unfortunately the main sources of error in this technique as applied to cytology seem to lie in the nature of the specimen itself rather than in the optical system, and the results are not as accurate quantitatively as was once hoped. Of the many medical applications of fluorescence microscopy, reviewed by J King, the detection of tubercle bacilli is one of the most familiar. A promising technique is that in which proteins conjugated with fluorescent dyes are used to study antigen antibody reactions.[2]

The value of phase contrast microscopy in elucidating the structure of living cells is well known, but R Barer illustrates a less familiar use: it can give a quantitative measure of the refractive index of parts of living cells, and in this way the concentration of solids can be deduced. An application of special interest to pathologists is the measurement of hæmoglobin concentration in single red cells and the study of its distribution among different members of a red cell population. F H Smith describes several types of interference microscope, which give results broadly similar to phase contrast, but they can sometimes be used to measure optical path (i e, the product of refractive index and thickness)—a quantity which can be related to the dry mass per unit area, so that cells can now be "weighed" under the microscope. Refractometry and interferometry are closely related methods which may be expected to yield much useful quantitative cytological information. D Causeley and J Z Young describe the flying spot microscope, and they refer particularly to the counting of cells and particles. A red-cell count can be done in only four seconds, but the degree of consistency is perhaps a little disappointing. X ray microradiography, discussed in this book by W C Nixon, may prove useful in biology, not so much because of its resolving power (which is as yet only comparable to that of an optical microscope), as because it may reveal new types of contrast by displaying the relative opacity of some tissue constituents to X rays, though not necessarily to light. It is also particularly useful for three dimensional stereoscopic views of quite thick specimens. There are still many physical difficulties to be overcome, and long exposures of the order of several minutes are usually needed.

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Microscopy is clearly very much alive and there are many new techniques waiting to be applied more widely in medicine

AUTO-ANTIBODIES IN RHEUMATISM

The hypothesis that rheumatic fever (and possibly other rheumatic diseases) are due to the presence of irregular antibodies to the patient's own tissues has always seemed attractive Cavelti[1] was among the first to claim the discovery of such "auto-antibodies" in the sera of patients with active rheumatic fever he used patients' serum and collodion particles sensitised with human heart antigen to demonstrate positive agglutination tests between the two, but Fischel and Pauli[2] were unable to confirm this work More recently, in Vienna, Steffan and his colleagues[3] have used a "Coombs reagent deviation test" to show that when a suspension of human heart tissue is incubated with serum from patients with active rheumatic endocarditis it absorbs a specific factor (presumably gamma globulin) from the serum A heart-tissue suspension treated in this way can significantly reduce the titre of a Coombs anti-human-globulin serum by absorption Similar "antibodies" reacting with mixed tissue suspensions of muscle, joint capsule, and heart were found in rheumatoid-arthritis sera by the same very indirect methods

Rejholec and Wagner,[4] in Prague, have now returned to the *collodion-particle technique in attempts to demonstrate* auto-antibodies in rheumatic-fever sera They sensitised collodion particles with saline extracts of mixed tissue from the organs of a cadaver—myocardium, heart valves, subcutaneous tissue, and joint capsules, and they noted that such "antigens" were very unstable and that preparations from many cadavers were unsatisfactory The sera of 38 patients with rheumatic fever were tested at various stages in the progress and treatment of the disease, and in each case the collodion-particle agglutination test was positive with at least one (and usually with all) of the "antigens" described, patients with clinical active myocarditis gave the highest titres The serum factor responsible for these reactions (whose specificity was controlled) was extremely unstable in vitro, disappearing within a week unless the sera were kept at −20°C This difficulty, and those inherent in the collodion particle agglutination method, make it unlikely that experiments will be attempted to correlate results obtained by this method and by that of Steffan

How far do such experiments substantiate an auto antibody hypothesis in rheumatic disease? It is doubtful whether the reactions attributed to rheumatic sera in experiments of this kind are really due to specific immunological phenomena The antigens presumed to take part in the reaction are completely uncharacterised, even in the broadest sense, muscle, heart valve, and joint capsule must share most of the body antigens between them It is perhaps useful to compare the present approach to the investigation of auto antibody formation as a cause of disease with that adopted in the probably related field of hypersensitivity The unravelling of the immunological fabric of allergy, while far from complete, owes much to the physical and biochemical characterisation of relevant antigens, which in turn has permitted quantitative and analytical study of serological activity in vivo and in vitro In the study of rheumatism, immunological research sadly lacks a defined antigen or group of antigens If, in fact, antigens do act as immuno logical *determinants of* rheumatism, real progress towards understanding its cause must await their identification

ANÆSTHESIA FOR BURNED CHILDREN

Because of the need for long and specialised treatment, children with severe burns are usually admitted to special units as soon as possible after the accident, and such units have their own anæsthetists But every anæsthetist should know how great the difficulties of anæsthetising a burned child can be, because the occasional case may reach any hospital

At the section of anæsthetics of the Royal Society of Medicine on Feb 1, Dr D W Shannon drew attention to the importance of resuscitation during the first forty eight hours after the child has been injured, when the difficulties to be met were those peculiar to resuscitation in children as well as those of the burns themselves When more than 10% of the skin area was damaged, the child's body could not adjust itself to the train of events set in motion, and unless treatment was begun rapidly and then sustained, deterioration would quickly set in Replacement of fluids and adequate oxygenation of the tissues were the twin essentials of therapy Burned children, Dr Shannon remarked, had a remarkable thirst for oxygen, arising not only from their normal physio logical requirements (which were much greater than those of adults) but from several factors, connected with burns, which were likely to affect respiration The respiratory muscles might be harmed, the air passages were often made œdematous by noxious fumes, spreading inflam matory œdema might press on the trachea, crusted sores in the neighbourhood of the nares often caused obstruction, and unwise dosage of drugs might induce a general depression Moreover, the whole picture was accentuated by oligæmic shock Effective resuscitation, with intravenous fluids and with oxygen, must therefore be supplemented by cutting down tissue needs, and strict curtailment of unnecessary movement and exami nation of the child was an important precaution

At the same meeting Dr H G Middleton emphasised that these children were likely to need many anæsthetics during their treatment, and familiarity with the anæs thetist (preferably in his theatre clothes during his visits between operations) was far better and often more effective than heavy premedication He also referred to the high incidence of other diseases in children who are burned—complications which in normal circumstances would suggest postponement of anæsthesia and operation until they had been treated But for the badly burned child, such complications must be accepted if life was to be saved Indeed, as the result of his analysis of the deaths at the Welsh Regional Burns Centre at Chepstow, Dr Middleton could exclude both anæsthesia and surgery as causes, in fact, he thought that they probably reduced immediate mortality

Unlike those who are being treated for many other emergencies, the "very poor risk" burned patient must be accepted for anæsthesia early if the mortality is to be reduced For the future, if the anæsthetist can keep his young patient alive during operation and immediately afterwards, then excision of full thickness burns, even earlier than is commonly done nowadays, might become the best treatment This would be a hard task, but the results would be even more rewarding than they are now

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Special Articles

CASUAL EXPOSURE OF NURSES TO X RADIATION

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B Sc Lond B Sc Lond, A Inst P
ASSISTANT PHYSICIST PRINCIPAL PHYSICIST

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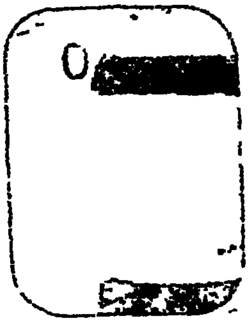
RADIATION-PROTECTION measurements in this hospital are largely carried out by means of film-badges, and those to whom they are issued include the nursing staff of wards where patients undergo treatment with radium and radio isotopes Most of these treatments are carried out in the special isotope ward, but occasionally such a patient may be nursed in one of the ordinary wards It has been noticed for some time that film-badges returned from these wards may show exposure to diagnostic X rays as well as to γ rays



The film badge holder contains two apertures through which radiation reaches the end sections of the film, the centre portion being screened by a filter. As the film is set about 1 mm behind the apertures radiation from different directions will be recorded in slightly different positions on the film We have found that exposure to diagnostic X radiation is usually at oblique angles Further, an X ray exposure, which is received in a short time and consists of low-energy radiation, appears as a clearly defined image, while γ-radiation in contrast appears as a diffuse image The accompanying figure is of a film showing these effects, in which the X-ray and γ-ray exposures can be measured separately, the appropriate calibration factor being used for each, Very few films show exposure to both X-ray and γ ray radiation so that in general X and γ ray exposures are easily estimated separately Table I summarises the information obtained from the film-badges issued in connection with radium and radio-isotope therapy over a period of 2 years

It is clear that if such exposure of nurses is typical of the nursing staff as a whole, the total amount of radiation involved is considerable Accordingly, an eight week test was arranged for two wards nursing surgical and radiotherapy patients The ward sisters knew that the object of the test was to ascertain the amount of diagnostic X radiation received by the nurses The rest of the nursing staff were not informed of the object of the test lest this knowledge should influence the result During the eight week period a scalp treatment with a radium mould was carried out in ward A, and a colloidal radio gold treatment in ward B, for which film badges would have been issued in any case Coöperation was excellent and the results obtained are shown in table II For comparison similar data from other departments over a period of two years are shown in table III

Doses Received

It is clear that the amount of radiation received is substantial, but it is unlikely that the results in table II are typical of the nursing staff as a whole The two wards investigated nurse a substantial number of patients who have undergone major chest surgery, and many of them have chest radiographs taken in the ward repeatedly, although the amount of such work during this particular period of eight weeks was considerably less than average If such an examination is undertaken in the few days following the operation, up to three nurses may be required to hold patient and film, and they are almost bound to be exposed to some of the direct beam of radiation The extent of this is shown by the observation that 5 out of the 137 film-badges recorded more than 300mr in one week That is, on average each nurse in these wards may expect to receive an occupational exposure of more than 300mr not less than 1 week in 28 or at least twice a year Further, the average amount of radiation per nurse-week is about 20mr The International Commission on Radiological Protection (1955) recommends that radiation workers should not receive more than 300mr per week where a substantial fraction of the body is irradiated For large populations (i e, groups of people not subject to the rigorous control specified for radiation workers) exposure should not exceed 30mr per week On the average, this condition is just fulfilled The average dose-rate of 20mr per week, as will be seen from table III, is considerably higher than that received by several groups of radiation workers in the same hospital

TABLE I—ANALYSIS OF 575 FILM-BADGES WORN BY THE NURSING STAFF IN CONNECTION WITH RADIO-ISOTOPE AND RADIUM TREATMENTS, OVER A PERIOD OF TWO YEARS

Ward	No of films issued	% of films showing exposure	Average recorded dose (mr)	Average dose per nurse-week (mr)	Number of nurses at risk
Isotope ward	455				8
X radiation		6 2	44	3	
γ radiation		59	10	6	
Other wards	120				800*
X radiation		13 3	77	10	
γ radiation		33	20	7†	

* Average number of nurses on *all* other wards who could be exposed to X radiation

† Average γ ray exposure per nurse week during radium and radio isotope treatments only

On average, a nurse is unlikely to receive as much as 30mr per week (ward A, table II) or as little as 3mr per

TABLE II—ANALYSIS OF 137 FILM-BADGES WORN BY NURSES ON TWO SURGICAL WARDS DURING AN 8 WEEK TEST WITH COMPARABLE FIGURES FOR THE ISOTOPE WARD FOR THE SAME PERIOD

Ward	% of films showing exposure	Average recorded exposure (mr)	Average dose per nurse week (mr)	Highest individual average* (mr per week)	Highest recorded dose † (mr)	No of times 300mr per week exceeded
Surgical A						
X radiation	33	89	30	220	350	4
γ radiation	4	123	5	45	120	
Total	37		35			
Surgical B						
X radiation	24	35	13	40	320	1
γ radiation	19	18	5	[illegible]	80	
Total	43		18			
Isotope ‡						
X radiation	2	10			10	
γ radiation	71	10	8	10	[illegible]	
Total	73		8			

* Averaged for each nurse over all the dose measurements made on her during the 8 week test

† Highest recorded dose for any single week

‡ Figures taken for the same 8 weeks as for the other two wards

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* Now at the Royal Northern Hospital, Holloway Road, London N 7

† Now at the Marie Curie Hospital London, N W 3

week (isotope ward, table I) The values of 10mr per week (other wards, table I) and 13mr per week (ward B, table II) are more likely to be typical All γ radiation received by the nursing staff from radio isotope therapy is accounted for, and over the whole group of 800 nurses amounts to an average of only 0 1mr per week The X radiation amounts to about 10mr per week, and both these figures must be compared with the natural radiation level of about 2mr per week (Spiers 1956) No doubt the amount of X radiation could be considerably reduced by accurate coning, but this is of necessity much more difficult in ward radiography than it is in the X-ray department itself The extensive use of clamps and mechanical aids would reduce the need for the holding of patients and films by hand

TABLE III—ANALYSIS OF 6160 FILM BADGE RECORDS OVER A PERIOD OF 2 YEARS

Department	Average dose (mr per week)	Highest weekly average* (mr per week)	Highest dose in any one week (mr)	% of films recording at least 300 mr	Approximate no of measurements	Approximate no of staff
Isotope ward	9	30	80		460	8
Radiotherapy	10	30	800	0 1	800	14
Isotope laboratory	10	35	250		850	6
Physics	40	185	540	1 5	800	6
X ray						
Radiologists	10	100	800	2 5	950	12
Radiographers	120	400	800	7 5	1300	16
Student radiographers	40	140	440	0 5	1000	11
	Mean 50			Mean 2 5	Total 6160	Total 76

* Averaged over 13 consecutive weeks

Deliberate Exposure

There is bound to remain the occasional case where a nurse must hold the patient or film If, in such a case, radiological examination is essential, the nurse should be provided with a lead rubber apron and lead rubber gloves There is no more valid reason for exposing a nurse to a primary beam than there is for a radiographer

It has for long been the custom, in both diagnostic and therapeutic radiology, for the radiographer to ask relatives or ward nurses to hold a patient in the beam of radiation, where this is essential This practice is clearly preferable to repeated exposures of the radiographic staff to the primary beam It is presumably based on the assumption that exposure of the nurse or relative will be a relatively infrequent occurrence and the effects negligible In view of recent evidence on radiation exposure levels in this country (Medical Research Council 1956), particularly the increasing number of diagnostic X ray examinations (Osborn and Smith 1956) and the induction of leukæmia by radiation (Court Brown and Doll 1956), this practice may need to be modified

We wish to record our thanks to Miss H M Downton, matron of University College Hospital, for her help in this work, and to Miss D W Cook and Miss J G Price, ward sisters, for their active collaboration Miss I Bull, M S R, gave invaluable help in the film badge measurements

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JOINT CONSULTANTS COMMITTEE

A MEETING of this committee was held in London on Jan 23, with Sir Russell Brain in the chair

Medical Membership of Hospital Boards

Among the matters under consideration was a circular issued by the Ministry of Health on Dec 31 informing hospital boards that the Minister had accepted the recommendation of the Guillebaud Committee that the medical membership of regional hospital boards should not exceed 25% of the total membership save in quite exceptional circumstances, and advising boards to observe the same principle in making appointments to hospital management committees The Joint Committee had previously urged the Ministry that the membership of a regional board should include at least 5 consultants actively engaged in the region concerned, and in addition a general practitioner and a medical officer of health, all nominated by the profession In a letter from the Ministry informing the committee of the Minister's decision it was stated that the Minister could not accept this proposal, but that he fully shared the committee's view that the medical members of the regional boards should consist primarily of active members of the consultant staff in the region, together with a general practitioner and a medical officer of health

The Joint Committee was profoundly disturbed at the Minister's decision, the more so as it appeared inconsistent with his acceptance of the principle that the medical membership should consist primarily of active members of the consultant staff in the region, who are by no means well represented on regional boards at the present time The committee thought it inevitable that the small number of consultants representative of those working in the regions must be still further reduced if the over-all number of medical members was to be reduced, while still including representatives of the universities and medical schools, and in addition a general practitioner and a medical officer of health

The committee felt strongly that any reduction in the medical membership of hospital boards would, of necessity, effect adversely the valuable part played by the profession in the administration and planning of the service, and that to place upon a smaller number of doctors the responsibility of serving on the boards and their various committees would make the burden intolerable

The committee decided, therefore, to ask the Ministry for an early opportunity of discussing the matter further It decided also to discuss with the Ministry again the question of medical advisory machinery at regional board level, in the light of the recommendations of the Guillebaud Committee, while making it clear that it did not regard such machinery in any way as an alternative to adequate representation on regional boards

Hospital Medical Staffs

Representatives from the registrars group of the British Medical Association attended the meeting to put before the Joint Committee their views regarding the problems associated with hospital medical staffing as they affected the prospects of registrars and senior registrars They pointed out that the salary scales recommended by the Spens Committee had been formulated on the assumption that consultant status would normally be reached at 32 years of age At the present time, however, senior registrars in the main specialties did not usually obtain their first consultant appointment until several years later than this, with a consequent loss in their total life earnings of £1700 for every year promotion was delayed beyond the age of 32 They urged that the introduction of a new career grade below consultant status would not provide a satisfactory solution of the problem since it would permanently lower the total life earnings of a proportion of new entrants into the hospital service They recommended that there should be a gradual run-down in the number of senior registrars which would ensure reasonable prospects of promotion after an average training period of four years Pending such a balance being obtained, and as a purely temporary expedient, they suggested that the tenure and salary scale of time-expired senior registrars should be extended, and newly appointed consultants given seniority on the incremental scale for every year over 32 at the time of appointment

Appointments in Venereology

A deputation from the venereologists group committee also attended the meeting to discuss with the committee the difficulties experienced in the staffing of venereal-diseases departments in areas where there is insufficient work to make a consultant appointment in the specialty practicable

Moral Obligation

The committee agreed to a proposal from the Ministry that the Appointment of Specialists Regulations should be amended to allow a consultant or senior hospital medical officer whose sessions are reduced, or whose contract is terminated through redundancy, to be offered an alternative appointment without the necessity to apply for the vacancy in open competition

Hospital Private Beds

The question of the steadily rising charges for hospital private beds was discussed and the committee decided to prepare a case for the introduction of a moderately priced private bed Reference was also made to the many anomalies in the schedules of operations contained in the Pay Bed Regulations, and instances were quoted of the way in which these schedules operated to the disadvantage of the patient rather than to his advantage It was agreed to submit a reasoned case to the Ministry for the abolition of the schedules

Other Matters

Among other matters discussed were the shortage of radiographers and physiotherapists, domiciliary consultations by pathologists the attendance of chairmen of hospital group medical advisory committees at meetings of hospital management committees, and the payment of fees for the examination of prospective employees at the request of employers

N H S SUPPLEMENTARY ESTIMATE

ACCORDING to the Supplementary Estimates,[1] published last week, a further £26,872,700 will be needed for the National Health Service in Britain in the present financial year This brings the net total cost to £529,014,830 An additional £15,008,000 is needed by hospital authorities, mainly to cover increases in remuneration, prices, and rates For the pharmaceutical services an additional £8,089,000 is needed, despite the change in charges (from Dec 1 last) from 1*s* per form to 1*s* per prescription The estimated total of payments to general medical practitioners is increased by £2,946,000, and that of payments to general dental practitioners by £1,635,000

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[1] 1956–57 Supplementary Estimate Civil Estimates and Estimates for Revenue Departments H M Stationery Office Pp 223 8*s* 6*d*

Public Health

MORTALITY A CHANGING PATTERN

J A FARRER

M B Melb

RECLINING peacefully in many a village church are records which go back many years before the introduction of our more up to date registration statistics

When we speak in terms of advancement in ways of living, with what are we comparing the present day? In fact what, in our present day, are we to compare? Are we to compare recent statistics with past impressions, or do we put our impressions into statistics and compare them with the impressions of the great novelists?

Because of the high proportion of intangibles, there are many difficulties in the way of anyone wishing to project the past on to the present However, from the following, relatively small exercise, I wish to draw attention to possibilities which others, more skilled than I and with access to more extensive records than I, may care to follow up

The material consists of the record of burials performed in a very rural Dales village[1] At first sight the books, with their parchment pages, appear only relevant to those wishing to seek information on the whereabouts of their ancestors But, from the year 1804, the ages at death have been inserted and it is from that time that my tables have been constructed

The first nine years' recording is somewhat more interesting in that the diagnosis has been inserted

Tables I–III show the number of deaths in each age-group the percentage which this number represents of the total deaths in this period, the actual numbers of male and female deaths, and the ratio of male to female deaths Table IV shows the deaths in 1953 in the whole

TABLE I—DEATHS IN CLAPHAM CUM NEWBY (1804–12)

Age group	Total	% of total	Males	Females	Ratio males	Ratio females
0–5	66	20 2	35	31	53	47
5–10	12	3 7	4	8	33 3	66 7
10–20	30	9 2	15	15	50	50
20–30	23	7 1	9	14	39 1	60 9
30–40	24	7 3	10	14	41 6	58 4
40–50	23	7 1	12	11	52	48
50–60	20	6 1	9	11	45	55
60–70	30	9 2	19	11	63 4	36 6
70–80	52	15 9	24	28	46	54
80–90	39	11 9	17	22	43 6	56 4
90–100	8	2 4	6	2	75	25
	327					

TABLE II—DEATHS IN CLAPHAM CUM-NEWBY (1813–37)

Age group	Total	% of total	Males	Females	Ratio males	Ratio females
0–5	153	17 1	82	71	53 6	46 6
5–10	27	3 0	10	17	37	63
10–20	72	8 5	29	43	40 3	59 7
20–30	79	8 8	43	35	54 5	45 5
30–40	60	6 7	35	25	58 4	41 6
40–50	48	5 3	17	31	35 4	64 6
50–60	78	8 7	32	46	41	59
60–70	106	11 9	45	61	42 4	57 6
70–80	157	17 5	77	80	49 1	50 9
80–90	104	11 6	49	55	47 1	52 9
90–100	10	1 1	5	5	50	50
	894					

TABLE III—DEATHS IN CLAPHAM CUM NEWBY (1837–65)

Age group	Total	% of total	Males	Females	Ratio males	Ratio females
0–5	190	21 3	102	88	53 7	46 3
5–10	37	4 2	22	15	59 4	40 6
10–20	69	7 7	33	36	47 9	52 1
20–30	82	9 2	38	44	46 4	53 6
30–40	55	6 2	23	32	41 8	58 2
40–50	51	5 8	19	32	37 3	62 7
50–60	61	6 9	28	33	45 9	54 1
60–70	106	12 0	49	57	46 2	53 8
70–80	148	16 6	78	70	52 6	47 4
80–90	81	9 3	38	43	46 9	53 1
90–100	7	0 8	6	1	85 7	14 3
	887					

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[1] Church Records Clapham-cum Newby Parish Church 1804–63

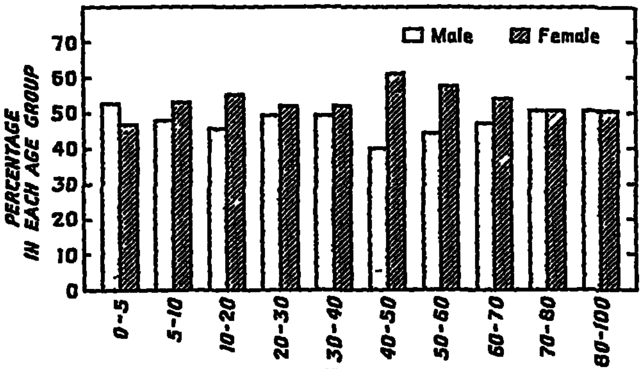

Fig 1—Ratio of male to female deaths in Clapham-cum Newby (1804-1865)

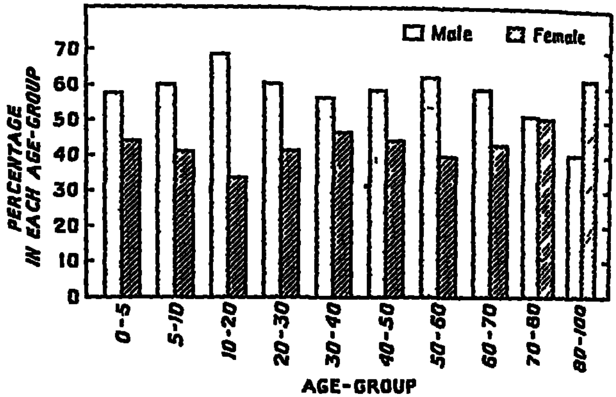

Fig 2—Ratio of male to female deaths in England and Wales (1953)

country,[2] From the totals in tables I–III, fig 1 was constructed This shows

1 In most age groups, female deaths predominate, the exceptions being a reversal in the first age group and equality in the last two

2 The only considerable sex difference is in the age groups 40–50

3 The sex difference in the age groups 20–40 is comparable with the total sex difference (48 4 male to 51 6 female)

TABLE IV—DEATHS IN ENGLAND AND WALES (1953)

Age group	Total	% of total	Males	Females	Ratio males	Ratio females
0–5	21,528	4 21	12 244	9284	56 7	43 3
5–10	1763	0 33	1043	720	59 2	40 8
10–20	2899	0 575	1769	1130	61 0	39 0
20–30	5967	1 18	3572	2395	59 8	40 2
30–40	10 132	2 01	5517	4615	55 5	45 5
40–50	24 738	4 9	14,120	10,618	57 4	43 1
50–60	54 994	10 9	33,711	21 283	61 2	38 8
60–70	105 160	20 9	61,094	44 066	58	42
70–80	159 165	31 5	79,806	79 359	50 2	49 8
80–100	117,183	23 2	46,614	70 569	39 7	60 3
	503,529					

Table IV, as prepared for 1953, has been represented in fig 2 The first item of note is, of course, a reversal of the proportion of male to female deaths Secondly, the whole pattern of ratios has changed

Lastly the tables have all been combined to show the changing pattern in another aspect (fig 3) This figure is based on the third column of the tables I, II, and III are reduced to a single set of figures represented by the white portions, and table IV is represented by the black portions

This bears out the general impression that mortality during the earlier years, particularly the first year of life, has been reduced

Discussion

When I began to examine these records I had very little idea whether anything of interest could be obtained But by the time the first three tables had been prepared, it became evident that, in spite of the relatively small numbers, there was a consistency in percentages (third column) over the years taken This consistency is also present, though not so exact, in the final column (ratio of males to females)

This pattern, I felt, could best be expressed in comparison with the present day figures shown in fig 3 but needed a rearrangement of the numbers for 1953 to make the scale comparable

When these had been completed, the next point meriting attention was the recording of the years 1804–12—the only years for which a diagnosis of the cause of death was recorded When the record had been prepared, it was evident that, though it was extremely interesting, no actual conclusions could be drawn

I had always thought that the rigours of childbirth had contributed largely to the mortality of the early 19th century yet in this series of some 327 deaths, only 2 were directly attributed to childbirth We must, of course, be careful in drawing general conclusions because medical knowledge has increased, but the records of births

TABLE V—CAUSES OF MORTALITY IN CLAPHAM CUM-NEWBY (1804–12)

Age group	0–5	5–10	10–20	20–30	30–40	40–50	50–60	60–70	70–80	80–90	90–100
Stone, gravel							1		2		
Consumption asthma	2	1	16	13	13	8	5	7	1		
Infirmity	1							17	38	36	9
Sudden death			1	1	1	1	2	2	1		
Chincough	4										
Dropsy					1	2	3	4	3		
Convulsions	20						1				
Fever in brain			1		1						
Accidental death	1	2	1		1	2	1		1		
Weakness	28		1					1			
Fever	2	2	4	4	2	2					
Inflammation of bowels and cramp in stomach	1	2		1	1	3	1		1		
Childbirth				1		1					
Smallpox	2	5	4								
Palsy						1			1		
Pleurisy									1		
Cancer						2					
Rheumatism							3				
Inflammation of throat	2								1		
Joint disease			1	1	1						
Epileptic fit			1								
Ague				1							
St Anthony's fire					1						
Broken leg									1		
Gangrene										1	

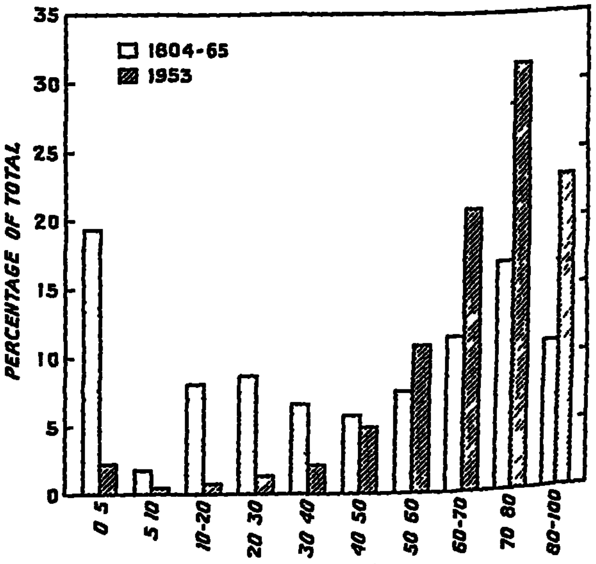

Fig 3—Ratio of deaths in Clapham cum Newby (1804-1865) to deaths in England and Wales (1953)

confirm that the small number of deaths in childbirth may well be accurate

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[2] The Registrar General's Statistical Review of England and Wales for the year 1953 Part I—Medical H M Stationery Office 1954 Table 16

Figs 1 and 2 show the pattern of male and female deaths for the period 1804–65, as compared with 1953 There is an alteration in the pattern which is hard to explain Part is, of course, accounted for by the fact that we are living in an era of more male births, in Clapham as in the rest of the country

Perhaps others may care to comment, or search

My thanks are due to the Rev C T Foster for permission to examine the records

Before Our Time

Thomas Lawrence

AT a meeting of the Osler Club held at the Royal College of Physicians on Jan 24, with Dr W S C Copeman, president of the club, in the chair, an address on Dr Thomas Lawrence was given by Sir Russell Brain, P R C P

Lawrence, he said, was born in 1711 into a family which played some part in national affairs from the middle of the 16th to the beginning of the 19th century His grandfather was physician to Queen Anne, and his father a captain in the Royal Navy Thomas Lawrence went to Trinity College, Oxford, decided to take up medicine, and became a student at St Thomas's Hospital and a pupil of Dr Nicholls, the popular lecturer in anatomy, whom he succeeded in that position at Oxford He also lectured in anatomy in London until he was displaced by the popularity of Hunter He then devoted himself to practice, and occupied numerous positions at the Royal College of Physicians, being elected president in 1767

The college library contains a number of Lawrence's works, both Latin and English Perhaps the most interesting is the *De Natura Animali* to which has been attached the manuscripts of Dr Johnson's corrections of Lawrence's Latin Lawrence's knowledge of anatomy is illustrated by his lectures, and his philosophical outlook by his discussions on the relation between the mind and the body

His election as president took place during the turmoil of the famous siege of Warwick Lane, when the Society of Collegiate Physicians, in protest against the tradition that only graduates of Oxford and Cambridge could become fellows of the College, broke in by force and attempted to take their places in comitia

Lawrence is known to us chiefly because of his friendship with Johnson, whose medical attendant he was Both Johnson's letters and Mrs Thrale's writings contain numerous references to him Both men were in failing health when Mrs Thrale accompanied Johnson to consult Lawrence who had that morning had a slight stroke She gives a graphic account of the interview Lawrence, who had suffered from angina as well as repeated slight strokes, retired from practice to Canterbury in 1782, and died there in the following year He was buried in the church of St Margaret, and a memorial tablet, with a portrait in relief, was placed in Canterbury Cathedral by his surviving children

Seeing Lawrence through the eyes of his contemporaries, we can construct a fairly complete picture of his personality He was a gentle, scholarly man whose hobbies were building model boats and playing the cello "In his endeavours to attain to eminence," writes Hawkins, "it was his misfortune to fail he was above those arts by which popularity is acquired and had besides some personal defects and habits which stood in his way a vacuity of countenance very unfavourable to an opinion of his learning or sagacity, and certain convulsive movements of the head and features that gave pain to the beholders and drew off attention to all that he said "

This address will appear in *Medical History* (see p 381)

The Widdicombe File

XXXVIII CURRICULOSIS

DEAR JAMES,

MY fraternal greetings I write to you however not as a brother but as, since your last Widdicombe, an accepted authority on the curriculum The G M C is thinking of relaxing its dead and iron hand and the Royal College of Physicians has set up its conference on medical education I hope they have had the sense to include you

The old war cries will soon be filling the air again—integration, correlation, the holistic approach, the basic validity of the doctor-patient confrontation and so on and so on Like you, I sniff the battle from afar and long to be doing, but, compared to you, I may not be quite so well pleased to have my piece listened to I began to compose you a memorandum, on such delectable topics as the need to retain the sixth year, and the introduction of a sixth year multiple option honours course for those who can complete the ordinary course in five years, and the black heresy of those who regard morbid anatomy as a dead subject But I became a little discouraged after a while all these things had been said before, and anyhow what did it matter? How much does the curriculum affect what we teach and what the student learns? I begin to believe that it matters a good deal less than the disputants pretend

Don't get me too far wrong Anyone who puts forward the current curriculum of any British medical school as an ideal which couldn't be improved is an idiot But I want to put forward some arguments, which are, I think, at least in part a poor thing, an ill favoured thing, Sir, but mine own, for the view that the curriculum has far less influence on the final content of the student's head (which is after all what matters) than we generally assume And the gist of the argument is simply this that this final content of the student's head reflects most closely not what his teachers taught him of their own subjects, but what they taught him of every subject but their own

Let me take your own subject of bacteriology We and you and most schools take a middle-of-the road view we teach a middling amount of bacteriology near the middle of the course But if we were radically minded we could find arguments for putting bacteriology anywhere in the course from preregistration to final year You could I am sure find excellent grounds for supporting a proposal to devote a full year of the medical course exclusively to microbiology I could on the other hand find excellent grounds (the proper study of mankind is man) for excluding it, as a separate discipline, from the course altogether I don't want to consider these arguments what I want to suggest is that, whether you taught bacteriology for three solid terms in the second year or I confined you to three optional lectures on epidemiology in the final year, the end result would not be so very different

You teach your bacteriology—and remember again that I'm taking this subject only as an example—to your students, James, in three principal ways There's the direct, the lectures you give yourself There's the deputy direct, by which I mean the lectures and practical classes and seminars given by your deputies, the junior members of your own department And there's the indirect the bacteriology that reaches them through those of their teachers who are not bacteriologists

It's not difficult to show that the second is more important than the first Partly it's quantitative: unless you're grossly understaffed your students will see far more of your juniors, and in far smaller groups, than they do of you no matter how much more practised and eloquent a teacher you are you are unlikely to overcome the sheer weight of numbers But there's a more subtle factor Your efficiency and your stature make what you say, however you strive against it, an Olympian utterance—something that must be true, something to be memorised rather than thought about Your rawest demonstrator is to the student someone human who can be wrong, who can be challenged and questioned The material he presents is only half digested and the very effort the student makes to digest it himself, though it wastes most of it, means that some will stick and stick for ever And so it comes about, James, that what you teach that same raw demonstrator is far more important than what you teach your students yourself

The importance of the third kind of teaching is perhaps not so evident But it works out I think something like this What you or even the youngest of your assistants teaches has always about it, however hard you try to get away from it, a faint aura of professionalism and laboratory unreality This isn't what proper doctors *think, this is just what bacteriologists think* It's to be swotted up for 3rd M B, then forgotten as soon as possible What is remembered, and remembered long after 3rd M B and Final as well, is the odd occasion on the ward when the report from the lab is awaited anxiously, when the textbook mumbo jumbo of *B thingumibobbii* and rising titres and falling sensitivities proves to mean something in terms of handling the patient, and when the clinician turns out to understand more than a little of what it is all about *That* part of bacteriology seems at once significant, something to *hold on to* And the same thing applies to other subjects Certainly to pathology—it's not what I teach them but what the surgeons and physicians and anatomists and bacteriologists teach them that sticks best Even among the clinicians it applies the smatterings of surgery retained by the physicians and of physician's medicine by the surgeons, the cardiology of the urologist and the neurology of the obstetrician, these irreducible minima of knowledge that seem to the student to be possessed by all his teachers, it is these that—rightly enough when you come to think of it—he regards as the irreducible *minima of* what he *must* learn himself If Sir Daniel Whiddon knows about the Nagler reaction, it must be important if not, who is the student to set himself up as better than Sir Daniel? And, *per contra*, if you or I don't know the difference between a Billroth I and a Billroth II, why should he worry about it?

There is a corpus of knowledge in every medical school, a highest common factor in the knowledge of all its teachers, that is by far the biggest single factor in forming and in stocking the minds of the students we produce It is repeated to him again and again under different disguises by different teachers (the Bellmen crying "what we tell you three times is true") and cannot but sink in *It is a prime responsibility* of every member of the staff to see that this corpus is kept alive and true and reasonably up to date To contribute effectively to this corpus you need three things you must have knowledge to contribute, you must have contact with the rest of the staff, and you must be successful as a practitioner of your own particular trade

The last is important The doctrines of the surgeon or physician whose patients do not get well, of the pathologist or radiologist whose diagnoses need too frequent revision, are always suspect It is in this that one of the chief dangers of the "pure" research worker in charge of a department lies His colleagues, unable to judge him by the pragmatic test of the success of his *ideas in practice, are slow in learning to trust him* as a source of information If he's outstandingly good of course, bridges will in time be built But in general a department devoted to pure research is almost as dead a loss to its medical school as one that does none at all (I think this even applies to the preclinical departments, which ought *somehow* to be brought into the hospital, but that is another story)

The value of clinicopathological conferences and the like lies chiefly in their hot-house forcing of this corporate knowledge in the staff of the school A student audience is only an excuse for a C P C it's the staff (on both sides) who are really educated

In this respect a medical school mirrors on a smaller scale the university of which it is a part You can have a university with no students, but you cannot have a university with less than three faculties The interchange of ideas between different disciplines is infinitely more important to the idea of a university than extremes of accomplishment in any one of them Moreover, though any cram college can teach students after a fashion, only a university can teach teachers It is a self-propagating enzyme system (that is the reason for its immortality) the proper nurture of its brighter entrants to take the place of their teachers is its one altogether inescapable function The teaching of the rest of the students is merely a valuable by-product They come to warm themselves at a fire they will never feed

As the head of a university department you have five main duties (I leave out administration, for that is only a means to the other ends) The first and chief is to be a good bacteriologist yourself The second is to teach your staff to be good bacteriologists in their turn The third is to communicate a distillate of your knowledge to your colleagues in other departments The fourth is to join in the education of whatever students come before you, adapting your instruction to the stage of their progress through the curriculum (remembering that, if there's anything in *what* I've *just said, it's* the interlarded fragments of pathology and pædiatrics and plumbing that they will remember best) The fifth and last and leastest, is to arrange the base details of that curriculum

The reorganiser of the curriculum is like a time and motion engineer in a watch factory he can save time, and produce a cheaper watch, but he cannot produce a better watch A reorganised curriculum may save time and energy, but it will not alter what is in the teachers' heads and it is what flows out of the full head of the teacher into the empty head of the student that matters, not the channels we contrive for the flow

You may say that in one respect the curriculum may circumvent this, if it cannot affect the contents of the head of the individual teacher, it can decide which teachers are to do the teaching It's partly true of course by adding or subtracting subjects we add or subtract teachers But even that is not as decisive as it sounds

Consider an extreme example we've already cited If you captured a whole year of the course for bacteriology, *you'd get wonderful results in 3rd M B*, but six months *later* you'd find it nine-tenths *forgotten* (just as now you can watch recent victors of 2nd M B visibly stripping themselves of superfluous anatomy till they arrive at the level their teachers of the clinical years seem to find adequate) But if, on the other hand, you were not allowed to teach any bacteriology, teachers of other subjects would find they had to introduce it into their own courses (As once at school, our maths being behind hand, our chemistry master taught us logs and our physics master nearly got us as far as calculus) Except for a few enthusiasts the first method would give you, the end results wouldn't be as grossly divergent as you might suppose Bacteriology is a necessary part of medicine, in that respect it arranges for its own teaching

It is much the same with new subjects If they are good and live and genuine they edge their way in willy-nilly Students listen avidly, teachers find it profitable to display their erudition on something outside their usual sphere The best registrars suddenly start side stepping into the novelty, and in self-defence the school has to appoint someone to its staff to take care of it It is being taught as much as it deserves usually long before the curriculum has even noticed it exists

Good luck to your discussion, James, I'm sure the grand debate will be the better of your contribution But don't waste too much time on it Remember only, as the Inquisitor nearly said, that bacteriology comes first

Yours,
PETER DAVEY

Parliament

Capital Punishment

ON Feb 1 the debate on the first private member's Bill of the day—a measure for the control of hire-purchase advertisements—lasted for five hours As a result of this exhaustive discussion the private member's Bill to abolish hanging lost its slender chance of survival On Feb 6 the third reading of the Government's Homicide Bill, which restricts but retains the use of capital punishment, was carried by 217 votes to 131, and sent to the House of Lords

In introducing the third reading Mr R A BUTLER, in his first speech as Home Secretary, said that the new defence provided in clause 2 would enable the courts to take account of the great strides that had been made in the understanding of the human mind, and to avoid treating as murder killings for which the accused ought not to be held wholly responsible This was part of the new approach to the problems of the mind which he thought would exercise both the Home Office and the House in the coming months and years He believed that the unexplored territory of the mind would be perhaps one of the most exciting of the adventures before the human intellect in the years to come, and as important in our relationships in the human sphere as nuclear development in the scientific He hoped that he might have the support of the House in any further moves in this direction in the humanising and understanding of relationships, whether in crime or in the other spheres for which he was responsible

In the course of the debate Dr REGINALD BENNETT returned to this clause about which he confessed he felt uneasy The new code on diminished responsibility seemed to him in conflict with the McNaughten rules yet the rules had not been abolished He feared that the courts in future would be baffled which of these mechanisms was to be invoked in murder trials If there was a prima-facie abnormality of mind did a charge of murder still stand? Or, if it was evident from unopposed medical evidence before a trial came to pass that the prisoner's mental condition was in other ways deranged, did the indictment drop to that of manslaughter? If there was a charge of murder, must the outcome of the charge be either that the prisoner was unfit to plead on arraignment —that he was guilty or not guilty or that he was guilty but insane—or was there the further alternative, when the charge was murder that he was guilty of manslaughter? Or did he really go for trial on a charge of manslaughter to which he could be guilty or not guilty?

An even greater difficulty, Dr Bennett suggested, was to decide on what basis and to what degree there was irresponsibility The provision in clause 2, was whether the accused

> " was suffering from such abnormality of mind (whether arising from a condition of arrested or retarded development of mind or any inherent causes or induced by disease or injury) as substantially impaired his mental responsibility for his acts and omissions "

Against that we had the McNaughten rules, which asked whether the accused was suffering at the time from such a defect of mind as to be unable to appreciate the nature of his act or the fact that it was wrong Which of these two standards came first? Did one supersede the other? Might it be assumed that in future in cases of homicide there would be no consideration of the McNaughten rules? The point was important because if the McNaughten rules applied, a man found to be suffering from a defect of reason would go to Broadmoor which was automatically an indefinite sentence If, however, his defect of mind was found to be one which justified a sentence for manslaughter, there would be no consideration of any treatment for his mental state except such as is incidental to an ordinary term of imprisonment

In winding up the debate Mr J E S SIMON, the joint under-secretary of State for the Home Office, said that the Bill provided a criterion which took cognisance of the fact that there were, humanly speaking, many degrees of mental responsibility for crime Till now the only legal criterion of mental responsibility for crime was provided by the McNaughten rules, and unless that rigorous test was satisfied, the death sentence was passed The Home Secretary, in deciding whether to recommend that the sentence should stand, applied a different test and one not prescribed by the law The Bill went far to reconcile that divergence

Turning to Dr Bennett's question as to the relationship between the two defences, Mr Simon said that the accused man might, on the face of it, be unfit to plead That was generally a matter which was initially determined by the prosecution, though it might be raised by the defence, and a jury was then empanelled to decide whether the man was fit or unfit to plead It was only if the man was fit to plead that any question of these defences arose, and then it was a matter for the man The prosecution could not raise any question at that stage as to his mental responsibility for the crime It was for him to say whether he would raise a defence which would lead to a verdict of "Guilty but insane" or whether he would raise the sort of defence which would lead to a verdict of manslaughter by raising a question of diminished responsibility The one was under the McNaughten rules It was a complete defence and the verdict was guilty but insane, which was equivalent to not guilty The diminished responsibility defence would lead to a verdict of guilty but guilty of manslaughter For this the sentence was not necessarily a fixed term It was a matter for the judge's discretion, on the evidence that was then given to him after the verdict, as to whether he passed a sentence for life if he could not determine the time necessary successfully to treat the prisoner He could sentence the convicted man to a term of years Equally he could, if he wished, put him on probation for the crime of manslaughter, and he could make a condition of the probation in a proper case that the man should submit himself to psychiatric treatment, or, indeed, any other medical treatment for a suitable time

Domiciliary Services for Old People

On Feb 6, under the ten-minute rule, Mr FRANK MCLEAVY introduced a Bill to amend section 31 of the National Assistance Act, 1948, so as to empower local authorities to provide meals and domiciliary and other facilities for old people

QUESTION TIME

Supplementary Estimate

Mr ARTHUR BLENKINSOP asked the Minister of Health how much of the Supplementary Estimate for the National Health Service was due to an increase in the number of medical and other staff of our hospitals —Mr DENNIS VOSPER replied None Provision for staff increases was made in the original estimate *With* insignificant exceptions, the extra expenditure on hospital running costs provided for in the Supplementary Estimate is in respect of increases in pay, prices and rates

Number of Prescriptions

Mrs L Jeger asked the Minister the number of prescriptions dispensed during the first month of the new charges, and the number for the corresponding period last year —Mr Vosper replied *An accurate figure is not yet available* From a representative sample it is estimated that the number dispensed in England and Wales during December, 1956, was of the order of 15 5 million The total number in December, 1955, was 19,349,115

Dental Hygienists

Mr Barnett Janner asked the Minister, as representing the Lord President of the Council, whether he would make a statement on the availability of dental hygienists for the general public in accordance with the provisions of the Dentists Act, 1956

Mr Vosper replied Some dental hygienists are already employed in the local authority and hospital dental services, but they cannot work with dentists in private practice until permitted by regulations made under the Dentists Act, 1956, by the General Dental Council The General Dental Council has asked the Privy Council to approve draft regulations which provide that dental hygienists shall not be allowed to work in private practice until such time as the requirements of the local authority and hospital dental services are, in the opinion of the General Dental Council, satisfied This limitation would not appear to accord with the intentions of Parliament as expressed during the passage of the Bill and the proposals have therefore been referred back to the General Dental Council for further consideration

Fees for Poliomyelitis Vaccination

Mr Moss Turner Samuels asked the Minister of Health whether, in view of the fact that the remuneration of general practitioners for the carrying out of the responsible duties and complicated arrangements required to collect, store, and administer the vaccine and keep the necessary records in connection with inoculation against poliomyelitis was unreasonably low, he would increase the present inclusive fee of 5*s* for the two inoculations required in each case to a more reasonable figure —Mr Vosper replied The vaccination will be performed as part of the general practitioner's comprehensive medical care of his patients for which he receives remuneration from his local executive council, the additional 5*s* fee is to be paid by the local health authority for the record of vaccination This is the present fee for records of other forms of immunisation and was agreed between representatives of local authorities and of the medical profession

Overseas Dental Students

Mrs Hill asked the Minister of Health how many students at present in British dental schools are from the Commonwealth and how many from foreign countries, and how many he estimates will practise in this country after qualifying —Mr Vosper replied The numbers from Commonwealth and foreign countries in English dental schools are 109 and 113, respectively I cannot estimate how many will practise in this country after qualifying

Senior Medical Inspector of Factories

Sir Leslie Plummer asked the Minister of Labour if he would now improve the grading of the post of H M Senior Medical Inspector of Factories, to reflect more accurately the importance attached to industrial health organisations and equated with the grading of the chief medical officer of the Ministry of Pensions and National Insurance and of the Colonial Office as well as with the Treasury medical adviser —Mr Iain Macleod replied *No* The present grading of the post of H M Senior Medical Inspector of Factories is based upon the recommendations of the Howitt Committee which reported in 1951 The salary has been adjusted in accordance with the recommendations of the Royal Commission on the Civil Service

Occupation Centres for Mentally Handicapped

At the end of 1955, 12,372 mentally handicapped people were attending occupation centres and 7877 others, mostly adult, were reported by local authorities to be suitable to attend when places could be provided At the end of 1956 there were 301 centres in full time and 69 in part time use Schemes for 41 full time centres have been approved and these may be expected to be working in the course of the next two years Proposals for 33 others are being considered

In England Now

A Running Commentary by Peripatetic Correspondent

You might think that transplanting a couple of gooseberry bushes a simple operation ? Not in our garden I was poised with my fork when the dustmen arrived and amongst them my old patient Tom Hoggart

" Are t' movin' goosegogs, doctor ? "

"-Yes, into the orchard, Tom "

" Thou'lt send 'em to their grave "

" Eh ? "

" Th' acid in t'ground They might show first year, small an' 'ard Followin' year they'll wither down Th' acid 'l draw 'em down to t'root ends "

At that moment my wife came rushing out of the house her hands and arms white with flour

" You're not moving the gooseberry bushes are you ?

" Why not ? "

" Every time anything looks as though it's going to take a hold in this garden you decide to move it Even weeds can't grow here, they haven't time "

" Relax, honey-child In three years these two bushes have produced five hard, hairy goosegogs They need a new start And that's what I'm giving them ! "

" It will be the children next," she said " You'll be sending them to boarding school "

As our eldest child is only $3^1/_2$ I considered this a remark of quite tangential irrelevance and was about to say so when Mr McGillivary, the smith, walked by I was in need of an ally

" Moving the gooseberry bushes, doctor ? "

" He's *always* moving *everything*," said my wife " Every time I come out into the garden the plan is changed I never know where to look for things "

" And isn't that what the ladies do in the house ? " said Mr McGillivary " When a man wants his pipe or his slippers or a piece of string or his screwdriver where are they ? Moved ! "

I smiled on Mr McGillivary Not for nothing had we thrown together the companionable dart at the *Golden Ball* I looked towards the orchard

" Where would you put them, Mr McGillivary ? "

" In the orchard The ground is sweet under the apple trees, and when summer comes their skins will be bursting with sugar "

* * *

The Church, the Army, the Law, and Medicine are all in their way connected with death The cloth discusses it, the warrior arranges it, the solicitor is ready for it, the doctor delays it (or tries to do so) These lugubrious conclusions arose from my recent visits to the third of *these fell sergeants The man of law's touch* was so light His remarks were far removed from the forebodings of the post-Victorian revivalist He spoke of some far off divine event When the event happened, you, me, the client would be obviously performing a gracious act (gracefully), and he was armed at all points cap à pie to carry on the good work with all propriety How comforting a speculation Everything prepared for Nothing, or only very little, to go wrong

Part of the solicitor's finesse comes from good training, from those articles, not the thirty-nine, for which as a penurious father I have just paid so much, but part surely from the fact that the lawyer acts after life, and the parson, the colonel, the doctor during life When the Law is in action during life its mills grind as slowly as those of God, its results may be as uncertain or as foggy as the case of Jarndyce *v* Jarndyce

If our profession could be as futuristic as the family solicitor is, how different it would be Luckily I suspect for ourselves, we are continually being held up to the ransom of necessary decision, and some of us can shut our eyes like the fighting man guided by some higher command, or like the cleric call upon some vision which not all mortals can share with him The sword of Damocles hangs by its thread, in Lincoln's *Inn* it has already fallen For us there are minefields everywhere the lawyer in his bulldozer is engaged in a mopping- and chopping-up proceeding

* * *

Yesterday during my matutinal period of reflection, my eye lighted on the rhythmically stamped cylinder of "Government Property" by my side, and I fell to thinking of the wonderful effect that slight and insistent propaganda can have Of all the expensive apparatus owned by the State, this cheap roll is the most jealously labelled Is this the source of our nation's difficulties? How little does H M Government understand the psychology of advertisement, how poorly does its material and site compare with that of the meanest drug-house! It is causing us to lose the respect we should have for things not our own We are being conditioned to throw down the drain what Whitehall has marked as its own

It may be the concern of Dr Hill in his new office to deal with this, lest the products of Government action block our national waterways and sewage canals No doubt the Ministry of Health will suggest that a shilling charge be put on each dispensation Lucky numbers and a monthly draw for tax-free prizes might overcome opposition to this, while some will be hoping that the discovery of an imperforate roll will bring the rewards of an imperfect sheet of stamps

* * *

WEST OF SUEZ

The Healthman's Moane

Whan that a manne thinketh that his foode
Is full of dirt and maybe is not goode,
Or mayhap feeleth that a piece of meat
Is froght with danger unto him that eat,
Or if it seemeth that a dung or spitt
Be full of Microbes lurking to transmit
The seeds of evil stynking of disease,
Whether it come from home or overseas,
Or if perchance 'twere that a mouse or ratte
A miller s flour or grain sacks has been atte,
There is a way vouchsafed whereby hee
May bring the noxious thing along to mee
It must in sooth be carried straightaway
For urgent matters can brook no delay,
Therefore do I affix to it a tabbe
And bear it instantly unto the Labbe—
A mean and sorry place of no great wealth
But natholess a proppe of public health
Wherein men using alchemy and smell
Can tell us whether bodeth ill or well
Each thing pertaining to the nation's meat
And drink withal, a veritable feat
The Labbe's kindly folk will do their best
To find if therein harbour plague or pest

When Healthmen find that they can get the juice
They put the Labbe to quite a bit of use
Needs must they get the wherewithal to go
But now the edict sayeth nay not so
A most disastrous tragedye indeed
Withholding from him what he sorely need
But unto such enactments must one bow
By using only what the law allow
Where Healthman s duty lieth in a towne
His channels may not be so greatly downe
But when amid the hills his places lie
In sooth can he but stand aside and sigh
Meseemeth it accordant to reasoune
The country Healthman is a sorry loone
For lo perforce he draweth in his horne
Trulye he wisheth he had never been borne
For eke withal the Healthman shall survey
The countryside from whence he draweth paye
And men in his employ must cart ye mucke
And garbage from men s houses in a trucke
Or else it shall be piled mountains high
And men will say it reacheth to the sky
The precious fluid must be used for thatte
To ask aught else is talking through a hatte
Behoves a man to put an utter bar
On milk or water carried from afar
What can be left till later must be stoppe
Affairs of health perforce must show a droppe

Letters to the Editor

NEONATAL COLD INJURY

SIR,—Dr Mann and Dr Elliott are to be congratulated upon their clear description (Feb 2) of what they have elected to call "neonatal cold injury" The term has the advantage of pointing to the most important single ætiological factor—chilling—while embracing a clinical picture which to the minds of many extends from an apparently uncomplicated hypothermia to an irreversible sclerema

I am glad that the authors mention that factors other than cold may help to precipitate the condition In some full-term infants who show this picture it is difficult to accept exposure as the most important operative factor I have seen two babies recently who illustrate this point

A male infant of 6 lb 1 oz birth-weight was born spontaneously by the breech His dissimilar twin died on the first day of life The survivor was apparently well until the fifth day, when he was noted to feed poorly and to feel cold He was red and had pitting œdema and a rectal temperature of 91°F He was transferred to the premature room where his temperature rose to 97°F within twelve hours, and without further treatment his temperature became stable within normal limits in a few days

The second patient, a boy of 6 lb 10 oz birth weight, was an assisted frank breech birth No abnormality was noted until the eighth day when he became lethargic, unwilling to feed, cold, and erythematous His rectal temperature was found to be 91°F Again recovery was rapid on his being transferred to the premature room

Both infants were born in the Simpson Memorial Maternity Pavilion and became hypothermic in a nursery the temperature of which was maintained by thermostatic control at 70°F. All other infants in the nursery were maintaining normal temperatures on each occasion The severest rigours to which they had been exposed amounted to brief periods of partial exposure during changing and weighing These can hardly be compared to the conditions prevailing in a new and inadequately heated prefabricated house in a snowstorm I have little doubt that the temperatures of these two infants would have fallen further had preventive action not been taken

There would appear to be in some newborn infants a deficiency of heat regulation because of which hypothermia may occur even under good conditions Obviously the cold injury will be more severe if the environmental temperature surrounding such babies is low or if the infant's condition is not quickly appreciated and rectified. There would appear to be some factor other than prematurity, infection, or cerebral birth injury responsible for this central derangement

I have treated this condition by short wave diathermy in a small series over the past two years with considerable success The response of laboratory animals rendered moribund by chilling and of hypothermic, not sclerematous, infants has been dramatic The treatment was devised primarily for the treatment of sclerema, but I have not as yet had the opportunity of using it in this condition Although I appreciate the hazards of increasing the metabolic rate in the presence of asphyxia, it has appeared to me a logical form of treatment in some such cases The coexistence of infection of the respiratory tract and elsewhere is common The hypothermic infant is less capable of dealing with invading organisms than the normal baby The growth of the bacterial invaders, however, is not greatly influenced by the fall in body-temperature Changes in the subcutaneous fat of the thorax add to the respiratory embarrassment The duration of survival of the 8 fatal cases in the series of 14 infants described by Mann and Elliott varied from 7 to 100 hours with an average of 40 hours For the reasons I favour radio-frequency rewarming and the simultaneous careful use of oxygen

The technique which has been evolved by Miss Sheila Cameron, M C S P, and myself is still experimental, and through-and-through heating by short wave diathermy is not advocated for general use Severe local burning may occur in the presence of wetness or if the coil is improperly spaced I have no doubt that a safe technique is now possible, and a full description of it and of the results obtained will be published later

Department of Child Life and Health, University of Edinburgh JAMES W FARQUHAR

HYPERTENSION PRESYMPTOMATIC DIAGNOSIS AND TREATMENT

SIR,—Many of us share Professor Sanjivi's interest in the early and uncomplicated phase of essential hypertension (Feb 2), and are concerned to know at what stage in the evolution of the syndrome it is right to intervene with a potent hypotensive drug The trouble with Dr Sanjivi's contribution to this problem is that, by the evidence of his representative case, his patients are not hypertensive in the proper sense of having an established high diastolic pressure They are " diastolic reactors "—people whose pressure may be found casually raised but can fall within normal limits in nice circumstances and during sleep In any case, an emotional reactivity of the diastolic pressure is a phenomenon of hypertension at all stages

In my sort of psychosomatic interviewing,[1] with the patient at rest on a comfortable couch and showing no manifest anxiety, the average diastolic swing has been 25 mm Hg during the discussion of his life situation, and swings of 45 mm are not uncommon The casual reading gives no indication of the potential seriousness or otherwise of this liability, because it may lie anywhere along the range according to circumstance In particular it is unreliable as a base line for assessing the effect of treatment

I do not believe that Dr Sanjivi has done more than demonstrate the fall in pressure as recorded by a particular doctor when he has established a good therapeutic relationship with a diastolic reactor That the pressure stays satisfactory when the reserpine is stopped is proof of this

I do not take issue with the use of reserpine when the hypertensive condition is severe, but I am sure that the way Dr Sanjivi proposes is unwise Firstly, if relief from worrying is a rationale, it must be said that in psychiatric practice reserpine has not proved itself better than amylobarbitone sodium[2] Secondly, it is not innocuous Smirk and McQueen[3] report that half their hypertensive patients complained of mild symptoms such as lassitude and some disturbance of sleep by nightmares, and a tenth had significant depression In general, the depression may demand psychiatric measures in 5–20% of cases, and suicide is not uncommon In our state of ignorance about the prognosis for a patient with a casual diastolic reading of 105 mm Hg, 115, or, for that matter, 125, in the absence of complications, I do not see that we shall help by introducing a definite hazard of depression or impulsive suicide

Hypertension is probably not a disease until it begets complications, and I think that a man may be a diastolic reactor throughout life without running into any more circulatory trouble than a normotensive person We cannot evaluate the " late results of early treatment " until we know the late results of being a youthful diastolic reactor in the absence of treatment In the meantime, unlike Dr Sanjivi, I believe we should regard diastolic reactivity as a benign process—or shall I say only a little less benign than life itself, which is rather apt to end in cardiovascular disease It is compatible with a normal life span and with normal activities The patient needs to be protected from the anxieties of his doctor about the ultimate prognosis A worried preoccupation with blood pressure readings, the premature imposing of restrictions, and the giving of drugs are potent sources of disabling anxiety symptoms

Except in the accelerated phase, headaches do not call for hypotensive measures They should be treated on their merits as tension or conversion symptoms Better than succumbing to the blandishments of the drug houses and writing a prescription is a little sympathetic listening to the social, occupational, and family troubles that may be responsible for hypertensive episodes and outbreaks of anxiety and depression The hypertension is best kept in the background, watched with masterly inactivity (or " hands folded ") for the approach of complications, whilst the patient is treated as a person who from time to time gets into emotional difficulties with people in his environment

Cranbrook, Kent JOHN HAMBLING

SIR,—Dr Sanjivi has discovered the fallacy of a name—" benign hypertension ", he rightly states that it often kills We all know that Malignant, benign, essential, renal hypertension are all variants of " hypertensive disease "

There is no need to rail against this terminology It is not meant to lead anywhere, and cannot therefore mislead Mr Smith may be a woodworker, pernicious anæmia is a harmless disease, and my grandmother may develop athlete's foot—no need to wax indignant, we all know what is meant Names and labels are useful, they are not substitutes for descriptions even where they sound descriptive

Dr Sanjivi having unmasked the devil that lurks behind " benign hypertension " should go one further and exorcise the gremlin that lives in his sphygmomanometer Whenever this instrument records above 150 mm systolic and 95 mm diastolic this gremlin whispers " disease " into the doctor's ear, and leads doctor and patient into the pharmacological wilderness Yet, nine times out of ten he is dealing with a harmless elevation of blood-pressure that is ephemeral, truly benign, and not " disease "

Sir, a misunderstood sphygmomanometer reading can be as misleading as a name taken at its face value Do not let us be misled by this facile but fallible gadget into the large-scale study of treatment of mostly healthy people Let us first find out who needs treatment ! What we need is not eleven cases treated over 11 or even 21 months We need ten times eleven cases, observed without meddlesome treatment over twice 11 years, with records not only of blood pressures but of urinary, fundal, biochemical, radiological, and electrocardiographic findings, set against the subject's heredity, constitution, environment, and occupation Out of that study might—or might not—come a simple sign that would indicate when " moderately elevated blood pressure " is the precursor of " hypertensive disease "

We would then still have to find out whether hypertensive disease is as amenable to treatment as the ubiquitous patient with a " headache and a tired feeling at the end of the day " and a blood pressure of 168/106

In the absence so far of such a discriminating sign it is our first duty not to submit healthy people to " certain simple restrictions of activity [what activity, and why ?] and diet " We must still investigate adequately those patients with increased blood pressure, particularly if their symptoms are more specific than " headache and tiredness ", we must evaluate our findings, temper them with our judgment, treat the few, and spare the many

London, W 1 G SCHOENEWALD

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[1] Hambling H J In Modern Trends in Psychosomatic Medicine (edited by D O Neill) London 1955 chap 12

[2] Hare F H Seager C P, Leitch A Lancet 1956 i 545

[3] Smirk, F H McQueen E G Ibid 1955 ii 115

INTERACTION OF DEPOLARISING AND NON-DEPOLARISING RELAXANTS

Sir,—We regret that circumstances delayed our reply to the interesting letter of Dr Churchill-Davidson (Nov 10) In this communication he took exception to the use of the term "unexpectedly increased sensitivity to *d* tubocurarine" used in our previous letter

In an attempt to prove that our findings should not have been classified as "unexpected" he cites observations on the changing response evoked by repeated doses of C10 in certain mammals[1] and by a single dose of the same compound in myasthenics[2] These observations were not unknown to us and as a matter of fact were links in the chain of thought leading to the present understanding of the mode of action of depolarising muscle relaxants These observations, however, do not make our findings obvious, and thereby unworthy of reporting, as is implied by Dr Churchill Davidson

Whether an observation is expected or unexpected depends on previous experience and mental outlook. We do not wish to argue this point, but would like to emphasise that, from observations on the changing character of the block caused by depolarising drugs in certain mammals, the differences observed in the type of block caused by these agents in myasthenic individuals, and the fact that neuromuscular block produced by prolonged administration of these agents can occasionally be reversed in man by anticholinesterases, it does not necessarily follow that increased sensitivity to non depolarising muscle relaxants should be encountered after prolonged administration of depolarising substances in all human subjects tested

If Dr Churchill Davidson, or anybody else, had formulated the hypothesis that "prolonged administration of depolarising drugs makes the endplate more resistant to depolarisation," *then indeed the findings of Dr Brennan*[3] *and those of ourselves* could not have been classified as "unexpected" Such a hypothesis, however, as far as we know, has never been suggested, and only after the findings of Thesleff,[4] Brennan,[3] and ourselves became available did we feel justified in advancing the above hypothesis

Additional experimental evidence obtained with the sciatic gastrocnemius preparation of dogs and cats[5] and further clinical observation in man confirmed our assumption that prolonged administration of depolarising relaxants (e g, suxamethonium and decamethonium) produces gradually increasing resistance of the endplate to depolarisation In man, this increasing resistance may first be manifested by the need to increase the dose of depolarising relaxant to maintain a myoneural block of unchanged intensity At this stage, the block is presumably still a depolarisation block, because it is intensified by anticholinesterases Increased sensitivity to non depolarising relaxants, however, is already evident at this time In certain human subjects, but by no means in all, the resistance of the endplate to depolarisation can increase further, and in these cases the original depolarisation block can change to a non depolarisation block reversible by anticholinesterases

The rate of change in the sensitivity of the endplate to depolarisation varies, not only with the species investigated, but also with individuals of the same species and different muscles of the same individual It is fortunate that in most instances acetylcholine, the "physiological transmitter" is still capable of depolarising the endplate, and thereby restituting myoneural transmission, at times when suxamethonium or decamethonium are no longer capable of producing depolarisation

While we have the pen in hand, we would like to take exception to the use of the term "dual" block. The word "dual," as commonly used, implies two different actions occurring simultaneously (e g, the nicotinic and muscarinic effect of acetylcholine) It is now evident that the type of block previously classified as "dual" is caused by progressive changes in the properties of the endplate These changes can occur with varying speeds in different species In view of the gradual change in the properties of the endplate and the nature of the block the term "biphasic" (originally suggested by Jenden et al.[6]) or "multiphasic" block would depict the events at the endplate more truly and would be less likely to lead to misunderstanding of the basic principle involved

Portsmouth, England   R J Hamer Hodges

Pittsburg, Pa, U S A   F F Foldes

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[1] Paton W D M Zaimis E Pharmacol Rev 1952 4 219

[2] Churchill Davidson H C Richardson A T *J Physiol* 1953 122 252

[3] Brennan H J *Brit J Anæsth* 1956 28 159

[4] Thesleff S *Nature Lond* 1955 175, 594

[5] Foldes F F Wnuck A L, Hodges R J H deBeer F J *J Pharmacol* (in the press)

[6] Jenden D J Kamijo K Taylor B D *Ibid* 1951 103 348

HOME CARE FOR SICK CHILDREN

Sir,—With reference to last week's article by Dr Lightwood and his colleagues, I must correct a wrong impression created by the statement that in the home-nursing unit set up in Rotherham in 1948 with which I was associated, there is no direct connection with the hospital services In fact great stress has always been laid on cooperation with the hospital services, and the home nurses used in the unit attend hospital for a brief refresher course before commencing work with the unit This point is shown quite clearly in the filmstrip made by Camera Talks showing the work of the unit

J Adrian Gillet

Dagenham Essex   Medical officer of health

"DOCTOR"

Sir,—It was with interest and amusement that I read Dr Graham's enlightening article (Feb 2) It is only to be regretted that the article was written by an F R C P and not an F.R C S—which would have perhaps added weight to the wise suggestion put forward

As an overseas doctor of medicine and a qualified surgeon, I am really struck by the importance surgeons attach to the title Mister This in itself may not be so important, and indeed may simply be classified as one of those "traditional" things that linger on and, in a way, add originality to the British way of life But does it not become ridiculous when the infection spreads downwards through all the layers of medical personnel ? A houseman insists on being called, or is called, Mister during his six months in the surgical wards, then he changes over to the medical firm and is addressed as Doctor, and perhaps does not very well know what to be called during his gynæcological training ! (Likewise, the ward sister, on obtaining an administrative appointment, insists on being addressed as "Miss")

These are amusing rather than fundamental anomalies But what is more serious is the use of the term Doctor in a derogatory way How often has a surgeon rebuked his houseman with that particularly stinging accent on the last word of "I told you to hold that retractor, Doctor" ! I know of at least one sister who addresses the surgeon as Doctor when she is cross with him, and as Sir or Mister when he is in favour with her

As Dr Graham says, the practice causes a good deal of confusion among the public, and who has not known the patient who has shyly asked us whether we should be called Doctor or Mister ? Worse still, surgeons have known the inconvenience of being reduced to a doctor's level during travel abroad, where all medical men are called Doctor

In the scale of medical degrees, strictly speaking only he who has obtained the M D degree of a university can be called "Doctor" But the general public tend to address all medical men as doctors, and the term can perfectly well be retained for this purpose, without harm to anybody If one had to search for logic, it is all surgeons *and* physicians who have not obtained their M D who should be called Mister leaving the Doctor privilege to those who have their doctorate

Perhaps the best solution is to take the public as the final arbiter for them a doctor is he who practises as a qualified and registered medical man, whether he is called upon to treat Johnny's measles, to repair mother's prolapse, or to remove grandpa's prostate

Southall Middlesex.   C Swan

Sir,—One finds nurses and other medical personnel refusing to address anyone with a doctor's degree as "Doctor," unless he has a medical qualification this happens not only in speech, but also in writing and reasons I favour radio-frequency rewarming and the simultaneous careful use of oxygen

The technique which has been evolved by Miss Sheila Cameron, M C S P, and myself is still experimental, and through-and-through heating by short wave diathermy is not advocated for general use Severe local burning may occur in the presence of wetness or if the coil is improperly spaced I have no doubt that a safe technique is now possible, and a full description of it and of the results obtained will be published later

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Sir, a misunderstood sphygmomanometer reading can be as misleading as a name taken *at its face value* Do not let us be misled by this facile but fallible gadget into the large scale study of treatment of mostly healthy people Let us first find out who needs treatment! What we need is not eleven cases treated over 11 or even 21 months We need ten times eleven cases, observed without meddlesome treatment over twice 11 years, with records not only of blood pressures but of urinary, fundal, biochemical, radiological, and electrocardiographic findings, set against the subject's heredity, constitution, environment, and occupation Out of that study might—or might not—come a simple sign that would indicate when "moderately elevated *blood pressure*" *is the precursor of* "*hypertensive disease*"

We would then still have to find out whether hypertensive disease is as amenable to treatment as the ubiquitous patient with a "headache and a tired feeling at the end of the day" and a blood pressure of *168/106*

In the absence so far of such a discriminating sign it is our first duty not to submit healthy people to "certain simple restrictions of activity [*what activity, and why?*] and diet" We must still investigate adequately those patients with increased *blood pressure*, particularly if their symptoms are more *specific* than "headache and tiredness", we must evaluate our findings, temper them with our judgment, treat the few, and spare the many

London, W 1 G SCHOENEWALD

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[1] Hambling J *In* Modern Trends in Psychosomatic Medicine (edited by D O'Neill) London 1955, chap 12

[2] Hare E H Seager C P, Leitch A *Lancet* 1956 i 515

[3] Smirk F H McQueen E G *Ibid* 1955 ii 115

worker never finds it necessary to distort or misrepresent facts in order to achieve simplification

In conclusion, I should like to reiterate that the scientific aspect of the controversy regarding Rh terminology is terminated, since all the facts are now readily available The only problem remaining is one of education

Brooklyn New York **A S WIENER**

TOWARDS PREVENTING SUICIDE

SIR,—The article by Dr Parnell and Dr Skottowe (Jan 26) and your annotation thereon are valuable in drawing the attention both of the medical profession and the public to the gravity of the problem I disagree, however, with one conclusion in your articles—that treatment should be admission to a mental hospital

In 1954 of 50 cases of attempted suicide admitted to the general hospitals of this group only 3 required subsequent admission to a mental hospital These figures were published with a suggested scheme of preventive action[1] to counteract some of this annual carnage

With the overcrowding of mental hospitals, many more psychiatrists should be included on the staffs of general hospitals, without them of necessity being attached, as now, to mental hospitals This is unlikely to come to pass as long as regional boards receive most of their advice on mental health policies from medical superintendents of mental hospitals, whose primary concern is naturally for the mental hospitals

Provided adequate psychiatric facilities are available at the general hospital, very few potential suicides need admission to a mental hospital The cooperation between the medical, anæsthetic, and psychiatric departments at this general hospital is such that three members of the resident medical staff and one clinical assistant general practitioner administer electroconvulsion therapy and apply other psychiatric therapeutic techniques to inpatients and outpatients under the direction of a consultant psychiatrist, and a number of beds are available in the medical wards for psychiatric cases

I agree that preventive social psychiatry holds the key, and it may well be that the public health services will in the future examine all school children psychologically, as they now do physically, and that adults may be similarly screened periodically

East Glamorgan Hospital
Church Village near Pontypridd **T S DAVIES**

RADIOACTIVE VITAMIN B_{12} IN THE DIAGNOSIS OF NEUROLOGICAL DISORDERS

SIR,—In their interesting paper last week Dr Berlyne and his colleagues rightly stress the value of absorption tests with radioactive B_{12} for distinguishing non anæmic patients with subacute combined degeneration from patients with other cord and nerve lesions It should, however, be emphasised that, valuable as these tests are particularly in the treated patient, they give only indirect evidence of vitamin B_{12} deficiency

Neurological lesions due to vitamin B_{12} deficiency may occur in "vegans" who are able to absorb vitamin B_{12} normally,[2] and patients without vitamin B_{12} deficiency may be unable to absorb normal amounts of the vitamin[3] For these reasons direct evidence of deficiency of vitamin B_{12} is desirable before making so important a diagnosis as subacute combined degeneration of the cord In non anæmic patients this can be obtained only by measuring the concentration of vitamin B_{12} in the serum Patients with subacute combined degeneration of the cord have very low serum vitamin B_{12} concentrations whereas patients with other neurological lesions have either normal or only slightly subnormal concentrations of vitamin B_{12} in the serum[4]

Of the methods available for studying absorption of vitamin B_{12}, Dr Berlyne and his colleagues selected the Schilling test as the most convenient It should, however, be remembered that this method has two minor disadvantages Firstly, its accuracy is entirely dependent on a patient's ability to collect the urine passed during a 24 hour period This may be difficult, particularly in confused or incontinent patients or in elderly females Secondly, the urinary excretion of radioactive vitamin B_{12} is considerably reduced in patients with renal disease,[5] so that the results of the Schilling test may be abnormal even though the intestinal absorption of vitamin B_{12} is normal[6]

Department of Pathology (Hæmatology)
Postgraduate Medical School of London **C C BOOTH**
D L MOLLIN

BIRTHDAYS OF SPASTICS

SIR,—Recently when reviewing spastics of school age, quite accidentally I noticed that their months of birth were not evenly distributed throughout the year Of the 62 spastics reviewed only 10 were born in the four months December to March The largest numbers were born in the period June to August (25) This difference hardly seems to be a matter of chance

There seem to be two possible causes for this uneven distribution Do spastics who are born in the cold months of the year tend to die at a very early age? In this respect the article by Dr Mann and Dr Elliott (Feb 2) might be of interest, particularly as spastic children are known to be sensitive to changes of temperature If in fact there are fewer actual births of spastics during the period December to March, one may have to think in terms of infections of the mother during pregnancy

It would be interesting to know, from those who devote much of their time to the care of spastics, whether this observation is confirmed

Public Health Department
Glamorgan **R T BEVAN**

PNEUMOTHORAX IN TRACHEOTOMY

SIR,—I was interested in Dr McMath's report[7] of pneumothorax complicating tracheotomy in a case of laryngo tracheo-bronchitis I was involved in the supervision of two cases of this nature, both patients died, and even at necropsy no tear in the parietal or visceral pleura could be seen

CASE 1—An infant, aged 11 months, who had been "croupy" for 5 days, became much worse despite treatment Rib retraction increased, the pulse rate rose to 160 per minute and he was pale and becoming restless

Accordingly tracheotomy was performed The tracheotomy tube was finally inserted after a little difficulty, but thereafter his condition did not seem to improve He was cyanosed and his ribs were still retracted An hour later examination suggested left sided pneumothorax His left chest was needled at once, but he died

Necropsy showed acute laryngo tracheo bronchitis with left sided pneumothorax and massive collapse of the left lung, subcutaneous emphysema around the wound in the neck and also a little in the mediastinum, no rupture of the pleura, and grossly enlarged thymus (32 g) which microscopically was normal

CASE 2—An infant, aged $6^1/_2$ months had been "croupy" for 24 hours He had slight indrawing of the ribs, and did not improve with treatment in a steam tent The following morning his pulse rate was 140 per minute, his colour was good but he was obviously exhausted and his ribs were still moderately retracted A tracheotomy was performed, but he collapsed about 15 minutes later, became cyanosed and died

Necropsy showed the anterior mediastinum ballooned with air, subcutaneous emphysema extending throughout the such people will not be corrected The public's use of Doctor is as a vulgarism they cannot be bothered to say *general practitioner* or *medical attendant*

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[1] Davies T S *Brit med J* 1955 ii 1326
[2] Badenoch J *Proc R Soc Med* 1954 47 426
[3] Baker, S J Mollin D L *Rev Hémat* 1955 10 181
[4] Mollin D L Ross G I M *Proc R Soc Med* 1954, 47 428
[5] Brus I Mollin D L Unpublished
[6] Schwartz M Personal communication
[7] McMath W F T *Lancet* 1956 ii 750

Addlestone, Surrey F Hilton

THE PLIGHT OF HOSPITAL PHARMACY

SIR,—All that Sir Hugh Linstead says (Feb 2) applies with equal force to physiotherapists, and indeed all of the so called auxiliaries It is surely time that a complete review was made of salaries and conditions of these grades, and a degree of reality introduced

Sudbury, Suffolk DAVID WHITE

SEPSIS IN THE NEWBORN

SIR,—The purpose of the investigation reported in the article by one of us,[1] to which your annotation of Jan 26 refers, was a very limited one to find out if, in a maternity hospital, a relatively simple technique for the routine care of the skin of the newborn could safely be substituted, during the first week or two of life, for the traditional technique involving regular bathing We found no increase in the incidence of various skin troubles (*including staphylococcal lesions*) *among the babies* cared for by the simpler method

Your annotation was mainly devoted to making two suggestions for remedying the fact that the investigation was " not conclusive as far as sepsis is concerned," and we would welcome the opportunity to make a brief reply to these suggestions

While it is undeniably true that, mathematically speaking, " an investigation lasting two years would have been more conclusive " (always provided that the one observer had had the stamina to see it through), we do not think that any corresponding practical advantage will inevitably result from such a prolongation of an investigation of this kind We certainly would not expect to encounter the acid test you so confidently predicted—" a flare-up with widespread infection and severe lesions " During the period of the past ten years, for which we have accurate day-to day records of the incidence of skin sepsis in the Princess Mary Maternity Hospital, there has been a good deal of unexplained fluctuation from time to time (no doubt partly attributable to unconscious differences between the standards of different observers) but there has been only one episode which might be described as a " flare up " In May, 1951, when a change was made in the technique for the routine care of the cord, there was a rapid rise in the incidence of skin sepsis so that in June 35% of the babies in the hospital developed one or more pustules during their stay (fortunately there were no " severe lesions ") The situation was promptly brought under control again by a further change in the technique for the care of the cord Past experience, therefore, would lead us to be wary of the *apparently innocent* change in technique which may lead to unfortunate and unforeseen consequences on a large scale But it would not lead us to expect " at least one flare up " every two years

It is also undeniably true that, as compared with the *follow up period* which we relied upon (the duration of the babies' stay in hospital), " a follow up of four months might have revealed some sepsis later " But even if there is any causal connection between the serious visceral or bony lesions which may appear later, and " *the relatively small skin lesion appearing* in the first week," which has healed rapidly, we would not have expected to find a different incidence of these later lesions in two groups of babies which had shown the same incidence of the initial skin lesions Furthermore, it is *one of the advantages of working in a provincial centre* that one should be able to obtain an accurate idea of the true incidence of such serious lesions With regard to staphylococcal osteitis, for instance, we know that during the past eight years only two babies under the age of 4 months, who had been born in the Princess Mary Maternity Hospital, have been *admitted to the pediatric* wards in the region for treatment This figure gives an idea of the meagre reward which we would expect to be gained by a four-month follow-up of all the babies discharged from the hospital during a period of two years

In short, we would like to suggest that the planning of an investigation of this kind ought to be based upon the solid foundation of a knowledge of the natural history of the conditions which it is proposed to study, in the particular institution concerned (rather than upon generalisations which may be true of some institutions, but not of others) and that it may be wiser to budget for a result which is " not conclusive " (but which will tell one what one wants to know), rather than to strive after some arbitrary standard of conclusiveness, and risk finding oneself *to be engaged in the laborious pursuit* of a will-o'-the-wisp

Princess Mary Maternity Hospital,
Newcastle upon Tyne

LAETITIA BRUCE
GERALD NELIGAN

THE Rh BLOOD-GROUPS

SIR,—I was pleased to read that Dr Nicholas (Jan 19) acknowledges that, irrespective of nomenclature, the use of " most likely genotypes " leads to paradoxes The point is that the paradox was introduced into blood-group literature by the CDE protagonists, as can be seen by consulting the book of Race and Sanger In my own writings I have always been scrupulous in distinguishing phenotypes from genotypes, and so have all other workers who thoroughly understand the subject, and who therefore avoid the CDE notations I trust that Dr Nicholas's letter means that he intends to persuade Dr Race and other CDE protagonists to abandon the use of " most likely genotypes " This will be the first *step in clearing up their confusion, and then* there are some two dozen additional paradoxes for which CDE protagonists are responsible,[1] which await Dr. Nicholas's attention

Your leading article of July 21 last year stated that the CDE notations have " given every satisfaction, being easy to remember and understand " This statement is based on a misconception, since when workers use the CDE notations it is *because* they *do not* understand the subject Those who thoroughly understand Rh-Hr serology and genetics have no difficulty with the correct Rh-Hr nomenclature, because this merely translates facts they already know into symbols Your editorial also states that " it seems unlikely that outside the United States pathologists and others will wish to change over from the Fisher-Race to the Wiener nomenclature—a change which would involve much effort " This statement is also incorrect, because almost all those who are now using the CDE *notations* are also using the co called " shorthand " notations What is entailed therefore is not to learn something new, but to discard something old which has been shown to be incorrect All intelligent workers will welcome such a simplification

In a recent article,[2] it is pointed out that the medico legal expert is expected to master all intricacies of Rh-Hr serology and genetics If such an expert uses the CDE notations, this demonstrates his *lack of* understanding of the subject, and may be used *by a* lawyer to challenge his qualifications The argument that the use of these symbols is needed to simplify the matter for the judge and jury is fallacious, because the competent

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[1] Bruce, L *J Obstet Gynæc Brit Emp* 1956 63 735

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[1] Wiener, A S The Rh Hr Types a Budget of Paradoxes *J forensic Med* (South Africa) 1955, 2, 221

[2] Wiener, A S Blood Grouping Tests in Disputed Parentage *Ibid*, 1956, 3 138,

worker never finds it necessary to distort or misrepresent facts in order to achieve simplification

In conclusion, I should like to reiterate that the scientific aspect of the controversy regarding Rh terminology is terminated, since all the facts are now readily available The only problem remaining is one of education

Brooklyn New York A S **Wiener**

TOWARDS PREVENTING SUICIDE

Sir,—The article by Dr Parnell and Dr Skottowe (Jan 26) and your annotation thereon are valuable in drawing the attention both of the medical profession and the public to the gravity of the problem I disagree, however, with one conclusion in your articles—that treatment should be admission to a mental hospital

In 1954 of 50 cases of attempted suicide admitted to the general hospitals of this group only 3 required subsequent admission to a mental hospital These figures were published with a suggested scheme of preventive action[1] to counteract some of this annual carnage

With the overcrowding of mental hospitals, many more psychiatrists should be included on the staffs of general hospitals, without them of necessity being attached, as now, to mental hospitals This is unlikely to come to pass as long as regional boards receive most of their advice on mental health policies from medical superintendents of mental hospitals, whose primary concern is naturally for the mental hospitals

Provided adequate psychiatric facilities are available at the general hospital, very few potential suicides need admission to a mental hospital The cooperation between the medical, anæsthetic, and psychiatric departments at this general hospital is such that three members of the resident medical staff and one clinical assistant general practitioner administer electroconvulsion therapy and apply other psychiatric therapeutic techniques to inpatients and outpatients under the direction of a consultant psychiatrist, and a number of beds are available in the medical wards for psychiatric cases

I agree that preventive social psychiatry holds the key, and it may well be that the public health services will in the future examine all school children psychologically, as they now do physically, and that adults may be similarly screened periodically

East Glamorgan Hospital,
Church Village near Pontypridd T S **Davies**

RADIOACTIVE VITAMIN B_{12} IN THE DIAGNOSIS OF NEUROLOGICAL DISORDERS

Sir,—In their interesting paper last week Dr Berlyne and his colleagues rightly stress the value of absorption tests with radioactive B_{12} for distinguishing non anæmic patients with subacute combined degeneration from patients with other cord and nerve lesions It should, however, be emphasised that, valuable as these tests are, particularly in the treated patient, they give only indirect evidence of vitamin-B_{12} deficiency

Neurological lesions due to vitamin B_{12} deficiency may occur in "vegans" who are able to absorb vitamin B_{12} normally,[2] and patients without vitamin B_{12} deficiency may be unable to absorb normal amounts of the vitamin[3] For these reasons direct evidence of deficiency of vitamin B_{12} is desirable before making so important a diagnosis as subacute combined degeneration of the cord In non anæmic patients this can be obtained only by measuring the concentration of vitamin B_{12} in the serum Patients with subacute combined degeneration of the cord have very low serum vitamin-B_{12} concentrations, whereas patients with other neurological lesions have either normal or only slightly subnormal concentrations of vitamin B_{12} in the serum[4]

Of the methods available for studying absorption of vitamin B_{12}, Dr Berlyne and his colleagues selected the Schilling test as the most convenient It should, however, be remembered that this method has two minor disadvantages Firstly, its accuracy is entirely dependent on a patient's ability to collect the urine passed during a 24 hour period This may be difficult, particularly in confused or incontinent patients or in elderly females Secondly, the urinary excretion of radioactive vitamin B_{12} is considerably reduced in patients with renal disease,[5] so that the results of the Schilling test may be abnormal even though the intestinal absorption of vitamin B_{12} is normal[6]

Department of Pathology (Hæmatology),
Postgraduate Medical School of London C C **Booth**
D L **Mollin**

BIRTHDAYS OF SPASTICS

Sir,—Recently when reviewing spastics of school age, quite accidentally I noticed that their months of birth were not evenly distributed throughout the year Of the 62 spastics reviewed only 10 were born in the four months December to March The largest numbers were born in the period June to August (25) This difference hardly seems to be a matter of chance

There seem to be two possible causes for this uneven distribution Do spastics who are born in the cold months of the year tend to die at a very early age? In this respect the article by Dr Mann and Dr Elliott (Feb 2) might be of interest, particularly as spastic children are known to be sensitive to changes of temperature If in fact there are fewer actual births of spastics during the period December to March, one may have to think in terms of infections of the mother during pregnancy

It would be interesting to know, from those who devote much of their time to the care of spastics, whether this observation is confirmed

Public Health Department,
Glamorgan R T **Bevan**

PNEUMOTHORAX IN TRACHEOTOMY

Sir,—I was interested in Dr McMath's report[7] of pneumothorax complicating tracheotomy in a case of laryngo-tracheo bronchitis I was involved in the supervision of two cases of this nature, both patients died, and even at necropsy no tear in the parietal or visceral pleura could be seen

Case 1—An infant, aged 11 months, who had been "croupy" for 5 days, became much worse despite treatment Rib retraction increased, the pulse rate rose to 160 per minute, and he was pale and becoming restless

Accordingly tracheotomy was performed The tracheotomy tube was finally inserted after a little difficulty, but thereafter his condition did not seem to improve He was cyanosed and his ribs were still retracted An hour later examination suggested left sided pneumothorax His left chest was needled at once, but he died

Necropsy showed acute laryngo tracheo bronchitis with left-sided pneumothorax and massive collapse of the left lung, subcutaneous emphysema around the wound in the neck and also a little in the mediastinum, no rupture of the pleura, and grossly enlarged thymus (32 g) which microscopically was normal

Case 2—An infant, aged 6½ months had been "croupy" for 24 hours He had slight indrawing of the ribs, and did not improve with treatment in a steam tent The following morning his pulse rate was 140 per minute, his colour was good but he was obviously exhausted and his ribs were still moderately retracted A tracheotomy was performed, but he collapsed about 15 minutes later, became cyanosed, and died

Necropsy showed the anterior mediastinum ballooned with air, subcutaneous emphysema extending throughout the mediastinum and along the abdominal aorta into the pelvis, and massive collapse of both lungs, which microscopically showed peribronchial cellular infiltration amounting to consolidation in some places

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[1] Davies T S *Brit med J* 1955 ii 1326
[2] Badenoch J *Proc R Soc Med* 1954 47 426
[3] Baker, S J Mollin D L *Rev Hemat* 1955 10, 181
[4] Mollin D L Ross G I M *Proc R Soc Med* 1954, 47, 428
[5] Bruce I Mollin D L Unpublished
[6] Schwartz M Personal communication
[7] McMath, W F T *Lancet* 1956 ii, 750

In these two cases the respiratory disorder had been present for some days, and it may be in such cases that the danger of pneumothorax is greatest Furthermore, a low tracheotomy was performed in both cases, and it is obviously easier for air to enter the cervical fascia and mediastinum with this low approach to the trachea

After opening the neck with the tracheotomy incision the tube must be inserted quickly, as the inspiratory efforts are still great until the trachea is opened Furthermore, the tube must be secured firmly, as if it slips out respiratory distress may begin and air be sucked in [3]

Renmark, South Australia　J G WILSON

A MISSED FRACTURE

SIR,—I would like to believe that Dr Stone intended his letter (Feb 2) to be taken as a piece of sarcasm If this is indeed the teaching in our medical schools today there is every excuse for the diminishing esteem with which our profession appears to be regarded by the public As Dr Stone says, the public has a right to treatment, and that treatment should be the treatment of whole human beings—not of arms or legs or skulls or what you will An adequately complete examination is not so time consuming as Dr Stone seems to think Anything less deserves every stricture that is coming to it and can certainly be regarded as evidence of lack of proper professional care No doubt we all of us fall short of the ideal on occasion That should not prevent us from recognising and regretting a lapse in professional standards

Marlborough College,
Wilts　T A A HUNTER.

SHORTAGE OF RADIOGRAPHERS

SIR,—As one of the older radiographic workers, I should like to comment on Dr Illingworth's letter (Jan. 5)

Dr Illingworth states that it is wrong to assume that the present shortage of radiographers is primarily due to inadequate remuneration, and that the dissatisfaction is largely confined to the few male radiographers

In my own small circle I know of three young married male radiographers, all with children, who have found other work simply because they could not make ends meet on their salaries as senior workers I also know of two others who have emigrated for the same reason As regards new entrants to the profession, I know that prospective male students, and their parents, lose interest when informed of the salary scale Exception is taken not so much to the initial salary (although this is on a par with that of a hospital porter) as to the absence of career prospects

Dr Illingworth says that radiography is essentially a job for a girl I wonder why "essentially"? Is it simply because a girl can afford to work for a smaller salary than a man? I can think of no other reason Personally, I think a man is the better proposition in the long run—better because, provided that he earns enough to keep himself and his family in reasonable comfort, he usually stays in a job for life, whereas the majority of women forsake it for marriage

It is true that the modern radiographer does not need to possess the electro technical knowledge which was required by the radiographer of former days, but surely Dr Illingworth will admit that knowledge of other kinds is required? I have been in X ray work for over forty years, both as an engineer and as a radiographer, and I am still learning

The other things which Dr Illingworth mentions are mostly related to professional standards Radiographers have had to fight for what little place they have in t sun, and it is surely unreasonable to expect them reduce their professional standards because of a shorta of radiographers, especially since they themselves are no way to blame for the shortage Why should we op our doors to the illiterate—assuming, of course, that t illiterate could do our work? Radiographers are doi no more, no less, than other professional bodies do A professional bodies, without exception, partly in t furtherance and the protection of their own interes strive to maintain as high a standard as they possib can In a democratic society their right to do so is bo recognised and upheld

When Dr Illingworth ridicules the idea of a pre entr qualification in English, and thereby infers that it shoul be done away with, he is asking radiographers to u their professional throats The salaries of radiographe are determined by Whitley Council machinery, and th machinery is extremely sensitive to such things as pr entry qualifications and length of training Where wou we stand if we reduced our standards? Surely it mu be realised by all that prestige and status mean just much to a radiographer as they do to any oth professional person

Swansea Hospital　DONALD R GOULD

AMIPHENAZOLE

SIR,—If Dr Ballantine's findings with amiphenazol (Feb 2) can be confirmed in a large series of cases, w will have a drug of great value in the treatment intractable pain In a series of ambulatory patients wh have received oral amiphenazole and large doses analgesics, some of the claims made by McKeogh an Shaw [1] have not been confirmed, especially as regard reduction of vomiting, constipation, and respirator depression However, I have, as yet, found no evidenc of addiction in any of the patients, during periods treatment lasting from 2 to 27 weeks

The acid test of prevention of addiction would be th ability to reduce the dose of analgesics without with drawal symptoms, but since pain was mostly due t malignant disease this was rarely possible

Analgesics have been stopped entirely in 5 patients In 2 instances because of lack of benefit where severe pain was only intermittent and was of short duration, and in 3 patients where relief was obtained by nerve section or alcohol block Their daily dose of analgesics was as high as 54 mg levorphanol or 250 mg methadone with 120–300 mg amiphenazole, and no side effects were observed during the withdrawal period, which did not exceed one week Levorphanol and methadone were the only analgesics which proved to be consistently effective by the oral route

Vomiting, which is a major problem when large doses of potent analgesics are given by mouth, does not appear to have been reduced by amiphenazole Its occurrence is unpredictable, some patients will tolerate enormous doses while others cannot retain even the smallest dose Vomiting responds very well to cyclizine or chlorpromazine, but chlorpromazine intensifies the soporific effects of the analgesics [2]

In view of the apparent prevention of addiction to analgesics by amiphenazole, the drug has been given to a few patients with severe post herpetic neuralgia, and the results have been most gratifying

One elderly patient, who attempted to commit suicide because of pain, was started on 18 mg levorphanol with 100 mg amiphenazole daily about six months ago She voluntarily reduced this to 13 5 mg levorphanol and 80 mg amiphenazole during the first few weeks and has continued on the same régime since

In view of the report by Dr Ritchie Russell and his colleagues (Feb 2) this treatment may be better reserved as a temporary measure, combined with intensive local therapy Patients could be made more tolerant to active treatment, and the analgesics stopped when no longer needed

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[3] Barrie M J Ibid, 1910, i, 990

[1] McKeogh J Shaw, F H Brit med J 1956, i 142
[2] Shaw F H Shulman A Ibid 1955, i 1367

Department of Anæsthesia,
University of Liverpool
JOHN W DUNDEE

PRACTITIONER AND LOCAL AUTHORITY

SIR,—I do not wish to revive the lively correspondence under the title "Clinicosis," but your editorial (Feb 2) warrants some comment

In quoting from Ramage's paper on this subject you express the view that "general practitioners *could* become responsible for some local authority services" In the sense of "competent to," I would agree, and, as a teacher, stress that it is not sufficiently realised that the medical student of today is taught much in the preventive field which the general practitioner alone can put into effective use

However, you state, equally dogmatically, that "from the correspondence most doctors think they *should* do this work" What really are the motives for this? In discussing the "take over" of clinic services you state

> 'but it is unlikely to happen for a long time unless general practitioners are given some *financial reward* [italics are mine] for providing these extra services As things now are, and as Ramage's inquiry illustrates it is doubtful whether the present size of general practitioners' lists allows them time for anything but a gesture at preventive work"

Further comment is hardly necessary, except to say that many general practitioners do not realise that preventive work often takes more time than curative, although unlike the latter its effects are likely to be cumulative One wonders whether the general public, who pay all the bills, would be convinced that at the moment the general practitioner has more time than he needs for his curative work The prerequisite for the general practitioner doing real preventive work would be a reduction in his curative case load

Department of Preventive Medicine and
Public Health University of Leeds
C W DIXON

UNMARRIED PARENTHOOD

SIR,—Dr Comfort writes (Jan 26) 'the devotion of moral agencies to the prevention of coition has often eclipsed their anxiety over the tangible suffering unwise coition may cause"

As one who has had some experience of one of these 'moral agencies'—the Church of England Moral Welfare Council—I am astonished at Dr Comfort's allegation, since moral welfare workers and councils are only too terribly aware that the amount of time and effort spent of necessity in connection with unmarried mothers and their urgent material problems leaves far too little time for the general educational work so essential amongst young people and which they feel should really be a first priority

Dr Comfort's suggestion that "the obvious first step' to reduce the present tragic unhappiness of the unmarried mother is "general contraceptive education" would prove an encouragement to young people to indulge in premarital coition as an interesting experiment rather than, as happens at present, as an uncontrolled emotion—thereby debasing the act to a far lower level than that on which it usually takes place Moreover it may be doubted whether universal knowledge of methods of contraception *would* appreciably reduce the illegitimate birth-rate since a high proportion of putative fathers and a not inconsiderable proportion of unmarried mothers are perfectly well aware of contraceptive methods but owing to carelessness, laziness, and lack of self-control and moral fibre, they urge or permit coition with little or no thought of the possible consequence

It seems doubtful if the tragedy of unmarried motherhood can be lessened by any means other than education—not in contraceptive methods, but in the proper relationship and respect one sex should have for the other and in the encouragement of the ideal that coition should be the culmination of the expression of the love of two persons who have accepted each other as a partner for life

Dr Comfort's suggestion that "the attempted prevention of sexual behaviour in young people" is one of the aims of moral-welfare organisations is as ludicrous as it is untrue "Sexual behaviour" is natural to both adults and young people This is fully recognised by moral-welfare workers who encourage it to progress on the right lines progress such as this does not lead to extramarital coitus, but the wider dissemination of contraceptive methods amongst unmarried persons suggested by Dr Comfort would, as I have previously suggested, by no means prevent unmarried motherhood, it would, on the other hand, almost certainly lead to an unnatural experimentation in the act of coitus, which should from the moral, practical, and æsthetic point of view be reserved for the culminating act of courtship and marriage

Goulceby near Louth,
Lincolnshire
E C CORDEAUX

SYRINGE CARRIER

SIR,—Dr Stark Murray (Feb 2) almost fully answers the criticism made by Dr McDonald and Mr Pirnie (Jan 26) of the syringe carrier which I described in your issue of Jan 12 He fails, however, to elaborate upon his statement that this syringe carrier is "unlikely to solve the problems of the anæsthetist"

Dr McDonald does not appear to have understood fully how this box works

The number of syringes and their variety are composed beforehand to suit the particular operating list with which it is intended to deal The box is then opened only long enough for one syringe to be extracted at a time The box is then closed The time taken to do this is less than that in which a surgeon removes a gown from a gown drum Would Dr McDonald therefore suggest that this method of sterilising gowns should be abandoned? The time taken to extract a syringe is about a fifth of the time taken to fill the syringe, carry it to the patient and inject its contents into a vein

Dr McDonald does not appear to appreciate that the anæsthetist, when handling sterile apparatus, wears cap and mask and washes his hands Unlike Dr McDonald I do not believe that there is any real risk of a dirty syringe being replaced in the box

At the moment I am carrying out a series of tests to establish whether the air in one of these boxes remains sterile from start to finish of an operating list

London, S W 3
L H LEHMAN

ERADICATION OF TUBERCULOSIS

SIR,—Dr J H Hudson's letter (Jan 12) stimulates me to reply to his point (c) He asserts that the director of a mass radiography unit has a statutory duty to notify pulmonary tuberculosis on the basis of X-ray examination alone May I say that such action, apart from the ethical considerations, would be clinically and administratively inadvisable, leading to false notifications and unnecessary anxiety to patients Surely pulmonary tuberculosis should not be diagnosed but only suspected on an initial film Infiltration and cavitation can be due to other causes besides the tubercle bacillus and if notification is to be made prematurely without clinical assessment of the patient and bacteriological examination of his sputum, the medical officer of health's notification register will become unreliable

The present-day chest service is established as a means of supplying accurate diagnosis and treatment of pulmonary disease I consider it would be a retrograde step if doctors reading X-ray films were to start notifying cases as tuberculous It would be reminiscent of the bad old days when tuberculosis was notified on the simple basis of a chronic cough

Newcastle upon Tyne H R THOMSON

TETRAETHYL LEAD POISONING

SIR,—Tetraethyl lead poisoning due to cleaning tanks is a disease that may affect seamen I can add to the four cases of Dr Boyd and his colleagues (Jan 26) that of a Polish sailor who was an inpatient in the Seamen's Hospital (under the care of Dr Alec Wingfield) from October to December, 1956

He had abdominal colicky pain, tightness in the chest, and vomiting His scleræ were slightly icteric, he had a hæmolytic anæmia (hæmoglobin 8 2 g per 100 ml, mean corpuscular fragility slightly decreased, reticulocytes 6%, active normoblastic marrow, serum bilirubin 2 mg per 100 ml), and 0 8% of his red cells showed the coarse punctate basophilia of lead poisoning Urinary lead excretion was 0 3 mg in 24 hours He said that the haze of rust in the atmosphere during scaling of the tank gave rise to cough with rusty sputum It was interesting to compare this seaman with a case of straightforward lead poisoning in an accumulator worker who happened to be in hospital at the same time this patient's complaint was also colicky abdominal pain (he had been *thought to have a perforated peptic ulcer*), but he *had* no anæmia and excreted no lead in the urine, though he showed characteristic coarse stippling of his red cells Both patients responded very definitely to therapy with intravenous *edathamil calcium disodium* ('*Versene*')

Devonport Laboratory,
Greenwich London G L ROBINSON

THREE CASES OF DYSURIA

SIR,—Dysuria is a symptom met by all of us daily The following three cases all presented with this complaint, and the final diagnosis was made only with some difficulty The patients were all young males

CASE 1—A boy, aged 3 years, a thin miserable child who was always unwell, was said to have dysuria and abdominal pain *There was no previous history of urinary symptoms*

He had a tender abdomen and pyrexia, but, as he always cried when approached, it was hard to say how much pain he was having His urine showed a cloud of albumin I *thought his pain was too severe to be due to urinary infection*, and I requested his admission to hospital as a possible acute abdomen

After admission, he was observed for 48 hours, and a precautionary *laparotomy was then performed* At the operation, at which a normal appendix was removed, it was noticed that the left kidney and ureter were enlarged Investigation showed a normal right kidney and a gross left *hydronephrosis* and mega ureter, which proved to be due to chronic pyelonephritis The kidney was removed, and the child is now very well indeed, cheerful and chubby, with rosy cheeks and a ready smile

CASE 2—*A youth of 19 complained of dysuria* Examination of his urine showed a cloud of albumin The abdomen was not tender and he was afebrile A tentative diagnosis of cystitis was made and he was given sulphonamides and potassium citrate Then began a series of bizarre symptoms, including jaundice which lasted 48 hours His temperature was normal by day, but rose in the evening to 100 or 101°F He was seen at home by a surgeon who advised admission

On admission his temperature was 100°F, he was now tender in the left iliac fossa, and his left kidney was palpable Next day jaundice reappeared and a physician thought that he had an obstructive infection of the kidney Intravenous pyelography showed a space occupying lesion of the lower pole of the left kidney On examination of the kidney after its removal this was found to be a clear cell carcinoma A year later he is very fit

CASE 3—Another boy, aged 17, who also complained of dysuria, was afebrile, and had no abdominal pain His urine contained albumin A tentative diagnosis of cystitis was made and he was treated with sulphonamides and potassium citrate Next day he had diarrhœa and nausea I wondered whether he had dysentery with superadded cystitis, or diarrhœa due to the treatment The question was answered next morning when he said that he had passed blood in his urine A sample sent to the laboratory was found to contain many tubercle bacilli He is now being treated for renal tuberculosis

Thus three of the major diseases of the kidney presented with the same symptom—dysuria Then followed a number of red herrings which diverted attention from the kidney

William Budd Health Centre,
Knowle, Bristol H I HOWARD

TREATMENT OF POST-HERPETIC NEURALGIA

SIR,—The successful treatment of post herpetic neuralgia by mechanical vibration, described by Dr Ritchie Russell and his colleagues (Feb 2), prompts me to report the following case of trigeminal neuralgia

A man, aged 51, developed a right trigeminal neuralgia in 1950, following a bilateral Caldwell Luc operation An alcohol injection of the gasserian ganglion in 1952 produced only temporary and minor relief of pain The pain became so intolerable that in July, 1954, the trigeminal nerve was divided in the posterior fossa This produced immediate relief of pain, but unfortunately after the operation left hemiplegia with right facial palsy developed Later the right cornea ulcerated and a tarsorraphy was necessary *The facial pain slowly returned, and though less severe, was still burning* He has not worked since the operation

The patient was admitted here in October, 1956, at the request of a neurosurgeon, as an intractable rehabilitation *problem At that time he was socially independent and could* walk short distances with the aid of one stick, he could not climb stairs or walk out of doors, dressing was difficult He had a typical left hemiplegia with some shoulder control although only flexion and abduction *to 90°* There was virtually no control over the elbow, wrist, or hand The left leg was spastic and weak, extended at hip and knee, and he had a dropped foot He was emotionally unstable On attempting any sustained effort he experienced paroxysmal pain which began in the right upper lip and spread rapidly over the whole right side of the face, it lasted 3–5 minutes, during which time he had to remain motionless, and it left an intolerable burning pain which lasted more than 30 minutes This pain was only moderately controlled by pethidine 100 mg *three to six* times per day, and was unaffected by sedatives or tranquillisers The limit of his exercise tolerance was 20 yards slow walking This made functional retraining or therapeutic exercise impossible

To help with his rehabilitation, procaine iontophoresis (2%, 4–5 milliamperes, 5 minutes daily), was given by a large electrode applied to the whole of the right face For the *following two hours it was possible to proceed* with vigorous exercises without a return of pain, and during this period drugs were unnecessary The iontophoresis was then given twice a day, and within a month he had made a good functional *recovery* from his hemiplegia He was able to walk well, with only minor spasticity (his dropped foot was controlled by a below knee calliper), and he had almost *normal* arm and hand function However, his pain remained severe

The patient was given a break for Christmas leave, and after a short remission the pain became so severe that he returned by ambulance, heavily sedated He complained that the pain was worse than before nerve section and was no longer controlled by pethidine The pain was brought on by any effort and by eating, and also occurred spontaneously He was seen again by the neurosurgeon who could offer no help other than the possibility of leucotomy

Knowing of the success achieved with mechanical vibration in postherpetic pains by *Ritchie Russell and his* co workers this was tried with a *hand operated* mechanical vibrator The patient applied it himself for 5 *minutes* every hour to the trigger areas Within 2 days he improved remarkably, *and* by 7 days *the only trigger spot remaining* was at the inner canthus of the eye, which was inaccessible to the head of the vibrator This area has now responded to sustained digital (self applied) pressure

For the past 3 weeks the patient has been virtually symptom free and can take exercise without pain. *For the* first time in years he is taking pleasure in work and play He has been provided with a mechanical vibrator to use at home

This case well illustrates the point made by Ritchie Russell and his colleagues—that local anæsthesia by procaine iontophoresis and mechanical vibration may be valuable in the treatment of intractable pain

Department of Physical Medicine and
Rehabilitation Devonshire Royal
Hospital, Buxton

Ronald Harris

PULLED ELBOW

Sir,—The clinical entity which Dr Salkind (Jan 26) describes is well known, and most of us have been taught to accept it as due to a subluxation of the head of the radius out of the annular ligament This belief, I think, is based on a false assumption which is implicit in Dr Salkind's account of the varying relationship in size of the radial head and neck The assumption is that the annular ligament is around the *neck* of the radius, whereas in fact it is around the *head* of the radius The annular ligament is attached in front to the anterior margin of the radial facet on the coronoid and behind to the posterior margin of the same facet The stability of the radial head within the annular ligament cannot, therefore, be influenced in any way by the relative size of the radial head to the neck

My views about Dr Salkind's interpretation of this clinical condition are further reinforced by my own experience that these cases spontaneously settle down in a few days irrespective of any form of treatment, manipulative or otherwise

County Hospital Lincoln

David F Thomas

REPAIR OF FEMORAL HERNIA

Sir,—I had the good fortune to be taught McEvedy's approach to femoral hernia by a surgical registrar at my last hospital

In Nigeria one has four or five hernias on an average operation list, and many are femoral Recently at the Civilian Hospital I saw two women with femoral hernias (in one case bilateral) about the size of a large grape fruit I used McEvedy's approach in both cases with utmost satisfaction Perhaps the only drawback to this method is the tendency to puckering of skin when the vertical incision is used

I was pleased to read the article by Dr Mouzas and Dr Diggory[1] and the letter from Mr Reay-Young[2] I also purchased a recent large textbook of operative surgery, but could find no description of, or even reference to, McEvedy's approach

Military Hospital
Kaduna, West Africa

J F Hickey

NEURONE SELECTION IN RELIEF OF PAIN

Sir,—I should like to call attention to the work of Dr Martonfy and Dr Balta[3] in the neurological department of this hospital We are using 10 ml of an aqueous solution of phenol (0 5%) injected through the first or second sacral foramen in all forms of sciatica, in herpes zoster, and in cancerous intractable pain The technique is that described by Bonica[4]

The principal difference between our method and that of Dr Maher (Jan 5) is that by our method the phenol diffuses into the perineural tissue, whereas Dr Maher injects it directly into the cerebrospinal fluid or the epidural dural tissue Our method has given very good results in 450 cases of sciatica and 54 of herpes zoster As a rule a single injection sufficed to relieve pain and allowed the patient to move and walk with ease The injection had often to be repeated in a day or two, but if as many as 3 injections were found insufficient the treatment was abandoned About 15–20% of our patients proved to be refractory

I have observed no disabling symptoms such as incontinence, and since the patients who were relieved have remained free from pain throughout the time of observation (one to two years) I have no hesitation in recommending this method for sciatica and herpes zoster

St István Hospital,
Budapest

T Lehoczky

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[1] Mouzas G L Diggory P L C *Lancet* 1956 ii 1073

[2] Reay-Young P S *Ibid* p 1217

[3] Martonfy J Balta G *Orvosi Hetilap* 1956 97 587

[4] Bonica J J The Management of Pain London 1953 p 352

DANGEROUS CONTAMINANTS IN STORED BLOOD

Sir,—I too am greatly relieved that Dr Discombe (Feb 2) agrees that the use of blood that has been tapped (under approved conditions) may be safely used more than 24 hours after the tapping

The scanty evidence available suggests that contaminants in blood in sufficient strength to be dangerous are exceedingly rare, and that they are in the bottle or cap before the blood is collected, as in Dr McEntegart's cases,[1] and are not introduced by tapping the bottle under approved conditions This somewhat dogmatic assertion is based on perhaps uncertain, but to my mind convincing, evidence, for in those regions where pilot tubes are not supplied very many bottles must have been tapped and used more than 24 hours after tapping there is no record of blood contaminated in this way causing death

Dr Discombe asks how many patients I have saved from contaminated blood by the film technique during the short time the technique has been in use no contaminated bottles have been found If, however, antespective action had been taken, and the blood-film examined before rather than after the blood had been given, the two patients recorded by Dr McEntegart might have survived The same applies to other patients who have died from infected blood[2 3] There are probably yet others, as not all deaths due to transfusion are recorded, and in some cases in which contaminated blood has been given the cause of death may have been missed

If I had to prepare blood for a member of my family I would certainly examine a stained film I would not worry if the bottle had been tapped previously by a trained worker in whom I had confidence and who had all facilities and if it had been properly refrigerated under continuous laboratory control I would never use a bottle that had been handled by a careless clinician

Pathology Department
Worthing Hospital

Read Aidin

AN AMERICAN IN BRITAIN

Sir,—It may be of interest to summarise my experience as an American Air Force physician during the past two years in Britain

At our station, which has roughly 3000 troops and 500 dependants, we see many hundreds of 'acute sore throats" In each case a throat-swab is cultured and generally no antibiotic is given unless a Lancefield group A organism is found We have found such an organism in only 26 cases in two years We have had no cases of rheumatic fever or of acute nephritis Standard treatment is one shot of 'Bicillin' (benzathine penicillin)

At our well baby clinic we see children roughly five times before the age of 3 years, and we try to apply a tuberculin skin test yearly We have found 4 positive reactors in two years, and these children (aged 4 years or less) are all being treated with isoniazid Progressive primary tuberculosis or other complication has not developed in any of them

We have had no cases of chilblains or similar cutaneous disorder, but many have reported skin complaints

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[1] McEntegart M G *Lancet* 1956 ii, 909

[2] *Brit med J* 1952, i 1036

[3] *Ibid* 1954 ii 934

(dryness, scaling, pruritus) apparently due to the local water, too little fat in the diet, and excessive washing with too strong a soap It has been a great relief not to have to worry about dog bites, because of the great rarity of rabies in the United Kingdom

We have seen many cases of what is generally called either *gastro intestinal flu or epidemic nausea, vomiting, and* diarrhœa (in children), and these cases have a certain similarity to the disease called winter vomiting sickness Meningism, however, has not been prominent

One interesting disorder is what we have come to call the 'paraffin complex," which is due to misuse of paraffin heaters Many of our people use these heaters in poorly ventilated rooms and may forget to trim the wicks This produces headaches, injected conjunctivæ, and difficult breathing Several children were treated for "recurrent pink eye" before the nature of the process was recognised

Our problems with venereal diseases, adult tuberculosis, and catastrophic disease (diabetes, infarction, serious trauma) *reflects, I believe, the expected incidence* in an adult population of similar age composition in England

From this brief survey it can be seen that, though our problems are pretty much the same, certain aspects are relatively fresh to us In closing I should like to thank the local medical personnel for their unstinted help It will indeed be a pleasure to entertain any that may visit us in the U S A

R A F Station,
Upper Heyford, Oxon

EMIL P TAXAY

Obituary

DOUGLAS ROBERT MacCALMAN

M D Glasg, F R C P E

Dr D R MacCalman had held chairs of psychiatry in Aberdeen and in Leeds His death at the age of 53 has come at a time when his knowledge and experience, especially in child guidance, will be greatly missed

He was the son of the late Rev D M MacCalman of Strachur Argyll, and he was educated at Glasgow Academy and at the University of Glasgow, where he was awarded the William Hunter medal in pathology After graduating M B in 1929 he held resident appointments at Glasgow Royal Infirmary and at mental institutions The following year he visited the United States and worked under Prof Macfie Campbell at the Boston Psychopathic Hospital and under Prof Adolph Meyer at the Johns Hopkins Hospital, Baltimore At Boston he took part in a large investigation into the cause of schizophrenia and he also studied variations in the blood-picture in different psychological states

On his return to this country in 1932 he became medical director of the Notre Dame child-guidance clinic in Glasgow The following year he took the M D with high commendation and in 1934 he joined the staff of the Royal Victoria Infirmary, Glasgow, as assistant physician for diseases of the nervous system He continued the work on the Rorschach test which he had begun in the United States

In 1935 he moved to London to take up the post of general secretary to the Child Guidance Council and psychiatrist to the Child Guidance Clinic

At that time the Council was financed and in every other way upheld by the Commonwealth Fund, and MacCalman's knowledge of the way things worked in America was of great value So also was his quiet determination to get child psychiatry on a sound footing in this country and he drew general physicians, and particularly pediatricians, as well as psychiatrists, academic psychologists, and the branches of the social services, into the work

In 1938 he was appointed the first (and only) Crombie Ross lecturer in psychopathology in the University of Aberdeen As a colleague later said "That region of hardy Calvinists and high thinking must have been a difficult field for a psychiatrist to cultivate But if his appointment was a bold experiment it was a successful one His assignment was to give instruction in the *causes and treatment of the* common neuroses, and to develop a child-guidance service and inpatient and out patient psychiatric services in the general teaching hospital At the height of the Normandy campaign in 1944 many psychiatric casualties found their way to the E M S hospital at Aberdeen, and MacCalman by early diagnosis and active treatment prevented the chronicity seen in the shell-shocked soldier By 1946, despite war-time handicaps, he had vindicated himself as a pioneer, and the University of Aberdeen promoted his department to professorial status and installed him as its first professor of mental health By the time he left in 1948 to take up his chair at Leeds the new department had been brought up to establishment, a comprehensive teaching programme organised, and the framework for an integrated mental health service constructed W M M, his successor, records

There is no feature of the present set up in Aberdeen that Douglas MacCalman did not either plan or foresee His effectiveness was all the more noteworthy because he was always so modest and unassuming His West Highland canniness and reserve concealed an astute and lively mind and his characteristic pawkiness many a time revealed itself in unexpected ways But his most outstanding quality during the years that I knew him was his fortitude

At Leeds he held at first the Nuffield chair of psychiatry, but in 1951, owing to ill health, he exchanged this for a part-time chair Much of the organisation of the psychiatric services in the Leeds hospital region shows evidence of his interests A flourishing child guidance department in the university psychiatric clinic gave him scope for his experience Last year he visited Australia as an adviser, and on his return to Leeds as part-time professor he supervised research projects which linked the university and the mental hospitals of the region He also fostered the Leeds Regional Psychiatric Association and he was active in the formation of the Mental Health Research Fund

E M C writes

MacCalman had a disarmingly quiet manner and a voice which was often difficult to hear Anyone supposing that he was unable to stand up to opposing opinion would deeply misunderstand the strength of his character Gentle he certainly was, but on occasion he could denounce sham and fumbling administration in terms of the keenest bitterness It was, however always done without rancour, and he always returned to the fight, tough and determined and deeply *intuitive as to the needs of the situation* whether in terms of a personal patient or of the laying on of a service

He died on Jan 31 He leaves a widow and a daughter

Appointments

BATES, MARGARET M, M B Camb, D P H: M O, public health department, London County Council
CORBETT, C C, M CH, N U I, D L O: consultant E N T surgeon, North West Durham and Durham group of hospitals
DAVIDSON, J I, F R C S I, D A: anæsthetist (S H M O), East Fifeshire, based on Kirkcaldy general hospitals
DAWKINS, JOAN M ST V, M B Lond, D I H, D C H: district M O H, Daventry
LEVY, RONALD, M B Leeds, D M R D: consultant radiologist, Sunderland group of hospitals
MALCOLMSON, K G, M B Belf, F R C S, D L O: consultant E N T surgeon, United Bristol Hospitals and the South Western Regional Hospital Board
MAIR, R S, M B Birm, M R C P, D C H, D I H: senior administrative M O, Nottinghamshire
NUTTIN, H L, M B Aberd, D P H: M O H, Beccles, Bungay, Halesworth and Leiston
PHILLIPS, J L F, M B Wales, D O M S: ophthalmologist, school health service, Stoke on Trent
WINFRID, I J B, M B Edin: M O, public health department, London County Council

Leeds Regional Hospital Board
HOWARD, J D, M B Sheff, F F A R C S, D A: assistant anæsthetist (S H M O), Scarborough, Bridlington, Malton and Whitby group of hospitals
PARKES, W J, M D Birm, M R C P, D C H: consultant geriatrician in Huddersfield group of hospitals
WARD, C S, M B Lond, F F A R C S, D A: part time consultant anæsthetist, Huddersfield area hospitals

Surrey County Council
PRYCE JONES, ELIZABETH, M B Leeds, D C H: assistant M O
QUANTRILL, D W, M B Birm, D I H, D T M & H, D OBST: assistant M O
YATES, S H, M B Sheff, D I H: assistant M O

Notes and News

COMMITTEE ON RADIOLOGY

A COMMITTEE to review the present practice in diagnostic radiology and in the use of radiotherapy in non malignant conditions has been set up by the Minister of Health and the Secretary of State for Scotland and has begun work. The decision to appoint this committee,[1] under the chairmanship of Lord Adrian, O M, accorded with a recommendation by the Medical Research Council's Committee on the Hazards to Man from Nuclear and Allied Radiation[2] The terms of reference of the new committee are

> To review the present practice in diagnostic radiology and the use of radiotherapy in non malignant conditions having regard to the Report of the Committee on the Hazards to Man of Nuclear and Allied Radiations and to make recommendations.

The members in addition to the chairman are

Prof J C McC Browne, F R C O G Sir Horace Evans F R C P Mr R J G Grewcock L D S Prof R J Kellar F R C O G Dr Peter Kerley Dr D R Maitland Prof W V Mayneord D SC Prof J S Mitchell F F R F R S Mr C Naunton Morgan F R C S Dr Kenneth Robson Mr T Holmes Sellors F R C S Mr G R. Seward M D S Prof F W Spiers D SC Prof E J Wayne F R C P Prof C A Wells F R C S Prof B W Windeyer, F F R

A JOURNAL OF MEDICAL HISTORY

IT is a pleasure to welcome at long last a major British journal dealing with *Medical History* Published by the antiquarian booksellers, William Dawson & Sons, and edited by Mr W J Bishop for many years librarian at the Wellcome Historical Medical Library, the first number of 90 pages is a handsome piece of work. Its decorative cover, incorporating a portrait of Thomas Linacre, worthily suggests the quality of the material it contains

This quarterly journal devoted to the history and bibliography of medicine and the related sciences is already the official organ of three history of medicine societies and of the Osler Club of London The five special articles in this number include an interesting account of Blue Books by Sir John Charles, and articles on the history of venous thrombosis on the plague in Cambridge, and on the health of James VI of Scotland and I of England There are also sections on texts and documents and on news notes, and queries, that may well be the strength of the journal Book reviews, society reports and a long list of medical anniversaries for 1957 are prominent features There are eight admirable full page plates The paper and type are excellent

There is at the moment a growing interest in medical history The new journal will be an added stimulant and it deserves full support both financial and literary from all who are interested in medical history or medical bibliography It is obtainable at £2 10s per annum from the publishers 4, Duke Street, Manchester Square, London, W 1

S H M O.s UNDERTAKING CONSULTANT DUTIES

COMMITTEE B of the Medical Whitley Council has agreed to consider claims for remuneration on the consultant scale submitted by senior hospital medical officers who are undertaking consultant duties[3] Application forms may be had from the secretary of the British Medical Association (B M.A House, Tavistock Square London W C 1) to whom the completed forms should be returned by March 2

HOSPITALS IN NORTHERN IRELAND

THE report for 1955[4] of the Northern Ireland Hospitals Authority shows that during the year admissions and out patient attendances were each about 1% more numerous than in the previous year The provision of new buildings at mental hospitals was helping to reduce over-crowding but, says the report, ' further building will be essential before the situation can be regarded as satisfactory ' Work continued on the planning of admission units for three mental hospitals

* * *

International Society of Internal Medicine

Sir Russell Brain F R C P has been elected president of this society The next meeting will be held in Philadelphia from April 24 to 26 1958

University of London

Dr M J Blunt, senior lecturer in anatomy at St Bartholomew's Hospital Medical College, has been appointed to the readership in anatomy at that college

Dr Blunt who qualified from Guy s Hospital in 1944 was resident surgical officer at Woolwich Memorial Hospital before he became lecturer in anatomy at the Royal Free Hospital Medical School He has also been visiting lecturer in anatomy at Queen Elizabeth College He took up his appointment at Barts last year His published work includes papers on the poster or wall of the inguinal canal and on the blood supply of the facial nerve.

Royal College of Physicians of Edinburgh

At a quarterly meeting of the college held on Feb 5, with Dr. A Rae Gilchrist, the vice president, in the chair, the following were elected to the membership

R F Gaymer M. A. O Halloran Misra Madhav Prasad James Allan, John Wilkinson Boris Levin Saifuddin Ahmed Elaine H McNeil Smith, Mohan Sankar Narayan Pathy Sharnagat Singh Khandpur Ram Dev Pasi B J Baldachin J R Roy A C Gibson Purnendu Samaddar Mukherji Flora M Bissett Smith J P F Fogarty N Z Sacks Tribhovanbhai Becharbhai Patel Anokchand Jain J H Learmonth Koratti Ardhanarishwara Krishnamurthy Bhim Prosad Mozoomdar W B Hudson Pitambar Dayal

Royal College of Physicians of Ireland

At a meeting of the college on Feb 1 the following were admitted to membership Elizabeth A. A. Awoliyi, W. D Linehan, R J P Skelly

British Medical Association

The annual meeting of the association will be held in Newcastle upon Tyne from Wednesday, July 10, to Friday July 19

Biochemical Society

A meeting of this society will be held at the Senate House of the University of London, W C 1, at 11 A M on Saturday Feb 23, when there will be a symposium on the structure and function of subcellular components

Central Council for Health Education

The council s summer school is to be held from Aug 20 to 30 at the University of North Wales, Bangor, on the promotion of health The speakers will include Dr J N Morris, Dr Wilfred Barlow, and Dr C O Carter Further particulars can be had from the medical director of the council, Tavistock House, Tavistock Square, London W C 1

Lady Tata Memorial Trust

The trustees of this fund invite applications for grants, scholarships, or fellowships for research on blood diseases, with special reference to leukæmia, in the academic year beginning next October Programmes of research on any aspect of malignant disease which may throw light on problems of leukæmia will be considered, and awards may be made to investigators of any nationality, working in any country where payment can be made Particulars and application forms may be had from the secretary of the (European) Scientific Advisory Committee of the trust, Chester Beatty Research Institute, Fulham Road, London, S W 3 Applications must be submitted before March 31

Society for General Microbiology

The general meeting of this society will be held at the Royal Institution, Albemarle Street, London, W 1, from April 15 to 17 At 6 P M on Monday, the 15th, Dr Andre Lwoff of the Pasteur Institute Paris, will give the Marjory Stephenson lecture on the Notion of Virus This lecture will be open to non members On Tuesday and Wednesday, the 16th and 17th, there will be a symposium on microbial ecology and the speakers will include Dr Jane Gibson, Dr E S Anderson, Dr C H Andrewes F R S, and Dr G S Wilson Further particulars may be had from the office of the society c/o Institute of Biology, 41, Queen s Gate, S W 7

International Symposium on Curare and Curarising Substances

This symposium will be held in Brazil from Aug 5 to 17 During the first week meetings will be held at the University of Brasil in Rio de Janeiro and during the second week visits will be made to Manaus (Instituto Nacional de Pesquisas de Amazonia) and to Belem (Instituto Agronomico do Norte) Further particulars may be had from Prof C Chagas, Instituto de Biofisica, Universidade do Brasil, 458, Avenida Pasteur Rio de Janeiro, Prof Daniel Bovet, Instituto Superiore di Sanita 299, Viale Regina Elena, Rome, or Prof P B Carneiro, Delegation du Brésil, UNESCO, 19, Avenue Kleber, Paris 16e

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[1] See *Lancet* 1956 ii 1[illegible]

[2] H.M Stationery Office 1956 See *Lancet* 1956, i 919

[3] *Brit med J* Feb 9 1957 suppl p 60

[4] Issued by the Authority Victory Buildings 44 Queen Street Belfast [illegible] 2s 6d

International Symposium of Clinical Psychopharmacology

Further particulars of this symposium, which is to be held at Milan from May 9 to 11, may be had from Dr S Garattini, Via A del Sarto, 21, Milan

European Organisation for Research on Fluorine and Dental Caries Research

A meeting of this organisation will be held at Malmö, Sweden, from June 15 to 17 Further particulars may be had from Professor Syrrist, Royal Dental School, Malmo

Education for Motherhood

A seminar for medical officers of health on health education for the expectant mother is to be held at St John House, Collingham Gardens, London, S W 5, from Feb 26 to March 1 Further particulars may be had from the medical director, Central Council for Health Education, Tavistock House, Tavistock Square, W C 1

Atoms and Health

The Royal Society of Health, with the United Kingdom Atomic Energy Authority, is holding an exhibition on this subject at 90, Buckingham Palace Road, London, S W 1, from Monday, March 18 to Friday, May 31 It will be open to the public on Mondays to Fridays from 10 A M to 5 P M

Hearing-tests for Cerebral Palsied Children

A film on this subject has been made at the Centre for Spastic Children, Chelsea in coöperation with the audiology unit of the Royal National Throat, Nose, and Ear Hospital The film is silent (16 mm, 650 ft), and a script to go with it can be obtained or a lecturer supplied from the centre, 61, Cheyne Walk, London, S W 3

American Broadcasts on British Medicine

During February and March, in its weekly broadcasts on Thursday evenings *For Doctors Only*, the New York Academy of Medicine is including a series of lectures on British medicine The lecturers are to be Sir David Campbell, Lord Cohen of Birkenhead, Sir Charles Dodds, Dr J R Duthie, Prof C F W Illingworth, Prof John McMichael, Prof Alan Moncrieff, Sir James Paterson Ross, Mr T Holmes Sellors, Prof B W Windeyer, and Prof L J Witts

Ministry of Health Appointments

Mr Dennis Vosper, the Minister of Health, has appointed Mr John Barter, M P for Ealing North, as his parliamentary private secretary He has appointed Mr P Benner to be his private secretary and Mr E F Cooper to be his assistant private secretary

Mr J K Vaughan-Morgan, the parliamentary secretary to the Ministry, has appointed Mr J P Cashman to be his private secretary

National Association for Maternal and Child Welfare

The annual conference of this association will be held at Church House, Westminster, London, S W 1, from June 26 to 28 The theme of the conference is to be safeguarding the health of mother and child, and the speakers will include Dr Charlotte Naish, Dr J W B *Douglas*, Dr W C Cockburn, Dr Ian Taylor, Sir Weldon Dalrymple Champneys, and Prof F R G Heaf Further information may be had from the secretary of the association, Tavistock House North, Tavistock Square, W C 1

International Poliomyelitis Conference

This conference will be held at Geneva from July 8 to 12 The subjects chosen for discussion include vaccination against poliomyelitis, enteric viruses producing disease simulating poliomyelitis, studies on cultured mammalian cells, general considerations of viruses, respiratory distress in patients with poliomyelitis, and care of patients severely stricken by poliomyelitis Further information may be had from the secretariat of the conference, *Hôtel du Rhône, Geneva*, Switzerland

French Government Exchange Scholarships

Under a reciprocal arrangement with the Centre National de la *Recherche Scientifique*, the Medical Research Council invite applications from British workers in medical science for two scholarships tenable at research institutions in France during 1957–58

The scholarships will carry a maintenance allowance of 50 000–70 000 francs a month *married men will receive a supplementary* allowance and provision will be made for travelling expenses Further particulars may be had from the secretary of the council, 38 Old Queen Street London S W 1 with whom applications must be lodged by March 31

Diary of the Week

FEB 17 TO 23

Monday, 18th

HUNTERIAN SOCIETY
8 30 P M (Mansion House, E C 4) Mr A W Badenoch The Surgery that Hunter Changed

UNIVERSITY COLLEGE OF LONDON, Gower Street, London W C 1
5 30 P M Mr T S Work, D SC, Biochemical Approach to the Problems of Protein Synthesis (First of two lectures)

POSTGRADUATE MEDICAL SCHOOL OF LONDON, Ducane Road, W 12
4 P M Dr W Ritchie Russell Pain

Tuesday, 19th

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields W C 2
3 45 P M Dr Frank Stansfield Anatomy of the Visual Pathway (Arnott demonstration)

ROYAL SOCIETY OF MEDICINE, 1 Wimpole Street, London, W 1
8 P M *Pathology Physical Medicine* Dr W S Tegner, D Bruce Cruickshank, Dr A T Richardson, Dr L E Glynn Rheumatoid Disease

BRITISH POSTGRADUATE MEDICAL FEDERATION
5 30 P M (London School of Hygiene and Tropical Medicine Keppel Street, W C 1) Mr A L Greenbaum, PH D Control of Fat Metabolism

ST MARY'S HOSPITAL MEDICAL SCHOOL, W 2
5 P M Mr Norman Morris Uterine Blood flow During Late Pregnancy and Labour

ROYAL ARMY MEDICAL COLLEGE Millbank London S W 1
5 P M Prof G W A Dick Attenuated Virus Vaccines

INSTITUTE OF DERMATOLOGY, Lisle Street, London, W C 2
5 30 P M Dr G B Dowling Scleroderma and Dermatomyositi

MANCHESTER MEDICAL SOCIETY
4 30 P M (Medical School, University of Manchester) *History of Medicine* Dr William Brockbank Debt of Medicine to Her Undergraduate Students

Wednesday, 20th

ROYAL SOCIETY OF MEDICINE
8 15 P M *General Practice* Dr Kenneth Irvine, Sir Geoffrey Marshall, Sir Clement Price Thomas Modern Outlook in the Management of Pulmonary Tuberculosis

POSTGRADUATE MEDICAL SCHOOL OF LONDON
2 P M Dr J H Humphrey Biochemical Mechanisms Underlying Hypersensitivity Reactions (First of two lectures)

INSTITUTE OF DERMATOLOGY
5 30 P M Dr Henry Haber Localised Disease of the Collagen

INSTITUTE OF DISEASES OF THE CHEST Brompton, S W 3
5 P M Dr Howard Nicholson Pneumonia

ROYAL MICROSCOPICAL SOCIETY Tavistock House South W C 1
5 30 P M Mr R J King, M SC Investigations of Mouse Ascites Cells by Ultraviolet Phase contrast and Interference Microscopy

NOTTINGHAM MEDICO CHIRURGICAL SOCIETY, 64, St James's Street Nottingham
8 30 P M Dr R M B MacKenna Common Problems in Dermatology

Thursday, 21st

ROYAL COLLEGE OF SURGEONS OF ENGLAND
3 45 P M Mr B E Greenfield Functions of the *Masseter* Muscle (Arnott demonstration)

BRITISH POSTGRADUATE MEDICAL FEDERATION
5 30 P M (London School of Hygiene and Tropical Medicine) Miss Honor Fell, F R S Physiology of Skeletal Tissue in Culture

ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE, 26 Portland Place, W 1
7 30 P M Dr W S S Ladell Physiological Aspects of the Heat Disorders

HYPNOTHERAPY GROUP
8 P M (1 Wimpole Street, W 1) Dr D M L Doran Dr Ian Hadfield Hypnotherapy From the Trainee Point of View

LIVERPOOL MEDICAL INSTITUTION, 114, Mount Pleasant Liverpool 3
8 P M *Pathological Meeting* Dr Edith Dawson Mammary Cancer in Young Subjects with Special Reference to Pregnancy

MANCHESTER MEDICAL SOCIETY
8 P M (Staff House University of Manchester) *Anaesthetics* Dr B L S Murtagh Anaesthetics and Midwifery

NORTH WESTERN TUBERCULOSIS SOCIETY
5 P M (Manchester Royal Infirmary) Dr Brockbank Asthma

UNIVERSITY OF ST ANDREWS, *Queen's College*, Small's Wynd Dundee
5 P M Prof C Bruce Perry Prevention of Acute Rheumatism

Friday, 22nd

ROYAL SOCIETY OF MEDICINE
4 P M *Paediatrics* Dr A White Franklin *Place of the Paediatrician in the Maternity Hospital* Dr John Murray Dr G H Lathe Dr A P Norman Haemolytic Disease of the Newborn
8 15 P M *Obstetrics and Gynaecology* Prof J McClure Browne, Mr Norman Morris, Mr John Sophian Ætiology of Pre-eclampsia

POSTGRADUATE MEDICAL SCHOOL OF LONDON
10 A M Mr Geoffrey Flavell Unusual Manifestations of Cancer of the Lung

REFLECTIONS ON CIRCULATORY CONTROL *

T Cecil Gray
M.D Lpool, F.F.A R C S
READER IN ANÆSTHESIA, UNIVERSITY OF LIVERPOOL

The story of modern anæsthesia can, I think, be summarised in one word—control During the past ten to fifteen years, new drugs have been introduced which, little by little, have enabled us accurately and surely to regulate the bodily mechanism of our patients, until today it is almost possible to manipulate basic physiology as one might play an organ—pulling out this stop or suppressing that in order to achieve an effective blend of safety for the patient and excellent conditions for the surgeon

After the first great discovery of general anæsthesia in 1846, which gave man some merciful control over the consciousness of his suffering fellows, the next most significant step was taken when Griffith and Johnson (1942), by the use of curare, demonstrated the clinical feasibility of the control of muscle tone It was very soon realised that there was no longer any excuse for the turbulent belly and the struggling surgeon, and by 1946 there should have been, in Frankis Evans's picturesque phrase, " no question of a vast abdomen moving in gusty waves " (Evans 1946)

But this was not just a new tool in the anæsthetist's bag, it had a greater significance than the mere smoothing out of a troublesome anæsthesia Time has shown that the effects of this discovery extend over a very wide field indeed One has only to think of the need which at once arose for better-trained anæsthetists who could be safely entrusted with this potent new therapeutic weapon, and as a result of this improved educational background the raising of the status of the anæsthetist, not only economically but (more important) in the esteem of his colleagues Still more important, however, were two new " controls " which were at once placed in our hands

It is true that before curare control of the respiration had been practicable by a combination of central nervous depression and excessive ventilation of the lungs But the procedure was not satisfactory, and, because of the widespread depression of bodily function produced by deep anæsthesia, it demanded a price With curare, respiratory control by peripheral paralysis of the muscles of respiration was possible, and even inevitable if curare was to be used safely and effectively Artificial ventilation of the lungs was imperative whenever curare was given, and thus anæsthetists became experts in controlled ventilation The floodgates to a great stream of research into the various types of artificial respiration were opened, and led to a renewed interest among clinicians in the physiological principles of pulmonary ventilation As a result too, anæsthetists have been able to make considerable contributions towards the treatment of diseases involving the respiratory apparatus, such as poliomyelitis, tetanus and various forms of poisoning

Perhaps, however it might be held that an even more significant result followed the introduction of curare In 1946 I wrote, " the age of deep anæsthesia with its attendant respiratory and circulatory depression and postoperative dangers should have passed away " The use of curare was in effect the first step in achieving control of the circulation—for all the anæsthetic agents of sufficient potency when given in the dosage required to achieve muscular relaxation, seriously disturb the regulation of circulatory stability All through the central nervous and cardiovascular systems these agents exert their effects—function is depressed From the vital medullary centres regulating vasomotor control and the heart-rate, through the servo-mechanisms in the aorta, carotid body, and great veins, down to the very pump itself, the myocardium—all are depressed by anæsthetic agents The kaleidoscopic fluctuations of the vast capillary bed are slowed and their responsiveness to hæmorrhage is lost Zweifach and his colleagues had shown in 1945 that deep anæsthesia abolished the response to transfusion after hæmorrhage As with hæmorrhagic collapse so also with autonomic reflexes—if afferent stimuli from the mesentery, mediastinum, or liver-bed produced reflex circulatory collapse—evidenced by low blood-pressure and bradycardia—the collapse, under deep anæsthesia, tended to persist On the other hand, the very light anæsthesia that was possible when curare was used left the protective reflexes unimpaired and the reflex control of vasomotion still sensitive and adequate for compensatory responses

It was appreciated that surgical trauma in so light a plane of anæsthesia might have its own hazards Crile (1921) had warned that the brain which was only half asleep might respond to trauma by initiating circulatory collapse But the experience of the past ten years has shown that light anæsthesia does not in fact conduce to circulatory collapse Thoracotomies are now often carried out under nitrous oxide/oxygen anæsthesia alone, and anæsthesia per se has never produced less deterioration of the circulation than at present

This very absence of " shock " in patients only just asleep turned our minds and thoughts to the study of the fundamentals of circulation and respiration, and even of mind and consciousness itself So light is our anæsthesia, with patients often moving frowning, or showing other reactions to stimuli, despite complete unawareness, that we have begun to wonder what indeed is meant by unconsciousness Is it perhaps, after all, only loss of memory from instant to instant ?

One recalls the words of John Snow (1847) as he contemplated the effect of the invention of anæsthesia

> " The power we have acquired, through the discoveries of our medical brothers in America of inducing at will and with perfect safety such a state of insensibility as we should probably have thought to be alarming cannot be without its influences on the progress of our knowledge of the diseases of which insensibility form a symptom. and of the function of the nervous system generally "

Induced Hypotension

The next advance in our control of the circulation stemmed directly from these developments As the circulatory dynamics were little affected by light anæsthesia, a new problem arose—bleeding Of course, at first, curare the new drug itself, was thought to be causative This was inevitable for any new drug is likely to be blamed for every unexpected reaction of the patient to whom it is given

Undoubtedly, failure to appreciate the need for adequate pulmonary ventilation played a part, but the light plane of anæsthesia now being used was the principal cause My colleague, Dr McLoughlin (1954), has shown that in these light stages of anæsthesia (1) the amount of bleeding is inversely proportional to the plane of anæsthesia, and (2) cyclopropane causes one and a half times as much bleeding as ether In Edinburgh around 1948 cyclopropane was extensively used, and Gillies (1952) himself has acknowledged that this undoubtedly contributed to their ready appreciation of the dry surgical field provided by total spinal block Evolution is, in a sense, inevitable, and it is idle to speculate on alternatives, but I hazard a guess that, had not curare

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* The Alex Simpson Smith memorial lecture of the West London Hospital Medical School delivered on Oct 30, 1956.

been introduced to anæsthesia, we should not now use induced hypotension

However that may be, to return to my previous simile of the organ, Gillies in 1948 pulled out a full diapason stop by demonstrating to anæsthetists, and (perhaps unfortunately) to surgeons, the practicability and apparent safety of deliberate lowering of the blood-pressure (Griffiths and Gillies 1948) The field of operation now approached the ischæmic pallor of the post mortem room, and when the original method of complete sympathetic block by high spinal anæsthesia was supplanted by the use of ganglioplegic drugs it was inevitable that this particular control would be used widely In hæmorrhagic operations the need for transfusion was reduced It seemed clear that one pint of blood retained in the circulation was worth two citrated and out of a bottle Neurosurgical, plastic, and otolaryngological operations, hitherto hampered by congestion, were facilitated, and enthusiasm has waxed strong Quite apart from the obvious advantage of a bloodless field of operation, it has been suggested (and this is always propounded by the advocates of every new anæsthetic technique) that hypotension induced by drugs protected against those circulatory responses which are so often misleadingly described under the general term "shock" (Wyman 1953) It is thought that this might be due to the blocking of afferent autonomic impulses or to the avoidance of the stress of over compensatory vasoconstriction and the free flow of blood through the capillaries

Dangers of Hypotension

With a new advance in clinical practice, a compromise has often had to be made between, on the one hand, submitting our patients to remedies incompletely investigated and, on the other hand, overlong delay in exploiting their salutary and beneficial effects In any case, in medicine, as in every other sphere, knowledge is doomed always to be incomplete and there cannot but be some empiricism in therapeutics

This empiricism was certainly exercised in the clinical application of hypotension, but I believe time has shown that widespread use of this technique is not justified More investigations than one (Armstrong Davison 1951, Van Bergen et al 1954) have yielded electrocardiographic evidence suggesting myocardial ischæmia during hypotensive anæsthesia, and Nilsson in Sweden (1953) obtained, by flicker fusion tests, evidence of subclinical cerebral damage during these operations There are certainly ample experimental data now to confirm the obviously expected interference with cerebral circulation (Saunders 1954, Hughes 1955) and a change in cortical function has been shown by alteration in the electro encephalogram (Van Bergen et al 1954) There is some danger of renal ischæmia where drugs are used to produce hypotension (Aas and Bergen 1949) or when the hypotension is prolonged (Armstrong Davison 1951) These and other similar investigations lead one to think that the a-priori reasoning on which the safety of the technique was first deduced was perhaps too naïve The argument was propounded in these terms

> The head of pressure driving blood through the capillary bed under normal conditions is of the order of 30 mm Hg The bulk of the peripheral resistance maintaining normal blood-pressure is in the arterioles, and, therefore, when all arteriolar tone is abolished (as in a condition of complete vasodilatation) and the patient is at rest under anæsthesia, the blood-pressure could be lowered considerably, without losing the requisite head of pressure to ensure capillary perfusion

The validity of this argument depends on the relation of the blood volume to the capacity of the vascular bed There is evidence that sometimes there may be disproportion during anæsthesia with low blood pressure, and then hypoxia is bound to follow (Van Bergen et al 1954) Furthermore, though it may be convenient in theory to look upon the human circulatory system in mechanical terms as a pump flushing a liquid through a series of pipes of variable diameter and resistance, there are factors, in particular disease, which make the analogy inapplicable

Therefore, though induced hypotension was at first enthusiastically welcomed by many surgeons and anæsthetists, it is not surprising to find that recent surveys have shown that this advance has exacted a price—some might say a heavy price Four years ago an editorial in one of the principal anæsthetic journals stated that there have been "unexpected deaths in apparently healthy people undergoing operations of no particular severity" (*Anæsthesia* 1952) Factual evidence for these "unexpected" deaths is now available The Association of Anæsthetists established, in 1949, a committee to investigate deaths during anæsthesia Of the first 1000 fatalities freely reported to that committee, 17 were in patients who had had hypotension While the committee cautiously reported that "it is not suggested that in any instance the use of intended hypotension was necessarily deleterious" (*Anæsthesia* 1953) from the data it would appear that in at least 5 patients the hypotension was probably gravely implicated, and in the remainder (which included cases of death due to reactionary hæmorrhage, cerebral and coronary vascular accidents, and anuric renal failure) the low blood pressure state probably contributed to death Four years ago Hampton and Little (1953) published the result of a questionnaire sent to 602 specialist anæsthetists in this country From the data collected, covering 21 000 patients submitted to hypotension, it appeared that this technique was implicated in a mortality-rate of 1 in 500 and a morbidity-rate of 1 in 38 In the United States a similar inquiry covered 6805 hypotensive anæsthetics and showed a mortality of 1 in 136 Even allowing for mismanagement and the wrong application of the technique, this is a morbidity-rate far greater than might be expected from normotensive anæsthesia, and an indictment that cannot be ignored

It is still widely claimed that in young and healthy people this technique is perfectly safe when used by experienced anæsthetists But youth and health do not necessarily go together, and disease is not always clearly apparent In this context a cardiologist has stated "that severe coronary heart-disease may be symptomless and produce no changes in the electrocardiogram and there is no reliable way of detecting it until myocardial ischæmia is produced" (Hayward 1952) He points out that "the state of the peripheral arteries gives no indication as to the health of the coronary vessels, and an increasing number of cases of coronary thrombosis is occurring in young, apparently healthy men, who at autopsy are found to have advanced coronary disease" He concludes by suggesting that in "certain types of operations where success may depend on the bloodless operative field the potential risk of the methonium compounds causing cardiac or cerebral ischæmia may have to be accepted"

These risks should no longer be taken In the first place, hypotension should be reserved for those cases in which it is clearly imperative because of the nature of the surgery this would limit it to neurosurgical, and perhaps some otolaryngological and plastic operations, and thoracotomies in the presence of aortic coarctation In the second place, even in these cases, I believe that the risks can be greatly reduced by combining hypotension with moderate hypothermia—that new "control" which has been given to us, control of the metabolism Sir James Learmonth who was in at the very birth of techniques for inducing low blood pressure, must have had this in his mind when he suggested that "a combination of the hypotensive and cooling techniques has many possibilities in facilitating and extending surgical procedures" (Learmonth 1953) It seems to me that the law of supply and demand applies just as much in the economy of the body human as in that of the body politic, and, if it is necessary to restrict the supply of blood to the tissues then, if damage is to be avoided with certainty, it is imperative to reduce the demand for blood At 30°C the body's oxygen consumption is about 50% of normal, and even at 32°C it is still reduced by 35%, our experience with hypothermia convinces me that to reduce the body-temperature to this level is safe and well within the competence of those who should practise induced hypotension It seems doubtful whether, except for the briefest periods, hypotension should ever be used without this additional safeguard It is time-consuming perhaps—but it seems that a couple of hours of preparation, which in practice can become of a very routine nature, is a small price to pay for the additional safety in those cases (and this I emphasise because I believe they are really not numerous) where hypotension is essential

Hypothermia

An enormous bibliography has accumulated on the subject of hypothermia and within the past eighteen months the Royal Society of Medicine has held no less than four meetings to discuss the subject I do not wish to cover the same ground again, for the usual effects of cooling should by now be well known I do, however, wish to give some evidence for the safety of cooling by the surface application of ice when it is combined with the administration of light anæsthesia and drugs such as chlorpromazine to ensure vasodilatation and freedom from shivering

Since 1953 I, and the anæsthetists associated with my department and the neurosurgical unit, have used hypothermia in over 250 patients The great majority, 180, have been patients undergoing neurosurgery in fact the neurosurgical unit is at present using this technique in 10–12 patients a month 46 have had general surgical operations, and the remainder have had vascular or cardiac operations In only one have we used the extra corporeal method

Methods of Cooling

It has been suggested that the method used to achieve hypothermia is "relatively unimportant" (Lucas 1956) I regard that as an oversimplification It seems likely that each method has its own indications and certainly each has its advantages and disadvantages The argument for some form of extracorporeal cooling in patients having cardiac or vascular surgery in the thorax is strong until the chest is opened and the diagnosis confirmed the patient need not be exposed to whatever risks are entailed in the cooling process It is perhaps less time consuming though both in animal experiment and in our patient we were surprised at the time required to cool and rewarm The vein-to-vein method (Ross 1954), modified by Sir Russell Brock (1956) in which blood is circulated from one vena cava through the cooling unit to the other vena cava, prohibits a very rapid lowering of temperature In these circumstances the heart is cooled more rapidly than the remainder of the body It is a fact that, with this method overenthusiastic cooling produces quite evident cardiac deterioration even while the general body temperature is high

After all by the surface method one can achieve enough cooling within two hours It seems to me that in the type of case for which hypothermia is used, the time factor should be relatively unimportant

It may be suggested that the extracorporeal method is more controllable Thus it is often alleged that the continued fall of temperature after removal of the ice makes surface cooling particularly unpredictable But this is much less of a problem if adequate vasodilatation is maintained by chlorpromazine or similar drugs, for in this way the gradient of temperature from the body core to the surface is considerably reduced Changes in posture during the cooling in order to prevent pooling of the blood probably also help, but the danger of this "after drop," as it has been called, is much lessened by its anticipation All our experience has endorsed the finding (Burrows et al 1956) that the degree of "after-drop" is related to the patient's build Lean patients with little adipose insulation cool rapidly and have little or no "after-drop," while the well-covered and insulated body cools slowly and the fall of temperature continues for some time after removal of the ice In the well-covered, perhaps the tyro would be well advised to stop active cooling, as Virtue (1955) suggests, at two-thirds of the required fall in temperature Shivering is no longer seen premedication with chlorpromazine and light anæsthesia have prevented this undesirable feature of surface cooling

Arrhythmias

A testimony to the safety of the method is the fact that except after intracardiac manipulation, we have had no case of ventricular fibrillation This seems to me not only evidence of controllability but also of interest because the 180 neurosurgical patients have not, in fact, had artificial ventilation (except when there has been acute respiratory depression, as when surgical manœuvres have interfered with the floor of the 4th ventricle) Vanderwater et al (1955) have produced results which suggest that, even though respiration is depressed and slowed in these circumstances, there is not necessarily a decrease in the pH of the blood, in fact there may occasionally be a tendency to alkalinity In contrast to the neurosurgical patients, all the others have been very actively ventilated It is, however, easy to demonstrate in dogs that ventricular fibrillation can be caused, below the critical temperature of 28°C, by sudden ventilation in cases where the respiration has been depressed I suspect that it is important to maintain steady ventilation and avoid sudden changes

Another sinister arrhythmia is bradycardia Intense bradycardia during hypothermia has been described in dogs by Cookson and Di Palma (1955) who believed it was due to direct depression of the sino auricular node That it was not due to vagal overactivity is suggested by the failure of vagotomy or atropine to reverse the condition We have seen this three times, and I am grateful to Dr Dundee for these cases 2 failed to

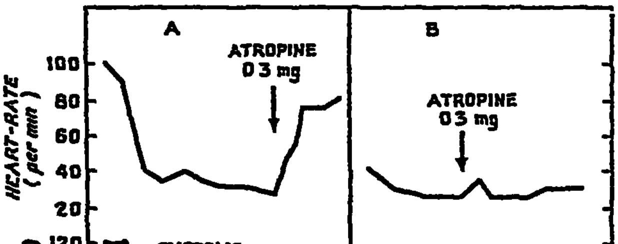

Fig 1—2 patients with bradycardia during hypothermic anæsthesia (A) Man aged 46 with a frontal lobe tumour bradycardia reversed by atropine (B) Woman aged 28 with an arteriovenous anomaly no change after atropine

respond to atropine, but in the other it was successful in removing the arrhythmia (fig 1)

Blood-coagulation

One of the complications of hypothermia which has exercised us has been its effects on blood-coagulation A patient whom we cooled by the surface method succumbed to intractable oozing which continued after the operation This was for portacaval anastomosis, and the hypothermia was used in an attempt to obtain a relatively dry field of operation In fact, the advanced liver cirrhosis, with a significantly reduced prothrombin index, contra indicated hypothermia He received 21 pints of blood, and he died forty-eight hours later, apparently from a transfusion reaction (Dundee et al 1953)

There are many references in the literature to uncontrollable postoperative hæmorrhage in animals (Helmsworth et al 1955) and to submucosal hæmorrhages in the viscera following hypothermia (Parkins et al 1954, Deterling et al 1955) The influence of a fall in temperature on the coagulation time of blood in vitro is well known (fig 2), but there is more to it than this Ross (1956) has drawn attention to the dangers of prolonged hypothermia and has shown that in dogs, at any rate, the proportion of recoveries from the hypothermic state falls very significantly after three to five hours He emphasises the particular danger of uncontrollable oozing

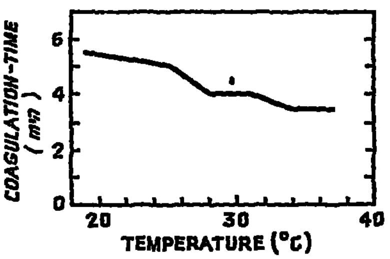

Fig 2—Effect of temperature on coagulation-time of blood as estimated by hair capillary method

During experiments to determine the steroid output at low temperatures, we have maintained 16 dogs, cooled by the surface method, at temperatures below 30°C for seventy-two hours 3 did not survive this period Of the remaining 13, we have attempted resuscitation in 9 without success, although they have survived for two or three days after rewarming Of these 9, 3 almost, but not quite, recovered consciousness At necropsy, apart from a boggy œdema of the tissues and transudation of fluid into the peritoneum and pleural cavities, hæmorrhage and congestion are the predominating features There is intense congestion in the liver accompanied by central lobular necrosis (fig 3), and in the kidneys (fig 4) accompanied by fluid exudation into the glomerular tufts The distal tubules show separation of the cells from the basement membrane, which is prominent and convoluted The suprarenals (fig 5) are characterised by vacuolation and loss of cells in the medulla, and necro in the cortex (fig 6). These changes are similar to (but more severe than) those described by Knocker (1955) in dogs cooled for up to three hours It cannot be stated that they are not due to hypoxia, for blood oxygen was not estimated, but in these experiments any sign of hypoxia would have been treated by assisted respiration

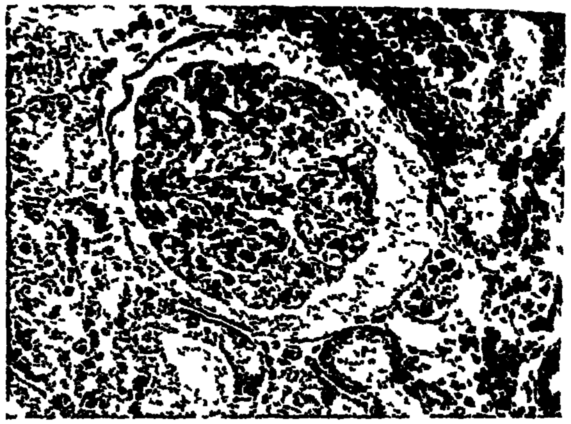

Fig 4—Kidney of dog (×360) maintained at 29°C for 72 hours. Congestion and exudate into glomerular capsule Prominence of basement membrane

Certainly the predominant characteristic—i e, reduction in the coagulation ability of the blood—could not be so explained The lungs are so congested that they can only be described as full of blood, and the bladder shows extensive submucosal hæmorrhages Oozing from each needle prick after withdrawal of blood samples and troublesome hæmorrhages from the wound edges were further evidence of the loss of clotting-power

Examination of the coagulation characteristics of the blood gave some explanation of these findings (fig 7) There was a slowing of the thrombin fibrinogen reaction and a fall in the platelet counts as the days passed, with corresponding changes in the coagulation time and prothrombin index

Though care was taken to maintain the electrolyte and fluid balance of these animals, they were not given protein, there may have been a loss of fibrinogen, associated with a general fall in plasma proteins But similar experiments in control dogs which were kept anæsthetised with pentobarbitone (though at normal temperature) for the same period showed that this was not the explanation These control dogs recovered rapidly and perfectly normally, and their blood coagulation characteristics were little altered (fig 8)

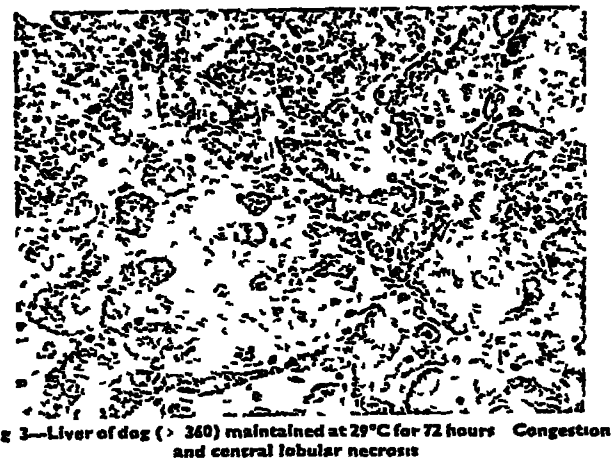

Fig 3—Liver of dog (× 360) maintained at 29°C for 72 hours Congestion and central lobular necrosis

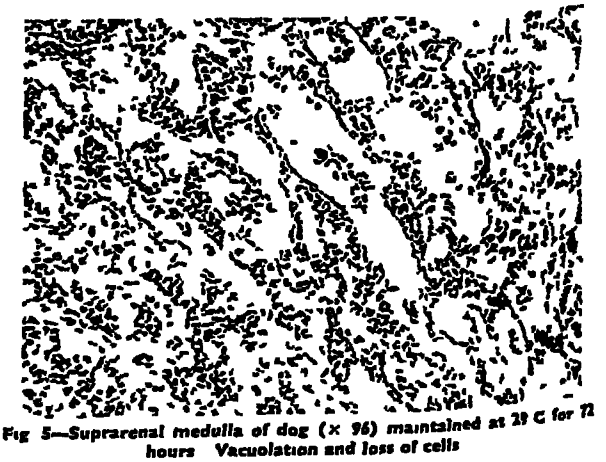

Fig 5—Suprarenal medulla of dog (× 96) maintained at 29 C for 72 hours Vacuolation and loss of cells

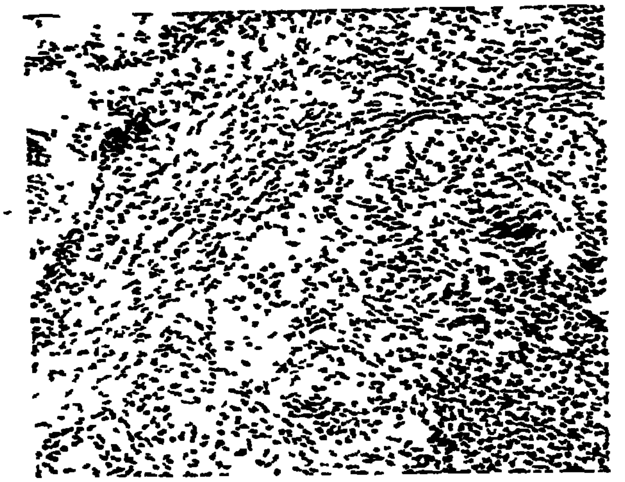

Fig 6—Suprarenal cortex of dog (× 96) maintained at 29°C for 72 hours Cell necrosis. Disappearance of typical cells.

The slowed fibrinogen-thrombin reaction in the cooled dogs might be due to loss of fibrinogen from depression of liver function, but Owren (1947) has shown that the optimum concentration of fibrinogen for blood-coagulation is 20% of that normally found. Fulton (1946) gives an even lower level. The possibility arises of the presence of a heparin-like substance Suomalainen (1954) in Finland has shown that during hibernation, hedgehogs have a greater prolongation of coagulation-time than can be accounted for by the fall in temperature This is associated with a proliferation of the mast cells which are deposited in the submucosa of the intestine and in the region of the bronchioles These cells are believed to liberate heparin. We have not yet estimated the heparin level of the blood of our animals but if it were increased this would account for all our findings A high heparin level might be due to liberation of an excess or to a delay in excretion of heparin at these low temperatures

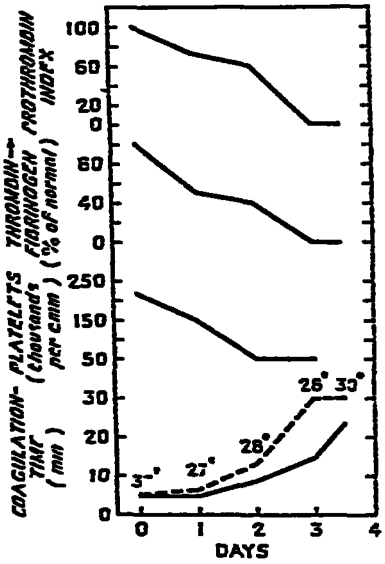

Fig 7—Coagulation characteristics of dog maintained at 29°C for 72 hours. The coagulation-time (hair-capillary method) is shown at the dog's temperature at the time of estimation and at normal body-temperature 37°C.

Practical Considerations

These observations may have little significance in regard to short periods of hypothermia—e.g., during operation—except to warrant care in patients in whom the blood-coagulation is not normal, but I think they may be of some importance where prolonged hypothermia is attempted in treating brain-stem injury or other conditions Very low temperatures should probably be avoided, and a check kept on the coagulation characteristics of the blood

With the exception of the single patient with reduced liver function that I have mentioned we have not seen this type of trouble with the 250 surface-cooled patients: and some have been kept at 30°C for up to four days

However all that may be, few will deny that these difficulties with blood-clotting are much less likely to be experienced with surface cooling than with the extracorporeal methods It is well known that the circulation of blood through tubes and valves leads to hæmolysis and loss of platelets and so interferes with coagulation This can be a real danger. Of 40 patients at the Mayo clinic maintained on a heart-lung apparatus during operations on the open heart (Kirklin et al 1956), 1 is reported to have died from intractable postoperative hæmorrhage It is suggested that this was due to the large amount of hæmolysis present (plasma-hæmoglobin 1.5 g per 100 ml.) The clotting elements of the blood were not investigated

There is reason to suspect that other workers have had more difficulty We have lost a patient from incoagulability of the blood after operation who was cooled by the simple apparatus described by Lucas (1956) modified by the use of siliconised rubber tubing instead of the less elastic vinyl plastic She was a girl aged 22 with pulmonary stenosis, treated by open valvotomy

Helmsworth and Cole (1956) have sought to show that changes of this nature in the blood are greater with surface cooling than with the extracorporeal method (see table) But their results might be misleading, because the estimation was made with the surface method at 23°C, and with the extracorporeal method at 28°C Apart from the possible effects of the difference in temperatures it seems certain that further circulation of the blood through the apparatus in order to achieve the extra 5°C of cooling would have altered the result very considerably and made it more justly comparable to that obtained with the surface method.

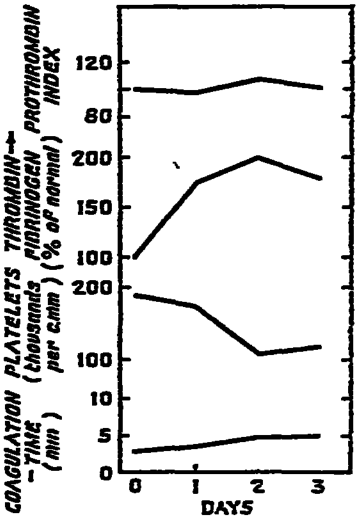

Fig 8—Coagulation characteristics of dog maintained anæsthetised with pentobarbitone for 72 hours at normal temperature.

CHANGES IN 11 ANIMALS COOLED BY IMMERSION (ABOVE) AND EXTRACORPOREAL CIRCULATION (BELOW) (ADAPTED FROM HELMSWORTH AND COLE 1956)

Immersion	Average at normal temperature	Average change at 23°C
Hæmatocrit (%)	46.4	[illegible]% increase
Platelet-count (per c.mm.)	324,700	50.7%
Leucocyte-count (per c.mm.)	12,6[illegible]	52.[illegible]%
Total eosinophil-count (per c.mm.)	3[illegible]	3[illegible]% decrease
Mean [illegible]	33.9	61%

Extracorporeal circulation	Average at normal temperature	Average change at 28°C
Hæmatocrit (%)	[illegible]	[illegible]% increase
Platelet-count (per c.mm.)	34[illegible]	34.[illegible]%
Leucocyte-count (per c.mm.)	12,[illegible]	51.2%
Total eosinophil-count (per c.mm.)	[illegible]	33.1% decrease
Mean [illegible]	32.2	4[illegible]%

What of the future of hypothermia ? It is foolish to prophesy, but I think that there is no doubt that it has established itself as irreplaceable as an adjuvant to hypotension in general surgery and especially in neuro surgery, and I reiterate that I believe that hypothermia should always be used, except perhaps for the briefest period of hypotension in young people In therapeutics it is likely to remain effective in treating cases of hypermetabolism Thyrotoxic crises are a rarity in these days, but we have found hypothermia extremely useful in the 2 cases we have met Similarly it has a place in the treatment of hyperpyrexial states, and in cases of brain or brain-stem injury associated with œdema

Heart-lung Pumps

In open cardiac surgery, there is a distinct decline in enthusiasm for hypothermia and an increasing tendency to favour some form of pump oxygenator to assume the function of the heart and lungs This has been particularly evident in the United States since the work three years ago by Miller et al (1953) and the great advances made by Lillehei and his associates (1955)

I am not at all sure, however, that hypothermia will be replaced by these methods The differential brain-cooling suggested and successfully used by the Japanese workers Kimoto et al (1956) would seem in theory to remove many objections to cooling Furthermore, the recent experiments on the supra-cooling of mammals raises the question of whether this approach has been fully exploited The introduction of extracorporeal circulation through a pump and mechanical oxygenator has all the hazards in regard to hæmolysis and altered coagulation to which I have referred

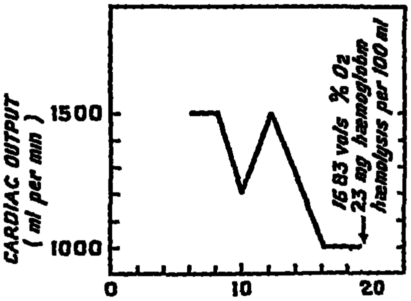

Fig 9—Dog s heart lung preparation perfused with human blood working against a peripheral resistance of 120–130 mm Hg Oxygen and free hæmoglobin estimated at 20 minutes

It seems that we are faced with a dilemma We require a pump with an output of the order of more than 2 litres a minute Such large-output pumps, however, entail circulation of the blood through the pump more frequently than do pumps of small output, and the cellular components of the blood are subjected to more trauma Perhaps the answer will he with moderate cooling and a pump giving the smaller order of output

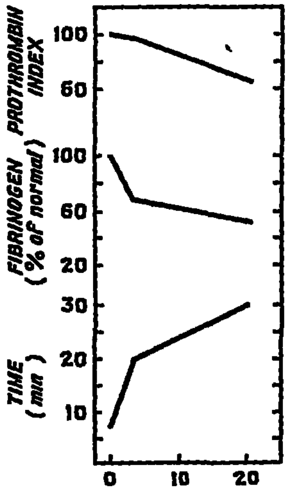

Fig 10—Dog's heart-lung preparation perfused with human blood Blood-coagulation studies

I should like to conclude by describing an attempt we have made to reduce these hazards For some years I have been carrying out various pharmacological investigations with the Starling heart lung preparation, and Mr Leslie Temple suggested that, in view of the success achieved with the heterologous lung oxygenator, the heterologous heart should be used as a pump Helped by generous donors of human blood, we have worked together on this project and, as with all such enterprises, have waxed alternately manic and depressive in our enthusiasm I think, however, we have established that the heart and lungs of the dog can be used to pump and oxygenate human blood We have not been able to demonstrate any incompatibility of the sample of human blood which has circulated in the preparation with a sample of the same blood which has not circulated This might, I think, be expected after the report, by Campbell et al (1956), on the successful use of the dog's lungs to oxygenate blood in cardiac surgery in 7 patients We have, however, been faced with several problems, such as the tendency of the lungs to become œdematous Acting on the experience of Campbell and his colleagues, we thought this could be overcome by adequate washing out with dextran, but our longest period with a good output and reasonable oxygenation has been forty-five minutes, and occasionally lung œdema comes on considerably earlier (fig 9) The heart and lungs are not so easy to wash out as the lungs alone, but our present technique of cooling the preparation before introducing the dextran and human blood is enabling us to get wash outs with only 7000 cells per c mm

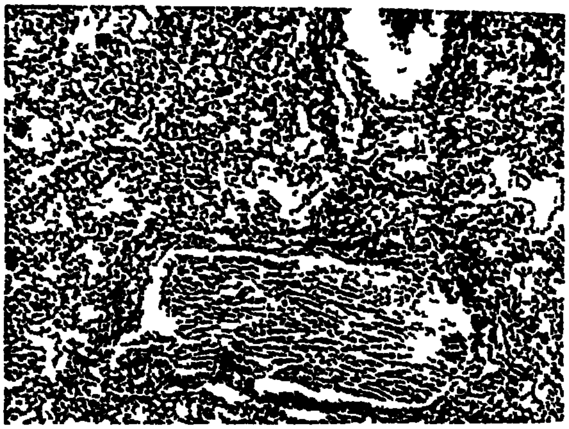

Fig 11—Dog's lung (× 95) after perfusion with human blood Congestion, œdema, and deposition of fibrinogen in pulmonary vessel

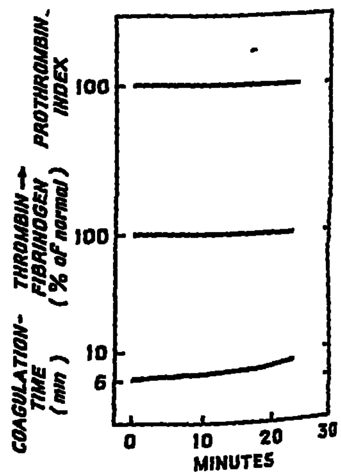

Fig 12—Dog's heart lung preparation perfused with human blood Blood coagulation studies after insertion of nylon filter in circuit

It was disappointing, at first, to find that hæmolysis and altered coagulation of the blood are experienced with this biological pump, just as with mechanised heart lungs The amount of hæmolysis has varied, and, though we have had some preparations with less than 2 mg of plasma hæmoglobin per 100 ml, usually there is about 136 mg We hope to reduce this considerably by using an all-plastic apparatus which is being prepared

The early preparations progressively lost fibrinogen, and the blood coagulation studies showed disturbing features (fig 10) The fibrinogen was being deposited in the lungs (fig 11), but the serious feature was the considerably altered prothrombin index But at the sug gestion of Dr Harry Wilson, of the department of pharmacology, we are now filtering the blood through nylon and seem to have overcome this difficulty (fig 12), though we have not established that the difference is in fact due to the nylon filter

It is too early to say whether this type of preparation has any future in clinical application It does hold out the possibility of a cheap and efficient heart lung pump, and one which in theory should be less destructive to corpuscles and carry its own servo regulatory mechanisms

Conclusion

My theme may be summed up in the word " control " I have above all endeavoured to control myself and to avoid that type of dogmatism which would have me labelled, as was the character in *Measure for Measure*, " a proud man, drest in a little brief authority "

I have suggested that induced hypotension, both on a priori grounds and in the light of recent surveys, demands a high price, and that surface cooling down to 30°C is, in experienced hands, practical and safe It should be regarded as an adjuvant to hypotension in most, if not all, cases I have expressed a foreboding that extracorporeal cooling will be found to incur its own hazards, which are likely also to attend the use of any mechanised heart-lung pump I have suggested a new approach to the heart-lung pump problem which remains to be explored

Dr Robert Coope, in his little book *The Quiet Art*, quotes a Negro's prayer, and it would be difficult to find a better morning supplication for all who are involved in this work and who, by constant endeavour and thought, are striving to improve the lot of our patients by more effective and safer control of the circulation

> " Lord, help me to understand that you ain t goin' to let nothin come my way that you and me together can't handle "

I would like to express my gratitude to my colleagues in the department for their very considerable assistance in the experiments from which I have quoted, and to Mrs Todd, the biochemical technician in my department, for the various blood investigations I am greatly indebted also to Mr H P Harding, of the department of veterinary pathology, for the examination of many pathological specimens and slides and to Mr W A Lee of the central department of photography, for the preparation of the photomicrographs Without the full coöperation of Dr D Lehane, of the Liverpool Regional Blood Transfusion Centre, it would not have been possible to have carried out the experiments with the heart-lung preparation, and I am extremely grateful to the generous donors who gave, and are continuing to give their blood for this work

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THE CHANGING PATTERN OF LEUKÆMIA

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THERE are striking differences in the published estimates of the relative incidence of acute and chronic leukæmia, extreme values for the acute form being 26% (Morganti and Cresseri 1952) and 61% (Gunz and Hough 1956) Undoubtedly part of this is due to the use of different criteria to decide which cases are to be included under the heading of acute leukæmia Another cause is the great difference in age at onset of the two forms of leukæmia, which makes it difficult, and sometimes impossible, to compare two series of cases Yet another difficulty is that there is evidence that the incidence of leukæmia varies with social status and geographical location (Hewitt 1955) There are other reasons for these differences which are not so obvious as those cited above For instance, there has been a change in the relative age-incidence of acute and chronic leukæmia since 1940, at least in the age group 15–55

Material and Methods

Our material consists of all cases of leukæmia which occurred in the Armed Forces between Sept 4, 1939, and Dec 31, 1955, and for which application for pension was made to the Ministry of Pensions and National Insurance We have thus obtained details of 655 cases, but there may be others Previous experience has shown that some cases are always missed from such a series, owing to errors in coding, &c , but no grounds have been found for suggesting that selective factors are involved in such omissions

For the present purposes the following data were recorded in each case sex, date and place of birth date of onset of leukæmia, date of death or duration of disease until Dec 31, 1955 Such a series is not entirely free from selection as regards the following factors

(1) *Sex* —Only 10 of the 655 were females , owing to their small number they were included with the males

(2) *Age* —This is necessarily limited to the ages of serving personnel In the present case the ages ranged from 18 to 63 years

TABLE I—RELATIVE INCIDENCE OF ACUTE AND CHRONIC LEUKÆMIA, ACUTE LEUKÆMIA BEING DEFINED AS A DURATION OF NOT MORE THAN *Six* MONTHS

Age at onset (yr)	Years of onset 1940–44			1945–49			1950–54		
	Acute	Chronic	Total	Acute	Chronic	Total	Acute	Chronic	Total
15–24	69 (*72·6%*)	26	95	37 (*71·2%*)	15	52	17 (*60·7%*)	11	28
25–34	68 (*64·2%*)	38	106	59 (*58·4%*)	42	101	16 (*55·2%*)	13	29
35 or more	35 (*41·2%*)	50	85	47 (*51·1%*)	45	92	22 (*61·1%*)	14	36
All ages	172 (*60·1%*)	114	286	143 (*58·4%*)	102	245	55 (*59·1%*)	38	93

Figures in parentheses are percentages of the acute type for each age group for each onset period

(3) *General Health*—The cases were drawn from a population who were, at the date of enlistment, considered to be of the standard of physical and mental fitness necessary for service in the Armed Forces. Since the comparisons to be made are entirely within the series, this fact is of no importance in the present investigation.

In every case we saw the hospital records including the hæmatological findings, and satisfied ourselves about the diagnosis of leukæmia. We consider that our series consisted entirely of cases of leukæmia, so far as could be ascertained by the diagnostic methods in use at the time of the investigation. On the other hand, we found wide differences of opinion on the histological type of leukæmia. We also noted cases diagnosed as aplastic anæmia where we have reason to regard the diagnosis with suspicion.

TABLE II—MEAN AGES AT ONSET OF ACUTE AND CHRONIC LEUKÆMIA, ACUTE LEUKÆMIA BEING DEFINED AS A DURATION OF NOT MORE THAN *Six* MONTHS

—	Years of onset 1940–44	1945–49	1950–54
Mean age, acute (yr)	28·7	31·7	33·1
Mean age, chronic (yr)	33·9	34·6	32·8

In view of the uncertainty expressed by most workers on the "typing" of cells in acute leukæmia we adopted an arbitrary definition; *a case of acute leukæmia was* one in which the disease did not last more than six months from onset to death. A further difficulty then arose—the determination of the date of onset. We have taken this as being the first date on which the patient complained of any symptom which is included in the standard descriptions of leukæmia (Whitby and Britton 1953, Wintrobe 1956).

Results

The cases were divided into three groups according to the year of onset, 1940–44, 1945–49, and 1950–54. This excluded cases arising before 1940 and since 1954 from this part of the investigation, leaving 624, which were again divided into age groups at date of onset 15–24, 25–34, and 35 years or more. The data are shown in table I.

It will be seen that the incidence of acute leukæmia, all ages, was remarkably constant in each of the five-year periods of onset, being 60·1%, 58·4%, and 59·1%. Comparison of the mean age at onset of the two types, however, showed an increase in the acute type and a decrease in the chronic (table II).

The increase in mean age at onset in the acute cases was found to be significant; the decrease in the mean age at onset in the chronic cases was found to be no greater than that expected from chance variations (see appendix).

The change in the age at onset of the acute type was mainly due to an increase in the proportion of acute cases in the older age groups, but there was also a decrease in the proportion in the younger ages (fig 1).

Such a change could be explained if the average age of Forces personnel had increased during the period under investigation. The age distribution of men in the Forces for 1941–54 inclusive was obtained from the Central Statistical Office, and the means calculated. For the three five-year periods 1940–44, 1945–49, and 1950–54 these were found to be 28·7, 27·0, and 23·9 years respectively. These mean ages, with the mean ages at onset of the two types of leukæmia, are shown in fig 2.

It will be seen that, far from explaining the observed changes, consideration of the mean age of the Forces personnel emphasises the extent of the changes which have taken place.

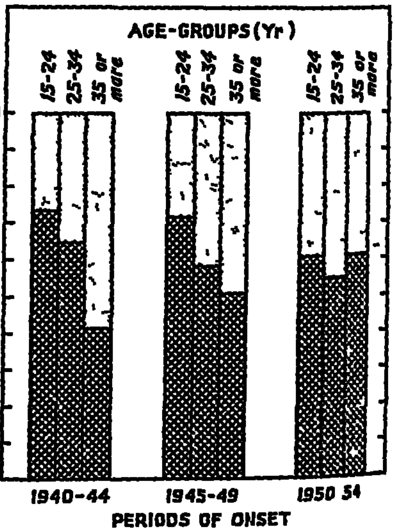

Fig 1—Change in incidence of acute and chronic leukæmia since 1940: stippled, chronic; hatched, acute.

It was appreciated that these results might have depended on our arbitrary six-months' definition of acute leukæmia, and that a different definition might not show any such change. Hæmatological opinion is divided on the classification of leukæmia by its duration. Some hæmatologists recognise a subacute type which lasts from six to twelve months, whereas others include cases lasting twelve months or less with acute leukæmia (Committee for Clarification of Nomenclature of Cells and Diseases of Blood and Blood-Forming Organs 1950). We therefore re-examined the data, defining acute leukæmia as that form of the disease which did not last more than twelve months. The results are given in tables III and IV.

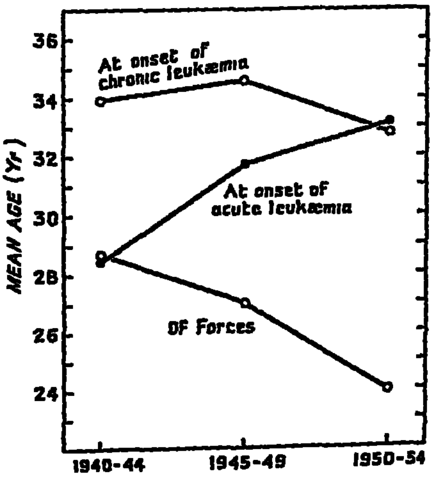

Fig 2—Mean ages of Armed Forces and at onset of acute and chronic leukæmia

It will be seen that the change in pattern with time is still present. It was found that the increase in the mean age at onset of the acute type had the same degree

TABLE III—RELATIVE INCIDENCE OF ACUTE AND CHRONIC LEUKÆMIA, ACUTE LEUKÆMIA BEING DEFINED AS A DURATION OF NOT MORE THAN *Twelve* MONTHS

Age at onset (yr)	Years of onset								
	1940–44			1945–49			1950–54		
	Acute	Chronic	Total	Acute	Chronic	Total	Acute	Chronic	Total
15–24	77 (*81 1%*)	18	95	45 (*86 5%*)	7	52	20 (*71 4%*)	8	28
25–34	79 (*74 5%*)	27	106	75 (*74 3%*)	26	101	20 (*69 0%*)	9	29
35 or more	45 (*52 9%*)	40	85	59 (*64 1%*)	33	92	27 (*75 0%*)	9	36
All ages	201 (*70 3%*)	85	286	179 (*73 1%*)	66	245	67 (*72 0%*)	26	93

Figures in parentheses are percentages of the acute type for each age-group for each onset period

of significance as with the previous definition, and that the decrease in the mean age at onset of the chronic type was again not significant (see appendix)

Discussion

Additional evidence which may be of importance for the explanation of this change in the pattern of leukæmia is contained in the tables of age-specific death-rates of leukæmia for England and Wales prepared by Dr R A M Case and Miss J T Pearson (unpublished) Calculations based on these tables show that the ages at which no real change in the mortality from leukæmia has taken place are from 20 to 34, and that these are approximately the same in both sexes (These changes, for males, are shown in fig 3)

It now becomes possible to bring together certain more or less isolated facts about leukæmia and to draw conclusions from them The facts are as follows

(1) The mortality from leukæmia in the general population is known to be increasing sharply, both in this country and in others

(2) There are two peaks in the mortality from leukæmia, in infancy and from middle age onwards, and this is true for both sexes

(3) In the age group 20–34 there has been virtually no change in the mortality from leukæmia

(4) Ionising radiation is known to be leukæmogenic both in animals and in man (Warren 1956, Medical Research Council 1956)

(5) Radiation is the only known leukæmogen to which every living thing on the planet is to some degree exposed (Spiers 1956)

(6) There has been an increase in the man made contribution to background radiation, both from the appurtenances of civilisation and as a result of nuclear explosions (Medical Research Council 1956)

(7) There has been a significant increase in the mean age at onset of acute leukæmia since 1940

From these facts we have drawn the following conclusions

(1) It is improbable that the increase in the incidence of leukæmia can be solely due to heavy doses of irradiation such as from radiotherapy or from close association with nuclear explosions The Medical Research Council (1956), investigating leukæmia and ankylosing spondylitis, found only 37 cases of leukæmia in a heavily irradiated population of 13 352 patients over a period of twenty years and it is obvious that there cannot be many such populations in existence

(2) Though we are not here dealing with the leukæmia of infancy, it seems probable that at least in some cases it is associated with irradiation in utero (Stewart et al 1956) Such irradiation is delivered to embryonic tissues and compared with background levels constitutes a high radiation dose

(3) We are left with an excess of cases of leukæmia occurring after the age of 35 in people who have not been subjected to heavy doses of radiation In the absence of evidence for genetic determination of these cases it is reasonable to assume that they arise as a result of some agent acting after conception. Such an agent may well be exposure to long term low dose radiation If we accept this hypothesis, it is necessary to postulate either a certain minimal cumulative dose or a time lag after the exposure to the responsible agent, and/or leukæmia to be the result of a somatic mutation. The results of experiments on animals suggest that a somatic mutation is the most probable explanation (Loutit 1957), and that in man there is a latent period before leukæmia is detectable by present techniques A latent period has been found in leukæmia occurring in cases of irradiated ankylosing spondylitis and in those following the Japanese atomic bombing Japanese cases were still occurring, apparently with undiminished frequency, ten years after the bombing (Medical Research Council 1956)

It is clearly to be understood that we are not advancing the hypothesis that all leukæmia is due to radiation, and we are well aware that the picture has been oversimplified Other possible leukæmogens have been suggested—e g, sulphonamides The use of these drugs greatly increased during the period of our investigation, but there does not, at present, appear to be any firm evidence that they are leukæmogenic We hope to be able to produce evidence on this point and later on other suggested leukæmogens At present we can only point out that a possible explanation of at least some of the

TABLE IV—MEAN AGES AT ONSET OF ACUTE AND CHRONIC LEUKÆMIA, ACUTE LEUKÆMIA BEING DEFINED AS A DURATION OF NOT MORE THAN *Twelve* MONTHS

—	Years of onset		
	1940–44	1945–49	1950–54
Mean age at onset acute (yr)	29 0	31 7	33 2
Mean age at onset, chronic (yr)	35 0	36 2	32 3

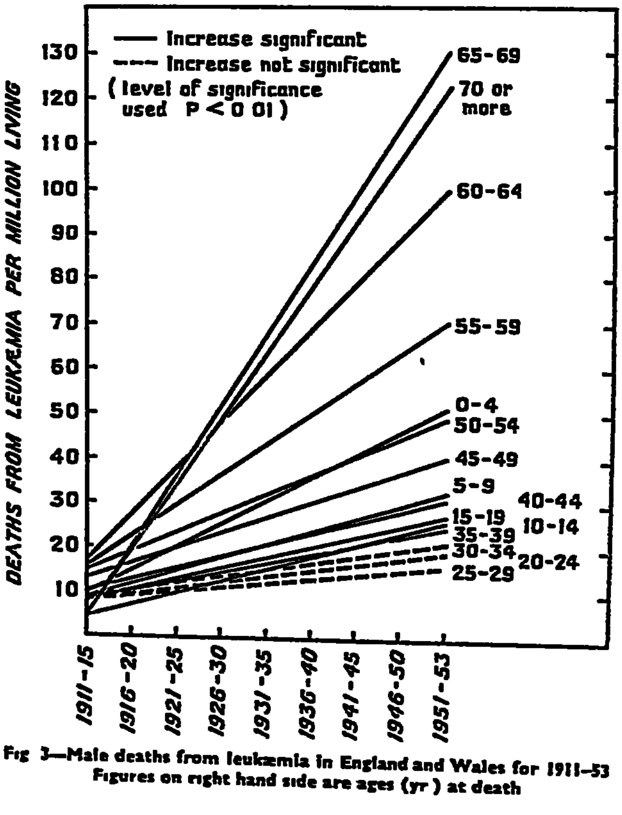

Fig 3—Male deaths from leukæmia in England and Wales for 1911–53 Figures on right hand side are ages (yr) at death

increase in the mortality from leukæmia, and of the advance in the age at onset of the acute type which we have shown to be taking place, is the increasing amount of man made radiation to which we are all subjected In particular we emphasise the increase in diagnostic radiology in the Western countries between 1900 and the present date (the period covered by the tables from which fig 3 had been prepared) We tried to estimate the amount of diagnostic radiation received by the patients in our present series, but the position was so complicated by the possibility of unrecorded routine mass radiography that the assessment of this particular factor proved to be impossible We appreciate that such a hypothesis is not a "good" one, in the sense that it cannot be subjected to experimental verification If, however, this hypothesis is correct, a continued increase in the incidence of leukæmia is to be expected unless exposure to man-made radiation is adequately controlled

Summary

624 cases of leukæmia arising in members of the Armed Forces in 1940–54 were examined

A significant increase in the mean age at onset of the acute type was found both with a duration of less than six months and with a duration of less than twelve months No significant change was found in the mean age at onset of chronic leukæmia during the same period

There was a decrease in the mean age of Forces personnel during the same period, which accentuates the change found in acute leukæmia

It is probable that environmental factors are responsible both for this change and for the known increase in the general mortality from leukæmia One such factor may be man-made additions to the background radiation

We wish to acknowledge our indebtedness to the Medical Research Council's working party on leukæmia research, under whose auspices this investigation is being made We are most grateful for helpful advice and criticism from Dr J V Dacie, Prof A Bradford Hill, Prof J S Mitchell, Dr E E Pochin, Dr F G Spear, and Prof L J Witts We have to thank Dr R A M Case and Miss Joan T Pearson for permission to use their unpublished work, the Central Statistical Office for details of and permission to publish the mean ages of Forces personnel, and the Ministry of Pensions and National Insurance for providing access to the relevant war pension records and for permission to publish the data extracted from them

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Appendix

Age specific Death-rates for Leukæmia (table v) —Tables of death rates for leukæmia for England and Wales for 1911–53 in five year periods and for each 5 year age-group from 0–4 to 70 or more male and female, have been prepared by Dr R A M Case and Miss J T Pearson as part of the programme of the Chester Beatty Research Institute From these tables we have calculated the "best straight line" for each 5 year age group, and each of these lines has been compared, by the χ^2 method, with a line drawn parallel to the X axis through the point Y = mean death-rate for the age group (The best straight line is here defined as that line for which the sum of the squares of the residuals is a minimum) These lines are shown for males in fig 3 The features to which we especially wish to draw attention are the non significant increases for the age groups 20–24, 25–29, and 30–34, and the rapidly growing significant increases for the older age groups

TABLE V—SIGNIFICANCE OF DIFFERENCES IN MEAN AGES AT ONSET

Type	Difference of mean ages at onset (yr)	Standard error of difference (yr)	Significance
"Acute" = not lasting more than 6 mos			
Acute	4 4	1 7	P less than 0 01
Chronic	1 1	2 0	not significant
"Acute" = not lasting more than 12 mos			
Acute	4 2	1 5	P less than 0 01,
Chronic	2 7	2 3	not significant

BLOOD PYRUVIC-ACID AND ALPHA-KETOGLUTARIC-ACID LEVELS IN LIVER DISEASE AND HEPATIC COMA

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THE liver is intimately concerned with intermediate carbohydrate metabolism, and the raised blood keto acid levels reported in severe liver disease (Amatuzio and Nesbitt 1950) might indicate failure of this process The application of paper chromatographic (Cavallini et al 1949) and enzyme methods (Segal et al 1956) have now allowed separate analysis of α-ketoglutaric and pyruvic acids Both these acids are transported from the periphery to the metabolic pool in the liver Raised levels of α-ketoglutaric acid in the blood have been reported in liver disease (Seligson et al 1952) and increases in both acids noted when there is complicating hepatic coma (Amatuzio and Nesbitt 1950, Carfagno et al 1953, Walshe 1955) In this paper the blood levels of pyruvic acid and α-ketoglutaric acid are reported in a series of patients with liver disease, with and without neuropsychiatric changes An attempt has been made to determine the mechanism of the changes in keto acid levels and to assess the usefulness of these estimations as a routine clinical procedure in the management of patients with liver disease

The blood ammonium level is often raised in hepatic coma (McDermott and Adams 1954, Traeger et al 1954, Phear et al 1955), and Bessman and Bessman (1955) have observed removal of ammonium by the brain and peripheral tissues as reflected by an arteriovenous difference This peripheral and cerebral removal of ammonium is probably due to combination of α keto glutaric acid and ammonia to form glutamic acid, which in turn is aminated by another molecule of ammonia to form glutamine Bessman and Bessman (1955) have suggested that in hepatic coma the unmetabolised ammonium combines with the α ketoglutaric acid of muscle and brain until the supply of this acid is exhausted Such a deficiency will eventually interfere with the efficient working of the Krebs tricarboxylic acid cycle in which α-ketoglutaric acid is an essential link The blood

TABLE I—NORMAL VENOUS KETO ACID LEVELS

Reference	Method	No of observations	Mean α ketoglutaric acid ± S.D. (µg per 100 ml)	Mean pyruvic acid ± S.D. (µg per 100 ml)
Seligson et al 1952	Chromatography of 2,4 dinitrophenylhydrazine derivatives after ethyl acetate extraction	18	200 ± 23	656 ± 151
Walshe 1955	Chromatography of 2,4 dinitrophenylhydrazine derivatives after ethyl acetate extraction	16	143 (range 86–302)	230 (range 160–280),
Smith and Taylor 1955	Chromatography of 1,2 diamino 4 nitrobenzene derivative	7	100 ± 20	310 ± 70
Segal et al 1956	Enzyme	26		660 (range 390–860)
Present series	Chromatography of 2,4-dinitrophenylhydrazine derivatives after ether extraction	19	57 ± 12	541 ± 111

keto acid levels were therefore compared with those of blood-ammonium The level of blood ammonium was also raised by giving oral ammonium chloride, and the effect on blood keto acid levels observed

Thioctic (lipoic) acid is a co enzyme essential for the formation of active acetate and so obligatory for the efficient working of the tricarboxylic acid cycle and hence for the metabolism of pyruvic acid (Ochoa 1954) In view of the increased pyruvic acid values noted in hepatic coma, thioctic acid has been recommended for its treatment (Rauch 1954, Steigmann and Canthuati 1956) Results in 4 patients are now reported

Case-material and Methods

38 patients with liver disease were studied, of whom 16 showed neurological changes 33 patients suffered from portal cirrhosis 1 from biliary cirrhosis and 2 from acute virus hepatitis A patient with typical neurological changes had a normal liver histologically and macroscopically, and a large extrahepatic portal systemic collateral circulation Another had deep jaundice associated with Hodgkin's disease of the liver and was in coma All patients received parenteral vitamin B supplements The control group (16) were members of the hospital staff or volunteer patients without liver disease or other conditions such as congestive heart failure or thyrotoxicosis, which are known to affect the blood keto acid level

The neurological condition was graded 0 (normal), 1 (minor disorders of consciousness and the motor system) 2 (gross disorders of consciousness and the motor system), or 3 (coma) The portal collateral circulations were assessed by transplenic portal venography (Atkinson et al 1955)

On 70 occasions blood from resting patients after an all night fast was drawn simultaneously from artery and antecubital vein On 20 occasions only venous blood was obtained Ammonium was estimated by a slight

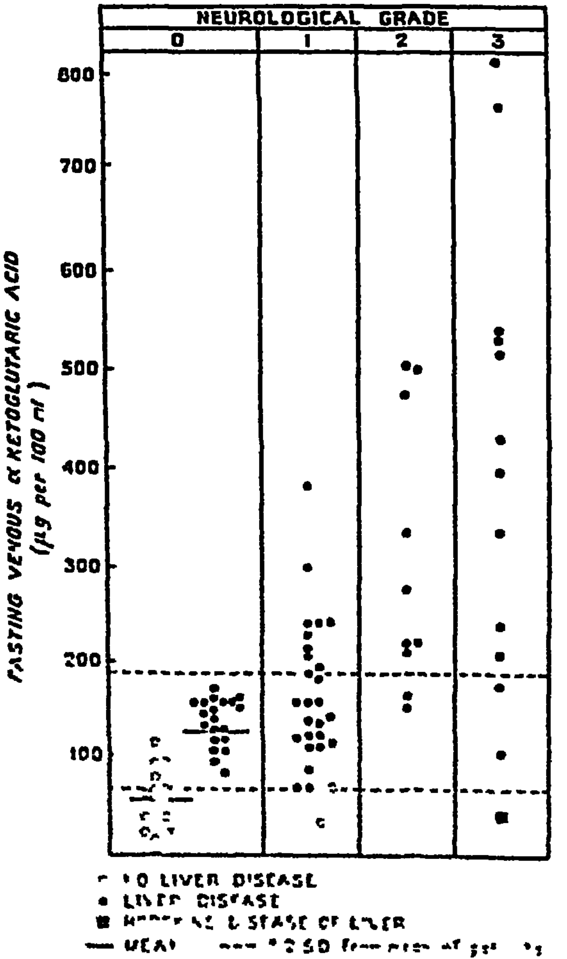

Fig 1—Fasting venous α-ketoglutaric acid levels related to grade of coma

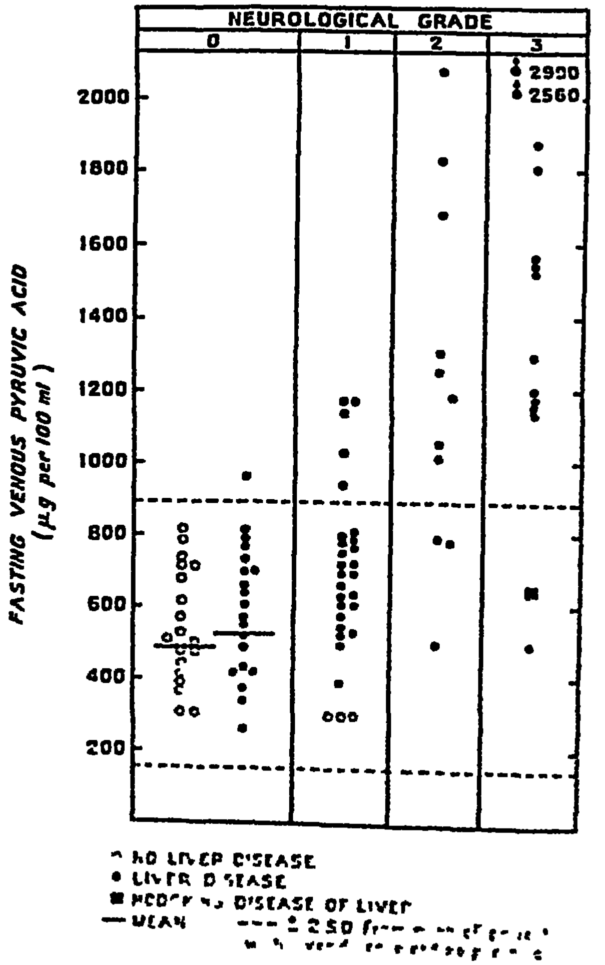

Fig 2—Fasting venous pyruvic acid levels related to grade of coma

increase in the mortality from leukæmia, and of the advance in the age at onset of the acute type which we have shown to be taking place, is the increasing amount of man-made radiation to which we are all subjected In particular we emphasise the increase in diagnostic radiology in the Western countries between 1900 and the present date (the period covered by the tables from which fig 3 had been prepared) We tried to estimate the amount of diagnostic radiation received by the patients in our present series, but the position was so complicated by the possibility of unrecorded routine mass radiography that the assessment of this particular factor proved to be impossible We appreciate that such a hypothesis is not a "good" one, in the sense that it cannot be subjected to experimental verification If, however, this hypothesis is correct, a continued increase in the incidence of leukæmia is to be expected unless exposure to man made radiation is adequately controlled

Summary

624 cases of leukæmia arising in members of the Armed Forces in 1940–54 were examined

A significant increase in the mean age at onset of the acute type was found both with a duration of less than six months and with a duration of less than twelve months No significant change was found in the mean age at onset of chronic leukæmia during the same period

There was a decrease in the mean age of Forces personnel during the same period, which accentuates the change found in acute leukæmia

It is probable that environmental factors are responsible both for this change and for the known increase in the general mortality from leukæmia One such factor may be man-made additions to the background radiation

We wish to acknowledge our indebtedness to the Medical Research Council's working party on leukæmia research, under whose auspices this investigation is being made We are most grateful for helpful advice and criticism from Dr J V Dacie, Prof A Bradford Hill, Prof J S Mitchell, Dr E E Pochin, Dr F G Spear, and Prof L J Witts We have to thank Dr R A M Case and Miss Joan T Pearson for permission to use their unpublished work, the Central Statistical Office for details of and permission to publish the mean ages of Forces personnel, and the Ministry of Pensions and National Insurance for providing access to the relevant war pension records and for permission to publish the data extracted from them

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Appendix

Age specific Death rates for Leukæmia (table v) —Tables of death rates for leukæmia for England and Wales for 1911–53 in five year periods and for each 5 year age group from 0–4 to 70 or more male and female, have been prepared by Dr R A M Case and Miss J T Pearson as part of the programme of the Chester Beatty Research Institute From these tables we have calculated the "best straight line" for each 5 year age group, and each of these lines has been compared, by the t^2 method, with a line drawn parallel to the X axis through the point Y = mean death-rate for the age group (The best straight line is here defined as that line for which the sum of the squares of the residuals is a minimum) These lines are shown for males in fig 3 The features to which we especially wish to draw attention are the non significant increases for the age groups 20–24, 25–29, and 30–34, and the rapidly growing significant increases for the older age groups

TABLE V—SIGNIFICANCE OF DIFFERENCES IN MEAN AGES AT ONSET

Type	Difference of mean ages at onset (yr)	Standard error of difference (yr)	Significance
"Acute" = not lasting more than 6 mos			
Acute	4 4	1 7	P less than 0 01,
Chronic	1 1	2 0	not significant
"Acute" = not lasting more than 12 mos			
Acute	4 2	1 5	P less than 0 01,
Chronic	2 7	2 3	not significant

BLOOD PYRUVIC-ACID AND ALPHA-KETOGLUTARIC-ACID LEVELS IN LIVER DISEASE AND HEPATIC COMA

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The liver is intimately concerned with intermediate carbohydrate metabolism, and the raised blood keto acid levels reported in severe liver disease (Amatuzio and Nesbitt 1950) might indicate failure of this process The application of paper chromatographic (Cavallini et al 1949) and enzyme methods (Segal et al 1956) have now allowed separate analysis of α-ketoglutaric and pyruvic acids Both these acids are transported from the periphery to the metabolic pool in the liver Raised levels of α ketoglutaric acid in the blood have been reported in liver disease (Seligson et al 1952) and increases in both acids noted when there is complicating hepatic coma (Amatuzio and Nesbitt 1950, Carfagno et al 1953, Walshe 1955) In this paper the blood levels of pyruvic acid and α-ketoglutaric acid are reported in a series of patients with liver disease, with and without neuropsychiatric changes An attempt has been made to determine the mechanism of the changes in keto acid levels and to assess the usefulness of these estimations as a routine clinical procedure in the management of patients with liver disease

The blood ammonium level is often raised in hepatic coma (McDermott and Adams 1954, Traeger et al 1954, Phear et al 1955), and Bessman and Bessman (1955) have observed removal of ammonium by the brain and peripheral tissues as reflected by an arteriovenous difference This peripheral and cerebral removal of ammonium is probably due to combination of α keto glutaric acid and ammonia to form glutamic acid, which in turn is aminated by another molecule of ammonia to form glutamine Bessman and Bessman (1955) have suggested that in hepatic coma the unmetabolised ammonium combines with the α ketoglutaric acid of muscle and brain until the supply of this acid is exhausted Such a deficiency will eventually interfere with the efficient working of the Krebs tricarboxylic acid cycle in which α-ketoglutaric acid is an essential link The blood

TABLE I—NORMAL VENOUS KETO-ACID LEVELS

Reference	Method	No. of observations	Mean α-ketoglutaric acid ± S.D. (μg. per 100 ml.)	Mean pyruvic acid ± S.D. (μg. per 100 ml.)
Seligson et al. 1952	Chromatography of 2: 4-dinitrophenylhydrazine derivatives after ethyl acetate extraction	18	200 ± 23	686 ± 161
Walshe 1955	Chromatography of 2: 4-dinitrophenylhydrazine derivatives after ethyl acetate extraction	16	143 (range 86–302)	230 (range 160–280)
Smith and Taylor 1955	Chromatography of 1: 2-diamino-4-nitrobenzene derivative	7	100 ± 20	330 ± 70
Segal et al. 1956	Enzymic	20		600 (range 380–860)
Present series	Chromatography of 2: 4-dinitrophenylhydrazine derivatives after ether extraction	19	57 ± 12	541 ± 141

keto-acid levels were therefore compared with those of blood ammonium. The level of blood ammonium was also raised by giving oral ammonium chloride, and the effect on blood keto-acid levels observed.

Thioctic (lipoic) acid is a co-enzyme essential for the formation of active acetate, and so obligatory for the efficient working of the tricarboxylic-acid cycle and hence for the metabolism of pyruvic acid (Ochoa 1954). In view of the increased pyruvic-acid values noted in hepatic coma, thioctic acid has been recommended for its treatment (Rauch 1954, Steigmann and Canahuati 1956). Results in 4 patients are now reported.

Case-material and Methods

38 patients with liver disease were studied, of whom 16 showed neurological changes. 33 patients suffered from portal cirrhosis, 1 from biliary cirrhosis, and 2 from acute virus hepatitis. A patient with typical neurological changes had a normal liver histologically and macroscopically, and a large extrahepatic portal-systemic collateral circulation. Another had deep jaundice associated with Hodgkin's disease of the liver and was in coma. All patients received parenteral vitamin-B supplements. The control group (16) were members of the hospital staff or volunteer patients without liver disease or other conditions, such as congestive heart failure or thyrotoxicosis, which are known to affect the blood keto-acid level.

The neurological condition was graded 0 (normal), 1 (minor disorders of consciousness and the motor system), 2 (gross disorders of consciousness and the motor system), or 3 (coma). The portal collateral circulations were assessed by transplenic portal venography (Atkinson et al. 1955).

On 70 occasions blood from resting patients after an all-night fast was drawn simultaneously from artery and antecubital vein. On 20 occasions only venous blood was obtained. Ammonium was estimated by a slight

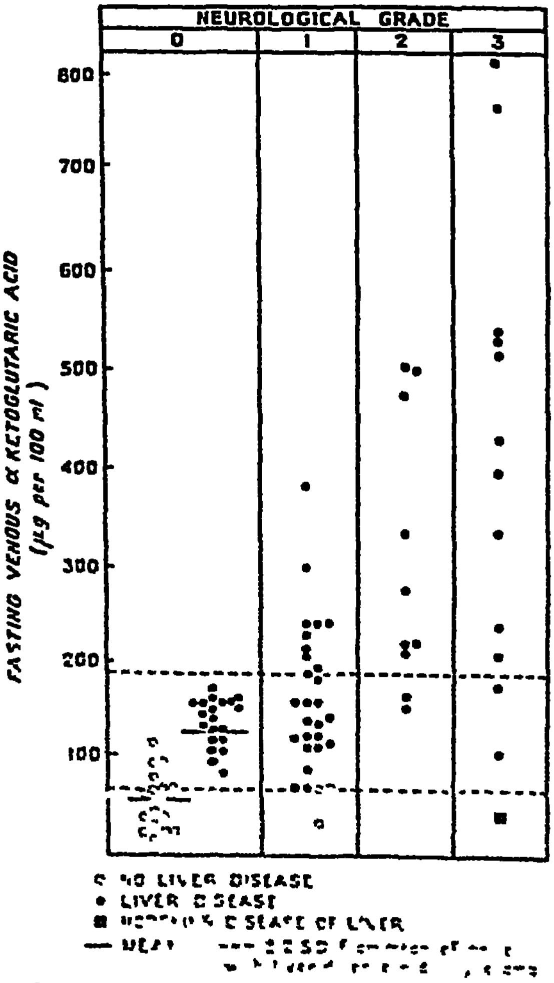

Fig. 1—Fasting venous α-ketoglutaric acid levels related to grade of coma.

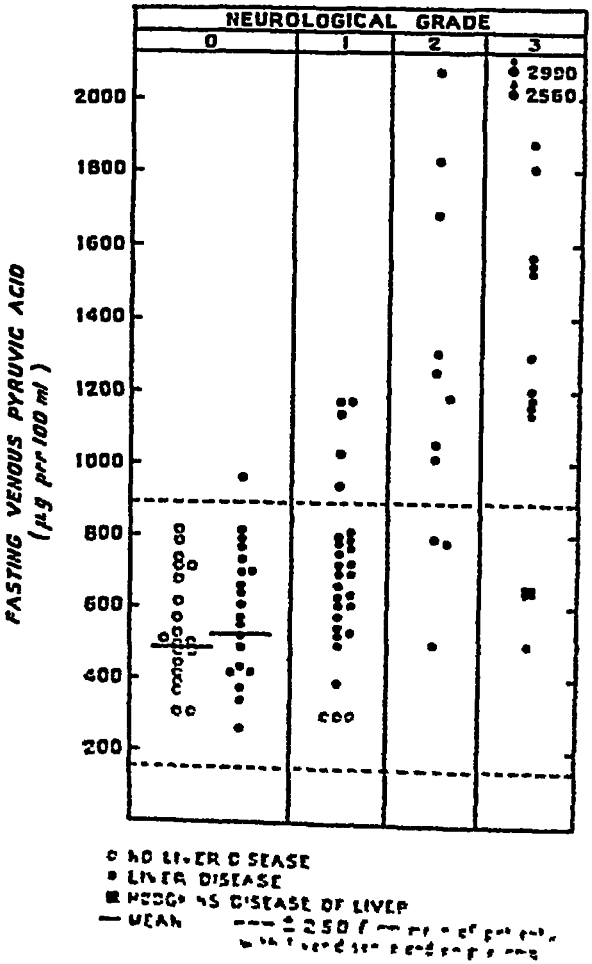

Fig. 2—Fasting venous pyruvic acid levels related to grade of coma.

modification of Conway's (1950) microdiffusion method (Phear et al 1955) Normal arterial values for this method are less than 1 μg per ml Pyruvic acid and α-ketoglutaric acid were estimated by a modification of the method of Cavallini et al (1949), the 2 4-dinitrophenylhydrazine derivatives were extracted with ether and separated by chromatography (de Groote et al 1955)

10 fasting subjects with cirrhosis of the liver were given 3 g ammonium chloride orally, arterial and venous α-ketoglutaric-acid, pyruvic-acid, and ammonium levels were estimated at once and thirty, sixty, ninety, and a hundred and twenty minutes later

Thioctic acid was given intravenously in doses ranging from 66 to 88 mg over periods of forty two to sixty hours Fasting blood and keto acid levels were obtained at the beginning and end of treatment

Results

Normal Blood Keto acid Levels

Like previous workers we found a wide scatter of values, especially for pyruvic acid (table I) The present values for blood α-ketoglutaric acid were lower than those previously published

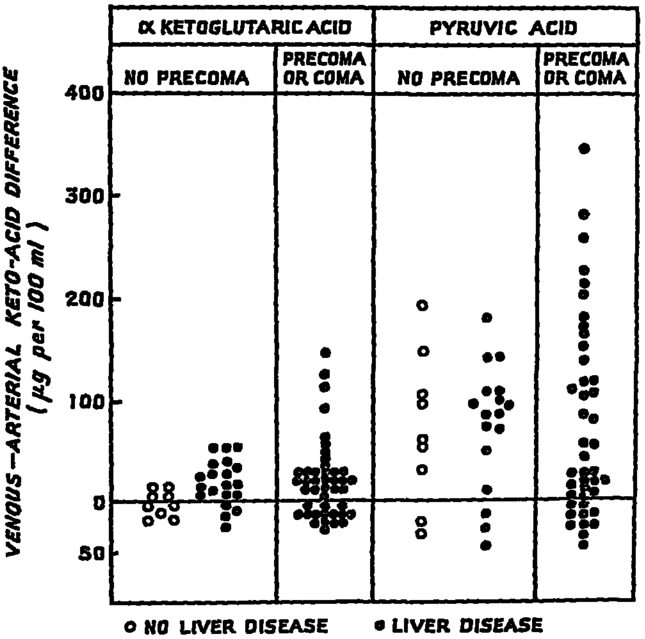

Fig 3—Fasting venous-arterial difference of keto-acids in relation to neurological state Values above the line indicate the peripheral tissues giving up keto acids

Venous α-ketoglutaric acid and Pyruvic-acid Levels and the Neurological Condition

Results of 73 estimations in 38 patients were correlated with the neurological condition at the time of sampling (figs 1 and 2) In patients with neuropsychiatric complications, a "raised" value of either keto-acid differed more than 2 standard deviations from the mean value obtained for patients with liver disease but without hepatic pre coma

Mean fasting venous α-ketoglutaric acid levels (fig 1) in patients with liver disease and no signs of impending coma was 131 μg per 100 ml ± 30, this is significantly higher than the control group (p = 0 01) Levels were raised in 8 of 30 patients in grade-I precoma, 8 of 10 in grade II coma, and 10 of 12 patients in grade III coma

A patient whose liver was invaded by Hodgkin's tissue had a normal level All the patients with grade I neurological changes and values less than 100 μg per 100 ml had relatively good liver function and a large portal systemic shunt, and were suffering from the syndrome of chronic portal-systemic encephalopathy (Summerskill et al 1956) The three lowest values were obtained from the woman with this syndrome who had a normal liver

TABLE II—VARIATIONS IN VENOUS KETO ACID LEVEL OF 4 FASTING PATIENTS WITH CIRRHOSIS OF THE LIVER

Patient	9 A M	10 A M	11 A M	Maximum variation from initial value (%)
	α Ketoglutaric acid (μg per 100 ml)			
1	251	240	240	− 4
2	64	64	73	+ 14
3	111	105	132	+ 19
4	174	169	183	+ 5
	Pyruvic acid (μg per 100 ml)			
1	775	710	740	− 6
2	483	468	412	−13
3	810	790	808	− 3
4	859	756	993	+ 16

Mean fasting pyruvic-acid levels (fig 2) did not differ between control subjects and patients with liver disease without neurological disorder Levels were raised in 5 of 29 patients in grade-I precoma, 7 of 10 in grade II coma, and 11 of 13 in grade III coma

With the development of neuropsychiatric symptoms the blood-level of both α-ketoglutaric acid and pyruvic acid tends to rise In patients with early neuropsychiatric changes, however, the scatter of results is so great that neither measurement is of practical value in the diagnosis of incipient hepatic coma

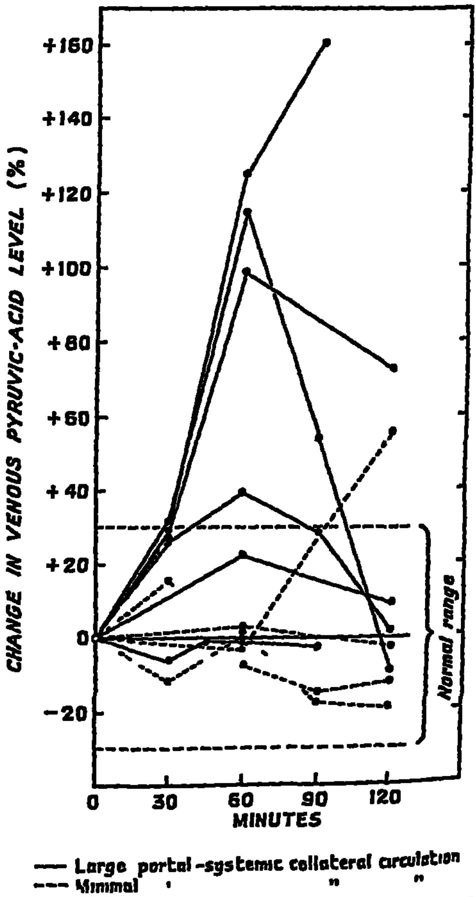

Fig 4—Change in venous pyruvic-acid levels after 3 g oral ammonium chloride (expressed as percentage of fasting value)

The peripheral venous-arterial difference of both α-ketoglutaric and pyruvic acids, in patients with liver disease, did not significantly change when there were neuropsychiatric complications (fig. 3). In particular, there was no evidence of an increased uptake of α-ketoglutaric acid by peripheral tissues in hepatic coma.

Relation of Blood Keto-acid Levels to Blood-ammonium Levels and the Effect of Ammonium Chloride

The arterial ammonium level is said to correlate more closely than the venous values with the neurological status of the patient (Bessman and Bradley 1955). Arterial ammonium levels, however, showed no significant correlation with those of venous α-ketoglutaric acid (r = 0.21, 50 observations) or venous pyruvic acid (r = 0.19, 43 observations).

The variation of fasting venous keto-acid levels over a two-hour period was studied in 4 cirrhotic patients (table II). The maximum variation of α-ketoglutaric acid from the initial value ranged from −8% to +10%, and for pyruvic acid from −13% to +16%; this is in close agreement with the observation of Segal et al. (1956) on venous pyruvic levels. We regarded an alteration of less than 30% for either acid as not significant.

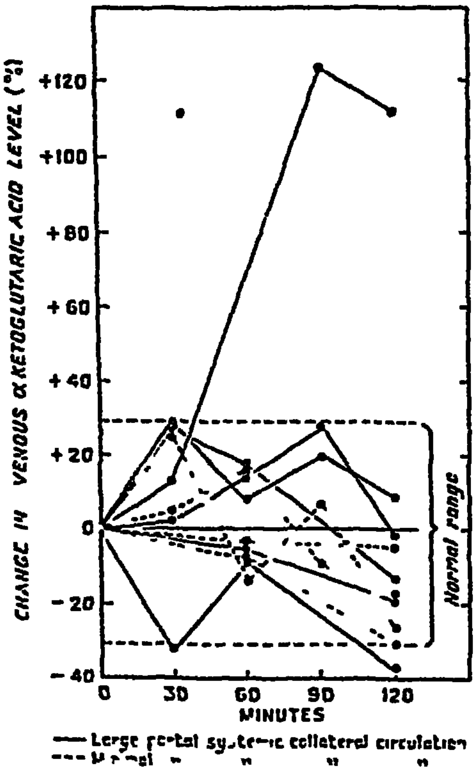

Fig. 5—Change in venous α-ketoglutaric-acid level after 3 g. oral ammonium chloride (expressed as percentage of fasting value).

In 6 patients with a large portal-collateral circulation arterial ammonium levels after 3 g. oral ammonium chloride exceeded [illegible] μg. per ml. [illegible] of these patients had [illegible] of venous pyruvic-acid levels, while 2 [illegible] change (fig. 4). [illegible] α-ketoglutaric-acid levels (fig. 5) [illegible] patient who showed the greatest [illegible] in venous pyruvic-acid values.

In 4 patients [illegible] portal-collateral [illegible]

TABLE III—EFFECT OF THIOCTIC ACID ON FASTING VENOUS KETO-ACID LEVELS IN HEPATIC PRE-COMA

Patient	Thioctic acid		Fasting venous α-ketoglutaric acid (μg. per 100 ml.)		Fasting venous pyruvic acid (μg. per 100 ml.)		Neurological grade		Remarks
	Dose (mg.)	Time (hr.)	Before	Values at end of infusion	Before	After	Before	After	
1	66	42	84	92	509	721	I	I	Chronic neuropsychiatric disorder
2	66	48	404	404	1288	1280	II	II	Alcoholic cirrhotic
3	85	60	476	352	1820	1015	II	I	Gastro-intestinal hæmorrhage controlled. Improvement followed
4	88	60	186	173	625	528	I	I	Chronic neuropsychiatric disorder

Thioctic Acid

Thioctic (lipoic) acid (table III) did not have a constant effect on the blood level of α-ketoglutarate in fasting subjects. The levels in patient 1 (initially normal) and in patient 4 (initially raised) did not change significantly; in patients 2 and 3 they fell slightly. Venous pyruvic-acid values fell significantly only in patient 3. This patient, the only one showing clinical improvement, was also having active treatment for bleeding œsophageal varices, and it was difficult to ascribe the benefit only to the thioctic acid.

DISCUSSION

The levels of blood keto-acids are greatly influenced by the nutrition of the patient and by vitamin-B deficiency. Glucose feeding may double the blood keto-acid level in patients in hepatic coma (Amatuzio and Nesbitt 1950). The patients we studied were fasting overnight and had all been given adequate vitamin-B supplements. Increased fasting α-ketoglutaric-acid levels in liver disease agree with the observations of Seligson et al. (1952) and Smith et al. (1953). The latter group report normal blood-pyruvic-acid values, but Seligson et al. (1952) found raised blood-pyruvate levels; precomatose patients were, however, included. In the individual patient values for either keto-acid were not sufficiently predictable to be of practical value in clinical diagnosis or in the management of hepatic coma. Levels have not hitherto been compared with the severity of the neuropsychiatric disturbance. It was interesting to find that in each neurological grade the mean level increased as the neurological state deteriorated. This indicates a progressive impairment of intermediate carbohydrate metabolism. This could be a reflection of failure of the liver to deal with a normal quantity of these metabolites or due to a general failure of intermediate metabolism so that the liver is called upon to deal with an increased load. Two important factors in the production of hepatic coma are liver-cell failure and a large portal-collateral circulation (Sherlock et al. 1954). The keto-acid levels correlated better with the severity of liver-cell failure than with the extent of the collateral circulation. Most of the comatose patients with low levels were suffering from chronic portal-systemic encephalopathy, in which shunting of portal blood into the systemic veins is of major importance and liver function is relatively good. Seligson et al. (1952) have also noted high levels of α-ketoglutaric acid in the blood of patients with acute hepatic [illegible] when liver-cell damage is the main factor. Blood ammonium reflects the shunting of portal venous blood into the systemic veins as well as the state of the liver cells (White et al. 1955). [illegible] that the blood-ammonium levels failed to correlate with the blood keto-acid levels.

Bessman and Bessman (1955) suggested that ammonium interfered with cerebral metabolism by withdrawing α-ketoglutarate from the Krebs tricarboxylic-acid cycle This cycle functions in peripheral tissues, yet there was no relationship between the venous α-ketoglutaric-acid and arterial ammonium levels, and ammonium chloride did not cause a fall in α-ketoglutaric acid levels or a contraction of the arterial venous difference of α-keto glutaric acid We confirmed the Bessmans' (1955) observation that ammonium is removed by peripheral tissues, it seems, however, that ammonium toxicity is not related to withdrawal of α-ketoglutaric acid from the tricarboxylic-acid cycle The rise of venous pyruvic-acid levels after oral ammonium chloride in some cirrhotic patients with a large portal systemic shunt suggests that in some circumstances, when a large amount of ammonium reaches the peripheral tissues, the ammonium ion interferes with intermediate carbohydrate metabolism

The rôle of thioctic (lipoic) acid in the citric-acid cycle has been fully reviewed by Ochoa (1954) Though a deficiency of the co enzyme in hepatic coma seems unlikely, it has been claimed to give encouraging results in treatment (Rauch 1954, Steigmann and Canahuati 1956) The effect in the 4 cases reported was unconvincing and extension of the trial did not seem warranted

Summary

In fasting patients with hepatic cirrhosis, mean levels of α-ketoglutaric acid in venous blood were raised, but mean levels of pyruvic acid were normal

Both levels rose progressively as the neuropsychiatric state deteriorated to hepatic coma

There was no correlation between the arterial level of ammonium and the venous level of α-ketoglutaric acid or pyruvic acid

No constant pattern in α-ketoglutaric-acid response (arterial or venous) was observed in 10 cirrhotic patients given 3 g oral ammonium chloride but in 4 of the 6 patients with a large portal systemic collateral circulation the venous pyruvic acid rose

Thioctic acid was given to 4 patients in hepatic pre coma without constant effect on the clinical state or blood keto acid level

We wish to thank Lederle Laboratories Division, Cyanamid Products Ltd, for generous supplies of thioctic acid, and the Medical Research Council for a grant for technical help Miss Y d'Almeida, B SC, and Miss J McLaren, B SC, gave valuable biochemical assistance

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A COMPARISON OF THE EFFECTS OF PHENOBARBITONE AND RESERPINE IN HYPERTENSION

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THE rauwolfia alkaloid, reserpine, is now generally accepted as an effective means of treatment in many cases of essential or renal hypertension (Doyle and Smirk 1954, Locket 1955) Reserpine is known to have some sedative or tranquillising effect (Kline 1954), and the possibility has not been excluded that the hypotensive effect may be due to sedation (Tuchman et al 1954) For this reason a small controlled trial was made to compare the effects of reserpine and phenobarbitone on blood-pressure

Methods

The patients submitted to the trial were 3 men and 8 women, aged 35–62, all of whom were considered to have essential hypertension on the basis of clinical, radiological, and bacteriological findings, 7 received reserpine ('Serpasil'), phenobarbitone, and control tablets, and 5 received only reserpine and control tablets The dosage of reserpine was 0 5 mg thrice daily, and that of phenobarbitone gr $^{1}/_{2}$ thrice daily, these dosages were thought to be roughly equivalent in sedative effect The drugs and control tablets appeared identical, so that neither the patient nor the examiner knew which tablet was being

BLOOD PRESSURES UNDER TREATMENT WITH PHENOBARBITONE AND WITH RESERPINE (ALL MEASURED WITH PATIENTS IN STANDING POSITION)

Case no	Control blood pressure (mm Hg)	Fall in mean blood pressure on phenobarbitone (mm Hg)	Fall in mean blood pressure on reserpine (mm Hg)
1	173 3 ±3 6 96 3 ±2 6	+6 3 −1 2	+9 7 +8 1
2	177 6 ±8 5 119 3 ±4 3	−6 7 −6 0	+23 7 +16 3
3	213 3 ±4 9 119 3 ±0 8	−10 0 −5 0	+16 6 +11 0
4	180 8 ±5 0 108 3 ±2 5	−8 2 −3 5	+23 0 +15 5
5	198 3 ±6 5 126 2 ±2 4	+5 5 +17 0	+2 1 +16 2
6	232 0 ±3 1 128 0 ±1 0	+19 0 +8 0	+37 0 +21 0
7	177 0 ±9 7 109 5 ±5 0	+11 7 +3 3	+5 0 +11 1
Mean		+2 52 ±4 2 +1 8 ±3 2	+16 73 ±4 6 +14 1 ±4 56
8	171 0 ±4 1 108 3 ±2 0		+19 [illegible] +13 6
9	167 5 ±3 1 108 2 ±2 2		+24 [illegible] +21 2
10	198 7 ±2 2 120 0 ±2 7		+20 4 +14 0
11	191 0 ±3 3 113 6 ±3 7		+27 5 +21 1
Over all mean			19 0 ±3 1 16 0 ±1 3

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taken and the order of taking the drugs was randomised. Each patient was treated for twelve weeks with each tablet and attended once weekly, at the same time of day each time. Blood-pressures were measured by the same person using the same sphygmomanometer each time. Blood-pressures were measured in the lying, sitting, and standing positions at each attendance.

When the results became available, it was evident that there was a considerable delay between the administration of reserpine and its effect on blood-pressure, sometimes amounting to four or five weeks. For this reason the readings during the first six weeks of each trial period were ignored, and only measurements in a "steady state" during the second six weeks were used as a basis for comparison.

Results

Blood-pressure.—For each patient the mean blood-pressure was calculated, with its standard error, for the last six weeks of each period in the standing, sitting, and lying positions. The mean pressures during the control period and the mean fall in blood-pressure in the standing position during the second six weeks of treatment with reserpine and phenobarbitone are shown in the accompanying table, from which it is evident that phenobarbitone produced a fall of blood-pressure in only 3 of the patients who received it, and over the whole group it had no significant effect on the blood-pressure, the mean fall being $\frac{2.5 \pm 4.2}{1.8 \pm 1.2}$ mm Hg. Reserpine produced a fall of blood-pressure in all the patients, and its effect was highly significant, the mean fall was $\frac{16.7 \pm 4.6}{14.3 \pm 1.5}$ mm Hg. The effects on blood-pressure in the sitting and lying positions were similar in every respect. In the sitting position the average falls of blood-pressure due to phenobarbitone and reserpine were $\frac{4.1 \pm 3.8}{1.7 \pm 2.6}$ and $\frac{19.8 \pm 4.6}{11.0 \pm 1.9}$ mm Hg respectively. Similarly the falls of blood-pressure in the lying position were $\frac{11.8 \pm 4.6}{4.7 \pm 2.6}$ and $\frac{23.2 \pm 6.2}{14.7 \pm 2.0}$ mm Hg respectively.

Weight Changes.—The weight changes varied, and though there was usually a weight gain on treatment with reserpine, this gain often persisted subsequently for more than twelve weeks. On average during the twelve weeks on phenobarbitone treatment there was no weight change, on control tablets a loss of 1/2 lb, and on reserpine a gain of 7.1 lb.

Side-effects.—3 of the patients complained of nasal blocking during treatment with reserpine, but no other symptoms were observed. There was no subjective history of depression and no objective evidence of mental retardation.

Discussion

The blood-pressure was relatively stable in each patient, as shown by the small standard error of the means during each period. This may have been due to the fact that the patients were attending regularly for some time before the period which was used for calculation, so that they became accustomed to the procedure.

Reserpine produced a significant (p<0.05) fall of diastolic blood-pressure in each of the 7 patients treated with reserpine and phenobarbitone, and a significant fall in systolic pressure in 5 of them.

Phenobarbitone caused a significant fall in systolic pressure in 3 patients and a significant fall in diastolic pressure in 2. Although the blood-pressure fell in 3 patients treated with phenobarbitone, none of these [illegible]

[illegible] phenobarbitone [illegible] the [illegible] [illegible] [illegible] postural

effect of reserpine on blood-pressure suggests that the mechanism controlling normal blood-pressure was unaffected.

Summary

The effects of phenobarbitone and reserpine on blood-pressure were compared in a small controlled trial in 7 patients with essential hypertension.

Phenobarbitone gr. 1/2 thrice daily had no significant effect on blood-pressure. Reserpine 0.5 mg. thrice daily produced a significant fall of blood-pressure in all 7 patients.

There was no postural fall of blood-pressure in patients treated with phenobarbitone or with reserpine.

We are grateful to Dr. C. D. Falconer, medical adviser to Ciba Laboratories, for supplying us with the tablets used in this trial.

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POLYNEURITIS AS A CAUSE OF "AMYOTONIA CONGENITA"

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AMYOTONIA congenita appears in infancy and is characterised by muscular weakness, hypotonia, loss or depression of reflexes, and contractures.

This clinical picture may be produced by various diseases, but in the majority—about 80% in Walton's (1956) series—it is due to some form of spinal atrophy or myopathy. Walton lists thirteen causes of the syndrome, and Brandt (1950) and Lizard (1954) add many general diseases which may be associated with muscular hypotonia in infancy.

In published accounts it is repeatedly stated that partial or even complete recovery is possible from amyotonia congenita, but the possibility of recovery from the pathological processes postulated in these conditions has never been adequately explained. All of Walton's (1956) cases which improved were classed as benign congenital hypotonia (benign congenital myopathy), which he does not regard as a "true myopathy." Nattrass (1954) concluded that of his patients who recovered from myopathy, the majority had polymyositis and the remainder benign congenital myopathy.

We report here three cases in which children with amyotonia congenita improved and were shown to be suffering from polyneuritis.

Case-reports

FIRST CASE

A boy aged 7½ years was admitted to the Hospital for Sick Children, Great Ormond Street, on June 5, 1956, under the care of Dr. Paulsen [illegible] a history of inability to [illegible] He was born of a normal family with [illegible] consanguinity. [illegible] normal [illegible] he was [illegible] normal [illegible] until the age of 2 months [illegible]

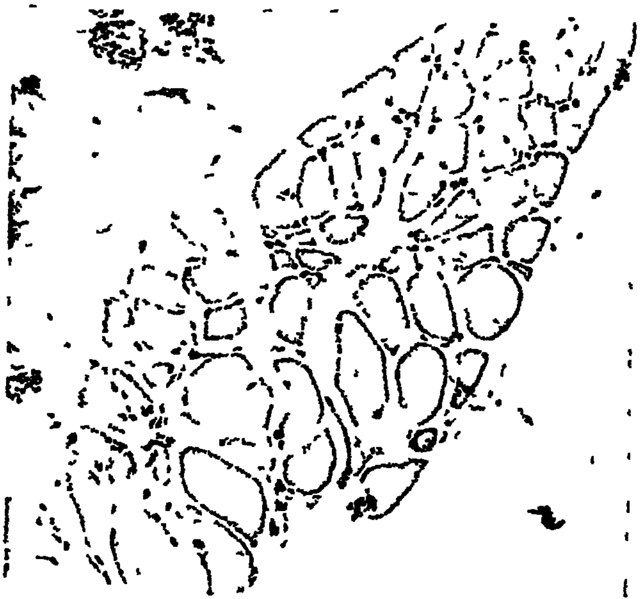

Fig 1—Case I transverse section of tibialis anterior muscle showing abnormal variation in thickness of muscle-fibres and prominence of subsarcolemmal nuclei (Hæmatoxylin and van Gieson ×154)

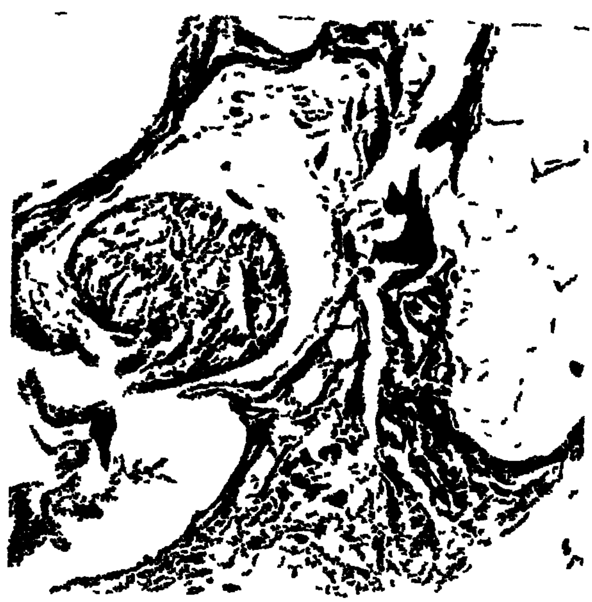

Fig 2—Case I transverse section of muscle and nerve bundle showing decreased number of myelinated fibres (Hæmatoxylin and van Gieson ×360)

weeks After this illness he continued to develop normally as regards gain in weight and mental function He had acquired full control of his sphincters at the age of 3½

After the gastro enteritis his spontaneous movements, particularly of his legs, were very slow to return and he was unduly limp Noticeable improvement was not observed until 15 months later, when he began to hold a rattle, to feed himself, and to sit with support A year later, at the age of 2½, *he could pull himself to his feet, and at the age of 4 he* began to walk, holding on to furniture

In the subsequent 3 years he learnt to write, to use his hands with considerable dexterity, and to stand unsteadily for a few seconds without support He never could raise his head when lying supine although he controlled it fairly well when erect

Apart from a thoracic scoliosis noticed at the age of 2½ years there were no other symptoms referable to his nervous or other systems He had been seen several times at Great Ormond Street and elsewhere since he was 2½ years old and was regarded as having amyotonia congenita

Examination

His mental state and speech were normal He walked only with support, on a wide base, with considerable ataxia and could stand alone unsteadily Romberg s sign was positive

He had slight asymmetry of the skull and moderate dorsal kyphoscoliosis, convex to the right He could not raise his head from the pillow

His *cranial nerves were normal except for a fine nystagmus* on full lateral gaze and weakness of his orbicularis oris muscle His sternomastoid and trapezius muscles were thin and weak His skeletal musculature was small, but there was no obvious wasting His limbs were hypotonic, and power was generally diminished in both arms and legs, more so distally and more so in the legs His trunk musculature was likewise weak Movement *of his limbs was ataxic, equally so* on both sides All his tendon reflexes were absent His abdominal reflexes were present and equal, and plantar responses flexor No sensory abnormality was discovered

He was slightly underweight (40½ lb), but no other abnormality was found

Investigations

His blood count, blood calcium, blood phosphorus, and blood-alkaline phosphatase were normal His urine was normal A radiograph *of his skull was normal* apart from slight brachycephaly and slight asymmetry Radiographs of his spine were normal except for dorsal scoliosis His intelligence quotient was 100 A sweating test was normal

His cerebrospinal fluid (C S F) was examined twice at an interval of 3 months On each occasion the pressure and dynamics were normal The protein content was 200 mg per 100 ml on the first occasion and 100 mg per 100 ml on the second An air encephalogram was normal

Electromyography (Dr A T Richardson) of his tibialis anterior muscles "*Occasional fibrillation potentials, and, on* volition, a reduced number of motor unit potentials, many of high amplitude *and long duration*"

Biopsy of tibialis anterior muscle (Dr W Blackwood) "There is abundant muscle tissue, although the fibres vary in calibre (not grossly) and the subsarcolemmal nuclei are prominent The nerve bundles contain only a few nerve-fibres (methylene blue) and few myelinated fibres (paraffin) In sections stained with methylene blue a few fibres going to nerve *endings* were *seen One of them shortly* before the nerve ending gave off an ultraterminal branch such as is seen after reinnervation The appearances suggest (1) a long-standing denervation with branching of residual nerve fibres to innervate muscle fibres other than those originally supplied, and (2) a partial sensory denervation of the muscle, because the degree of apparent loss of myelinated *nerves from the nerve bundles seems proportionately* much greater than the number of denervated muscle fibres" (figs 1 and 2)

The detailed history of this patient revealed a relatively rapid onset of the motor disability and slow recovery The clinical and laboratory findings were typical of polyneuritis, and the diagnosis was confirmed histologically by denervation atrophy with reinnervation of muscle and lesions of both motor and sensory fibres The only equivocal finding was the fine nystagmus on full lateral gaze Perhaps this was the consequence of a slight residual weakness of the *external ocular muscles, but* possibly it was due to anoxic damage sustained at birth

SECOND CASE

A boy, aged 4 years, was admitted to the National Hospital Queen Square, under the care of Dr Macdonald Critchley on July 20, 1955, with a history of weakness of the limbs since *infancy and disordered pronunciation* since he began to speak at the age of 1 year

He was adopted at the age of 3 weeks No family history and no history of pregnancy and delivery were available He had had pneumonia at 15 months and otitis media at 2 years From both these illnesses he recovered *completely* Nothing abnormal was noticed in the first few months save that he *frequently* vomited after his feeds This symptom ceased after he was weaned at 6 months

The onset of his motor disability is *difficult* to date but when he was 6 months his foster parents *first began to concern* themselves at his not sitting up and at his lack of movement It was not until *he was 18 months old that he made* much use of his limbs, at this time he began *to crawl* and to stand with support Not until he was 3 years old did he use his hands freely to manipulate his toys *In the few months before his* admission he had learnt to feed himself and could walk about [illegible] yards alone. Since he first began to speak he had also had [illegible] particular difficulty in pronouncing L, R, [illegible] and S. His [illegible] parents reported that there had been slight improvement in his movements since the age of [illegible] years. On direct questioning it was learnt that whereas he had always been [illegible] the [illegible] soles of his feet, they had in the last few months become ticklish. No other symptoms were elicited.

Examination

He was normally developed, cooperative, and very intelligent. He had a "lolling" type of dysarthria and tended to omit L and R. He could stand but walk unsupported, but his stance was unsteady, and Romberg's sign was positive. His gait was broad-based and ataxic, and he had a waddling appearance due to an exaggerated lumbar lordosis. His cranial nerves were normal.

He was flabby, and obvious wasting was present only in the small muscles of his hands. He had generalised hypotonia with moderate hyperextensibility of all the joints of his limbs. All his skeletal muscles were weak, more so distally. There was moderate ataxia in all his movements. All his tendon reflexes were absent; his abdominal reflexes were present and plantar responses flexor. He had impaired joint-position sense in his fingers and impaired two-point discrimination on his soles but no abnormality elsewhere. General examination was normal.

Investigations

His haemoglobin and urine were normal. His erythrocyte-sedimentation rate (Westergren) was [illegible] mm. in 1 hour. His c.s.f. was under normal pressure and there was no block. It contained [illegible] mg. of protein per 100 ml. but was otherwise normal.

No definite abnormality was found on electromyography of his quadriceps and tibialis anterior muscles. Biopsy of the [illegible] muscles was normal.

The history is of delay in the acquisition of movement first noticed at the age of [illegible] months, with subsequent improvement, and without other symptoms. The clinical picture of ataxia, weakness and wasting, areflexia, [illegible] sensory [illegible] associated with a raised level of protein in the c.s.f., and the history of obvious improvement strongly suggest [illegible].

[illegible] CASE

A girl, aged [illegible] years, was admitted to the Hospital for Sick Children under the care of Dr. [illegible] in [illegible] with a history of delay in walking.

She came of a healthy family with no consanguinity and no history of any nervous or other disease. The whole family [illegible] had lived in Singapore for three years before admission. Pregnancy [illegible] and [illegible] were normal and [illegible] movements vigorous. Delivery was at full term and labour was normal. The milestones were passed at the normal time up to the age of [illegible] months. She was noticed at the age of 11 months [illegible] when she sat up. She could not stand until she was [illegible] months of age and could not walk until she was [illegible]. She had full control of her sphincters at the age of [illegible] and was speaking in sentences at the age of [illegible].

From the age of [illegible] her walking very slowly improved. She was always unsteady on her legs and had a rolling gait, and easily [illegible] to the floor. At [illegible] she could walk about [illegible] yards by herself, and her usual means of progression was on [illegible]. Her parents had noticed no disorders in the use of her hands or arms.

On the voyage to England from Singapore her instability on her feet led her parents to carry her everywhere, and at the end of the voyage she was walking very much worse than before. There had been no disturbance of her general health, nor had she complained of any symptoms during this time. There had been no loss of [illegible].

This setback was largely overcome by energetic physiotherapy in [illegible] weeks in hospital. No other symptoms were elicited.

Examination

She was of normal mentality and development, and on admission she sat, she could not stand, and did not [illegible]. Her cranial nerves were normal. She had no wasting of her arms, which were hypotonic. There was slight weakness of the small hand muscles and of finger movements. She had mild ataxia on carrying out the finger-nose-finger test. There was weakness of flexion and of extension of the trunk. The muscles below the knee and the intrinsic muscles of the feet on both sides were slightly wasted, and the tendo Achillis slightly shortened. She had moderately severe weakness in both legs and could not dorsiflex or evert her feet. All her tendon reflexes and abdominal reflexes were absent and plantar responses flexor. She made errors in the appreciation of joint-position sense in the fingers and toes and in two-point discrimination in the fingers. General examination showed no other abnormality.

Investigations

Her blood count and urine were normal. A [illegible] test was normal. Radiographs of her skull, spine, and feet were normal. Her [illegible] was normal. [illegible] of the [illegible] showed [illegible] her legs, [illegible]. Her c.s.f. was [illegible] at [illegible] months. The pressure, dynamics, and [illegible] were normal except for a protein content of [illegible] mg. per 100 ml. on [illegible] occasion.

Electromyography of the tibialis anterior muscles (Dr. [illegible]) [illegible]. Fibrillation potentials [illegible]. On volition there was a reduced interference pattern of motor

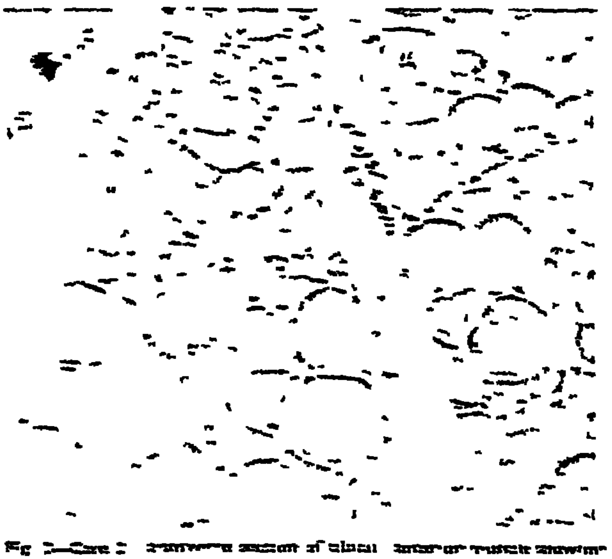

Fig. 2—Case 2: transverse section of tibialis anterior muscle showing abnormal variation in the size of muscle-fibres and prominence of subsarcolemmal nuclei. (Haematoxylin and eosin [illegible].)

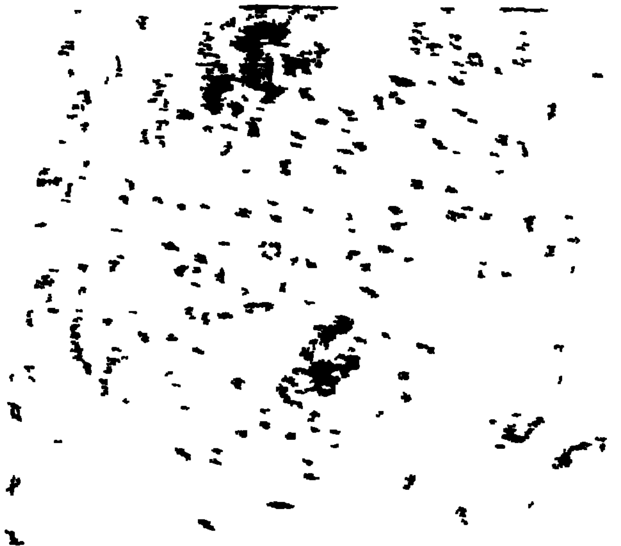

Fig. 3—Case 2: transverse section of nerve bundle showing decreased number of myelinated fibres. [illegible] are arrowed. [illegible] 210.

unit potentials of 5–10 m sec Occasional large polyphasic potentials were seen "

Biopsy of the left tibialis anterior muscle (Dr W Blackwood) "The muscle fibres show considerable variation in calibre and many groups of slender hypernucleated fibres The nerve bundles are poorly myelinated The appearances are those of denervation " (figs 3 and 4)

Follow up

3 months later, during which time her Achilles tendons had been lengthened and she had received much physiotherapy, there was no significant change in the physical signs, but she could stand and walk with support and had become more mobile

The history is of delay in the acquisition of movement, first noticed in the second 6 months of life, with subsequent slow improvement in a child who was otherwise normal

The evidence that she had polyneuritis is the clinical picture of widespread symmetrical paresis, worst distally and in the legs, muscle wasting, absent reflexes, mild sensory disturbance in the extremities, and absent flare in the triple response elicited in the extremities, with a raised C S F protein, and electromyogram and biopsy characteristic of denervation

The setback on the voyage back from Singapore to England we attribute to the interruption of physiotherapy rather than to a relapse of polyneuritis, because the symptoms were confined to the legs, sparing the trunk and arms, were not associated with any constitutional or other disturbance, and were rapidly relieved by physiotherapy

Discussion

The diagnosis of polyneuritis in these cases rests upon the clinical and laboratory evidence The history of the onset of the illness in each case is that the parents noticed a delay in the acquisition of movement without retardation of development in any other direction In case 1 detailed questioning established that the onset of the illness followed an attack of gastro enteritis, but no such information was elicited in the two other cases The course of the illness in all three cases was slow improvement The clinical picture was of widespread symmetrical lower motor-neurone paresis, worse in the legs than in the arms and more severe distally than proximally Associated with this were loss of the tendon-reflexes and, in two cases, mild but unequivocal sensory disturbance in the digits There was no muscular tenderness In all three cases the C S F was under normal pressure, there was no suggestion of a block, and the protein content was raised Denervation of muscle was shown by electromyography and by biopsy in cases 1 and 3, and damage to the peripheral sensory system by biopsy in case 1 and by absence of the flare from the triple response in case 3 All three patients were of or above average intelligence There was no sign of damage to the central nervous system No case showed disturbance of the sphincters or of general health , nor was there any skeletal or other disorder

All these patients conformed to the clinical criteria of amyotonia congenita All had been seen from time to time since the onset of their illness by competent physicians, and had been given the usual discouraging prognosis This, in two cases, had led to reluctance on the part of the local authorities to invest their limited resources of physiotherapy and education in such unpromising material Considerable correspondence was needed before the patients could benefit from these facilities The lamentable effects of neglect of physiotherapy are shown in case 3, who almost entirely lost the ability to walk as a result of being taken off her legs for 3½ weeks The importance of recognising this group of cases needs no further emphasis

The diagnosis of polyneuritis in these cases had not been seriously considered, because the clinical picture did not conform to that of acute polyneuritis in infancy (Casamajor and Alpert 1941, Andersen 1947, Brandt 1950), they were too young for a reliable sensory examination, the C S F had not been examined, and polyneuritis as a cause of amyotonia congenita is conspicuously rare in the literature

Ford's textbook (1952) and the review by Adams et al (1953) mention the possibility that amyotonia congenita is sometimes due to unrecognised polyneuritis, but they do not cite such a patient Sobel (1926), Brandt (1950), and Tizard (1954) mention polyneuritis as a possible cause to be borne in mind Bernhardt (1907) discussed two such cases and Leclerc (1907) another in which polyneuritis was the most likely diagnosis Leclerc's case was not unlike case 1 in that the symptoms were first noticed after bronchopneumonia at the age of 7 weeks and slow but steady recovery ensued

As many who have written on this topic point out, to establish an ætiological or pathological diagnosis in a case of amyotonia congenita there is need for repeated and meticulous examinations In spite of the common difficulty in differentiating between symptoms suddenly noticed and symptoms suddenly appearing, the retrospective history, as in case 1, in Leclerc's (1907) case, and in some of Nattrass's (1954) cases, may suggest an onset too rapid for a myopathy or for a " spinal atrophy " Later in the course of the illness the history of improvement is likewise a useful pointer

The main features of the paresis are its widespread distribution at an early stage and the presence of a degree of ataxia unusual in a myopathy of comparable severity We were fortunate in that our patients were old enough to be good sensory witnesses In the absence of this aid to diagnosis the triple response is the simplest test of the integrity of the peripheral sensory system

The most important single investigation is the examination of the C S F A raised protein level is an important finding with which to support the diagnosis The persistence of the increase of protein in the C S F for long periods after acute polyneuritis is well known, but the length of time in the present cases is remarkable

Electromyography and muscle biopsy usually establish the presence of denervation atrophy, and occasionally biopsy provides evidence of damage to sensory nerves Such procedures distinguish this small group of cases from the various types of spinal atrophy, myopathy, and myositis At a later stage in the illness chronic familial polyneuritis, and perhaps Friedreich's ataxia, have to be distinguished In the cases we have reported above the main points are the early onset, the improvement, the early involvement of the trunk musculature, and the raised level of protein in the C S F

As regards pathology and ætiology we have no observations to contribute beyond those already mentioned

The treatment of these patients is that of any polyneuritis—maintenance of the general health, the prevention and treatment of intercurrent illness, the prevention or correction of deformity, and training in movement Physiotherapy must be skilful and regular

The possibility that polyneuritis may closely mimic the clinical picture of the more usual causes of amyotonia congenita lends added support to the views expressed by other workers that this term should be discarded or confined to descriptive use in much the same way as the terms anæmia and glycosuria are used In particular it should be emphasised that this name implies no defined pathological process and indicates no definite prognosis

Summary

The history of the syndrome called amyotonia congenita is briefly outlined, and the fact that improvement is possible is emphasised

Three cases of amyotonia congenita are reported and shown to have been due to polyneuritis

The diagnosis of such cases is discussed, and the importance of examining the cerebrospinal fluid is emphasised

Electromyography and muscle biopsy will usually reveal denervation, and the elicitation of the triple response is suggested as a part of the sensory examination in such cases

It is important that physiotherapy be regular and skilled

The ætiological diagnosis of amyotonia congenita is briefly discussed, and the limitations of the term are explained

We wish to thank Dr Paul Sandifer and Dr Macdonald Critchley for their encouragement and advice, Dr W Blackwood for his helpful interest, Dr A T Richardson for the electromyograms, and Mr J A Mills for the photomicrographs

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INCIDENCE OF COMPLICATIONS AMONG ELDERLY HOSPITAL PATIENTS

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How do old people fare in hospital? Little has been written about this, compared to the numerous accounts of the hazards facing an infant in a large hospital nursery or a soldier in a small dormitory Yet, the number of old people in this country is increasing, and more and more beds instead of being for the chronic sick, are being turned over to acute geriatric units, where the emphasis is on treatment rather than long term care The average length of stay of most of the patients in our unit is only a little longer than in the general medical wards[1] This change in the use of beds raises its own problems

Are old people less able to bear hospital discipline and procedures than the young and middle aged? Are they more liable to develop complications than younger patients? What complications occur in hospital and what proportion of patients are affected? Is it wise to admit old people for a while, so as to give their relatives a rest? Should an acutely ill patient always go to hospital where there is round-the clock nursing and medical care, or should he be nursed at home?

In an attempt to answer some of these questions, a survey was made of the complications arising in patients in our unit during twelve weeks from July to October

TABLE I—ANALYSIS OF COMPLICATIONS

—	Male	Female	Fatal	Delaying	Total
Chest infections	8	5	5	2	13
Urinary infections	1	5			6
Eye infections	2	1			3
Upper respiratory tract infections	2	1			3
Carbuncle		1			1
Confusion	1	6		1	7
Falls					
Fractured femur		1		1	1
Fractured ribs	1			1	1
Cut temple	1				1
Effusion on knee		1			1
Facial bruise	1				1
Bedsores	3	5		2	8
Superficial burn	2				2
Contractures	1	1			2
Calliper ulcer	1			1	1
Incontinence	1				1
Submandibular sialadenitis	1				1
Cerebral thrombosis		2			2
Coronary thrombosis		1	1		1
Pulmonary embolism		1	1		1
Œdema of tongue		1			1
Ammoniacal dermatitis	1				1
Surgical emphysema (from bedsore)		1			1
Total	27	33	7	8	60

Observations

The unit has two wards, one male and one female, each with 30 beds All conditions arising during the survey, which had been absent on admission and which were not clearly related to the patients' original disease, were classed as complications Control series were obtained from general acute medical wards and a geriatric half-way house

Geriatric Admissions

During the period of the survey there were 86 admissions and 82 discharges The length of time the patients had been in hospital on death or discharge is shown in the chart 45 patients developed complications (table I)—12 of whom developed more than 1 complication (table II)

TABLE II—INCIDENCE OF SERIAL COMPLICATIONS

No of complications	No of patients		
	Male	Female	Total
1	12 *(63%)*	21 *(80%)*	33 *(73%)*
2	6	3	9
3	1	2	3
Incidence of serial complications	7 *(37%)*	5 *(20%)*	12 *(27%)*

Percentages in parentheses equal incidence in each group

4 men and 2 women were admitted to give their relatives a rest from home nursing They all developed complications

Controls

At the half-way house attached to the hospital 26 old people live The average length of stay here is measured in years, not weeks During thirteen weeks the following complications occurred

Complications	*Male*	*Female*	*Total*
Acute bronchitis	2	1	3
Bronchopneumonia		1*	1
Effusion on knee	1*		1
Acute intestinal obstruction		1*	1
Extensive bruise		1*	1
Scrotal cellulitis	1*		1
			1
	4	4	8

* Patient admitted to hospital

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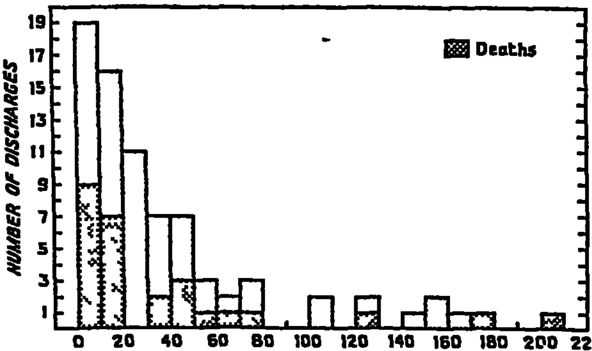
[1] Amulree (Lord), Arnold P, Polak A *Lancet* 1952 ii 191



Duration of stay of 82 patients discharged during twelve-week survey 4 of the 82 are not shown in this abridged chart They were discharged at 240 days and (by deaths) at 259, 437, and 529 days

In one general acute medical ward 30 beds were observed for twenty-two weeks Approximately half were for men and half for women Patients of all ages are admitted, but the average age is about 58 The average stay is 34 days Among the 136 patients observed, the following complications occurred

Acute bronchitis	1
Pulmonary embolism (1 death)	5
Confusion	2
Hæmatemesis	1
Fracture dislocation of head of humerus	1
Blepharitis	1
Conjunctivitis	1
Carbuncle	1
Otitis externa	1
Diabetic hypoglycæmic attacks	1
	15

Interpretation

As the duration of the survey is only slightly longer than the average length of stay in the geriatric unit (78 days) the incidence of complications cannot be related directly to admissions During the twelve week survey *on 60 beds, 60 complications* were observed, so that I complication occurred in each bed in twelve weeks This period may be called the complication interval But beds were vacant from time to time Allowing for this the complication interval =

$$\frac{\text{Number of patients} \times \text{days in hospital (4758)}}{\text{Number of complications (60)}} = \textit{79 days}$$

The complication interval in the general medical wards was 298 days, and for cases in a half-way house it was 282 days

The prospect of a patient developing a complication may be calculated indirectly The average duration of stay of geriatric patients was 72 days—very close to the complication interval (79 days) In consequence during the stay of 100 patients $\frac{72}{79} \times 100 = 91$ complications would be expected In the survey 45 patients developed 60 complications between them, so the number of patients required to develop 91 complications is $91 \times \frac{45}{60} = 68$ patients

From this it appears that 68% of patients admitted to our geriatric unit develop complications Worked out on the same basis, the incidence of complications for general medical admissions is just over 11%

Among the patients in the geriatric unit during the survey there were 30 deaths, of which 7 (23%) were due to complications The fatal complication interval may be calculated on the same principle as the simple complication interval

$$\frac{\text{Number of patients} \times \text{days in hospital}}{\text{Number of fatal complications}} = 680 \text{ days}$$

The percentage of patients developing fatal complications was 11% Thus in a geriatric unit of 80 beds 1 complication may be expected every day and 3 deaths from complications each month

Discussion

It is calculated that 2 out of 3 patients admitted to a geriatric unit develop 1 or more complications and that 1 patient in 10 dies of a condition acquired in hospital

The complication interval is roughly four times shorter in an acute geriatric unit than in either a half way house or an acute medical ward In each geriatric bed 1 complication occurs on average every 11 3 weeks

Of the 67 women in the geriatric ward 26 (39%) developed complications and of 74 men 19 (26%)—i e, women are affected more commonly than men in the ratio of 3 2 However the proportion of men that have a further complication is approximately twice as great (table II)

Age, in patients over sixty five, does not seem to affect the incidence of complications, *for the average age* of patients with and without complications was the same

Of 60 complications, 26 were due to infection, including 13 chest infections of which *5* were *fatal* *The chest infec*tions were unlikely to be due to seasonal exacerbations of chronic bronchitis, for the survey was made between July and October Four out of five urinary infections in women followed catheterisation In these patients "*catheter fever*" and pyuria developed after urine (sterile on culture) had been withdrawn This cannot be blamed entirely on the nurse's technique, for the same nurses working in other hospital departments do not introduce infection

12 complications were due to *falls* or to confusion These are classed together because I think that they are partly due to the same thing Taking a slightly demented old person out of his own home and putting him in a large ward, expecting him to climb in *and out of a hospital bed,* subjecting him to a routine that is strange and at times alarming, and asking him to try to walk with few and unfamiliar hand holds, puts a big *strain on* his ability to remain upright and sensible

The patients who were admitted to give their relatives a rest all developed complications

The survey is *not* large enough to show *all the forms* that complications take, nor the frequency of each The interval between admission and the onset of complications varied greatly and did not appear to be significant

Summary

It is calculated that two out of every three patients admitted *to* a geriatric unit develop conditions from which they were free on admission In a general medical ward only one patient in ten develops complications

The complication interval (the time between complications for *any* geriatric bed) was roughly eleven weeks—four times shorter than in either general medical wards or a half-way house

A quarter of all deaths in this unit were due to complications

Women were more commonly affected than men in the ratio of 3 2, but men more commonly had several complications

Nearly half the complications were due to infection

I thank Lord Amulree for his help and encouragement in writing this paper

LATENT HÆMOLYSIS IN RHEUMATOID ARTHRITIS *

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THE rate of red blood cell destruction is increased in many diseases in which a hæmolytic process is not the predominant factor—e g, cirrhosis of the liver (Chaplin and Mollison 1953) and uræmia (Emerson 1948, Chaplin and Mollison 1953) In some of these conditions a hæmolytic state may be inferred from the results of routine laboratory tests Latent hæmolysis may be present in other conditions in which the serum bilirubin level is within normal limits, and in which reticulocyte counts are normal or only *slightly increased* *In such* cases red cell life span must be measured directly to demonstrate a hæmolytic mechanism

Mollison and Patterson (1949) transfused sensitised red cells to 2 patients with rheumatoid arthritis *and found* that in both cases the transfused cells were *eliminated* at an increased rate The experiment was repeated using unsensitised cells and in 1 case the transfused cells were eliminated in about fifty days In 1 severe case of rheumatoid arthritis investigated by Brown et al (1944) transfused cells were not destroyed abnormally quickly When the present investigation was started no further report on red-cell life span in rheumatoid arthritis had appeared Since that time Bunim (1954), using cells tagged with radioactive chromium, and Freireich et al (1954) and Alexander et al (1956), using the Ashby technique, have reported that the life span of normal red cells in the circulation of rheumatoid patients is diminished

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* Based on a *thesis for the degree of* M D in the Queen's University of Belfast

Material and Methods

In the present investigation the life span of normal red cells in the circulation of 15 patients with anæmia and rheumatoid arthritis was measured The effect of intravenous iron therapy on the anæmia was studied in 7 of the 15 cases Marrow-iron examination, which is a means of distinguishing the iron-deficient from the non-iron-deficient patient (Hutchinson 1953), was carried out in each of the 7 cases before blood-transfusion or the administration of iron The effect of intravenous iron therapy was studied over a test period of about a month, either before the start of or after the conclusion of the transfusion experiment in each case About one gramme of an iron preparation for intravenous use (saccharated oxide of iron in colloidal solution, either ‘Ivron’ or ‘Ferrivenin’ containing 20 mg colloidal iron per ml) was administered in from six to ten injections over a period of eight to ten days

The 15 patients examined were inpatients at the Royal Bath and White Hart Hospitals, Harrogate 13 were classified as having “very” active disease, the remaining 2 had “moderately” active disease In classification the following factors were considered the degree of joint pain and tenderness, the presence of general constitutional symptoms and the erythrocyte-sedimentation rate (E S R)

Red-cell life span was measured by Dacie and Mollison's (1943) modification of Ashby's technique Anti-M sera in the form of powdered globulin (Lederle) were used for differential agglutination (Ebert and Emerson 1946, Mollison 1951a) Pre transfusion (‘blank”) counts with these sera varied from 3000 cells per c mm to 10,000 cells per c mm All recipients were of blood group M or MN The cells from 800–1200 ml. of blood from normal donors (group N) were transfused in each case either as whole blood or in the form of a concentrated red cell suspension The blood had been stored in acid citrate-dextrose solution for six days or less in 12 cases, but in 3 instances was up to ten days old Estimations of surviving transfused cells were made twenty-four to forty-eight hours after transfusion, again after a few days, and thereafter at convenient intervals For the first post transfusion estimation 4000 cells were counted, afterwards 2000 cells were counted until near the end of the follow up period when cells were relatively scarce and 1000 cells were counted

Red-cell-survival Experiments

The figures obtained for red-cell survival were plotted graphically against time In the single case in which the number of transfused cells diminished steadily with time, the mean red cell life span was estimated by fitting a straight line to the points by inspection and noting the point at which the line cut the time axis In the remaining cases, in which the slopes of elimination were curvilinear, the mean red cell life span was calculated by the simple method devised by Dornhorst (1951) and described by Mollison (1951b) The observed values for transfused red cells were each multiplied by $\frac{120}{120-t}$ where t is the number of days after transfusion These corrected values were then plotted graphically against time and the area under the curve was measured between 0 and 120 days This area was then divided by the initial height to give the mean cell life

TABLE I—RED CELL LIFE SPAN ESTIMATIONS

Case no	Age (yr)	Sex	Disease activity before transfusion	Hb (g per 100 ml)	P C V (%)	M C H C (%)	Reticulocytes (%) (max count)	Serum bilirubin (mg per 100 ml)	Mean red cell life span (days)
1	62	M	Mod	10 1	37	27	1 2	0 2	93
2	56	F	− − −	9 0	34	26	2 8	0 4	60
3	58	F	+ − −	9 3	34	27	1 8	0 2	30
4	56	F	− − +	9 0	33	27	1 3	0 2	61
5	58	F	− + −	9 0	33	27	1 2	0 4	70
6	55	F	− − −	10 2	36	28	1 7	0 2	60
7	54	F	− + −	10 2	36	28	1 1	0 2	90
8	42	F	− − −	8 5	30	28	0 6	0 2	105
9	48	F	− − −	8 5	29	29	1 4	0 2	40
10	17	F	+ − −	10 9	40	27	1 0	0 2	65
11	38	M	Mod	9 3	36	26	0 8	0 2	108
12	68	F	− + −	8 8	29	30	1 5	0 5	54
13	55	F	+ − −	11 5	38	30	3 5	0 9	28 32
14	38	F	− + −	10 1	37	27	1 1	0 3	70
15	65	F	+ + −	11 5	39	30	1 2	0 2	98

Other Tests

Reticulocytes were counted, antiglobulin reactions were carried out, and cold-agglutination titres were measured using the methods described by Dacie (1950) Serum-bilirubin and fæcal-urobilinogen estimations were made by the methods of King (1951) Red-cell osmotic fragility was determined by the technique of Creed (1938) Marrow punctures were performed in the manubrium or first or second parts of the body of the sternum under local anæsthesia Histological sections prepared from aspirated marrow fragments were stained for iron using the method described by Hutchinson (1953) With regard to iron content the marrows were roughly classified as showing “none,” “a small amount,” “a moderate amount,” or “a large amount” of stainable iron

Results

The results are given in table I It is generally agreed that the normal life span of the red cell is 100–120 days (Callender et al 1945, 1947, Mollison 1947)

In 5 of the 15 cases the red cell life span was ninety days or more Of these patients, 2 (cases 7 and 8) showed distinct clinical improvement after transfusion In 2 further patients (cases 1 and 11) there was evidence of iron deficiency in that no stainable marrow iron was demonstrable in either case and 1 (case 11) responded to iron therapy In these 2 cases disease activity varied from moderate to slight The remaining patient (case 15) had very active arthritis initially, her condition improved somewhat after transfusion, but the disease remained moderately active throughout the period of the transfusion experiment

The rate of red cell destruction was increased in 10 of the 15 cases examined These 10 patients had very active arthritis The rate of destruction varied from about two to four times normal In case 13 the rate of destruction was measured twice and each time was found to be about four times normal In this case the reticulocyte count was 3 5% and the serum-bilirubin level was at the upper limit of normal In the remaining patients, with 1 exception, the serum bilirubin levels were within normal limits and reticulocytes were 2% or less The exception was case 2, in which a reticulocyte-count of 2 8% was found once In 6 cases in which fæcal urobilinogen was estimated no excess was found Red cell osmotic fragility was normal in 6 cases in which the test was carried out

TABLE II—RESPONSE TO INTRAVENOUS IRON RELATED TO RED CELL LIFE SPAN

Case no	Sex	Marrow iron (amount)	Response to iron therapy *	Red cell life-span (days)
1	M	None	+	93
2	F	Large	–	60
3	F	Mod	–	30
4	F	Large	–	61
5	F	Small	–	70
6	F	Mod	–	60
7	F	Mod	–	90

* Increase in Hb level of 2 g or more per 100 ml

The response to iron therapy is related to red cell life-span in table II In assessing the effect of intravenous iron therapy, an increase in hæmoglobin of 2 g per 100 ml or more was arbitrarily taken as indicating a response (Coleman et al 1955) In 5 patients (cases 2–6) stainable iron was demonstrated in the bone-marrow, there was no response to intravenous iron therapy, and red-cell life span was diminished In case 7 the marrow contained iron, there was no response to iron therapy, but red cell life span was diminished little if at all This patient had improved clinically after blood transfusion In case 1 iron deficiency was a factor in the production of anæmia, as the absence of marrow iron and the response to iron therapy indicated, disease activity varied from moderate to slight throughout the period of observation and red cell life span was only slightly reduced

Deductions from Mean Red-cell Life-span

In cases where the red-cell life-span was normal or only slightly reduced, the anæmia arose from inefficient hæmoglobin production by the bone marrow due to iron deficiency, marrow dysfunction, or a combination of these two factors In some instances there was evidence of spontaneous improvement in anæmia

In case 8, for example, the packed cell volume before transfusion was 30% A week after transfusion the packed-cell volume was 36%, eight weeks afterwards it was 40%, and about twelve weeks afterwards it was 37%

In view of the obvious difficulties when marrow output is not steady throughout the period of observation, no attempt has been made to correlate life span and marrow-red-cell output in these 5 cases

When mean red cell life is reduced, the production of red cells needed to maintain a steady output is related to normal production by the expression

$$\frac{\text{Observed red cell count}}{\text{Normal red cell count}} \times \frac{\text{Normal mean red cell life}}{\text{Observed mean red-cell life}}$$

(Chaplin and Mollison 1953) For the purpose of this calculation, the normal red-cell count was taken to be 5,000,000 per c mm This figure is said to be a fair average, irrespective of sex (Whitby and Britton 1953)

Thus marrow output was found to be about one and a third times to twice normal in 8 of the 10 cases In the remaining 2 patients, red-cell output was calculated to be between three and four times the normal (table III) In making these calculations, it was assumed that red cell production was steady at the time when observations began (Chaplin and Mollison 1953)

Although the red-cell output was found to be increased in all 10 cases, the red cells produced were deficient in hæmoglobin as shown by lowering of the mean corpuscular hæmoglobin concentration

TABLE III—CALCULATED RED CELL OUTPUT IN CASES WITH A DIMINISHED RED CELL LIFE SPAN

Case no	Mean red cell life span (days)	Red cell production (ratio to normal)
2	60	1 6 1
3	30	3 5 1
4	61	1 5 1
5	70	1 3 1
6	60	1 6 1
9	40	2 0 1
10	65	1 7 1
12	54	1 6 1
13	(a) 28	
	(b) 32	3 5 1
14	70	1 5 1

Discussion

Latent hæmolysis, demonstrated by abnormally short survival-time of normal red cells, is a factor in the production of anæmia in certain cases of active arthritis The results of the present study agree with those reported by Mollison and Patterson (1949), Freireich et al (1954) and Alexander et al (1956) Evidence that there is an intrinsic red cell defect in rheumatoid patients is described by Bunim (1954), who found in a single case that red cells from a rheumatoid patient had an abnormally short life span in the circulation of a normal individual Freireich et al (1954), however, reported that red cells from rheumatoid donors survived normally in normal subjects in the few cases which they studied Alexander et al (1956) state that red cells from rheumatoid donors survive longer in rheumatoid recipients than do cells from healthy donors They suggest that this may be due to some special characteristic of the red cells from rheumatoid donors Mollison (1956), however, points out that this longer survival-time of rheumatoid cells is not surprising as red cells taken from any patient with a hæmolytic process are a selected population compared with red cells from a normal donor, and their survival is expected to be better Alexander et al further observed that the administration of corticotrophin in doses sufficient to control the clinical signs of the disease did not prolong the survival-time of normal red cells in rheumatoid patients In the present study corticotrophin was not given to any patient, but red cell life span was reduced little, if at all, in patients in whom sustained clinical improvement took place after transfusion

An increased rate of red-cell destruction has been described in the active phase of rheumatic fever (Reinhold 1954) and in nephritis (Chaplin and Mollison 1953) Hæmolysis in association with acute disseminated lupus erythematosis has been reported (Michael et al 1951, Dubois 1952) Hæmolytic anæmia is a feature of thrombotic thrombocytopenic purpura (Muirhead et al 1948, Dacie 1954a), and hæmolysis in association with periarteritis nodosa has been described (Dameshek and Rosenthal 1951) These diseases have been included by one worker or another in the "collagen disease" group, but, although fibrinoid necrosis is common to them all, it is unlikely that they have a common ætiology (Duthie 1954)

Compensatory Erythropoiesis

The bone-marrow in uncomplicated hæmolytic disease is capable of producing about six to seven times the normal amount of hæmoglobin (Crosby and Akeroyd 1952) In the present 10 cases in which hæmolysis was shown, the calculated red cell output was in most cases one and a third times to twice normal Myeloid erythroid ratios, determined in 5 of these 10 cases, varied from 1 8 1 to 4 1, and sections prepared from aspirated marrow showed normal cellularity Thus the bone marrow response to hæmolysis in these cases of arthritis was less than would be expected if marrow function were normal Hæmolysis in these cases of arthritis was associated with the production of red cells which were deficient in hæmoglobin as shown by a low mean corpuscular hæmoglobin concentration The exact nature of this defect in hæmoglobin synthesis is unknown It is not apparently due to lack of iron, as marrow iron stores were demonstrated and intravenous iron therapy failed to correct the deficiency in certain cases in the present study (table II) The diminished life span with slight increase in marrow output in these cases is somewhat similar to the pattern of anæmia in hepatic cirrhosis (Chaplin and Mollison 1953) Freireich et al (1954), using radioactive tracer techniques, estimated that iron utilisation and red cell production were normal in cases of rheumatoid arthritis in which the red cell life span was diminished Bunim (1954) agrees that anæmia in rheumatoid arthritis results, in certain cases at least, from increased blood destruction without adequate compensatory production The results of the present study agree generally with the observations of Bunim (1954) and Freireich et al (1954)

Reticulocytes, Bile Pigment, Metabolism, &c

The laboratory tests which usually indicate the presence of hæmolysis were negative in the present cases Reticulocyte counts greater than 2% were found in only 2 cases, serum-bilirubin levels were within normal limits in all 10 cases, and fæcal urobilinogen levels were not excessive in the 6 cases examined The osmotic fragility of the red cells, measured by a routine laboratory method, was normal in the 6 cases investigated Normal reticulocyte counts and serum-bilirubin levels have been reported in latent hæmolytic states associated with malignant and infective conditions (Brown 1950) and cases of leukæmia and lymphoma (Ross et al 1951) Dacie (1954b) states that serum bilirubin and fæcal urobilinogen levels are unreliable as evidence for the presence of hæmolysis in a mild hæmolytic state In the present cases, although studies of bile pigment metabolism and reticulocytes did not suggest that hæmolysis was taking place, direct measurement of red-cell life span demonstrated the existence of a hæmolytic mechanism

Serology

In the present cases direct and indirect antiglobulin reactions were negative and cold agglutination titres were within the normal range The direct anti-globulin test was negative in the 2 cases of rheumatoid arthritis investigated by Mollison and Patterson (1949), but Dacie (1954c) mentions a type of " non specific " positive anti-globulin reaction in rheumatoid patients Ball (1952) found positive sheep cell agglutination tests in a large number of patients with rheumatoid arthritis and in certain cases of acute disseminated lupus erythematosis In view of this finding he felt that this agglutinating factor might be an auto antibody, but he was unable to obtain a positive anti-globulin test in the few cases of arthritis investigated The possibility that an underlying immunological mechanism is a factor in the production of collagen diseases is suggested by the work of Glynn and Holborrow (1952a and b), who have shown that in animals injection of a polysaccharide-streptococcus vaccine led to the production of specific antibodies to the homologous polysaccharide Theoretically an inflammatory reaction in connective tissue might possibly result from union of antibodies of this type with the polysaccharide of ground substance Duthie (1954) points out, however, that so far there is no direct evidence for the presence of antibodies of this type in human disease

Factors Possibly Influencing the Increased Rate of Red cell Destruction

The curvilinear slopes of elimination of the transfused cells suggest that an extracorpuscular factor is responsible for hæmolysis in these cases of rheumatoid arthritis Intravascular aggregation of red cells has been observed in the conjunctival vessels of patients with rheumatoid arthritis (Laine and Zilliacus 1950) This pathological change in blood flow—" sludging " (Knisely et al 1947)—has been described in various infective and malignant conditions as well as in blood disorders (Knisely et al 1947, Laine and Zilliacus 1950) Bloch and Powell (1952) consider that this type of intravascular aggregation is caused by a substance adherent to the red cells which might cause red-cell agglutination and make the cells susceptible to phagocytosis and consequently to hæmolysis Wasastjerna et al (1954), however, consider that this " sludging " factor is concerned more with rouleaux formation than hæmagglutination Miller and Whittington (1942) state that the plasma viscosity can be taken as an index of the power of the plasma to cause red-cell aggregation and rouleaux formation Plasma viscosity, like the erythrocyte sedimentation rate, is a non-specific response, affected by alterations in plasma-proteins and very little by the non-protein constituents (Eastham 1954) The effect of increased plasma viscosity on blood destruction in rheumatoid arthritis is not known, but in the present study persistently high plasma viscosity levels were found in cases in which there was a diminished red-cell life span

Kellgren (1952) has suggested that peptides liberated from disruption of the collagen polysaccharide complex may be responsible for the toxic and inflammatory features of rheumatoid arthritis There is no direct evidence for this hypothesis, but toxic metabolites may possibly be responsible for hæmolysis in rheumatoid arthritis , substances of this type may be factors in the causation of hæmolysis associated with uræmia, liver disease, and carcinomatosis (Dacie 1954d) In these disorders gross morphological abnormalities of the red cells are sometimes seen—a fact which Dacie (1954d) considers a further possible indication of a toxic factor Apart from hypochromia and slight anisocytosis and poikilocytosis, no morphological abnormalities have been detected in the peripheral blood of rheumatoid patients

Conclusions

In some cases of active rheumatoid arthritis an increased rate of red cell destruction is a factor in the production of anæmia

The hæmolysis is insufficient to cause anæmia in patients whose bone-marrows are uninhibited, and inadequate compensatory red cell production by the bone marrow apparently plays a part in the causation of anæmia In rheumatoid arthritis hæmolysis is often associated with the production of red cells which are deficient in hæmoglobin—a deficiency which in the present study was not corrected by intravenous iron therapy

The presence of hæmolysis in these cases could not have been inferred from the results of routine laboratory tests Direct measurement of red cell life span was necessary to demonstrate the existence of a hæmolytic mechanism

The curvilinear slopes of elimination, when the red-cell life span estimations are plotted graphically, suggests that an extracorpuscular factor causing random destruction of cells, irrespective of their ages, is responsible for hæmolysis In the absence of any identifiable immune mechanism the exact cause is unknown, but a diminished life span seems to be associated with pronounced disease activity When sustained clinical improvement takes place or disease activity is only moderate or slight, red-cell life span is diminished little if at all

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References overleaf

POST-GASTRECTOMY STEATORRHŒA AND PATCHY JEJUNAL ATROPHY

J W PAULLEY
M D Lond , M R C P

F A FAIRWEATHER
M B Lond

A LEEMING
M B St And

From the Ipswich Hospitals

CHRONIC inflammatory changes and atrophy of the jejunal mucosa associated with idiopathic steatorrhœa have been reported by one of us (Paulley 1952a and b, 1954) This observation was contrary to the current teaching that there were no abnormal changes in sprue or steatorrhœa—a concept dating from Thaysen's (1932) monograph Since 1954 further cases here, and unpublished data from G D Hadley and M Shiner in this country and F Gardner in the U S A (personal communications) have confirmed these changes

For some years the hypothesis has been entertained (J W P) that those cases of post gastrectomy syndrome in which steatorrhœa develops and the patient loses weight may have been latent cases of idiopathic steatorrhœa before operation—the supposition being that gastrectomy is provocative in predisposed subjects by causing unaccustomed conditions in the upper intestine To test this hypothesis, for the past year wedges of jejunal mucosa have been taken by our surgical colleagues during gastrectomy A possible correlation between the state of the mucosa and the patient's subsequent course is being sought To date, of 61 patients submitted to gastrectomy, 5 had abnormal mucosa Of these 5, the abnormality was gross in 2, both of whom, when traced, were found to have steatorrhœa, to be under weight, and to be dissatisfied , 1 gave a history of loose pale foul stools for a year or more before operation, and the other was said to have had colitis ten years before, and had had a high random fæcal fat two years before This work, which is still proceeding, may explain part of the 10% failure-rate after gastrectomy

Case-record

A man, aged 51, was admitted on June 18, 1956, complaining of variable pains, increasing weakness, and pale foul diarrhœa He was depressed, pigmented, and emaciated (body weight 5st 5 lb), with blue sclerotics He had had an enormous appetite since gastrectomy two years before

The past history, obtained from the patient and his wife and brother, was as follows He was the youngest of three brothers and had fragilitas ossium His mother made a fuss of him because of his numerous fractures, and he was devoted to her , his father was an alcoholic His mother told his wife that he had always had a weak stomach, and his wife described attacks of pale diarrhœa intermittently since she married him in 1935 , he had lost much time from work He said he first had " colitis " in 1920 He was never quarrelsome and would avoid rows at any cost His brother, when asked if he was soft hearted, said " he would give himself away " He added that the patient had dwelt on his pains and illnesses all his life When his mother died in 1941 of cancer, the bottom fell out of his life, and he became depressed thinking he had cancer of the bowel Later he thought he had cancer of the throat and of the brain To the time of his death his belief that he had cancer was never dispelled In 1950 he attempted suicide by cutting his wrist , previously he had tried to poison himself, was later admitted to hospital with anæmia and melæna, after treatment was transferred to a mental hospital, and remained under outpatient psychiatric observation for the next five years He had had no sexual relations with his wife since 1940 for fear that " she should catch cancer "

In 1952 he sought surgical advice for a suspected duodenal ulcer In 1954 he saw the same surgeon, who performed an anterocolic Polya partial gastrectomy , only scarring was found He then weighed 9 st 11 lb Almost at once he began to lose weight, and nine months after his gastrectomy he weighed 7 st 13 lb , after fifteen months he weighed 7 st 3 lb Eighteen months after gastrectomy, cholecystectomy was done because of persistent pain At laparotomy gall bladder adhesions were found In February, 1956, his weight had fallen to 6 st 12 lb Steatorrhœa was suspected at the time of cholecystectomy and was confirmed in June, 1956, when a casual fæcal fat reading was 50 9 g per 100 g total fat, and a fat balance showed only 70% absorption Radiography after a barium meal showed coarse folds and spattering of barium in the small bowel

Dr Shiner kindly carried out jejunal biopsy (Shiner 19[illegible]) To our surprise the specimen did not show the expected

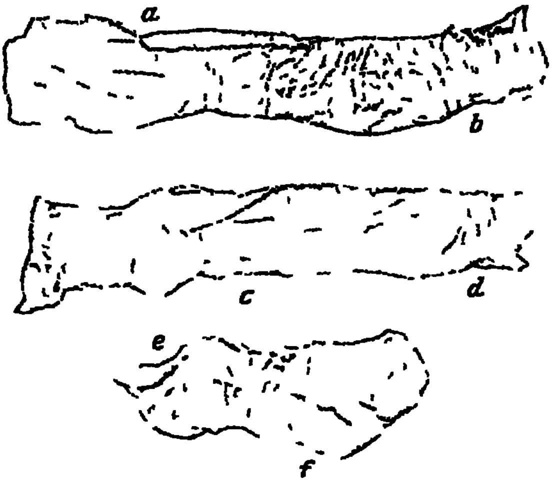

Fig 1—Jejunum, showing normal and atrophic areas

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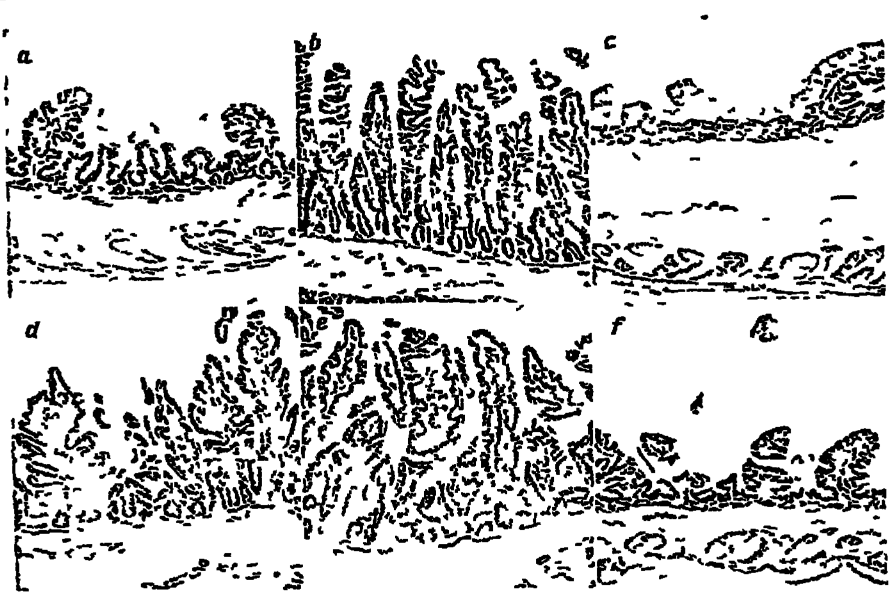

Fig 2—Microscopic appearances of jejunal mucosa (sites shown in fig 1) (*a*) atrophy, (*b*) normal, (*c*) gross atrophy (*d*) irregular villi, moderately abnormal, (*e*) somewhat irregular villi, moderately abnormal (*f*) gross atrophy

grossly abnormal changes of cellular infiltration and atrophy It was considered to be within normal limits

Despite every effort with gluten free diet, steroids, antibiotics, and modified insulin shock the patient failed to respond and died from terminal pulmonary embolism Permission for necropsy was obtained and the gut was preserved in formal saline shortly after death

Necropsy

The stomach was atrophic and the duodenum and stoma were normal The small gut was 15 ft long, everywhere its wall was thin. In the proximal 18 in the mucosa showed rugæ, though not so closely set as normal, to touch it had the normal velvety feel Below this there were many areas 6–12 in long where the mucosa appeared to be completely smooth (fig 1) and was not velvety to touch Toward the ileocæcal valve more normal mucosa was found The large intestine showed somewhat similar changes There was no ulceration The pancreas, liver, and suprarenals were normal

Microscopy confirmed gross mucosal atrophy in the areas macroscopically atrophic, and a near normal mucosa in the other areas, but the spacing, shape and size of the villi in some of these areas were irregular (fig 2)

Discussion

This man presented as a case of post gastrectomy steatorrhœa and malnutrition, but he and witnesses told of symptoms typical of steatorrhœa for many years before his operation, and he had shown emotional and personality disorder, which is common in steatorrhœa (Paulley 1949, 1952a and b, 1954) Gastrectomy precipitated a phase of gross malnutrition and steatorrhœa culminating in his death When jejunal biopsy was done there was little doubt in our minds that this was a case of idiopathic steatorrhœa aggravated by gastrectomy The almost normal mucosa was a complete surprise and quite counter to our experience and that of others in idiopathic steatorrhœa It seemed that either the diagnosis was wrong or the mucosal changes were patchy, and that we had failed to strike an abnormal area, although we had taken six specimens from different points to $1^1/_2$ feet below the stoma Shortly afterwards the case was discussed with Dr N Buyssens, of Antwerp, who said that he had seen patchy intestinal atrophy in 4 patients 1 of whom had proven idiopathic steatorrhœa, and the others malnutrition possibly with steatorrhœa

Probably our failure to obtain a biopsy specimen from an atrophic area was due to the smoothness of the mucosa rather than a failure of the tube to reach the right place The extreme thinness of the wall in the atrophic areas underlines the importance of not exceeding the negative suction pressure of –5 mm Hg recommended by Shiner to avoid perforation It now seems that a normal jejunal biopsy is not entirely dependable

Summary

Early results support the hypothesis that post-gastrectomy steatorrhœa is influenced by the state of the jejunal mucosa before operation Evidence so far suggests that surgeons should beware of gastrectomy in patients with a history of bowel looseness Jejunal biopsy may prove a useful screening measure before gastrectomy

A case is described of post-gastrectomy syndrome with steatorrhœa and malnutrition in a patient with a convincing history of intermittent steatorrhœa for many years before gastrectomy Jejunal biopsy was normal Necropsy revealed areas of gross atrophy of the intestinal mucosa separated by relatively normal areas

A negative jejunal biopsy may be misleading

On no account should excessive suction be applied during tube biopsy

We are most grateful to Mr A R Hill, Mr G F Langley, Mr R S Monro, and Mr P B Counsell for their help and also to A C Thackray, of the Middlesex Hospital, for the photomicrographs

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TREATMENT OF GLUTETHIMIDE POISONING

WITH BEMEGRIDE AND AMIPHENAZOLE

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GLUTETHIMIDE (α-phenyl-α ethyl-glutarimide, ‘Doriden’) has recently been introduced as a non-barbiturate hypnotic The usual dose of 0 25 to 0 5 g (1 to 2 tablets) gives five to eight hours' sleep The tablets disintegrate rapidly and the patient usually falls asleep in fifteen to thirty minutes Side effects are few Occasional nausea and rashes have been reported Lane (1955) found no alteration in the blood picture, in the urine, or in the thymol-turbidity and cephalin flocculation tests resulting from long continued administration of nightly doses of 1 0 g One of the advantages of glutethimide in normal doses seems to be the absence of respiratory depression

There have been few reports of poisoning Gerster et al (1955) described the case of a soldier aged 20 who took 60 tablets (15 g) in an attempt to commit suicide He was treated with picrotoxin, prophylactic antibiotics, and intravenous fluids, and recovered Two cases treated with bemegride (‘Megimide’) and amiphenazole (‘Daptazole’) have been reported by von Planta and Klingler (1956) The first patient, a man of 29, had taken 20 tablets, the second, a woman of 23, had taken 22 tablets, and both recovered In view of the need for information on the effect of bemegride and amiphenazole on coma other than that due to barbiturate (*Lancet* 1956), I report a further case

Case-report

A married woman aged 38 was admitted in coma having taken 40 glutethimide tablets (10 g) and 16 aspirin tablets (4 8 g) fourteen hours previously On admission she was unconscious with widely dilated pupils (which did not react to light), a divergent strabismus, and absent corneal reflexes All limbs were flaccid with absent reflexes The plantar responses were not obtained and there were no withdrawal reflexes She was not cyanosed and the peripheral circulation was good Respirations were moderately deep, the rate being 12 per min , the pulse rate was 115 per min , blood pressure 120/90 mm Hg, temperature 98°F There were no abnormal signs in the heart, chest, or abdomen Soon after admission she had an attack of laryngeal spasm with carpo-pedal spasm, resembling classical tetany and lasting about two minutes

Gastric lavage was done but no tablets were returned in the washings Prophylactic penicillin was given and glucose-saline infused 225 mg (15 mg in 1 ml) amiphenazole was given intravenously in the course of twenty minutes, with increase in the depth and rate of respiration (20 a minute) 4 ml (12 mg) picrotoxin was given with no effect

Three hours later her condition was unchanged , spasms were occuring every five to ten minutes Treatment with bemegride and amiphenazole was started, 50 mg bemegride and 15 mg amiphenazole being introduced into the tubing of the drip about every three minutes In one and three quarter hours, after a total of 750 mg bemegride and 225 mg amiphenazole had been given, the patient moved her right arm slightly and the knee jerks were just obtainable During this period, she continued to have intermittent tetanic spasms of all limbs Chvostek's and Trousseau's signs were absent , the blood calcium was normal (9 8 mg per 100 ml , diffusible 4 7 mg) , there was no alkalosis (indeed, there was acidosis—alkali reserve 45 3 ml CO_2 per 100 ml plasma) , and intravenous calcium gluconate had no effect There was also intermittent fine tremor of the hands The spasms continued during the course of the next three hours 200 mg bemegride was then given in twelve minutes , this increased the frequency of the spasms After an interval, 60 mg amiphenazole was given in 12 minutes, and there was no increase in spasms 200 mg bemegride and 60 mg amiphenazole were then given together over twelve minutes with increase in the frequency of the spasms and in the activity of the knee jerks

Twelve hours later, the patient was still having intermittent spasms, but the swallowing reflex had returned and she moved her arm slightly in response to venepuncture The left plantar response was extensor After another two hours there was a withdrawal reflex of the left leg, but this disappeared within an hour Forty one hours after she had taken the glutethimide, an electro encephalogram (E E G) was recorded before, during, and after the injection of bemegride and amiphenazole (see later) Seven hours later the pupils started to react to light and the strabismus disappeared After a further two hours she began to talk, and then became restless and required 4 ml paraldehyde for sedation

Next morning there were no abnormal signs at all apart from rapid nystagmus to either side This disappeared in twenty four hours She was very depressed and had to be transferred to a mental hospital

The Electro encephalogram

Forty one hours after taking glutethimide (patient still in coma) —The most persistent component was symmetrical 5 to 6 c per sec activity which was fairly generalised, though of slightly higher amplitude (about 40 µV mean), in the frontal regions Frequent runs of delta activity were seen here with a peak amplitude of up to 150 µV, but at no time were these truly paroxysmal No faster components were seen The intravenous injection of 100 mg bemegride preceded by 30 mg of amiphenazole produced a short term diminution of amplitude of the slow activity and this coincided with a partial return of her withdrawal reflexes The record returned to its former state thirty seconds after the end of the injection A further 100 mg bemegride and 30 mg amiphenazole had a similar transient effect on the E E G

Eighty four hours after taking glutethimide (patient clinically recovered) —The E E G findings had changed dramatically and were substantially within the limits of normal variation for an alert subject Runs of slow activity appeared during the latter stages of the recording, but were almost certainly due to drowsiness

Electrolytes

There was a slight acidosis soon after admission, probably due to the aspirin, but by the following day the alkali reserve had returned to normal The serum-potassium was low (12 5 mg per 100 ml , 3 2 m eq per litre) but this had returned to normal after ten days

A full blood count and liver function tests were normal two weeks later

Discussion

This patient was admitted in deep coma fourteen hours after taking 40 tablets of glutethimide (10 g) and 16 aspirin tablets (4 8 g) Despite the large dose of glutethimide, respiration was not grossly depressed This may be partly attributed to the stimulation of respiration by aspirin (Farber et al 1949), but I believe that glutethimide in this case did not depress respiration to the same extent as an equivalent dose of barbiturate Respiration was regular Gerster et al (1955) reported hyperthermia, electrocardiographic changes, and tachycardia , but in the present case there were no signs of disturbance of temperature regulation of the cardiovascular system, of the blood picture, or of liver function

An interesting feature was the *tetanic spasm* of the limbs, lasting several minutes, together with laryngeal spasm

Gerster et al (1955) observed that all intratracheal interference had a bad effect on respiration, but in our patient intubation was not attempted and laryngeal spasm was apparently spontaneous Between spasms the patient remained flaccid, and Trousseau's and Chvostek's signs were negative The serum calcium was normal, there was a mild acidosis, and the spasms were not relieved by intravenous calcium gluconate

The spasms were present before treatment, and persisted for twelve hours after the administration of bemegride and amiphenazole , they are presumed to be due to glutethimide Their frequency was increased by bemegride given alone or in combination with amiphenazole but not by amiphenazole alone

Bemegride and amiphenazole were given by the method of Shulman et al (1955) The knee jerks returned in one and three quarter hours, by which time 750 mg bemegride and 225 mg amiphenazole had been given The corneal and pupillary reflexes were the last ones to reappear, twenty-six hours later—about four hours before the patient regained consciousness A total of 1350 mg bemegride and 570 mg amiphenazole was given

The observations suggest that in glutethimide poisoning bemegride and amiphenazole stimulate reflex activity as well as respiration Amiphenazole in particular, increases the depth rather than the rate of respiration The alteration in the electro encephalogram is only transient if the drugs are used intermittently, and it is probably preferable to treat cases by continuous infusion as described by Clemmesen (1956) The only metabolic disturbance noticed was a decrease in the serum potassium, which has been recorded in the treatment of barbiturate poisoning with bemegride and amiphenazole (Shulman et al 1955) No mental disturbances were observed which could be ascribed to the treatment

Summary

A case of poisoning with 10 g glutethimide (' Doriden ') and 4 8 g aspirin is reported Frequent short lived attacks of laryngeal and tetanic limb spasm were thought to be due to glutethimide

Treatment with bemegride (' Megimide ') and amiphenazole (' Daptazole ') resulted in the return of reflex activity, increased respiration, and caused transient alteration in the electro encephalogram

These drugs are recommended in the treatment of poisoning by glutethimide

I am grateful to Dr C N Armstrong for permission to publish this case   I should also like to thank Dr B McStay and Dr J Wilson for their help in the treatment, and Mr J. W Osselton for reporting on the electro encephalograms

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ACUTE PANCREATITIS IN A CHILD AGED 3 YEARS

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IT has long been recognised that acute pancreatitis may occur in children, although it is extremely rare except in association with mumps

Farnham (1922) collected 119 cases of mumps pancreatitis, of which 117 recovered   Dey (1951) reported a case of acute hæmorrhagic pancreatitis in a child aged 22 months, on laparotomy he found bloodstained fluid in the peritoneal cavity, widespread fat necrosis, and a hard swollen pancreas   No serological investigation was made, but the patient's sister was admitted to another hospital with mumps at the same time

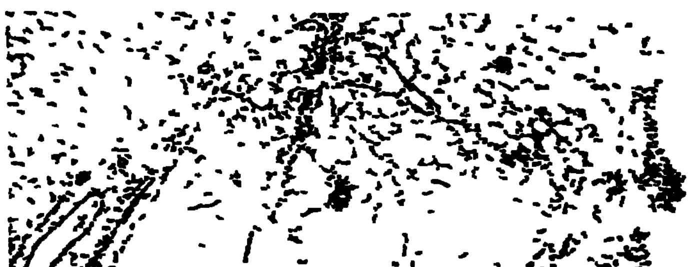
About 18 cases have been reported in children under the age of 13, who, so far as could be ascertained without serological tests, were free from mumps   Dobbs (1935) added 1 of his own to 14 collected cases aged 2–13

I report here a case in a child, aged 3 years, apparently without mumps

Case-report

A girl born on Sept 19, 1950, was admitted to the Victoria Hospital for Children, Tite Street, London, on April 5, 1954

History—Four days before admission she vomited several times and complained of abdominal pain   Three days before admission she developed a cough, and on the day of admission her abdominal pain became very severe and colicky, and she was completely constipated   Her mother stated that she had had a similar illness two years previously


Fat necrosis of greater omentum   (Hæmatoxylin and eosin ×45)

She was the third of five children   There had been no recent illness at home, nor was she known to have been in contact with any infectious disease

Examination—She was a flushed well developed child with a cough, temperature 99 4°F, pulse rate 100, and respirations 28 a minute, weight 33 lb 6 oz   She had enlarged injected tonsils and cervical adenitis   She was extremely tender round the umbilicus and there was general abdominal guarding There was no rigidity, and no mass was felt in her abdomen Her rectum was empty, but on bimanual examination fæces were felt in the colon above   No other abnormality was found

Tonsillitis with mesenteric adenitis was diagnosed

Progress—Next day her abdominal signs were less generalised, the tenderness being greater in the right hypochondrium No abnormality was found in her urine   A throat swab grew scanty β-hæmolytic streptococci   Her hæmoglobin was 70% A white-cell count showed 8100 cells per c.mm   A chest radiograph was clear

Next morning (April 7) her pulse rate rose and she looked pale, shocked, and ill and had fairly severe attacks of pain The tenderness was still worst in the right hypochondrium, and the right rectus muscle was now in spasm   In view of the change in the clinical picture it was thought that the child might have an acutely inflamed high appendix or even cholecystitis   Laparotomy was therefore advised

Operation (April 7)—A right mid-paramedian incision was made under general anæsthesia   There was no free fluid in the abdomen, but widespread fat necrosis was seen on the parietal peritoneum and greater and lesser omenta   The lesser sac was opened, and the pancreas was found to be hard, enlarged, and œdematous, its surface being covered with widespread fat necrosis, mostly appearing as white specks as big as a large pin head and making the surface of the pancreas feel like emery paper   The parietal fat necroses were very much larger, and one was removed from the greater omentum for microscopy   The gall bladder was extremely tense but was emptied by pressure and was without doubt the cause of the local tenderness   No stones were palpable in the biliary tract

Postoperatively, on April 8, the patient's serum amylase level was 160 units per 100 ml   Biopsy confirmed the diagnosis of fat necrosis (see figure)   A mumps complement fixation test showed no antibodies to the mumps virus at a titre of 1   5 in serum collected on the 4th and 5th days of the illness The patient convalesced uneventfully and has since remained well

Discussion

In view of the serological tests it can be stated with certainty that the cause was not mumps   The tenderness localised to the right hypochondrium on the second day in hospital was due to the tense gall-bladder   At no time was there any cyanosis or jaundice, and it is doubtful whether the diagnosis could have been suspected preoperatively   The child had had a similar attack, which settled, two years previously

In Dey's (1951) case there had been no previous history, the white cell count was 24,000 per c mm, and bloodstained fluid and fat necrosis were found on laparotomy   The pancreas was hard and swollen, but the biliary system was normal

Steiner and Tracy (1943) found an association between pancreatitis and diabetic coma in 10 children examined post mortem   They also cited 4 other cases of pancreatitis found among 26 children who died in diabetic coma   There was no association with diabetes in either the present case or Dey's (1951) case

In the 14 cases collected by Dobbs (1935) no cause was found in 6, an impacted gall stone was responsible in 1, there had been trauma in 3 (a cart running over the abdomen in 2), roundworms were certainly responsible in 1 case (a Hindu girl, aged 12 years had two round-worms removed from the pancreatic duct through an incision in the pancreas) and probably responsible in 2 cases, and 1 case was probably due to a septic embolus in the pancreas

Summary

A case of acute pancreatitis in a child aged 3 years is described. Serological tests excluded mumps

Biopsy showed fat necrosis

The child convalesced satisfactorily and has been symptom free for more than two years

I wish to thank Dr C Pinckney for asking me to see and operate on his patient and for allowing me to publish the case, Prof T Crawford for his photomicrograph, and Dr A Dudgeon for the comprehensive serological tests

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Medical Societies

MANCHESTER MEDICAL SOCIETY

Social Pathology of Coronary-artery Disease

ON Jan 23 Dr J N MORRIS (London), in an address to the sections of medicine and pathology, suggested that coronary atheroma was rife before the first world war but ischæmic heart disease was less common than now A national survey of necropsies on middle aged men had shown an excess of ischæmic myocardial fibrosis in "light" workers dying of cancer, injuries, &c This excess was particularly evident among patients with solitary scars of large healed infarcts—an observation which might give a link with the previously recorded excess of "sudden deaths" and other rapidly fatal ischæmic heart-disease in sedentary workers, such as bus-drivers and clerks

What might be called the "appeal to epidemiology" was persistently refusing to confirm hypotheses of a single or simple dietary ætiology for ischæmic heart disease In the present climate of opinion such a negative rôle was exceedingly uncomfortable ! But it was not possible, in time series or other series, to correlate what was known of the mortality from coronary heart disease with what was known of trends in fat consumption Thus, the great variations of mortality among Western countries having similar high fat intake disposed of any story that total fat consumption was the critical factor Changes in animal-fat consumption in the United Kingdom during the present century could be related to the changes in coronary atheroma found in the London Hospital records, but they showed no relation to the Registrar General's figures of mortality from coronary heart disease The trend of consumption of butter-fat in the United Kingdom showed absolutely *no relation*, the steep increase in coronary deaths since 1943 was only one illustration of this Changes in vegetable-fat intake followed the mortality experience more *closely*, and changes in hydrogenated fat intake were even more closely reflected in the mortality figures, except for the social-class distribution of coronary mortality, which did not agree with the pattern of margarine intake International experience was even more contradictory Norwegians, who ate a lot of margarine, seemed to have far less fatal "coronary thrombosis" than New Zealanders, who ate very little Perhaps the fish the Norwegians ate protected them, but this did not seem to help Aberdeen, which registered twice the coronary death rate of Oslo

In terms of the total of essential fatty acids themselves, the only available data for the United Kingdom gave no support to the hypothesis that the population was now suffering from an absolute or relative deficiency of essential fatty acids, and international comparison again showed anything but a homogeneous picture More and better statistics of disease and of food trends were urgently needed, and it was hopeful that the World Health Organisation had now entered this field

Reviews of Books

Handbook on Poliomyelitis

JOSEPH TRUETA, M D, D SC, F R C S, Nuffield professor of orthopædic surgery, University of Oxford, A B KINNIER WILSON, M B, M R C P, D P M, member of the scientific staff, Medical Research Council, MARGARET AGERHOLM, B M, assistant, Nuffield department of orthopædic surgery, Nuffield Orthopædic Centre, Oxford. *Oxford Blackwell Scientific Publications* 1956 Pp 139 20s

THIS is a compact and pleasantly readable book containing a wealth of up-to-date information

The first section includes history, virus studies, epidemiology, pathology, clinical manifestations, and diagnosis, and there are valuable sections on treatment in the acute stage and on specific preventive measures Nearly a quarter of the text is taken up by chapters dealing with the diagnosis and management of cases with complications affecting the respiratory muscles The final chapters deal with the treatment of cases during the transitional, recovery, and chronic periods The authors have avoided the temptation to present every aspect of complex surgical procedures, and instead have set out the arguments for particular forms of management and treatment in a way that is satisfying without being provocative

The book will be read with pleasure even by those with only slight knowledge of the subject, and to the expert it will rarely fail to supply in concise form such information as he seeks

Outline of Fractures

Including Joint Injuries JOHN CRAWFORD ADAMS, M.D., F R C S, *consultant orthopædic surgeon,* St Mary's Hospital, London Edinburgh and London E & S Livingstone 1957 Pp 248 27s 6d

THIS is the companion volume to the author's Outline of Orthopædics, published last year, and like this earlier book it is intended for the medical student and the general practitioner Mr Adams has an incisive mind and a lucid style, which will make this a popular book for the student

Possibly the insistence on brevity has sometimes been carried almost too far, so that the student may have to turn to larger textbooks for clarification for instance, the section on the circulation in an injured limb might well be expanded Future editions—which will surely be *demanded*—might include some further advice on handling a fractured limb at the first aid stage, in the chapter on general features of fractures a summary of the differences to be found in children might be included, and the illustration showing the never effective spring clips holding the bands on the Thomas splint should be changed

This generally excellent book can be warmly recommended to the medical student

Clinical Examinations in Neurology

By members of the Sections of Neurology and Section of Physiology, Mayo Clinic and Mayo Foundation for Medical Education and Research, Rochester, Minnesota. Philadelphia and London W B Saunders 1956 Pp 370 52s 6d

THIS book contains a useful account of methods of clinical examination in neurology and of the interpretation of physical signs There is a brief account of electro-encephalography, of the electrical testing of muscle, and of the methods of obtaining cerebrospinal fluid but neuro-radiology is not dealt with The book follows conventional lines, but it is clearly written and provides a valuable introduction to neurological case taking

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Modern Treatment Yearbook (London Baillière, Tindall, & Cox 1957 Pp 312 25s)—As Sir Cecil Wakeley, its editor observes in a preface, the yearbook's aim is to present the general practitioner with the advice of experts on up to date treatment Those who are familiar with it will know how seldom it misses the mark Among the contributors to the new volume, Dr P M I Bishop acts as a Young Person's Guide to the Endocrine Orchestra and Dr J B Harman writes helpfully on the treatment of incurable malignant disease

THE LANCET

LONDON SATURDAY, FEB 23, 1957

Industrial Lung Cancer

The study of industrial pulmonary cancer has special significance at present, when much effort is being expended in many countries to determine whether environmental factors, such as atmospheric pollution or tobacco-smoking or both, are the essential causes of the world-wide increase in lung cancer. Every well-conducted study of an industrial hazard yields some information about the nature of the exposure or the response of the tissues to that exposure, and in six industries the hazard of lung cancer is well proved; in many others there is suspicion but no proof.

The story of the Schneeberg and Joachimstal miners' cancer is an old one, and it was this disease which firmly established the association between industrial exposure and pulmonary cancer. Today we have no further reliable information about the real cause than we had when the condition was first described in 1879. The ore concerned, pitchblende, has a uranium content of about 70%, but it also contains small quantities of oxides of rare earth metals, together with thorium, lead, zinc, manganese, silica, iron, cobalt, and nickel. The high uranium content suggests that radioactivity is at least partly responsible for the induction of the tumours, but there is no proof of this, and attempts to demonstrate radioactivity in affected lungs have failed.[1] There is also much uncertainty as to whether fibrosis does or does not precede the cancer. Another group exposed to danger are gas-retort workers. KENNAWAY and KENNAWAY[2] showed that they were about three times more liable to cancer of the lung than the general male population during the years 1921–38. The number of people employed in this way was not great, but the association seemed to be a real one. DOLL[3] found that recorded deaths from lung cancer in gas-works pensioners were nearly twice as many as would be expected from a comparison with the general run of men in London. The excess mortality lay principally among employees engaged in the production of gas and the treatment of waste products—i.e., among men actually working in the retort houses.

A third type of industrial lung cancer that has long been recognised in Germany is that found among those working on the production of chromates. In recent years the same liability has become apparent in the United States; and BIDSTRUP and CASE[4] have lately drawn attention to a similar hazard in Great Britain. They surveyed the causes of death among the employees in three factories in different parts of the country, and they found that deaths from cancer of the lung were between three and four times more numerous than they were among the general male population of England and Wales of the same age-groups. The deaths of 12 chromate workers were ascribed to lung cancer: the diagnosis was confirmed by necropsy in 4 cases and by biopsy in 3 more; in 5 others it was made on clinical and radiological findings. The industrial process involves extraction of chromium from the ferrous ore known as chromite or chrome iron-stone, which contains 30% or more of chrome oxide, and 15% of ferric and silicon oxides. The pneumoconiosis due to inhalation of insoluble chromium compounds (or chromitosis) is said to consist of a spotty fibrous thickening of the peribronchial and interstitial tissue, where the chromium dust particles are deposited.[5] In exposed workers, the chromium content of affected lungs is higher than that of other organs.[5,6] It is interesting to note that although perforation of the nasal septum and skin ulceration are well-known signs of over-exposure to chromate compounds, malignant tumours have not been described in the nose or skin of chromate workers.

Asbestos and nickel are two other substances associated with an increase in lung cancer. Workers in the asbestos textile industry suffered in former years from a severe form of pulmonary fibrosis, now known to be related to the subsequent development of lung cancer[7,8]; and similar findings have been reported from Germany, Canada, and the United States. Some ores contain ferrous and silicon oxides in high proportion; other ores, notably that found in Canada, contain only small amounts of iron oxide. The short fibres of the Canadian ore are said to be more dangerous than the long fibres of some other ores.[9] In this form of industrial cancer, there is no doubt that fibrosis precedes the malignant process; and it is also clear that the exposed female is susceptible to the disease. Cancers of the nasal passages and lung have been described among nickel-refinery workers in South Wales. Nearly all the tumours arose in workers exposed before 1924, when the plant was reconstructed. The men were exposed to nickel dust and to nickel-carbonyl vapours, but it is not known which was the responsible agent. AMOR[10] stated that refined nickel-copper ores were free from radioactive matter. Pneumoconiosis has not been recorded as a precursor of this type of cancer.

There has been controversy about the part played by iron ores in industrial lung cancer, but the recent work of FAULDS and STEWART[11] goes a long way towards indicting iron-ore mining as a cancer hazard. Ferric oxide is the chief constituent of the hæmatite ore mined in Cumberland, and the ore also contains 10–12% of silica. From 1932 to 1953, 2401 post-mortem examinations were made in Cumberland on men over the age of 30. Of these, 180 were on hæmatite miners and 17 (just under 10%) were found to have carcinoma of the lung; of the remaining 2221 necropsies on men over 30 who had not been hæmatite miners, 45 (2%) revealed cancer of the lung. This four- to five-fold increase among the miners is highly significant. FAULDS and STEWART also pointed to other data which support the view that the cancers were related to the mining In 12 of the 17 cancers, the primary site was regarded as being in the peripheral part of a lobe (either upper or lower) (The densest areas of fibrosis and the tumours were much easier to locate accurately when the lungs were inflated before fixation and full-size sections cut according to the technique of Gough and Wentworth[12]) It, was concluded that "the distribution of primary tumours *in the lungs of hæmatite miners closely follows that* of the areas where sidero-silicotic fibrosis is most pronounced and where it *presumably originated*" But Faulds and Stewart also noted that carcinoma usually arose in lungs which were *not* the seat of the most advanced general fibrosis, suggesting that an optimum or focal fibrosis is more conducive to the development of bronchial cancer Thorough chemical examination of lung tissue removed at death showed that cancerous lungs had the highest silica content, but their iron content was not appreciably greater than normal Finally, a careful search for radioactivity in the ore and in cancerous and non-cancerous hæmatite lungs proved fruitless, so it seems that radioactivity can be excluded as a cause or even a contributory *factor in lung cancer in hæmatite miners*

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The way is now open to a more detailed study of the industrial lung cancers that are already known and to a vigilant watch for new chemical hazards Post-mortem examination of the lungs has already yielded much information, but there is scope for more detailed inquiry into the distribution of the tumours, their relation to pre existing fibrosis, and their histological character, and these aspects must be coupled with careful chemical analysis and measurements of radioactivity So far no suitable experimental animal has been found Vorwald[13] claimed to have induced squamous carcinomas in the bronchus of the rat by causing the animals to inhale a dust of soluble and insoluble beryllium compounds, and this seems to be the nearest experimental approach to the human disease yet achieved A helpful guide to what is known about industrial lung cancer has lately been provided by Hueper[14]

The Liver in Hæmochromatosis

In classical hæmochromatosis an inborn error of metabolism is thought to be responsible for the extensive deposition of iron, in the form of hæmosiderin, in the viscera and skin, and hepatic cirrhosis and diabetes mellitus are among the consequences The total amount of iron in the body, normally about 4 5 g, is greatly increased and may reach as much as 30 g Since the normal daily intake in the diet is 5–15 mg, complete absorption and retention of the dietary iron for eight to twenty-five years would be *necessary to reach the levels observed in hæmochromatosis*, but it is doubtful whether either absorption or *retention is ever complete*, so that an even longer period of disturbed iron metabolism is probably required

It has long been recognised that a superficially similar picture can follow the administration of very large quantities of iron compounds by mouth or, more especially by injection The hæmosiderosis which results is said to differ in many ways from hæmochromatosis, particularly in the absence of cirrhosis and diabetes and in the more restricted distribution of the iron deposits Much is also known about how repeated blood-transfusions can similarly load the body with iron Sheldon's opinion[1] was that excessive destruction of blood and storage of iron did not produce classical hæmochromatosis but only a simple hæmosiderosis without tissue damage, and there is experimental evidence to justify his view But, as Pengelly and Jones[2] lately remarked, there are now enough published reports of cases of transfusion siderosis with "fibrosis" if not definite cirrhosis of the liver to suggest that hæmosiderin can damage cells—at any rate liver cells Now that blood is available for transfusion in almost unlimited quantities many patients with hypoplastic and hæmolytic anæmias can be kept alive for years (Pengelly and Jones's patient, in whom the full clinical picture of hæmochromatosis developed after nine years of regular transfusions, had a hypoplastic anæmia) The inability of these patients to increase their iron excretion above the normal level of 0 5–1 3 mg daily *leads to the accumulation of iron in quantities which* eventually reach the range found in typical idiopathic hæmochromatosis, so that the hepatic cirrhosis and the diabetes can appear[3 4] On the other hand, a recent appraisal of the situation by Rather[5] suggests that mere overloading with iron may not alone be sufficient to evoke the full picture The crux of the matter is that no one has succeeded in *producing diffuse fibrosis of the liver by simple overloading with* iron compounds In his own experiments Rather studied rats kept on a diet containing either 4% or 16% of protein to which was added 6% of ferric citrate In the control rats on similar diets but without the ferric citrate the iron content of the liver ranged from 32 to 111 mg per 100 g dry weight In the rats receiving the iron supplement the corresponding figures were 720–3180 mg The experiment lasted approximately five hundred days Despite such long and excessive feeding with ferric salts and the accumulation of enormous quantities of iron in the liver, there was *no evidence of hepatic cirrhosis or even of significant liver damage* It seems that, at least in the rat something more than an alimentary overload of iron is needed to produce a condition like classical hæmochromatosis

There is no reason to believe that the patient with idiopathic hæmochromatosis has been exposed to an excess of iron in the diet, and the accumulation in the tissues is presumably the result of increased absorption from a normal diet This increased absorption has been *convincingly demonstrated by* Peterson and Ettinger[6] by giving radioactive iron and estimating the activity of the unabsorbed iron in the stools They found that normal absorption was between 1% and 4% of the intake, whereas in 2 patients with hæmochromatosis it was 20% and 40% respectively The way in which the absorption of iron from the gut is controlled is still obscure The apoferritin-ferritin system of control described by

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[12] Gough J Wentworth J E *J R micr Soc* 1949 69 231
[13] Vorwald A J Proceedings of the 7th Saranac Symposium on Pneumoconiosis 1952
[14] Hueper W C US Department of Health, Education and Welfare Public Health Monograph no 36 1956

[1] Sheldon J H Hæmochromatosis London 1935
[2] Pengelly, C D R Jones, P *Lancet* 1956, ii 445
[3] Schwartz S Blumenthal S A *Blood* 1948 3 617
[4] Wallerstein R O Robbins S L *Amer J Med* 1953 14 256
[5] Rather L J *Ibid* 1956 21 857
[6] Peterson, R E Ettinger, R H *Ibid* 1953, 15, 518

Granick[7] can certainly be overcome by giving large quantities of iron, but, even when the intake of iron is relatively small, absorption can be strikingly increased by appropriate changes in the diet. By substituting a diet of corn grit and 20% lard for one of Purina dog chow, Kinney et al[8] were able to produce considerable hepatic siderosis in rats who had 2% ferric citrate added to their food. The effective diet in this experiment was apparently deficient in lipotropic factors and produced not only an increase of iron absorption but significant fatty infiltration of the liver—a condition known to lead to hepatic cirrhosis if it is severe enough. The inference seems to be that something which leads to cirrhosis may simultaneously interfere with the normal intestinal mechanism for the control of iron absorption. The incidence of hepatic siderosis in malnourished Africans[9] supports this conclusion, but the absence of any sign of nutritional deficiency in the Australian survey by Althausen et al[10] suggests that the fault in intestinal control may be initiated in other ways. The enhanced absorption of iron by cats in which the pancreatic duct has been ligated was first reported by Taylor,[11] and the observation was confirmed in dogs.[8] This finding suggests that the involvement of the pancreas in hæmochromatosis, if not a primary fault, may well promote a vicious circle.

It is not yet clear how much iron the liver cells can stand. Sudden large doses of iron salts have been shown experimentally to cause acute liver damage,[12] and children dying of ferrous-sulphate poisoning may have conspicuous toxic changes in their livers. But slowly mounting quantities of iron can be tolerated for a long time by an otherwise normal liver, and the present weight of evidence is against the view that the iron deposits are alone responsible for the hepatic damage in hæmochromatosis.

The Adrenal Cortex in Hypertension

Some relation between the blood-pressure and the adrenal glands had been recognised for about a hundred years when Addison first described the feeble pulse in the disease which now bears his name and in which both adrenal glands are destroyed by caseous necrosis or atrophy. Later the sphygmomanometer amply confirmed the low blood-pressure in Addison's disease. In 1895 Oliver and Schafer[13] demonstrated the remarkable rise in blood-pressure which followed an injection of an extract of adrenal medulla and when, some years later, Abel[14] isolated a crystalline "epinephrine," it was generally believed that this substance was responsible for the maintenance of normal blood-pressure and also for hypertensive states. It has been shown beyond doubt, however, that Addison's disease is due to the destruction of the adrenal cortex and that normal blood-pressure can be restored by cortical extracts. In recent years some have advocated a hypothesis which considers the action of adrenaline as synergistic to that of the corticoids,[15] and the adrenal gland as a single functional unit. This view is the *Leitmotiv* of Chwalla's book[16] on hyperfunction of the adrenal, but the evidence to support this attractive hypothesis is meagre, and other workers in this field prefer to concentrate their attention on the adrenal cortex and its hormones. Goldblatt[17] found (and it has since been confirmed) that the hypertension which follows constriction of the renal arteries can be reduced to normal levels by bilateral adrenalectomy. This effect of adrenalectomy has been attributed to the elimination of cortical hormones.[18–20] The mineralocorticoids are the hormones which raise the blood-pressure, and deoxycortone is the one which has been most closely studied. These hormones are apparently responsible for the hypertension produced by many neoplasms of the adrenal cortex, particularly those associated with a Cushing syndrome. Further important observations are that hypertension, with its pathological effects, can readily be produced by deoxycortone in Addison's disease and in adrenalectomised animals, but with difficulty or not at all in the presence of normal adrenals. Moreover, hypertension was produced by deoxycortone but not by crude extract of total adrenal cortex.[21] From these findings, Soffer[22] concluded that the adrenal cortex produced an additional blood-pressure-balancing fraction, as well as the hypertensive factor.

Understandably, these developments have directed attention to the morbid anatomy of the adrenal glands in essential and in renal hypertension, and a thorough investigation of this subject has lately been recorded by Dawson.[23] He has studied 90 adrenals from people with normal blood-pressure, 90 from patients with essential hypertension, and 44 from others with renal hypertension. The investigation included weighing the organs, measuring the thickness of the capsule and each of the three zones of the cortex, and staining by routine methods and those designed to display fats. Dawson also used digitonin precipitation, the polarising microscope, and the Ashbel-Seligman method, which is believed to demonstrate ketone groups. The average combined weight of the glands was 15·3 g in essential hypertension and 15·7 g in renal hypertension, compared with 11·8 g in the normotensive group. The enlargement was due to hyperplasia of the zona fasciculata, associated with an irregular arrangement of the cells, which were hypertrophied and vacuolated and contained abundant lipid. The changes in renal hypertension differed from those in essential hypertension mainly in the greater extent of the zona reticularis; the difference seemed to be quantitative rather than qualitative. The zona glomerulosa was not affected in either form of hypertension. Signs of exhaustion of the cortex were seen in renal but not in essential hypertension. It may be, however, that the presence or absence of lipids is not conclusive evidence of activity or exhaustion,[24] and to get a more accurate picture fat stains may have to be combined with histochemical demonstration and quantitative estimation of the dehydrogenase activity, using the tetrazolium-salt method, which gives reliable results with post-mortem material

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[7] Granick S Bull N Y Acad Med 1954, 30 81

[8] Kinney T D, Hegsted D M Finch, C A J exp Med 1949, 90 137

[9] Gillman J Gillman T Gastroenterology 1947 8 19 see leading article Lancet 1952 i 650

[10] Althausen T L Doig R K Weiden S, Motteram R, Turner C N Moore A Arch intern Med 1951 88 553

[11] Taylor J Stiven D Reid F W J Path Bact 1935 41 397

[12] Luongo M A Bjornson S S New Engl J Med 1954, 251, 995

[13] Oliver G Schafer E A J Physiol 1895 18 230

[14] Abel J J Johns Hopk Hosp Bull 1902 13, 29

[15] Grollman A. The Adrenals Baltimore 1936

[16] Chwalla R Die Ueberfunktion der Nebennieren Vienna, 1955

[17] Goldblatt, H Ann intern Med 1937 11 69

[18] Collins D A Wood F H Amer J Physiol 1938, 123 224

[19] Page I H Ibid 1938 122 352

[20] Williams J R Diaz J T Burch, J C, Harrison T R Amer J med Sci 1939 198 212

[21] Grollman, A Harrison, T R, Williams, J R J Pharmacol 1940 69 149

[22] Soffer L J Diseases of the Endocrine Glands London, 1951

[23] Dawson I M P J Path Bact 1956 72 393

[24] Baar H S Schweiz Z Path Bakt (in the press)

DAWSON believes that the changes in the adrenal cortex in hypertension are secondary, "since it is difficult to conceive of a primary adrenal change in renal hypertension" This reasonable assumption seems more likely to be true than that of CHWALLA,[16] who holds that the hyperplasia of cortex and medulla comes first, and predisposes to a variety of diseases, among them hypertension Even if the cortical changes can reasonably be taken as secondary effects, there is little to point to their significance Are they evidence of an increased formation of blood-pressure-raising hormones to counteract the effect of the primary disease and thus improve the blood-flow, or do they indicate compensatory formation of a hormone that depresses the blood-pressure[2] Such a hormone has not yet been isolated but its existence was suggested by SOFFER[22] because of the different actions on the blood-pressure of deoxycortone on the one hand and total cortical extracts on the other It is unlikely that the changes in the cortex indicate a cortical control of the secretion of medullary hormones, because hypertensive individuals excrete in the urine adrenaline in similar amounts to normal people[25]

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[25] *Lancet*, 1956 ii, 981

Annotations

A FLYING-SQUAD COMES OF AGE

THIS week the 21st anniversary of the Newcastle Obstetric Emergency Service was being marked by celebrations which included the presentation of a portrait to Emeritus Professor E Farquhar Murray, who took a leading part in its inception This flying squad service was brought into being mainly to save lives that might be lost during the journey from home to hospital—notably through the third stage complications of hæmorrhage, retained placenta, and shock There are now flying-squads based on over a hundred and seventy maternity hospitals or units in England and Wales, and third stage complications account for three quarters of the calls, which amount in all to about 1% of domiciliary deliveries Complications are often unpredictable, but experience has shown that, because of the enhanced risk, patients who have previously had third stage complications, pregnant women who are expecting twins, and grand-multiparæ should not be booked for home confinement

From a modest 11 cases in 1936 (the first full year of operation), the number of cases dealt with by the Newcastle service grew to a record total of 146 in 1955 The Newcastle scheme, directed since 1950 by Prof Harvey Evers, has been the prototype for many elsewhere —but not for all, since the best form depends on local geographical and other factors In Newcastle each call is answered by an experienced obstetrician, and nowadays he is accompanied by an anæsthetist, whose help has proved invaluable A senior sister from the antenatal department of the Princess Mary Maternity Hospital (on which the service is based) also attends The flying-squad is comprehensively equipped, and the patient is rarely moved to hospital Calls come from up to sixty miles away, and for this large area a policy of simple resuscitation and rapid transfer to hospital by ambulance (which has been adopted by some other flying squads) has never been applied

Improved antenatal care and selection of cases for delivery in hospital would somewhat reduce, but could not abolish, the calls on obstetric flying-squads The service started in 1935 by Professor Farquhar Murray and his associates is now recognised as a permanent and indispensable feature

CHLOROQUINE IN RHEUMATOID ARTHRITIS

THE discovery that antimalarial drugs may be beneficial in rheumatoid arthritis stems from one chance observation and two theoretical ideas Reporting that mepacrine was helpful in lupus erythematosus, Page[1] mentioned a patient in whom a polyarthritis of rheumatoid type improved at the same time as the skin lesion. Lupus erythematosus, especially the systemic type, is certainly outstanding among the diffuse mesenchymal diseases in the closeness with which any associated arthropathy may resemble rheumatoid arthritis Hence it was natural that mepacrine, although more clearly effective in the discoid than the systemic form of lupus erythematosus, should be tried in rheumatoid arthritis.[1] Haydu,[3] in the belief that the tissue requirements for adenosine triphosphate are increased in rheumatoid arthritis, tried chloroquine because, like other methods known to be effective, it inhibits adenosine triphosphatase That adenosine triphosphate is involved in this way in the pathogenesis of rheumatoid arthritis is at present no more than a suggestion based on certain hypothetical considerations Freedman,[4] who has lately recorded his experience with chloroquine in rheumatoid arthritis, is attracted by the view that rheumatoid arthritis is an infective condition, and that antimalarial drugs may have a chemotherapeutic action

The rationale of treatment with chloroquine is thus insecure, but Freedman's claim to have demonstrated its efficacy is based, unlike that of other investigators,[3 5 6] on a properly controlled clinical trial, and must be carefully examined The trial included 66 patients, and in most of them the effect of treatment was measured throughout a period of sixteen weeks Patients were allocated at random to the experimental and control groups All received a regular dose of aspirin and ascorbic acid The experimental group were given 200–300 mg daily of chloroquine, and the control group an equivalent number of dummy tablets Assessments of response were made without knowledge of the type of treatment The chloroquine patients improved to a degree which was *statistically significant* as far as tenderness of joints, strength of grip, and dexterity were concerned, but there was no definite change in the time taken to walk a measured distance, in the hæmoglobin level, or in the erythrocyte-sedimentation rate As Freedman himself points out, the improvement in the chloroquine group was modest Clinically there was (as would be expected) some improvement in both groups, but statistical analysis showed that only the change in the chloroquine group was significant It is not clear whether the difference between the degree of improvement in the two groups reached significance The two groups were not evenly matched, since the chloroquine group contained rather more patients with disease of recent onset and with slightly more active disease As Duthie et al[7] have shown, this would tend to weight the outcome in favour of chloroquine treatment Freedman held that this factor could not account for the difference between the treated and control group, but he does not give figures

Sixteen weeks is a short sample of the natural history of rheumatoid arthritis Any drug which influences the disease even briefly is of great interest, but only a longer trial can establish or refute the practical value of any treatment Freedman did, in fact, treat a group of patients for a longer period This part of his investigation was, however, uncontrolled, and serves mainly to establish the superiority of chloroquine over mepacrine in terms of toxic effects Freedman wisely concluded that the trial did not definitely prove the value of prolonged treatment with chloroquine in rheumatoid arthritis, but he believed that his data warranted a larger investigation

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[1] Page F *Lancet* 1951 ii 755
[2] Freedman A Bach, F *Ibid* 1952 ii, 321
[3] Haydu G G *Amer J med Sci* 1953 225 71
[4] Freedman, A *Ann rheum Dis* 1956, 15 251
[5] Oka M J *Ann med intern Fenn* 1953 42 215
[6] Lacapere J Monier H Vial G *Rev Rhum* 1954 21, 360 Fletcher W R
[7] Duthie J J R Thompson M Weir, M M, *Ann rheum Dis* 1955, 14 133

HELP IN THE HOME

TODAY any report worthy of the name—whether about old people or babies, hospitals or clinics, general practitioners or consultants, the family or the isolate, tuberculosis or mental disease—is likely to recommend "the development of the domiciliary services" In a world of almost frightening scientific progress and mechanical complexity, it is perhaps rather consoling that the answer to many urgent medical problems should be the simple words "more help in the home" But their simplicity is deceptive, and some of the difficulties, achievements, and resources which they cover will be found by the attentive reader of the recent report on London's health [1]

The three principal services which offer help in the home are the home nurses, the home helps, and the health visitors In London the home nurses are provided by 27 voluntary associations acting as agents for the London County Council through the Central Council for District Nursing in London At the end of 1955, 572 whole- or part time nurses were available, of whom 49 were men This force paid nearly 2 million visits, giving an average of 13 visits daily and a case load of 24 for each nurse 41% of the patients were over sixty-five years of age and 6% were children under five Besides providing the associations with a grant of 93% of their expenses, the L C C lent them 21 cars, and at the beginning of 1955 it appointed a supervisor who has during the year visited all the associations and where necessary advised in day-to day problems Through the British Red Cross Society the L C C also lends nursing equipment for patients who are getting care in their homes The demand for expensive and unusual equipment is growing because many chronic sick and disabled who were formerly held to be hospital cases are now able to live at home For example, as a result of the work of the National Spinal Injuries Unit at Stoke Mandeville Hospital, many more paraplegics are now able to look after themselves

The home help service is also growing steadily if slowly At the end of 1955, there were 3148 helps—the equivalent of 2029 full-timers—compared with 2996 and 1866 respectively in 1953 Over 80% of their work in 1955 was for the aged and chronic sick This service is short of staff, but, thanks to the policy of giving some assistance to all in need, only 61 applications had to be deferred or refused in 1955 compared with 161 in 1954 Night helps sit with patients in their homes to allow relatives to get some sleep but, surprisingly, the demand on this useful aid is not heavy, and in 1955 the 48 new applications were met

The scheme, started as an experiment, to provide help in a family crisis so that the children need not be received into care is being extended and is now offered for families with only one child (Previously it was limited to families with at least two children) The demand on this service is not yet as heavy as was expected—5 families (16 children) in 1955—but early morning and evening help, arranged to cover the gaps between school hours and parents' working hours, was supplied for 205 new families in 1955 compared to 85 in 1954 At the end of the year a scheme was being started to prepare selected home helps to work with the health visitors and teach the rudiments of housecraft to inexperienced mothers in homes which are in danger of breaking down The success of this preventive work is most clearly shown in the detailed reports from the boroughs, which record that in two L C C divisions it was possible to avoid taking 75 and 135 children into care

These divisional reports also show how much the 375 health visitors are contributing and how their work is widening In many London boroughs there are monthly reviews of problem families and potential problem families who with a little timely help can make a reasonably speedy return to normal One division also records that the health visitors are finding it possible to give more time to the lonely ailing old people Informal meetings are being held with the local family doctors at health and welfare centres Another successful experiment was to attach a health visitor for part of her time to a group practice Valuable domiciliary work is being done by health visitors in connection with the diabetic unit at King's College Hospital, and several health visitors have started classes in antenatal relaxation and exercise

These extra pairs of skilled hands, offering timely aid in a home for even a few hours a day, have freed many hospital beds and spared many families from anxiety, exhaustion, and separation

LARYNGEAL GRANULOMA AFTER INTUBATION

A GRANULOMA involving one or both vocal cords is a rare complication of endotracheal anæsthesia In recent years it has been gaining recognition as a clinical entity and this increase reflects the wider use of intubation in modern surgery Discussing these granulomas, Epstein and Winston [1] record 10 cases treated at the Royal National Throat, Nose and Ear Hospital in London All the patients were adults, and women outnumbered men by 4 to 1 The relatively small laryngeal aperture in the female may make women more susceptible Direct injury to the larynx during the introduction of the tube seems to play only a small part, since most granulomas followed an easy intubation, often performed with the aid of muscular relaxants Pressure of the tube in the glottis is probably the most important cause, and this view is supported by the fact that the granulomas always arise on the vocal process of the arytenoid and by the demonstration [2] of the spring-like action of the flexible endotracheal tube, which exerts pressure posteriorly in the larynx, increasingly so as the head is flexed The rigid bronchoscope, on the other hand, lies against the anterior commissure, and a granuloma has never been recorded as a sequel to bronchoscopy

The vocal process of the arytenoid forms a rigid unit, the mucoperichondrium is firmly adherent to the cartilage it covers and there is no subepithelial connective tissue layer to allow the epithelium to move on underlying structures Injury in this region leads to ulceration and the formation of non specific granulat on tissue Constant trauma from the opposite vocal process causes the granulation tissue to proliferate, and it becomes epithelialised and presents as a sessile granuloma Healing takes place by fibrosis, which narrows the base until the granuloma becomes pedunculated This process may continue until the granuloma is shed and expelled Usually it remains, causing irritation, hoarseness, and sometimes stridor

When an ulcer is seen on the vocal process after an operation involving intubation, the development of a granuloma may sometimes be prevented by insisting on strict voice rest At a later stage, the removal of a sessile granuloma exposes a large bare area which gradually heals by granulation, so that the granuloma may recur Provided the airway is adequate, removal should, therefore, be deferred until the granuloma is pedunculated, and it should be followed by absolute vocal rest

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[1] London County Council Report of the County Medical Officer of Health and Principal School Medical Officer for the Year 1955 Issued from County Hall, S E 1 Pp 193 2s 6d

[1] Epstein S S Winston P *J Laryng* 1957 71 37

[2] Barton R T *New Engl J Med* 1953 248 1097

NEW POPULATIONS, OLD PATTERNS

SIX family doctors have surveyed their practice in a new housing estate 15 miles from the centre of London [1] It is the first time that such a community has been the subject of a survey of this kind, by practitioners aware of the possible influence of the new surroundings on the people who have come to live in them

Information was recorded on a modification of the N H S medical-record envelope continuation sheet, then coded, transferred to punch cards, and sorted mechanically A random 25% sample was taken, including 4800 people living in 1018 houses in the area The consultation-rates and numbers of patients consulting were classified by social group as well as by sex and age The results of previous work were confirmed The presence on the estate of families rehoused on grounds of ill health did not apparently raise the consultation rate, perhaps because the low average age of the community cancelled out any such tendency The extent of the "hard core" of the practice is interesting 16% of the registered patients accounted for half the consultations, and the 7% who took up 30% of the consultations represented the real bedrock This aspect of the practice is to be further examined, and an analysis of the causes of these consultations would be of particular interest

It is surprising to learn that as many as 99 prescriptions were issued for every 100 consultations Only about 5% of the registered population consulted the doctor *without* obtaining a prescription—and most of these consultations were for reasons other than sickness The prescription-rate seems high, and analysis of the prescriptions issued, by an arbitrary estimate of their value, might be a useful means of future study

More inquiries of this kind are needed, and we hope for further news from this particular community

VITAMIN-D POISONING

VITAMIN D is often prescribed or taken in large doses, despite the known dangers, for conditions such as arthritis and skin tuberculosis for which more effective and safer treatment is now available Scharfman and Propp [2] have lately described 4 patients with vitamin-D intoxication in which a normochromic and normocytic anæmia was a presenting feature They concluded that this anæmia was probably secondary to the azotæmia which in turn depended on renal impairment caused by the hypercalcæmia of vitamin D poisoning, which may often be unsuspected Debré and Brissaud [3] mentioned anæmia as one of the features in their series of 27 children who had been poisoned by vitamin D

Another suggestion,[4] based on animal experiments, is that excess of vitamin D and cholesterol may be related to the development of atherosclerosis It would be virtually impossible to substantiate this work in man, but it may provide a link with Sinclair's thesis [5] that many modern dietaries are deficient in the essential polyethenoid fatty acids (E F A) and that cholesterol consequently becomes esterified with abnormal or unusually saturated fatty acids which the body finds difficult to dispose of and which could cause atheroma Sinclair has taken his argument a step further [6] by attributing a part in the ætiology of infantile hypercalcæmia to E F A deficiency Sensitivity to vitamin D has been suggested as a cause of infantile hypercalcæmia Sinclair has pointed out that roller dried milk, such as National dried, is relatively low in E F A and rich in vitamin D and that this combination might enhance the action of unesterified vitamin D and thus lead to hypercalcæmia Such a consequence might be regarded as a physiological penalty for our persistence in feeding babies with milk designed for the young of another species, and to which too much vitamin D has been added

Infantile hypercalcæmia is virtually unknown in the United States, where babies are more often fed on evaporated milk or on modified dried milk formulæ, which are richer in E F A and contain less vitamin D But lack of E F A cannot be the only factor since millions of babies are fed on National dried milk and only a few get hypercalcæmia, something else seems necessary to initiate the hypercalcæmia Infection [8] and adrenocortical dysfunction [9] have been suggested as possibilities

These new findings are a reminder that vitamin D is not without its dangers and that there is nothing to be gained by giving amounts vastly in excess of physiological needs [10] Ideal growth and the prevention of rickets in infants can probably be achieved by a daily dose of about 500 international units, and if the vitamin is to be prescribed for older children and adults a similar dose should suffice and should not, as far as we know at present, do any harm

TIRED YOUNG NURSES

IN the autumn of 1954 correspondents in the *Nursing Mirror* discussed whether young nurses are overtaxed and overstrained A few months later, as a result of these letters, a committee, representative of all grades of nurses in training-schools, was set up under the chairmanship of Mr H A Goddard, the director of the Nuffield Investigation Team, to consider the problem further In their report, published this week, the committee attribute much of the overstrain and fatigue of these young women (and men) to mental and emotional rather than physical causes They point out that the nurse, unlike other students, is cut off from her ordinary home life and spends her whole time in an "abnormal atmosphere of sickness and in an 'artificial' community"

To lessen this strain they suggest that for the first year the student nurse's training should follow more closely the conventional academic pattern The nurse should enter the hospital without any preliminary training, but she should live in a hostel not run by the hospital authorities, keep college terms, and go home for vacations She should be on duty for regular hours and her first year should be spent in lectures and ward work entirely under supervision "with no responsibility for ward" At first sight this restriction on contact with patients may seem yet another stitch in the nurse's academic gown But the committee's report shows that there may well be a real need to protect the young nurse from some of the rigours of hospital work The committee sent to 5284 nurses in the South West Metropolitan Region a questionnaire dealing with such subjects as their hours of work, ward equipment, catering arrangements The 1965 replies show, for instance, that half of the students in general hospitals work overtime either regularly or often, compared with just over a quarter in mental hospitals In mental deficiency hospitals all students do some overtime and half of them "often or regularly" Slightly over a third of the students have lectures in off duty times These rigours are no doubt due not to harshness but to shortage of staff and the

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[1] Brotherston J H F Chave, S P W *Brit J prev soc Med* 1956 10 200
[2] Scharfman W B Propp S *New Engl J Med* 1956 255 1207
[3] Debré R Brissaud H E *Ann Méd* 1949 50 417
[4] De Langen C D Donath W F *Acta med scand* 1956 156, 317
[5] Sinclair H M *Lancet* 1956 i 381
[6] Sinclair H M *Ibid* 1956 ii 101
[7] See leading article *Ibid* 1956 i 1062
[8] Creery R D G Neill D W *Ibid* 1956 ii 1357
[9] Anderson J Brewis I G Taylor W Personal communication (see ref 8)
[10] British Pædiatric Association *Lancet* 1956, ii 136

Special Articles

SIX WEEKS IN SIX WEEKS OUT

A Geriatric Hospital Scheme for Rehabilitating the Aged and Relieving their Relatives

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M B Belf, D P M
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Caring for an aged invalid, who can easily become a neurotic tyrant, is a fruitful cause of domestic strain, leading often to breakdown of the relatives' health This has serious social implications which demand more attention than they now receive In the Wolverhampton inquiry, Sheldon[1] suggested short stay hostels and permanent homes as means of lifting the relatives' burden Our experience at Langthorne Hospital, however, suggests that an alternative way of dealing with the situation may be preferable Certainly something must be done, because at present the cost of strengthening the old and weak is far too often a weakening of the young and strong

The extent of strain in the family circle can be assessed only by visiting the home In 1955 I paid 902 such visits, and I found that in 120 (13%) domestic stress was the principal reason why admission to hospital was sought But, whereas the general practitioner thought in terms of permanent accommodation in hospital, many relatives said that they had no wish to shelve their responsibilities and only wanted a rest—especially a night's unbroken sleep Many seemed to be living on phenobarbitone, and quite a few were having treatment from a psychiatrist These were the circumstances which led us to establish in our hospital what is now known as the social rehabilitation unit

The Unit

The section for women contains 24 beds and is decorated and equipped to produce an atmosphere of social well-being and happily lacks the formality of the average hospital ward The dayroom is pleasant and not too spacious, and has a homely air, open coal fires are provided in the ward and dayroom and are a great social amenity The arrangements and the organisation of the staff are intended to encourage self-reliance of every kind There are aids towards participation in work During their stay, patients have the benefit of chiropody and physiotherapy, and visit the daily activities section of the occupational therapy department, where they are encouraged to cook, wash and dry dishes, sweep the floor, and make a bed Similar accommodation is provided for 10 men and like techniques are employed

Admission

There are no direct admissions to the unit A patient is first seen in his own home and his suitability for this special type of environment is assessed If he is considered suitable, we explain to him and to his relatives that permanent accommodation will not be given Instead, he is to spend six weeks in hospital, followed by six weeks at home and then be readmitted for another six weeks Discharge and readmission will continue in this way as long as is necessary At the end of the stay in hospital the relatives are always given the date for readmission This is of great practical importance because the entire household can be reorganised and routines established which add depth to living not only for the patient but more particularly for the relatives

The table shows a list of the disabilities of 100 patients treated on these lines during the past eighteen months

The Patients

30 patients have died—80% of them during the first and second temporary stays This suggests that the death rate conforms to the usual pattern seen in the general wards of a geriatric unit The disabilit encountered are the usual ones in this particular categor In this series the patients with old hemiplegia, osteo-arthritis, or old fractures of the femur were apt to generate much stress A few comments may be of interest

Old hemiplegia—The average duration of the disabilit was three to four years In the early stages of the illness treatment had been active, but the hospital concerned soon l interest and therapy was discontinued The morale of the patients was low because no attempt had been made to he them to live with their disability 80% were chairfast, ma because the sound limb had become weak through disuse Many were aggressive, making the atmosphere in the household intolerable

MAJOR DISABILITY IN 100 AGED INFIRM PERSONS CAUS DOMESTIC STRESS

Disability	70 women (average age 78)		30 men (average a	
	Patients	Deaths	Patients	Deaths
Old hemiplegia	14	6	8	0
Osteo arthritis	23	2	4	1
Parkinson's disease	5	3	4	[illegible]
Old fracture of femur	11	4	2	0
Cardiac illness	12	3	7	[illegible]
Old cerebral thrombosis	5	5	5	2
Total	70	23	30	7

Old fractures of femur—In 8 patients the fracture had been sustained twelve to eighteen months before the domiciliary visit Orthopædic treatment had been excellent and weight bearing had been achieved, but in order to avoid further fall the relatives had persuaded the patients to remain a little longer in bed each day All had disuse atrophy of both limb The mental health of this group was excellent but they were subject to outbursts which caused serious friction, resulting in 3 instances, in the break up of the family

Osteo arthritis—70% of these patients were obese, and enthusiastic attempts to reduce weight had merely resulted in the production of psychosomatic symptoms causing great tension in the home They were reluctant to lose their symptoms, and many of the relatives had suffered great strain.

Results

As stress and strain in the household was the principal reason why admission to hospital had been sought, we felt that a questionnaire to the relatives after the patient's fourth temporary stay in hospital might help u to estimate the value of the scheme Here are a few case

Case 1—Mr A, aged 70, had a useless left arm and hand (an old disability due to poliomyelitis) gross osteo arthritis of hips and knees, flexion contracture of legs, and incontinence of urine He was mildly confused at times, there were aggressive outbursts, and his wife had an acute anxiety state He has been admitted seven times for temporary stay

Reply to questionnaire (by wife)—Arrangement of g help This is the first real rest I have had in two years H attitude to me has improved and he is much easier to man I am very grateful

Case, 2—Mrs B, aged 69, was chairfast because of Parkinson's disease, and was unable to feed herself Bout of urinary incontinence produced emotional crises Husband had given up a very good job to care for her, she demanded constant attention The family doctor asked for permanent hospital accommodation because the situation was intolerable She has had seven temporary stays

Reply to questionnaire (by husband)—I consider temporary stays of great assistance They have enabled me to take on a part time job and I feel ten years younger ' When my wife returns home she is much easier to manage She volunteers to wash the dishes and does so successfully She is still chair fast but is more reconciled to her disability She likes going into hospital as she feels it helps me She is not afraid any more as she knows that she will not be kept in hospital permanently

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[1] Sheldon J H The Social Medicine of Old Age London 1945 p 197

Case 3 —Mrs C, aged 89, had fractured her left femur in 1950 She had achieved full weight-bearing in 1951, but then lost interest and often fell Her son kept her in bed as he felt she would fracture her good leg She became difficult and incontinent, and dirty in her habits Her son, much attached to his mother, had spent part of his income in getting help for her Her son's wife was overwrought and anxious and this tension was communicated to their only son who was working for his 11+ examination When the patient was seen she was bedfast, with disuse atrophy of the right leg and flexion contracture of the left

Reply to questionnaire (by son) —Temporary stays of very great assistance The procedure has saved my wife from another breakdown in health Giving her six-week periods of rest has changed the atmosphere in my home to the benefit of my wife, my son, and myself We are all amazed that my mother can now walk again When she comes home for a temporary stay our nights are undisturbed My mother is very happy with the arrangement as she benefits from the company of other old people and the change in surroundings We are all very grateful and hope that this service will be extended to others

Replies to 70 questionnaires have been received and they are all couched in like terms They may be summed up in a phrase used by the daughter of a patient She says "The temporary stay procedure has made a difference to me between existing and living" It is worth recording that 30% of these patients were cared for by daughters Reports from general practitioners are equally heartening Only 3 patients have so far become "permanent" after the fourth temporary stay, as the domestic situation had changed In the present series 67% of the patients continue to enjoy the arrangement

Observations on the Experiment

The experiment owes its success to a therapy catering for the emotional and social needs of the patients and their relatives, and not merely the physical rehabilitation of the patients The latter is always tried, but the results are disappointing, for these patients are suffering from disabilities of many years' duration Teaching them to live with their disabilities is an important part of therapy

When these patients are first seen in their own homes they seldom know how much anxiety they are causing in the household They have one fear—that the relatives no longer want them and that they are going to be tucked away in hospital and forgotten When the temporary stay is explained to them they are at first suspicious but eventually agree to try it

Within forty-eight hours of admission social contacts are made, conversation flows, and experiences are exchanged The morale of the newcomer is quickly raised as she hears about the facilities available and the part she will play in the kitchen activities When she is told by several members of the group that they will be going home in a few weeks' time for a temporary stay she knows that this too will be her experience The aged infirm are often lonely and welcome those of their own age group with parallel memories, activities, and capacities, they feel out of place in a household where everyone is younger and active When relatives visit the unit they find the patient an entirely different person, who is pleased to see them and expresses, perhaps for the first time in years, how much she likes them They react accordingly and make the patient feel that when she returns home for a temporary stay she will be accepted as a member of the family circle Family affection is thus preserved A burden has been lightened and a sense of responsibility maintained

Sheldon[1] estimated that 7 7% of the old people were causing great strain on the younger generation, in my own series the figure is 13% The burden will, I believe, continue to grow, because there will be more aged in the community Incapacity, rather than old age, is its true measure, and no matter what medical and social progress is made, relatives will be required to share it Geriatric centres could, in the way we are trying, give intensive medical and temporary social care to a considerable proportion of infirm patients, and reduce the need for long-stay annexes

Summary

The aged infirm are increasing in number, and the stress imposed on relatives caring for them is not fully appreciated The measure of this stress can be assessed only by a domiciliary visit In 1955, 902 such visits were paid, and in 120 (13%) cases stress in the home was the principal reason why admission to hospital was sought Many relatives only wish the burden to be lightened and the temporary-stay procedure, which is described, does this

A few of our case histories illustrate the type of medical and social problem, and replies to a questionnaire sent to relatives show that a great need has been met

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THE GAZIER PLAN

FROM A PARIS CORRESPONDENT

SOMETHING seems to have gone wrong with the game of musical chairs which has for so long been a part of French politics the present government is still in power, after more than a year Unless the music stops very shortly—and this seems unlikely—parliament will amend the 1945 law governing the French social security system Already the proposed amendments—the "Projet Gazier" as they are called after the Minister for Social Affairs—are being studied by the relevant government departments before it is discussed by the Assemblee Nationale in the next few weeks The medical profession is up in arms against it the Confédération des Syndicats Medicaux, the French equivalent of the B M.A, has unanimously adopted a resolution flatly rejecting it, l'Ordre des Médecins, the French General Medical Council, has opposed it, and the venerable Academie de Médecine has "denounced the danger of administrative regulations which could jeopardise the proper treatment of patients and the mission and dignity of the medical profession"

What is it all about? French medical practice is based on four principles the patient should be free to choose his doctor, the doctor should be free to prescribe without limitations of any sort, strict professional secrecy should be maintained, and the doctor should be at liberty to decide his fee with the patient It is around this last principle that the battle is raging

THE PRESENT SOCIAL SECURITY SYSTEM

In 1945 the original law on social insurance (1928) was recast and made more comprehensive social insurance became social security Unlike the British system, French social security rejects the principle of universality, but where it operates (in the large majority of cases) it covers all needs "from the cradle to the grave" It even anticipates the cradle by providing financial incentives to have large families

In the matter of medical benefits, the principles governing the original law remained unchanged The patient pays a fee to his doctor, whether physician or surgeon, for each item of service, and he is reimbursed 80% of a theoretical fee given on a scale established by the social security organisation These theoretical fees are supposed to be fixed by agreement between the local branch of the social security organisation and the local chapter of the medical association In practice, agreements have been reached only in a few instances, because the social-security organisation insists on fees which the doctors say are much too low Since the law provides three categories of exemptions for doctors, most patients are reimbursed for only 50–60% of their outlay for a general practitioner and less for a specialist—except when they go to hospital

THE ORIGINAL PROPOSALS

The present government, supported by trade unions, holds that the existing system needs reform, and in the minds of most doctors the cure proposed will destroy medicine as a liberal profession Clumsy handling by the government has made matters worse

The government's key idea is to establish a precise scale of fees and to make it compulsory for all but 15% of doctors, who will be free to charge what they want on the understanding that their patients will not be reimbursed for anything except medicines The minister feels that by sacrificing "freedom for fees" he saves the other three principles which, in his opinion, are more fundamental

Most French doctors think it is extremely difficult to codify rigidly medical consultations, since each is essentially different If fees are standardised, doctors will be obliged to see more patients to maintain their present standard of living and in consequence patients will receive poor attention The older and more experienced man will be unable to charge more and the younger man with higher qualifications will likewise be handicapped The French feel strongly that the family doctor is the first line of defence against disease The more he can tackle, the less will be referred to hospitals, which should be reserved for difficult cases or special treatments The French medical profession is united in the belief that nothing must be done that will lower the standard of general practice and lead to "assembly-line" medicine

What of the 15% of doctors who would be outside the scheme? The profession believes that the creation of a special category whose services will not be reimbursed destroys the principle of "freedom of choice" All consultants will be in this category, and it is argued, therefore, that all but the wealthy will be discouraged from seeking a second opinion by private consultation

Another difficulty is being foreseen France is the country of competitive examinations, and there are many hurdles that the would be consultant must clear, what will happen, it is being asked, to those with excellent training and long experience but who have not made the grade simply because there were not enough jobs to go round? They will have to go into general practice without being allowed to charge more than their colleagues who took up practice immediately after qualifying Will this not deter the younger members of the profession from taking the examinations? Moreover, as many declare, a flat 15% cannot fairly be applied to all regions of France, since there are more consultants in university towns than in the country

Among other less fundamental objections to the Projet Gazier is the suggestion that it would be better to hitch the agreed fees to a sliding scale based on the cost-of-living index and the general wealth of the country Few doctors find solace in this plan

SECOND THOUGHTS

The final draft has not yet been submitted to parliament, and already changes are being made For example, it is now suggested that patients of "free fee" doctors be refunded on the basis of the legal rates, and that the "free fee" doctors will represent 15% of medical practitioners for the whole of France and not by region Moreover, provision is proposed for the recognition of specialists and consultants who may not possess the relevant degree or diploma but whose personal merit warrants recognition Finally, the latest plan is that doctors' fees will follow the cost-of-living index (which is manipulated by the government) and the purchasing power index established by the Institut National de la Statistique (which is free from manipulation) No doubt the final draft will be further amended by parliament

THE PATIENT'S VIEWPOINT

For the patient, who is also a taxpayer and a contributor to the social security scheme, some of these discussions seem theoretical He pays his dues and would like to get his money's worth "If this scheme is adopted," he asks, "will I be refunded 80% of my doctor's bill?" The answer must be an emphatic "no" The deficit of the social security system is increasing yearly and nothing short of reorganisation will stop it Having tasted military medicine, he dislikes anything that resembles the front line "sorting" type of medicine if that is what the scheme will amount to, he does not want it He does not like hospitals very much and prefers to be nursed at home He knows that hospital medical care will be the very best, but somehow he dislikes the common ward He realises that the social security system needs overhauling, but in spite of a cumbersome administration it works well enough—if only he were refunded more

MORE THAN FEES

No one disputes that something must be done to streamline the French social-security system, and many feel that major surgery is needed As the doctors see it, however, the proposed reform is tinkering with the fundamental problem it is an attempt by the government to lighten the sick man's burden—at the doctor's expense The medical profession interprets these moves as more than a challenge to their fees France is one of the few Continental countries where medicine has retained its traditional liberal character, and the great majority of French doctors will resist any effort to change the existing pattern

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Medical Education

THE UNIVERSITY HOSPITAL

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THE close association of universities and hospitals is a late development in this country as compared with in Germany and the United States There is general agreement that the meteoric advance of medicine in America in the present century is due largely to its linkage with the universities, and this is one of the reasons for the current trend towards strengthening similar university linkages in Britain It would be wrong to pretend, however, that the problem is an easy one, or that it is automatically solved by the application of a formula which works in other countries where the historical background and present conditions are different It is easy too to fall into the error of repeating clichés, or using words such as "research," "teaching," or "duty to one's patients" merely as slogans, or even as weapons with which to beat one's opponents The brief observations which follow are merely an attempt to define and clarify some of the problems

Some Definitions

A hospital is "an institution for the care of the sick," and a university (to paraphrase slightly the words of Adlai Stevenson) "an institution whose function is the search for truth and its communication to succeeding generations" The functions of the hospital and the university in a university hospital are thus complementary rather than antagonistic A hospital's work is concerned with the present, a university's with the future The hospital's primary duty is to the sick people who seek its aid The university is largely responsible for the doctors, and hence for the medicine, of the future

So far from there being a conflict between these two objectives, the long-term perspective associated with the university ideal should result in a higher standard of care for patients , and the general experience shows that it in fact does

Integration

The problem thus becomes one of integration It must be recognised that mere placing together does not constitute integration It may even mean the reverse, as illustrated, to take a political example, by the history of the modern State of Israel A similar state of affairs may obtain when a university department is established in a hospital The teaching hospitals of this country have a long and honourable tradition, built on the democratic ideals of individual freedom and responsibility Many of those working in these hospitals fear the establishment of an authoritarian professional system on the Continental model The reaction to this fear may be the isolation and insulation of the university's clinical departments Though they may do excellent work under these conditions, they obviously fail to have the influence they should on the hospital as a whole The remedy would seem to be for the university to recognise the strength and value of the democratic tradition in the teaching hospitals, and seek to harness these qualities in the service of the university ideal. The university department should be neither authoritarian nor insulated, but rather coordinating and catalytic

Research

Research is usually divided into pure and applied Conant [1] gives, as the main examples of this subdivision in the modern world, university research, which is primarily concerned with the discovery of fundamental principles, and industrial research, which is primarily directed towards the solution of immediate practical problems Medicine is an applied science, and therefore much of medical research must approximate to industrial research Since there is no lack of immediate practical problems in all branches of medicine research in a university hospital should be regarded as a general activity in which the university department has a special rôle Apart from the investigation of its own practical problems, the special functions of the university department are the providing of posts for, and the training of, research-workers, and the search for fundamental principles To perform these functions, the department needs research facilities and research assistants under its own control, as well as a liaison with the preclinical and hospital research departments

Teaching

The teaching hospitals of this country are by tradition regarded as primarily concerned with undergraduate medical education—the term “ primarily ” often being interpreted as “ almost exclusively ” As a result, little attempt has been made by the universities of this country to define and control postgraduate medical education This is in striking contrast with the United States, where, since the end of the last century the universities have closely guided the course of higher medical education Probably the attitude of the teaching hospitals of this country has been determined by their looking on postgraduate education mainly as a matter of cram courses for higher examinations, with all the interference with undergraduate education that these courses often cause, whereas such courses really constitute a relatively unimportant part of postgraduate education A greater interest in postgraduate education by university hospitals would be fitting to the position of this country as the heart of a great commonwealth Moreover, some control by the universities of the appointment of registrars may be the only solution of the registrar problem

As regards undergraduate education, there are large questions of principle content and technique which I shall not broach here But the point to emphasise is that the university department should be concerned not merely with teaching in its own unit, but with the mobilisation of teaching ability and material in the hospital as a whole As regards postgraduate education, the special functions of the university department should be the provision of facilities for and the encouragement of research

Suggested Academic Organisation of University Hospital

Much of the voluminous writing on medical education, while enunciating ideals which meet with general approval, is vague when it comes to their application An attempt will therefore be made here to outline a scheme of integration between university and teaching hospital, starting from the principle that the democratic traditions of the teaching hospital should be preserved but its relations with the university strengthened

Under the chairmanship of the dean of the medical school and responsible through the academic board to the school council, the clinical professors might constitute a clinical education committee Under this committee, each clinical professor would be chairman of a medium-sized subcommittee, widely representative of the clinical teachers in the corresponding subject, and advising on all aspects of education—e g , lectures, the full use for medical education of the clinical material in all departments of the hospital, and the organising of staff meetings This last function, and the fostering of the tradition of all grades of staff assisting at such meetings, should be regarded as especially important To emphasise his coordinating function, the full title of a professor should be “ professor of medicine, and chairman of the medical education subcommittee ”—and similarly for the other professors The above committees should meet regularly, but ordinarily this should not be necessary more than twice a year Owing to their representative character, the advice they give through the dean to the school council is not likely to give rise to difficulty when conveyed by the school council to the hospital

The University Unit

Some such organisation as the above should ensure that the university unit exercised the maximum catalytic and coordinative influence on teaching and research in the hospital as a whole This would be achieved too by a form of partnership, and without impinging on the individuality and resultant vitality of the other units As regards the organisation of the university unit itself, it should have some additional beds as compared with other clinical units (chiefly to provide clinical facilities for its research assistants), and facilities (if possible close to the wards) to enable it to fulfil its special functions in clinical teaching and research

Private Practice

Finally, brief reference must be made to private practice Too much importance has probably been attached to this question by the universities in the past indeed there has been a danger of a clinical professor being defined merely negatively as someone to whom private practice is forbidden A clinical professorship should clearly be substantially a whole time job, but the desire of the university to protect him from private practice sometimes contrasts with the excessive calls the university often makes on his time for administrative work, examining, and visiting The pros and cons of allowing some limited private practice have often been argued, and I shall not go into them here In my opinion, however, the main disadvantage of cutting off the clinical professor from all private practice is that it makes him different from his colleagues in kind, and not merely in degree, and hence makes integration of the university department and the hospital as a whole more difficult If the universities would adopt a less rigid attitude, this would give the teaching hospitals the opportunity to experiment, without their adopting such extramural devices as the appointment of directors rather than professors The present power of the universities over medical education is so great, if they choose to use it, that they should have no difficulty in reviewing and controlling experiments carried out under their ægis

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[1] Conant J B The Citadel of Learning New Haven 1956

CONCLUSIONS

The universities should devote their attention not merely to the establishment of university units in teaching hospitals but to their integration with the hospital to produce true university hospitals The Continental authoritarian professorial system is unsuited to the democratic medical traditions of this country, and attempts to introduce it are undesirable On the other hand, the non integrated professorial unit, though capable of excellent work, does not by itself make for a true university hospital The time is ripe for universities to encourage experiments, aiming at the establishment of such integration

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Public Health

PEDICULOSIS CAPITIS

A COMPARISON OF TWO REMEDIES

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IT seems strange that, despite progress with insecticides, pediculosis capitis should still be so prevalent among school children Official national figures showed that of those examined in the schools of England and Wales in 1953 1 9% were found to be verminous[1] Beare[2] points out that the prevalence varies, and that often more than half of a school population are infested He quotes a fairly constant annual figure of 8% from the total school population of Belfast

One of us (I D M N) has circularised principal school medical officers of county boroughs of England and Wales The information they have kindly supplied shows that in 77 county boroughs for the four years 1951–54 the proportion of children with nits or lice ranged from 0 5 to 22 9%, the averages being 6 9%, 6 8%, 6 2%, and 5 5% in 1951, 1952, 1953, and 1954 respectively For 34 counties the corresponding averages were 2 7%, 2 7%, 2 2%, and 1 9%

In considering such figures one must recognise differences of definition In some areas the presence of one nit classifies a child as "dirty," excluding it from school until clean, whereas in others a child is not "dirty" unless lice are present

The principal school medical officers of the county boroughs also told us what preparations were used in their school health service Taking the one mentioned first in each return (for many mentioned two or even three), we found that the following were those most commonly used

1 'Suleo' hair emulsion containing 2% dicophane (D D T) and 1% pyrethrums *B P C*
2 'Lorexane' concentrate, containing 1% gamma benzene hexachloride ('Gammexane')
3 'Lorexane' head lotion, containing 0 2% gamma benzene hexachloride
4 'Esoderm' medicated shampoo, containing 1 0% dicophane
5 Dicophane (in various bases and strengths)

TRIAL OF PREPARATIONS

Over 400 infested Brighton school children were treated alternately with either suleo hair emulsion or esoderm medicated shampoo Bearing in mind the difficulty some workers[3] had experienced in obtaining similar results with the same preparation in different parts of the country, it was decided that all the examinations and re examinations should be done by one nurse and all the shampooing and applications by another, both had had long experience in this work This ensured that all the classifications of infestation would be reasonably constant and that the two preparations would be used under similar conditions During the trial the results were computed after each hundred cases or thereabouts, and they remained fairly constant throughout No choice of preparation was allowed, and within the same family children were treated with different preparations

The parents were asked, in a letter from the school medical officer, not to interfere with their children's hair in any way, except as recommended by the manufacturers for each preparation All the children were re examined after two weeks

RESULTS

It appears from the table that esoderm medicated shampoo gave better results than suleo hair emulsion

Of the four common preparations mentioned above esoderm is the only one which washes the hair as well as attacking the vermin in it It has, therefore, the advantage that the infested person can return to the community at once with a "clean" head

Esoderm was probably the most difficult to use clinically, in that it entailed a shampoo and the hair had to be dried It was found, however, that the detergent base assisted in the removal of nits

GENERAL OBSERVATIONS

In comparing published statistics, a difficulty arises because the number of infested children can be expressed either as a percentage of the total number of examinations or as a percentage of the school population at the time Moreover, when figures are given, the procedure of inspection should be stated In some schools head inspections are made at the beginning of term while in others they are as frequent as once a month Again the whole school may be inspected or only the junior department

Some local authorities accept full responsibility themselves for cleansing, others place the onus entirely on the parents In our opinion, the onus should be placed on the parents, with guidance from trained staff Curnow,[4] like some others, uses the threat of court action for persistent offenders, but most medical officers prefer to leave the matter in the hands of staff who, by instruction and persuasion, can usually make the most difficult families see reason The families in the lower

RESULTS OF TREATMENT WITH TWO PREPARATIONS

	Sulco		Esoderm	
	Before treatment	After treatment	Before treatment	After treatment
Nits	90 (43 2%)	28 (13 4%)	125 (55 8%)	14 (6 [illegible]%)
Many nits	75 (35 9%)	2 (1%)	69 (30 8%)	1 (0 4%)
Lice and many nits	27 (12 9%)	1 (0 5%)	14 (6 2%)	—
Lice and nits	14 (6 7%)	1 (0 5%)	6 (2 7%)	—
Few or very few nits	[illegible] (1 3%)	53 (25 1%)	10 (4 5%)	34 (15 2%)
Clean	—	126 (60 3%)	—	175 (78 1%)
Total	209	209	224	224

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[1] Report of the Chief Medical Officer Ministry of Education for 1952–1953 H M Stationery Office 1954 p 141
[2] Beare J M *Practitioner* 1956 176, 484
[3] Busvine J R, Burn J L, Gamlin, R *Med Offr* 1948 79 121
[4] Curnow, R N Annual Report of the County Medical Officer of Health, Cornwall, for 1952 Truro, 1953

social classes, and problem families, may often be the most cooperative, making full use of the services provided, in such situations particularly, it is important to have the right kind of adviser

It does not matter whether the staff who undertake this work are trained nurses or not, provided they have the right personality School nurses are scarce, but most authorities, certainly in urban areas, should have no difficulty in finding suitable people to carry out the work In this field there is an absolute argument for the nursing staff of the school health service and the public-health service to be one

Reinfestation takes place mainly in the family circle, the same children requiring treatment time after time Hence, some attempt should be made to examine and treat the other members of the household In attempting this it is very helpful to be able to advise the use of a preparation which is acceptable to all members of the household In our experience there is no doubt that a preparation which washes the hair as well as disinfests is the one of choice

We should like to thank Dr W S Parker, medical officer of health for Brighton, for facilities for the trial, and Dr F Langford, county medical officer of health for East Sussex, for help with the figures from county councils

Life Tables

The life tables volume[1] of the Registrar-General's Decennial Supplement for England and Wales, 1951, contains English life tables no 11, prepared by the Government Actuary The tables, published for males and females separately, are based on the 1951 Census populations and on the mortality experience in England and Wales as a whole in the three years 1950–52

In addition to the main tables for the country as a whole, life tables on an abridged scale are published for Wales and for Greater London The expectation of life of a boy at birth has increased by nearly 15 years in the past 40 years, for a girl the increase is more than 16 years These increases are largely the result of improvement in infant mortality For men aged 60 the expectation of life on 1950–52 mortality is about 14$^3/_4$ years, an increase of only $^3/_8$ of a year on the figure 20 years earlier, whereas for women it is now 18 years, an increase of 1$^1/_2$ years Alone of all the major conurbations Greater London experienced lighter mortality than England and Wales as a whole The sharpest geographical contrast was between the Merseyside conurbation, with mortality for men 21% above the national average, and the Eastern region (mainly rural), with mortality for men 14% below the national average

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[1] Registrar General's Decennial Supplement England and Wales 1951 Life Tables H M Stationery Office Pp 37 3s

Medicine and the Law

Could a Child be Born ?

FROM A CORRESPONDENT

THOUGH the courts ought not to feel themselves bound to give effect to every scientific thesis, yet clearly the Law should not so ignore medically accepted facts as to violate common sense Recent recommendations of the Law Revision Committee (a body consisting of judges and practising and academic lawyers who consider matters referred to them with a view to legislative reform) aim to make more realistic certain aspects of the Rule against Perpetuities

Though generally the Law was sympathetic to property rights and encouraged freedom of disposition, yet it early recognised that no good came from allowing testators and settlers to tie up their land through generations unborn Otherwise dynasty-forming ambitions would prompt patriarchs of the past to settle their land first on living children, and then down through their children's children so that successive estates might spring to life in the future and no one have the power to break the shackles on free transfer The Rule as developed provides that where an estate is to arise in the future it must vest within the perpetuity period This is taken as the duration of a chosen life which exists at the date of the testator's death (if the settlement is by will) plus 21 years Any life may be chosen including one *en ventre sa mère*, or even a number of lives so long as they can be traced so that it will be known when the last life ends At the end of the 21 years a period of gestation may be added The future estate must vest—if it is to vest at all—inside this period If there is any possibility that it will vest outside the period then the gift fails So keen was the law to keep settlers within bounds that it would not even allow a period to wait and see whether in fact the estate did vest in the period or whether the unlikely chimera would appear

One assumption made for this purpose (though it is not always made in other issues) is that of life long fertility Wherever a woman might have a child who would affect the vesting, then a doctor cannot be heard to say that after a certain age, however conservatively estimated, no child could be born Sarah is the exemplar and evidence of disabling deformity including, semble, removal of the uterus would not help a beneficiary to show that there was no chance of a rival claimant

Thus in *Re* Dawson 1889 a gift was made to the children of the testator's daughter (D) who attained 21 and the grand children of D who attained 21 born of D's children who died under 21 A hypothetical grandchild might attain 21 outside the period, if D had a child after the testator's death who died under 21 leaving children who in turn might become beneficiaries at 21 The birth of a child to D after the testator's death was improbable since D was 60 when the testator died, but it was held that the mere improbability that D would have a child was not enough to close the class entitled, and so the whole gift violated the Rule against Perpetuities

The cases have been concerned with a woman of 62, spouses of 66, and, in Jee *v* Audley 1787, with spouses both 70, yet it was said here to be of great inconvenience and a dangerous experiment to allow conjecture on such matters as their ability to have children, and evidence was excluded It was said in *Re* Dawson that similarly medical evidence of incapacity for other reasons than age would be excluded, and it could not be shown that a man was sterile

If the new recommendations are adopted they will make changes in assumption without affecting the main objects of the Rule It is suggested that a court shall presume that a woman who has reached the age of 55 is not capable of having a child, and that a boy or girl under 14 *shall similarly for the purposes of the Rule* be regarded as lacking capacity This will allow the courts to decide when the settlement or will is in dispute that a woman as in *Re* Dawson will not have future children so that the property will be capable in law as well as fact of vesting within the period But, since the unusual may happen, this presumption should be rebuttable by proof that a woman over 55 is pregnant at the time of the proceedings when the validity of the vesting must be decided Similar evidence may be brought when, for *example, a girl of 13* can be shown to be pregnant But though this may be thought to be a more likely eventuality than the other it will perhaps not often be invoked, since legitimate children are usually referred to, and where English Law is to govern the question, a child under 16 cannot have a legitimate child

Thus medical evidence will be required sufficient to satisfy the court that the presumption should be rebutted at the time when the validity is in question, and the court's decision shall be accepted even if subsequent events *prove it to* have been wrong—though without prejudice to the child's right to property not in the event void for perpetuity

It now remains to be seen whether Parliament adopts the recommendations

In England Now

A Running Commentary by Peripatetic Correspondents

February fill-dyke has done well so far My gardener's anxious voice when I drive away in the morning, "Go steady through the water, doctor" reminds me of our old coachman as we set off on our ponies for the meet "Now Miss Glady, don't you 'arrap 'er about"

Last night I was safely at home when a knock at the door revealed an agitated young man with bare feet and trousers rolled up above his knees, standing in the porch

"Can I telephone for a tow? The road's flooded"
"It does"
"They don't give you any warning"
"No they don't"
"I've driven the car right into it"
"So have I before now"
"It's very cold"
"I always carry wellingtons"
"My father's in the car, I hope he won't try to follow me"

So did I, but while the young man was wrestling with "inquiries" and the intricacies of our country telephone, father arrived, roaring the engine, hooting and spluttering, with smoke, steam, and a blaze of headlights They left, this time with a warning, "There's another flood about 400 yards up the road"

* * *

From a stay at home doctor's postbag

I had a wonderful time in West Australia After a fortnight in Borneo, where I was in the jungle doing some work on the infertility of Muruts (since the British Government has stopped them head hunting they have lost their pride and become dirty, so when they get married at an early age, after an abortion or childbirth, the women become septic and get a parametritis, hence sterility), I flew on to Darwin where I landed in the middle of the night

In spite of what is said about Darwin I liked it I spent two days there dodging the flies and then flew on to Port Headland If you know where Port Headland is, you will realise it is on the edge of the outback I flew round with the flying doctor there for about a fortnight in a small aeroplane that went backwards when the wind blew It also went in every direction, up and down and sideways, but I penetrated all over the outback I went into some very distant places, including Marble Bar, Nulgaine, and Jiggilo, which, in case you don't know, is on the edge of the desert

After that I flew down to ———, had a very interesting two days with the local doctor, and then spent twenty four hours whaling I took some excellent pictures of this After I arrived back about midnight, went to my pub, and had got the smell of whale oil off, it was obviously too late to ring the doctor to thank him I was due to fly off the next day, but just as I was about to set off news came through that he had been drowned in tragic circumstances With two friends he had gone fishing and had been swept away by the sea

Clearly I couldn't fly out of ——— in circumstances like this, so I stayed on and took over the local practice for nearly a week This included two obstetric cases and one infanticide Fortunately no major surgery was needed, I shouldn't have been able to do it if it had been, but I had some difficult and interesting medical cases

Eventually I arrived in Perth thoroughly exhausted, and caught the ship which called up the west coast of Australia We left Australia at Broome, and forty eight hours out the ship's doctor burst into my cabin at 7 A M and asked me to see a man with a perforated gastric ulcer After I'd collected my wits I went along to a fellow passenger's cabin and after considerable cogitation announced that I didn't think he had a P G U but hepatitis—possibly early infective hepatitis However, I spent a very miserable day thinking that the ship was steaming further away from medical aid and I was cooking an acute death I must say I was glad to wake up the next morning to find the patient still alive and with definite localising signs Eventually he turned out to have an amœbic abscess, a diagnosis which I did in fact suggest later in the course of the voyage

That I think is all the news except that I may be in London in February on my way to New York, but it will only be for about two days

* * *

Tremors of the human body, whatever their cause, are easily recognised Earth tremors are different Some ten years ago, I was on holiday when, at 8 o'clock in the morning, my bed—in fact my whole house—shook violently, although I was some 55 miles south of the area where the tremor was greatest My second experience was ten days ago when I was doing outpatients in a town some 50 miles south of Derby The room I was in felt as though it was being bumped from side to side for about three seconds No-one took much notice even when I said to my house-physician "That is an earthquake!" The sister registered incredulity but greeted me next morning with an apologetic "You were right!"

* * *

I don't think we have done ourselves any good by pinching the title of doctor You only have to look up the *O E D* to see how its meaning has become vulgarised and of course everyone knows that the vet doctors a *tom-cat* *Then we have to contend with the frightful* people who greet us with a hearty "Hello, Doc!" By all means in the future let us be known as physicians Hello, Phiz!

* * *

The police had considered that my evidence might be needed in the case So for three hours before and two hours after the luncheon interval I sat in the public seat my thoughts uneasily preoccupied with the debt of work accumulating in my absence The case was dismissed, inside of ten minutes, without any contribution from me

At teatime my wife was reading aloud from the correspondence columns of the local paper Several readers who had been kept waiting unduly long at doctors' surgeries seemed to be asking for an appointment system "I see their point at present with unusual clarity," I said as I departed to do the sizeable list of visits that would have been completed in the morning, had circumstances allowed

* * *

Point the forceps up a little, Barlow Thank you so much Cut Shorter! A little shorter, Barlow, don't be afraid I am very good tempered About 1/8 inch Ah! I see our ideas of absolute measurement are quite, quite different Cut the gut just sufficiently far away to keep the knot happy

Now I know what you mean, Sir

Good! I felt confident that in time I would find a formula which would appeal to you And now if you will, just for a moment, take your head out of the field of operation Thank you, Some day, Barlow, and quite by accident of course, I shall scalp you Nurse, wipe Mr Barlow's brow We have no evidence to show his sweat is sterile Now there's an idea for your M D thesis—*The Flora on the Surgeon's Brow*—rather like the opening bar of a Sitwell poem

The Flora on the Surgeon's Brow
Oleum Olei, Olea, Oleon

I once wrote a poem in my student days a rather sad little piece I think I can recall the first line "Why, Oh why did the wicked Hormone?" which is prettily scanned, don't you agree?

Indeed, Sir, rather like *Balder Dead*

I see no relevance *My* verse was serious

Yes, Sir

If you lean very heavily on the patient's chest, Barlow he stops breathing Have you noticed?

Sorry, Sir!

Cut Shorter! No, not off Just shorter Again Cut it's really quite extraordinary once you get a pair of scissors in your hand, Barlow, you change from a very decent quiet young man into a thyrotoxic barber Relax my boy Hold your breath and count five hundred very slowly

Yes Sir Sorry, Sir

Don't apologise An apology establishes guilt which will in time, give you a complex of inadequacy When are you going on holiday, Barlow?

On the 24th, Sir

I shall miss you my boy We shall all miss Mr Barlow, won't we sister?

Letters to the Editor

BRONCHIAL CARCINOMA

SIR,—Mr Nicholson and his associates (Feb 9) deplore the average delay of six months between the onset of symptoms and the attendance of patients at their clinic They misguide us when they state that "we must strive to persuade the public to recognise and take heed of these symptoms early, and not to neglect them for six months"

The delay in diagnosis of carcinoma of the lung is not due to the failure of patients to report their symptoms to their doctors It is largely due to the failure of the medical profession as a whole to diagnose carcinoma of the lung at an early stage This long delay is experienced in almost all surgical centres It is due to the essential difficulties in diagnosis, which requires special techniques available only in thoracic surgical units The present tendency for general practitioners to refer chest cases to chest clinics, which have evolved from the old tuberculosis dispensary, in order to get an X ray, has contributed largely to the delay

An analysis of the causes of delay in *referring the* 135 cases submitted to operation for carcinoma of the lung at the London Hospital in 1954 showed an average delay from first symptom to attendance at the department of thoracic surgery of 6 4 months This delay was made up as follows

From first symptom to consulting general practitioner.	1 5 months
From seeing general practitioner to seeing chest physician	1 1 months
From *seeing chest* physician to seeing chest surgeon	3 8 months

A further analysis of these figures revealed that the average delay between physician and surgeon was 2 months for those cases which proved to be inoperable at thoracotomy, 4 months for those who had a pneumonectomy, and 5 5 months *for those* who had lobectomy. The delay was greatest in those most likely to benefit from surgery

The difficulties in diagnosis are the real problem Diagnosis requires special techniques available to surgeons but not to most physicians If general practitioners could have chest X rays for their patients independently of consultant physicians the delay between first symptom and operation might be appreciably shortened General practitioners who suspect that their patients have carcinoma of the lung should be encouraged to send them direct to surgical centres There are enough fully trained thoracic surgeons to deal with the problem There could be a great economy, a benefit *to patients*, and less frustration if there existed an independent radiological service so that general practitioners could have a direct report on which they could exercise their own responsibility Radiology is now an essential part of clinical examination

London W 1 **VERNON C THOMPSON**

TOWARDS PREVENTING SUICIDE

SIR —Dr Parnell and Dr Skottowe (Jan 26) have raised an important issue and have re emphasised the warning signs of possible suicide I am always put on the alert when ideas of guilt, self depreciation and self-accusation, associated with *tension* and agitation, are in evidence and if the patient does not get any relief from unburdening Again, if a patient is preoccupied with one organ or one system and is convinced that the disorder is serious, then one should realise that he is a potential suicide

It is a fallacy to think that the patient who talks about killing himself will not do so Insomnia is also of great importance, especially if the person is very concerned about it Patients often have grave doubts about the hypnotics prescribed they fear that drugs will damage their brain It is well to spend some time explaining to the patient that the medicine prescribed can be successfully dealt with by the body, and cannot possibly cause harm Dr Parnell and Dr Skottowe did not mention the Rorschach test, which is said to be a useful addition to psychiatric examination in predicting suicidal tendencies Many papers on Rorschach findings in cases of attempted suicide have appeared within recent years It has been pointed out that preoccupation with heavy grey colouring of the blots, usually on more than one figure and almost always on fig 4, suggests suicidal trends Marguerite Hertz, of Cleveland, Ohio, believes that Rorschach testing detects more suicidal risks than are recognised by behaviour signs or other symptoms

In regard to the case quoted by Dr Wilkinson (Feb 9) it is interesting to note that in Rorschach studies there is a suggestion that outwardly directed aggressiveness and hostility are less characteristic of suicidal patients While I agree with Dr Sawle Thomas (Feb 9) that many depressed patients are successfully treated by outpatient electroconvulsion therapy, the thorough going psychotic depressive with suicidal ideas is a *serious risk*, and should be treated in a mental hospital In my experience it is during the period of recovery, when the emotional field is still variable, that suicide occurs, extra caution should be exercised and it is better for the patient to be away from home

Dr Lawrence (Feb 9) mentions the important relationship between alcoholism and suicide I regard alcoholism as a form of physiological suicide Certain patients have unconscious drives which allow them to kill themselves by alcohol It is not surprising that on occasions the process is speeded up by overt attempts which are often successful Of course, the causes given for self-destruction are much too contradictory to be of any use *in understanding the suicidal drive* Sometimes it may be easy to understand how persons suffering from psychotic and nervous illnesses can commit suicide, but it is very difficult to understand the unexpected suicide The great majority of suicides are "normal" people and the reasons given for their attempts, such as problems of love, finance, or bereavement, are merely "triggers which have fired the loaded gun"

Severalls Hospital
Colchester **ROBERT H F SMITH**

SIR —The article by Dr Parnell and Dr Skottowe, and the correspondence which followed it, seem to assume that the prevention of suicide is always desirable Is that assumption justified? Dr Pullar-Strecker reminds us (Feb 9) that 130 years ago it was legal to bury suicides at a cross roads with a stake through their bodies Presumably that reflected the attitude of very many people at the time But public opinion has moved far since then, and I suggest that it is still moving

Many have come to realise that it is utterly hypocritical to condemn the individual suicide on the ground of the "sanctity of human life" while all the nations are prepared to send their young men to die in war And many are frankly questioning the too facile assumption that suicide always betokens an unsound mind Are we not moving towards a time when many of those who, by reason of the infirmities of old age, are no longer able to make a worth-while contribution to the community in which they live and to enjoy life, will fearlessly ask themselves whether it is not better to "cut the painter" rather than join the ever-increasing host of those waiting to die in old people's homes, mental *institutions*, or the homes of kindly (or not-so kindly) friends and relations? It seems to me that the social and economic stresses and strains of our rapidly ageing population must inevitably lead to such questionings, and, as a probable result, to a rising suicide rate, at least among the old It would be of interest to know if the high suicide rates of Switzerland and Denmark show any evidence of such a trend

Suicide unrelated to old age is of course another story, and requires different consideration But here again I suggest that we should be on our guard against the assumption that the premature termination of life is necessarily an evil thing, and must denote unsoundness of mind By all means let us try to prevent the suicides that derive from temporary depression or other form of mental derangement, but let us also move towards a more reasonable public opinion on the basic right of human beings to have a say in the disposal of their lives There would seem to be a place for some measure of death control (subject to proper safeguards) as well as of birth-control

Farnham Royal, Bucks LEONARD COLEBROOK

STEVENS-JOHNSON SYNDROME

SIR,—In his paper of Feb 9 Dr Short rightly points out that in Stevens-Johnson syndrome a fatal outcome should be uncommon Both in major and minor forms, this often recurrent syndrome of skin, mucous membrane, and sometimes pulmonary lesions tends to occur *d'emblee*, and, though there may be relevant antecedent infection and treatment with sulphonamides or other drugs, the proving of their specific relation to the onset of this illness is rarely possible Early recognition and treatment of the severer cases with adequate amounts of cortisone or corticotrophin (A C T H), with or without antibiotics, has appeared in our cases to cut short this distressing condition so that fatalities have not occurred

But the term Stevens Johnson syndrome is being used as a firm, if descriptive, diagnosis in more serious and fulminating conditions such as acute systemic lupus erythematosus, severe sulphonamide sensitivity reactions, and polyarteritis nodosa—of which Wegener's granulomatosis is probably a variant—in which skin, mucous membrane, and pulmonary lesions form only part of a more general disease The hæmorrhagic, necrotic, and gangrenous skin and oropharyngeal lesions described in Dr Short's case 1 are classical lesions of polyarteritis nodosa, the bloating of the face from œdema (likened elsewhere to cadaveric decomposition), the inevitable visceral involvement by infarction, the leucocytosis, and the albuminuria and cylindruria are confirmatory, and the necropsy findings are indisputable As in acute systemic lupus erythematosus, these cases are a clamant indication for cortisone or corticotrophin—the value of which Dr Short has not disproved The initial daily dosage is that which controls the activity of this disordered immunity reaction and has in my experience been from 200 to 300 mg or more of cortisone or an equivalent amount of corticotrophin Control of secondary infection with antibiotics such as penicillin or aureomycin is clearly necessary, but sulphonamides are proscribed

Might I finish with a plea for consultation, in all these severely ill cases, with dermatologists, who, less blinded perhaps by the secondary infective phenomena, might possibly sooner recognise the basic condition ?

Aberdeen IAN W CALDWELL

THE B C G LESION IN *SARCOIDOSIS*

SIR,—I was most *interested* in the paper by Dr Forgacs and his colleagues (Jan 26) My findings[1] with regard to the rate of development of the B C G lesion, its characteristics, and its failure to convert the Mantoux reaction were identical to those reported by Forgacs et al in three cases of sarcoidosis so tested Further, two other examples of diseases in which a negative Mantoux reaction is common—leprosy and acne agminata (lupus miliaris disseminatus faciei)—reacted in a similar fashion

About 10% of normal individuals who are tuberculin-negative do not become tuberculin positive after B C G vaccination, and I suggested at the time that the particular constitutional peculiarity may have some bearing on the future development of sarcoidosis Now that B C G vaccination has been performed on a large scale for some years, it should be possible to institute long-term follow-up of these individuals to test the hypothesis

London, W 1 PETER BORRIE

MASSIVE THROMBOPHLEBITIS

SIR,—Mr *Catchpole (Feb 16) seems to doubt* the association of venospasm with massive thrombophlebitis In the following case, seen some years ago, there was severe venospasm

A middle aged man, who had been in bed for some [illegible] on account of a medical condition, suddenly complained of excruciating pain in the left leg On examination a short time afterwards, the leg was slightly œdematous, and markedly cyanosed up to the groin Peripheral arterial pulses were present, and the foot was covered with multiple small petechiae The most striking feature was distension of the pretibial veins, which seemed to be under almost arterial pressure At the end of half an hour, the pain, cyanosis, and venous distension disappeared completely for several hours, only to recur for a further hour or so some hours later Approximately six hours later the condition recurred for a third time, and on this occasion did not disappear, thus finally constituting the typical picture of massive thrombosis of the common or internal iliac vein

The staged evolution of this disease picture can only be explained by the occurrence of intermittent severe venospasm, though this was probably reactive to established clot formation

Leicester Royal Infirmary H J GOLDSMITH

PRESSOR AMINES IN THE URINE

SIR,—The estimation of the urinary excretion of adrenaline and noradrenaline is the most satisfactory test for the presence of a phæochromocytoma Despite the recent report by Litchfield and Peart[1] of a case in which there was no excess of pressor amines in the urine, the estimation is becoming a routine investigation in patients with severe hypertension

Whichever of the several available methods is used for the test, the laboratory results must be considered in relation to the patient's clinical state, and it must always be remembered that the diagnosis is not finally established by the laboratory, but by the physician in charge of the patient This is especially the case if a full history does not accompany the urine specimen to the laboratory

In the course of urinary pressor amine estimations[2] on nearly 2000 patients, of whom 20 proved to have a phæochromocytoma, we have come across certain well defined difficulties and feel that attention should be drawn to these

We have recently found that a hypertensive lady with asthma, who used a 2% adrenaline spray, excreted sufficient adrenaline in her urine *for the result of our assay* to suggest the presence of an adrenal tumour Subsequent tests in this patient gave normal figures, while another, *non-hypertensive,* asthmatic using an isoprenaline spray was found to have an abnormal amount of noradrenaline in her urine *Patients* should clearly not be receiving any sympathomimetic drug during the collection of urine specimens for assay

Other drugs may also interfere with the test Burn[3] has shown that the pressor-amine excretion may be greatly increased in the twenty-four hours following a phentolamine test, and we consider that samples should not be collected for at least three days after this, and (until further information is available) after any similar test

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[1] Borrie P *Brit J Derm* 1952 64 357

[1] Litchfield J W Peart, W S *Lancet* 1956 ii, 1283
[2] Moulton R Willoughby, D A *Ibid* 1955, ii, 16
[3] Burn G P *Brit med J* 1953 i 697

Forssman[4] has found a considerable increase in noradrenaline output following a coronary thrombosis. We have recently found a raised noradrenaline level (to the very high figure of 0·5 µg. per ml.) in the urine of a known hypertensive who had collapsed as a result of a cerebrovascular catastrophe from which he died a few hours after the specimen had been collected. No phæochromocytoma was found post mortem. We have also found a raised noradrenaline level in the urine of a hypertensive patient who had had a subarachnoid hæmorrhage. Repeated determinations failed to confirm the original high levels and other tests did not indicate the presence of a tumour. Single high readings always require confirmation on further specimens.

So long as such limitations are appreciated, the estimation of urinary pressor amines remains the most reliable single test for a phæochromocytoma. It is the only satisfactory method for screening large numbers of patients, but the results must always be critically assessed.

Medical Unit, University College Hospital Medical School, London, W.C.1

R. MOULTON
M. L. ROSENHEIM
D. A. WILLOUGHBY

THE REMUNERATION CLAIM

SIR,—Dr. Noel Alder (Feb. 9) draws attention to a recent meeting of the Brighton and Mid-Sussex Division of the British Medical Association, where it was decided to form a local committee of the British Medical Guild which would organise our withdrawal from the National Health Service, if this action should become necessary. At this meeting a number of members advocated resignation from the service if the new Minister of Health proved to be as intransigent as his predecessor. I think the attitude of these members fairly reflected the temper of the meeting as a whole; Dr. Noel Alder, however, regards resignation as "shameless blackmail" and deplores the use of "trade-union tactics".

What would Dr. Alder have us do? Continue to watch our distinguished leaders suffer indignity and discourtesy at the hands of successive Ministers, and their permanent officials, while they plead our case? I am sure he must dislike this humiliation as much as the rest of us.

Dr. Alder, and those who think like him, should remember that the majority of the profession voted against accepting the terms of service in 1948, and those who were in favour at least believed the Spens recommendations would be adhered to. By now the most ardent advocates of the N.H.S. have their doubts, while the rest of us search for a way out or hope for reform.

I am not alone in thinking that a forced withdrawal may be our salvation; our profession should now know what to do with a second chance.

Hove, Sussex. PATRICK HALL SMITH

PRESCRIBING PHENINDIONE

SIR,—The anticoagulant drug phenindione, is familiar under the trade name 'Dindevan' as scored tablets in one strength only—50 mg., from which dosage schedules in multiples of 25 mg. may be arranged. There is now a need for a weaker strength if advantage is to be taken of the more accurate stabilisation of patients by means of Owren's modified method of estimating the "one stage prothrombin time".[5]

The advantages claimed for this method of controlling anticoagulant therapy are that it is sensitive to dosage increments of 10 mg. and thus allows stabilisation of patients whose dosage requirements do not coincide with multiples of 25 mg. Trends towards overdosage are obvious and the correct dose can often be decided two to three days earlier than with the older method.

The makers (Evans Medical Supplies Ltd.) are ready to supply a 10-mg. tablet of dindevan to meet this need. With this new strength, however, difficulties for the prescriber and pharmacist may arise.

The *British Pharmacopœia 1953* (Addendum 1955) directs that "if the quantity [of phenindione] contained in a tablet is not stated, tablets containing, in each, 50 mgm. shall be supplied or dispensed." If this directive were followed, the pharmacist would supply tablets which might be five times the strength of those intended.

So that there may be no doubt as to what should be supplied, prescriptions or orders for this drug should state the precise dose in milligrammes, or the strength of the tablet required.

United Oxford Hospitals.

ROSEMARY BIGGS
W. TRILLWOOD

SOIL, FOOD, AND HEALTH

SIR,—It is a pity that in your excellent annotation of Jan. 19 you should have fallen into the usual error of criticising organic husbandry on incorrect assumptions. In fact it does not depend on making compost; nor does it depend on *not* using mineral fertilisers; nor does it involve a reduction in the intensity of production. These fallacies arise out of a failure to appreciate the principles upon which organic husbandry is based.

Under natural conditions the fertility of the soil is dependent upon the soil organisms which, by their activities, convert the minerals, which are present in most soils in unlimited quantities, into a form in which they are available to plant life. The degree of activity of the soil organisms is dependent upon their food supply, which consists of decayed and decaying organic matter, both animal and vegetable.

The principle of organic husbandry is to exploit this mechanism to the full. This is accomplished first by making good any deficiencies in the mineral content of the soil—especially lime, phosphates, and (when necessary) trace elements—and then to feed the soil organisms so that they in turn can feed the crop. This is accomplished: (1) by deep-rooting leys which, by their extensive root system, produce a large bulk of organic matter as well as bringing up the minerals from the depths of the soil; and (2) by applying as much organic matter as possible to the surface layers of the soil, chiefly by means of the grazing animal, but also by the application of previously matured dung or compost which is more immediately available as a source of food.

The value of such applications lies not in the amount of minerals that they may contain, but as a means of feeding the soil and thus ensuring the release of the minerals that it already contains. There are a number of large scale farms in this country where no soluble mineral fertilisers are used, and little if any compost, but whose yields compare favourably with the best in the country.

Inorganic husbandry on the other hand seeks to short-circuit the natural process by supplying the necessary minerals in a soluble form that is immediately available to plant life. It is based on the presumption that we know exactly what minerals, including trace minerals, any crop requires; in what form, and in what balance—and that even if we don't it doesn't much matter.

Now that it is becoming increasingly recognised how many states of ill health are basically deficiency diseases, even including some infective processes, the above assumptions appear to be at least highly questionable from the medical point of view.

Although it is true that high yields can be forced easily and fairly cheaply by the use of soluble mineral fertilisers, it is also true that the products so grown are different in their chemical composition from those grown by natural means, and especially in the structure of their proteins. Whether such differences are harmful or not is surely a matter of vital importance to the future of preventive medicine, and we should therefore give all the support we can to research work such as that which is being carried out at Haughley

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[4] Forssman, O. *Acta med. scand.* 1954, suppl. 296.
[5] Owren, P. A. *Schweiz. med. Wschr.* 1954, 29, 822.

Keats House Guy's Hospital,
London, S E 1 T T STAMM

UNMARRIED PARENTHOOD

SIR,—The approach shown by Dr Cordeaux's letter last week is unphysiological Young men, whether they know it or not, have to experiment to discover which of the socially acceptable patterns of eating and drinking available suit them best, the need for similar experimenting in the doubly difficult (since two people have to be satisfied) field of sex must be obvious

Every branch of medicine must carry its quota of preventable tragedies, but until the adoption societies can meet all the demands they receive for children I do not feel that that of the unmarried mother is very serious, and I would prefer to ask your readers' sympathy for couples who, because they are so well aware of the responsibilities of marriage, or perhaps cannot see a way of assuming them without jeopardising a worth-while career, defer matrimony until the late 30s Many such couples, influenced by the propaganda of moral societies, abstain from intercourse in the misplaced trust that the mature affection and respect they feel for one another must lead to satisfactory physical consummation

No serious person doubts that morality is of the highest importance to any civilised society But morality is not the same as dogma, and moral agencies that dabble with sex without submitting *their dogmata to continual* scrutiny in the light of changing circumstances and increasing knowledge must carry a large share of responsibility for the divorces, delinquencies, frustrations, and ill health that spring directly from the failures in sexual adjustment

London N W 1 J F TUTHILL

X RAYS AND LEUKÆMIA

SIR,—I should like to congratulate Dr Rabinowitch on his thoughtful letters (Dec 15 and Jan 26) and also to offer some further observations of my own

It is perhaps unfortunate that Dr Alice Stewart's preliminary communication (Sept 1) on the possible relationship between malignant disease in childhood and diagnostic X rays in pregnancy received so much publicity Many doctors and—with more excuse—patients seem to have accepted headline announcements such as "X-ray Examinations as Cause of Cancer in Children" as proof that a case has been established Much apprehension has been caused and there is evidence of a growing tendency to discard one of the most valuable diagnostic procedures in the elucidation of difficult obstetric problems Personally, I can see no grounds for such fears in Dr Stewart's article, for the following reasons

1 Only 85 of the 547 cases of leukæmia or cancer were exposed to antenatal irradiation

2 45 of the 547 controls were similarly irradiated, without any known ill effects to the fœtus It is a reasonable assumption, therefore, that at least 45 of the malignant cases received a similar harmless dose of X rays This leaves only 40 (7 3%) of the 547 cases in which leukæmia or cancer might have been caused by diagnostic irradiation

3 There is reason to doubt whether Dr Stewart's cont are acceptable It is well known that X ray examinat are much more commonly performed in the first pregna than in subsequent ones, to be strictly comparable the fore the case and control groups should have b matched for parity This point was raised by Dr Ellis a Dr Lewis (Sept 15), Dr Stewart's reply being that "th were deliberately not matched for birth rank" and that "t child population dying of leukæmia and cancer nowad *includes a disproportionately large number of* first b children and twins" But, if the control group had contai a *similar* "*disproportionately* large number of first b children and twins," we should have expected *more* than of the 547 mothers to have been X rayed during pregn —perhaps even 85—in which case Dr Stewart's argu falls completely to the ground

In my opinion, Dr Stewart has provided no convin proof of any danger to the fœtus during antenatal X r examinations I would strongly suggest, therefore, th there shall be no change in the attitude of obstetric and radiologists towards X rays in pregnancy un such time as Dr Stewart completes and publishes h investigations

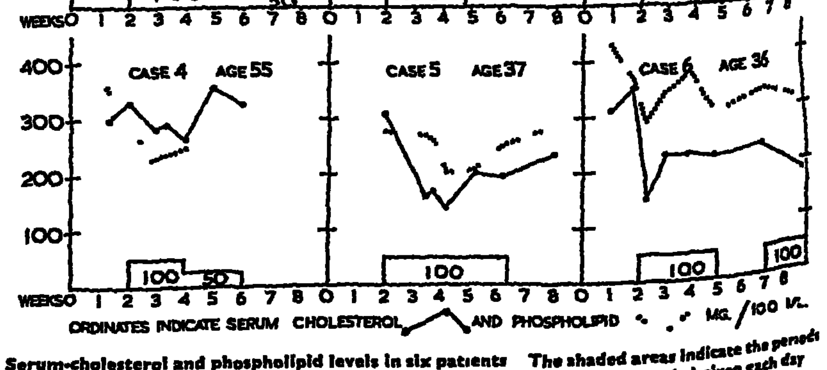
Harrogate FRANK REID

SUNFLOWER-SEED OIL AND SERUM-LIPIDS

SIR,—Bronte Stewart et al [1] reported that oral admin istration of sunflower seed oil or of a marine animal o lowers the level of cholesterol and β lipoproteins in th serum, even when a high-fat diet is taken The iodi value of the oil they used was 130-138, and its linoleic aci content 60%

We have given sunflower seed oil to six men, with occlusive vascular disease (Its iodine value was 137 5, and it contained 59 3% linoleic acid, with palmitic 5 6%, stearic 2 2%, arachidonic 0 9%, and oleic 32 0%) Al but case 4 were treated as outpatients and had been o a low-fat diet for some months previously The daily consumption of the oil (usually *100 g* in three or fou doses) and the period of administration are shown in th chart Apart from occasional diarrhœa and slight tem porary nausea there were no gastro intestinal disturb ances, and no undue difficulties in continuing the treatment

Oral administration of sunflower seed oil to this small group of patients, in whom the initial serum cholesterol



Serum-cholesterol and phospholipid levels in six patients The shaded areas indicate the periods during which sunflower-seed oil was given the figures represent the dose (g) given each day

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1 Bronte Stewart, B Antonis, A, Eales, L Brock, J F La 1956, i, 521

EFFECT OF SUNFLOWER SEED OIL ON CHOLESTEROL AND PHOSPHOLIPID LEVELS

Case	Age	Diagnosis	Serum levels before oil treatment (mg per 100 ml)		Maximum fall achieved (mg per 100 ml)	
			Cholesterol	Phospholipid	Cholesterol	Phospholipid
1	39	Angina of effort	270–323	269–288	92	Not significant
2	33	Thromboangiitis obliterans	352–400	300–320	30	Not significant
3	48	Intermittent claudication	232–258	204–257	41	75
4	55	Coronary thrombosis	300	360	64	130
5	37	Coronary thrombosis	286–370	220–300	220	97
6	35	Coronary thrombosis	290–380	238–375	167	74

and phospholipid levels were not excessively high, produced varying responses, those of cases 2 and 3 being the least striking (see table) In the others serum-cholesterol levels fell appreciably, with a tendency to rise during treatment in case 5 When the treatment was stopped (cases 1, 2, 5, and 6) or the dose of oil was reduced (case 4), these values tended to rise again promptly

In case 4, anticoagulant therapy, which had ceased only four days before sunflower seed oil was given, may have influenced the earlier cholesterol concentrations Anticoagulants had also been given in case 5—five months previously

Other patients with much higher initial serum-cholesterol and phospholipid levels have given more encouraging results with this treatment

These results correspond with those of Bronte-Stewart et al, and seem to support their suggestion that serum-lipid levels may be materially affected by the dietary intake of unsaturated fatty acids

We wish to thank Mr A D Wilson, of Unilever Ltd, who supplied the oil, together with analytical data concerning its composition We also thank Dr Robert Gaddie, biochemist, General Hospital, Birmingham, for several of the blood analyses

Queen Elizabeth Hospital
Birmingham.

G E OWEN WILLIAMS
GARFIELD THOMAS

RADIOACTIVE VITAMIN B_{12} IN THE DIAGNOSIS OF NEUROLOGICAL DISORDERS

SIR,—The most direct methods of confirming the diagnosis of subacute combined degeneration of the cord are those which demonstrate an inability to absorb vitamin B_{12} or a deficiency of it in the serum Dr Berlyne and his colleagues (Feb 9) describe a test of vitamin-B_{12} absorption which makes small demands on skill and labour, although it requires expensive apparatus

We think however, that there is more to be said for gastric analysis than Dr Berlyne and his colleagues say, and we would like to emphasise yet again the fallacies in conventional tests of gastric function

(1) The tube must be in the body of the stomach and not coiled near the cardia To ensure this it is best to pass the tube (once the tip is in the œsophagus) with the patient prone The final position should be checked either by a radiograph or, more easily, with a magnet tipped tube and compass [1]

(2) The secretory stimulus must be prolonged as well as powerful, so that where secretion is slow there is time for the antacid effect of saliva and other non acid secretions which the fasting stomach may contain to be overcome This requirement is not met by a single injection of histamine [2] We give, if necessary, four injections of 0 5 mg of histamine acid phosphate at intervals of twenty minutes

(3) Acidity is most adequately estimated with a pH meter If indicators have to be relied on it is probably better to use several One can then detect increases of acidity which, although not quite large enough to turn Töpfer's reagent (pH 3), suffice to show that secretion has occurred Nevertheless we have always been able, except in absolute achlorhydria where the pH remains between 6 and 8, to obtain samples acid to Töpfer's reagent, and we test each sample at the bedside with this indicator

We have used gastric sampling in this way in cases where subacute combined degeneration was suspected, and have had help from it similar to that which Dr Berlyne and his colleagues have had from their test with radioactive vitamin B_{12} In particular, we have demonstrated the ability to secrete acid in 3 patients who, as result of ordinary testing, had been described as having "histamine-fast achlorhydria"

We hope that Dr Berlyne and his colleagues will use a gastric test of the kind we describe in conjunction with their further studies, which may then not render gastric analysis "outmoded"

Royal Infirmary,
Cardiff

A H JAMES
C A PALLIS

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[1] James A H Lancet 1951 i 209
[2] Watkinson G James A H Clin Sci 1951 10 255

MANUAL ARTIFICIAL RESPIRATION IN THE SITTING POSTURE

SIR,—I was interested to read the article by Dr Henning Ruben (Jan 19) May I, however, query his statement that "during the intermittent flexion of the body the abdominal viscera press not only on the diaphragm but also on the vena cava, thus possibly helping to pump the blood towards the heart" Should this stimulation of the circulation be put forward in a manner suggesting that it is good treatment? Would it not tend to overload the right side of the heart which is already having difficulty in pumping blood round the inactive lungs? In such cases, stimulation of the circulation is usually recommended *after* breathing has recommenced

Ashby de la Zouch   A H M CAMPBELL

NEW DRUGS, OLD DANGERS

SIR,—Your leading article of Feb 9 wisely advises us to use a new drug "only when there is a clear indication for it, and when hospital trial has firmly established its superiority over its more familiar predecessors," adding that "then the occasional reaction is a risk that is justified"

By implication the drugs quoted have not passed these tests—phenylbutazone, probably because there are safer alternatives available, and chlorpromazine and meprobamate probably because the disability to be relieved often scarcely justifies the known risk But we wonder whether carbimazole has not a more established place? Like many widely used drugs unfortunately it is occasionally toxic, but probably less frequently than any available similar anti thyroid drug [1] one alternative (perchlorate) may be less toxic, but a full assessment of its risk is not yet available, and its different anti thyroid action gives a less satisfactory clinical control

Proper supervision of the use of such a drug should include provisions to ensure the early and full treatment of any toxic effects, and it is possible that some of the fatalities from carbimazole and similar drugs have occurred when these have failed—either when the carbimazole has not been stopped on the first symptoms [2] or when the infection complicating the agranulocytosis has not been controlled [3] To any patients given carbimazole we give clear instructions to stop taking the drug and report immediately if pyrexia, sore throat, or other unusual symptoms develop, and blood counts on these visits are essential, though of little help at other times Should agranulocytosis be discovered, as you say, "blood transfusion and penicillin are always advisable," but it is the antibiotics that matter and penicillin may not suffice If within 24–48 hours the patient is not improving, fuller antibiotic resources must be used Over previous years when treating agranulocytosis due to methylthiouracil, we have on occasion needed to add streptomycin or aureomycin to lower the fever and arrest the infection We trust that your gloomy statement that "if recovery is going to take place, polymorphs return to the blood within 2 to 3 days" will not suppress vigorous *pursuit of adequate antibiotic treatment in such patients,* for we have seen full recovery after the complete absence of polymorphs from the blood for over 12 days

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[1] Burrell C D Fraser R. Doniach D *Brit med J* 1956, i, 1453
[2] Burrell C D *Ibid* p 1456
[3] Tait G B *Lancet*, Feb 9 1957 p 303

Postgraduate Medical School
of London W 12 **RUSSELL FRASER**

Middlesex Hospital London W 1 **DEBORAH DONIACH**

CLINICAL PICTURE OF SICKLE-CELL DISEASE

SIR,—Your admirable leading article of Feb 16 on sickle cell disease contains statements on the proportions of different hæmoglobins in certain hæmoglobinopathies which might mislead pathologists in their investigations should they not be familiar with the subject

In sickle-cell anæmia the red cells contain 75–100% of hæmoglobin S and 0–25% of fœtal hæmoglobin—and not 0–25% of normal hæmoglobin A In sickle cell/hæmoglobin C disease the proportion of hæmoglobin S is greater than that of hæmoglobin C—and not about 50% each In sickle cell/thalassæmia the proportion of hæmoglobin S may vary from 25 to 90% or more, but it is true to say that the condition is symptomless and not a "disease" when the proportion of hæmoglobin S is below 50% In either case hæmoglobin A is frequently not "a small remainder" but may be present in a significant proportion

St Bartholomew's Hospital,
London, E C 1 **H LEHMANN**

CHEMICAL CARCINOGENS AND THEIR SIGNIFICANCE

SIR,—We have read with great appreciation Dr J W Cook's succinct account last week of the present status of this subject and agree with his suggestion that the study of chemical carcinogens is likely to prove one of the most profitable forms of cancer research There are, however, two statements which do not take into account all the experimentally proved facts, and which, carrying the authority of Dr Cook, may give a misleading impression

The carcinogenic hydrocarbons undoubtedly act locally at the site of direct application, but to describe this as a characteristic ignores the induction of mammary cancer by cutaneous intranasal, intraperitoneal, and intragastric administration of methylcholanthrene, and of ovarian cancer by cutaneous treatment with dimethylbenzanthracene [1–4]

The idea that the mechanism by which polycyclic hydrocarbons "transform normal cells into cancer cells" is associated with their becoming firmly attached to skin proteins cannot be easily sustained in view of the finding that such protein binding may also occur with non-carcinogenic substances of related chemical structure [5 6]

Department of Pathology
University of Birmingham **J W ORR**
D L WOODHOUSE

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1 Orr J W *J Path Bact* 1943 55 483, *Ibid* 1946 58 589
2 Marchant J Orr J W, Woodhouse D L *Nature Lond* 1954 173, 307
3 Howell J S Marchant, J Orr, J W *Brit J Cancer,* 1954 8 635
4 Shay H Aegerter F A Gruenstein M Komarov S A *J nat Cancer Inst* 1949 10 255
5 Woodhouse D L *Brit J Cancer,* 1954 8 316, *Ibid* 1955 9 418
6 Heidelberger C Moldenhauer M G *Proc Amer Ass Cancer Res* 1955 2 21

BIRTHDAYS OF SPASTICS

SIR,—Our experience certainly differs from that of Dr Bevan (Feb 16) Birthdays of the last 30 childr admitted *to this hospital* with cerebral palsy w distributed as follows January–March, 14, Apri June, 3, July–September, 15, October–December, 1

Alexandra Hospital,
Luton, Bedfordshire **H B LE**

TETRAETHYL LEAD POISONING

SIR,—The case described by Dr G L Robinson in h letter last week is not really typical of tetraethyl le *poisoning because neither a marked anæmia nor punct* basophilia are characteristic of this form of lead poison and the central nervous system is always affected

Scaling of tanks which have contained leaded pe usually results in exposure to inorganic lead salts co bined with other lead compounds which are the re of the breakdown of tetraethyl lead It would seem th the brief description of this particular case is s stantially that of ordinary lead poisoning

It should also be mentioned that lead can alw found in the urine of normal people who have had specific exposure, since this metal is invariably pres in very small amounts in the atmosphere and food of a industrial community Accurate methods of analy have proved these facts

Finally I doubt very much if any case of ordinary plumbism with normal kidney function would have *typical symptoms and signs unaccompanied* by a excretion of lead in the urine in excess of normal

Associated Ethyl Company Ltd,
Medical Services
20, Berkeley Square, London, W 1 **PHILIP BOYD**

A MISSED FRACTURE

SIR,—Dr Hunter last week suggested that my lett of Feb 2 might be taken as "a piece of sarcasm" Although I may have rather "laid it on," what I wish to do was to draw attention once again to the difficulties confronting a junior casualty officer and to suggest that everyone should not rush to criticise him every time he made a mistake It is time that some increased form of protection was afforded to these doctors in their work or there very soon won't be any

Newcastle upon Tyne **J F STOW**

SYPHILITIC AORTIC INCOMPETENCE

SIR,—Dr J C Leonard and Dr W G Smith are to be congratulated on their excellent study of the progno and effects of treatment of syphilitic aortic incompetence (Feb 2), and few people will quarrel with their main conclusions

Nevertheless their recommendation that it is probably best to give at least one full course of arsenic or bismuth to every patient, in addition to systemic penicillin requires some comment *The figures on* which this recommendation is based are, in their own words " small that it is impossible to be certain that the resul are of definite significance This does *not* seem to be a adequate reason for reintroducing in the treatment of t condition highly toxic drugs such as the organic arsenicals Severe reactions to these drugs were common, sensitivity frequently developed, and fatalities were far from rare Patients with syphilitic aortitis are usually middle aged or elderly and, in the past, proved particularly susceptible to the ill effects of this treatment

Surely, if better results are desired in the treatment of syphilitic heart-disease, it would be more reasonable to try to obtain them by increasing the dosage of penicillin up to at least 8–10 mega units, by giving a course of intramuscular bismuth, and possibly by repeating the course of penicillin on one or more occasions

I believe most physicians who have treated such patients, and all with any extensive experience of senical therapy, consider that there is now no indication r the use of these dangerous drugs in the treatment of philis

Whitechapel Clinic
London Hospital, E 1

J K OATES

ANTIMALARIALS AND RHEUMATOID ARTHRITIS

SIR,—Dr Allison and Dr Ray Bettley (Feb 9) are to congratulated on drawing our attention to chronic leg ceration in rheumatoid arthritis and suggesting that rhaps this association is not rare They show underandable caution in their interpretation of the finding of E cells in 4 of their 6 patients who otherwise would ave been regarded simply as suffering from long standing eumatoid arthritis, with rheumatoid nodules and ippling deformities to substantiate the diagnosis

Pathologists now have sufficient experience to enable em to identify L.E cells which would be acceptable as ch to their colleagues The significance of this cell is ow being freely discussed between them and clinicians, ; the cell specific to lupus erythematosus or not ? While his controversy is pursued, I must point out that patients ith rheumatoid arthritis are being crippled now linicians accept the value of chloroquine and certain ther antimalarials in disseminated lupus erythematosus urge them to try these drugs in rheumatoid arthritis have shown that they are of value in a short-term ontrolled investigation[1] and am endeavouring to stablish their long-term value, of which I am convinced n clinical grounds

Hackney Hospital
London E 9

A FREEDMAN

*** We discuss Dr Freedman's trial of chloroquine in n annotation on p 414 —ED L

ERYTHROCYTE-POTASSIUM LEVELS IN RHEUMATOID ARTHRITIS

SIR,—I was interested to read the preliminary communication by Dr Knudsen and Mr Thomas (Feb 2)

We are carrying out a similar investigation here in connection with the use of adrenal corticoids in chest disease Our method is likewise to calculate the erythrocyte potassium level from the whole blood-potassium and the hæmatocrit value, using heparinised venous blood and undertaking the estimations with as little delay as possible, although with different dilutions (1 in 500 for whole blood-potassium and 1 in 50 for plasma potassium samples) The group we have analysed so far consists of patients with pulmonary tuberculosis, who are symptom free but are receiving chemotherapy 69 estimations have been made in this group, with a mean erythrocyte potassium level of 105 m eq per litre The distribution of values around the mean fits very closely the pattern of a normal (Gaussian) curve, with a standard deviation of 5 m eq per litre We have to date found a negative correlation between the erythrocyte-potassium levels and hæmatocrit readings (r = –0 57) We are also investigating a normal control group, consisting of hospital staff and patients with chest disease who are receiving adrenal corticoids

Clare Hall Hospital
South Mimms Barnet

S GILLIS

"WINTER VOMITING DISEASE"

SIR,—I read the paper by Dr Haworth and his colleagues[2] with great interest and would like to refer to my own experience[3]

In an agricultural settlement, with a population of 1400 102 cases occurred during the three summer months of 1954, 83 of the patients were children up to 16 years of age and the age group particularly involved was the 3–6 year olds

The illness was principally characterised by sudden onset, vomiting, extremely severe headache, vertigo, meningism, temperature up to 38 5°C, absence of any other complications, and rapid recovery A lumbar puncture in a 5 year old girl with a definite Kernig's sign and absent knee jerks showed 21 cells per c mm, 28 mg protein per 100 ml, and no organisms Adults particularly complained of "pressure behind the eyes" and very severe headache Because of dizziness, which persisted for up to three days, the patients scarcely dared to turn the head A few patients had a mild relapse after six or seven days The incubation period was probably seven days

We, too, were unable to detect the causal agent In the same year cases of West Nile fever were reported in Israel Investigation was made in this direction, but with negative results

Ein Harod, Israel

A KALLNER

DISCREPANCIES IN THE ERYTHROCYTE-SEDIMENTATION TEST

SIR,—The discrepancies in the E S R test in rheumatic fever found by Dr Alexander and Mr Andrews (Feb 2) have been fully described by, among others, Enocksson et al,[1] Wilander,[2] Strom,[3] von Kaulla,[4] Nielsen,[5] and Oestner[6] I found the same phenomenon during a study of the E S R in defibrinated and undiluted blood[7]

Oestner explains its occurrence as follows

> In undiluted blood, in which the content of fibrinogen, globulin, and erythrocytes is greater than in diluted blood, particularly when the absolute values of protein are high, such large aggregates of erythrocytes are formed that these can close off completely the lumen of the sedimentation tube The sedimentation process is thus impeded, Sometimes, when an aggregate breaks loose, sedimentation can then continue, giving rise to characteristic forms in the sedimentation curve, which are not found when diluted blood is used

Naturally this phenomenon is not specific to any particular disease

Wilhelmina Gasthuis
Amsterdam Netherlands

A S GROEN

TREATMENT OF DISSEMINATED SCLEROSIS WITH ACTIVE AND INACTIVE DRUGS

SIR,—Seyffert[8] reported the results of treating disseminated sclerosis with phenothiazine derivatives The effect in the chronic cases was good, spastic symptoms were especially relieved I have compared the effects of a similar derivative, 'Lacumin' (*n*-methylpiperidyl 3-methylphenothiazine), with those of a placebo in 90 patients suffering from the disease

There were 33 men and 57 women, aged 24–64 years (mean 40 2) For several years they had all belonged to a special disseminated sclerosis society in Gothenburg The diagnosis was established by examinations at the neurological clinic in 54 cases The others had previously been examined at out patient departments by neurologists or in connection with the present investigation The duration of the disease varied between 2 and 30 years (mean 9 4) The degree of disability varied from slight dysfunction (slight weakness and disturbances of gait mild eye symptoms) to pronounced disturbances of gait and inability to move except in a wheel chair Most patients needed crutches All had been told about the nature of their disease Most had tried various remedies As a rule the patients kept in touch with each other, and had meetings once a month

At first lacumin was given to one group of patients After some time a rumour circulated that these tablets had unpleasant side-effects The placebo (which was called 'Lacumin P') was then introduced as a drug which had exactly the same effect as the lacumin tablets, but no side effects At the same time it was pointed out that the side effects were not serious

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[1] Ann rheum Dis 1956 15 251
[2] Haworth J C, Tyrrell D A J, Whitehead J E M Lancet 1956 ii 1152
[3] Kallner A Harefuah Aug 15 1954

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[1] Enocksson B, Gjertz A, Schnell A, Torgersrund T Acta med scand 1936 88 435
[2] Wilander O Ibid 1938 94 258
[3] Ström J Ibid 1938 96 365
[4] von Kaulla K N Ibid 1939 98 374
[5] Nielsen G Ibid 1942 111 66
[6] Oestner K Ibid 1942 suppl 127
[7] Thesis Amsterdam 1953
[8] Seyffert H M Münch med Wschr 1955 97 1623

All the patients were examined neurologically before the tablets were distributed In most cases, a similar control examination was performed at the end of the treatment 12 patients could not attend in person, but sent a detailed report (by filling in a questionnaire) about their condition The dose of both drug and placebo was 1 tablet (50 mg) 4 times a day—i e , that used by Seyffert[8] The treatment lasted about 4 weeks with each type of tablet

No definite objective changes in the neurological condition could be found in any patient with either lacumin or lacumin P The most manifest result was that most of the patients had side effects with lacumin resembling those of atropine, such as tiredness, difficulty in accommodating, and dryness in the mouth In many cases we had to reduce the dose after 1–2 weeks' treatment to 1 tablet twice a day or even 1 tablet at night

Table I shows that most patients found that their condition was made worse by lacumin (general impairment of function with reduced ability to move and tiredness) Those who had improved stated that they were more agile, they slept better, their balance had improved, and they had less trouble with micturition Amelioration and exacerbation seemed independent of the severity of the disease, and of the symptoms When the lacumin was stopped, the side effects disappeared, but the amelioration or exacerbation of the disease remained for some time

TABLE I—RESULTS OF TREATMENT OF DISSEMINATED SCLEROSIS WITH LACUMIN AND PLACEBO (LACUMIN P)

Subjective effect	Lacumin	Lacumin P
Only side effects	8	
Better	13	35
Worse	47	2
No effect	15	18
Total	83	55

TABLE II—RESULTS OF TREATMENT OF 48 PATIENTS WITH DISSEMINATED SCLEROSIS WITH LACUMIN AND PLACEBO (LACUMIN P)

Subjective effect	Lacumin	Lacumin P	Total
Better	8	32	40
Worse	34	2	36
No effect	6	14	20
Total	48	48	96

$\chi^2 = 45\ 6$ $P < 0\ 001$

Lacumin P in most cases gave a feeling of improvement (increased euphoria, strength, and agility) 4 patients considered lacumin P to be indispensable Only 2 said they were worse (buzzing in the ears, increased tiredness, nausea, impaired sense of balance, increased frequency of micturition, and pricking sensation all over the body)

The results in the 48 patients who received both lacumin and the placebo are shown in table II The placebo gave a better result than lacumin, and this tendency was statistically highly significant

We must be especially critical when estimating the therapeutic effect of a drug in patients with disseminated sclerosis Spontaneous variations are common, and most of them must not be interpreted as the effect of the treatment The results of this investigation show that lacumin helped in few cases and the improvement could not be objectively verified As a rule, the side effects of the drug were pronounced, in many cases the drug had to be stopped In most cases, however, a small dose of lacumin had a favourable, slight sedative effect

The results show in a convincing way that subjective improvement can be obtained by treatment with a substance which is, pharmacologically, completely inactive This was probably because the patients strongly believed in the new treatment, and it could easily be believed that the placebo tablets were better than lacumin as they had no side effects The patients *belonged to a society and many kept in touch with each other, which may have led to suggestive influence*

Neurological Clinic,
University of Gothenburg, Sweden LARS-H BLOMBERG

Parliament

The Exchequer and the Local Authorities

ON Feb 12 Mr HENRY BROOKE, Minister of Housing and Local Government, announced that the Government had completed their review of local-government finance and outlined the conclusions which they now propose *to put before the local authorities*

The Government's proposals, he said, were designed to strengthen the local-government system In doing this it was essential to improve the financial relationship between the central Government and local authorities The ratio between Exchequer grants to local authorities and their revenue from local rates, which thirty years ago was 1 to 2 was now 6 to 5 Not only had this remarkable shift reduced the financial independence of local authorities and their degree of direct responsibility to their own ratepayers, in addition, much of the Exchequer aid was on a percentage basis towards the expenditure incurred on specific services Percentage grants, whatever their merits, carried two disadvantages First, there might be danger of excessively detailed central supervision over spending, secondly, there was no certainty from year to year what the Exchequer might be asked to contribute He was sure that the greater the independence of local authorities in the raising and the spending of their money, the better for the good health of local government The Government, after a thorough investigation, did not think it practicable to devise a satisfactory new source of local revenue Nor did they believe it right to earmark for the direct benefit of local authorities any tax that was now levied nationally Rates were in this country a well established instrument of local taxation There were still some difficulties to be overcome in the rate system, but it provided a sound basis for local finance, and no better system of local taxation has been propounded

After describing the proposed changes in the rates to be paid by industry and freight transport, Mr Brooke went on to discuss the financial relationship between the Exchequer and local authorities Here a major recasting was intended which would entail a radical revision of the structure of Exchequer grants, as well as some reduction of the grants to take account of the new rate income With a few exceptions, specific grants would be replaced by a general grant of an amount fixed in advance for a short period of years, though not necessarily at the same level for each year of the period The general grant would be distributed to all county and county borough councils in England and Wales, and to county and town councils in Scotland, by reference to objective factors (mainly of *weighted population*) which were readily ascertainable and afforded a fair and reasonable measure of the relative needs of each authority

With this change, local authorities would acquire a great increase of responsibility in determining the money to be spent on the various services, in accordance with local needs Local government would become more truly local The Government's aim was to foster and stimulate a vigorous and independent local government, and to give members of councils a greater incentive to take a lively interest in their local expenditure by placing much *more of it under their own control* Under the proposals the Government had in mind, the amount of general grant-in-aid, not tied in any way to individual services, would, at present levels of expenditure, rise from less than one-sixth to close on two-thirds of the total Exchequer grants to local authorities

A Chance to Reconsider Retirement

One of the provisions of the National Insurance Bill, the text of which was published on Feb 15, allows retirement pensioners (men under 70, women under 65) who decide to go back to work to revoke their declaration of retirement They will then be eligible to earn pension increases against their final retirement

QUESTION TIME

Onset of Surtax

Mr John Hall asked the Chancellor of the Exchequer what as his estimate of the gross salary which in 1938 would ive given a married man with two children the same purhasing value after tax as he received today from a gross lary of £2000—Mr J Enoch Powell replied For a arried man with two children a gross salary of about £620 1938–39 would have given about the same purchasing power, ter tax, as a salary of £2000 at the present time Mr Hall. oes the Minister think that a level of purchasing power of 320 is the right level at which to start surtax? Is he aware hat it is because we in this country have the highest taxation the Commonwealth on brains that so many of our able oung men and women are thinking of emigration?—Mr owell The starting level for surtax is a matter for the udget which I cannot anticipate

Prescriptions in Dermatological Clinics

Mr Philips Price asked the Minister of Health whether e was aware that in dermatological clinics throughout the ountry the average prescription requiring more than one reparation is higher than any other type of clinic, and hether, in view of the heavy burden that this puts on atients suffering from skin trouble in comparison with other ypes of cases, he would abolish making a charge of 1s on ll items in excess of a certain figure—Mr Dennis Vosper eplied My information is that there is some tendency for he average number of items for these prescriptions to be igher than the general average, but I am not satisfied that any special action is needed in addition to the existing arrangements to give assistance when it is required.

Prescription Charges

Mr H E Randall asked the Minister of Pensions and National Insurance how much of the Supplementary Estimate of the National Assistance Board is due to National Health prescription charges—Mr J A Boyd Carpenter replied About £150,000

Composite Packs

Mr Ness Edwards asked the Minister what were the composite packages now issued on one prescription—Mr Vosper replied The undermentioned sets of apparatus or dressings, each of which includes two or more articles, may be ordered as one prescription

Atomiser
Colostomy apparatus
Douche
Hypodermic syringe
Smog mask
Multiple pack dressing
Perfusion fittings
Suprapubic belt
Higginson s enema syringe
Urine sugar analysis set
Vaporiser

Dental Students

Mr M R Kimball asked the Minister how many dental students began their training in 1954, 1955, and 1956, and to what extent the number of students fell short of the future needs of the profession?—Mr Vosper replied The numbers who started the first year of their professional course at English dental schools in the academic years 1954–55, 1955–56, and 1956–57 were 381, 494, and 509 respectively the Committee on Recruitment to the Dental Profession estimated that Great Britain needed 800 new dentists each year, of which, on the basis of present distribution, the share of England and Wales would be about 700

Dental Hygienists

Mr D K Freeth asked the Minister what progress had been made with the training of ancillary dental workers.—Mr Vosper replied More than 200 dental hygienists have been trained for employment in the Forces and in the public dental service and hold my certificate of efficiency, further arrangements for the training of dental hygienists are held up until the General Dental Council have made regulations to widen the scope of their employment

Foreign Dentists

Mr N A Pannell asked the Minister when regulations would be introduced which would make it possible for those foreign dentists whose degrees or diplomas are not as yet accepted as sufficient qualification for registration to qualify by special examination—Mr Vosper replied The General Dental Council has submitted regulations to the Privy Council for approval An amendment of the regulations to accord with the views of Parliament that the examination might be mainly practical has been suggested to the council for consideration at its next meeting on March 27 and I hope it will then be possible for the regulations to be approved and introduced

Increases for War-disabled Pensioners

Mr Henry Hynd asked the Minister if he was aware that the recent award of special age allowance to war pensioners is being deducted from their National Assistance payments, and whether this is done by his authority—Mr Boyd-Carpenter replied In the case of war disability pensioners receiving National Assistance who qualify for the special age allowance, 20s of the pension will already be disregarded in the assessment of their resources for National Assistance purposes The amount by which a pension exceeds 20s is taken into account by the National Assistance Board in accordance with the National Assistance Act

Institutional Confinements

During 1955 the number of institutional confinements in England and Wales was 440,857, which was 64 75% of the total

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Obituary

PERCIVAL HARTLEY

Kt C B E, M C, D.Sc Lond, F R.S

Sir Percival Hartley, who died in London on Feb 16 at the age of 75, had been associated with medicine from the time he joined the Lister Institute in 1906, and had made substantial contributions to the work of the profession

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Those privileged to have known Hartley will always remember him by his friendliness, courtesy, and modesty, All the patients were examined neurologically before the tablets were distributed In most cases, a similar control examination was performed at the end of the treatment 12 patients could not attend in person, but sent a detailed report (by filling in a questionnaire) about their condition The dose of both drug and placebo was 1 tablet (50 mg) 4 times a day—i e, that used by Seyffert [8] The treatment lasted about 4 weeks with each type of tablet

No definite objective changes in the neurological condition could be found in any patient with either lacumin or lacumin P The most manifest result was that most of the patients had side effects with lacumin resembling those of atropine, such as tiredness, difficulty in accommodating, and dryness in the mouth In many cases we had to reduce the dose after 1–2 weeks' treatment to 1 tablet twice a day or even 1 tablet at night

Table I shows that most patients found that their condition was made worse by lacumin (general impairment of function with reduced ability to move and tiredness) Those who had improved stated that they were more agile, they slept better, their balance had improved, and they had less trouble with micturition Amelioration and exacerbation seemed independent of the severity of the disease, and of the symptoms When the lacumin was stopped, the side effects disappeared, but the amelioration or exacerbation of the disease remained for some time

TABLE I—RESULTS OF TREATMENT OF DISSEMINATED SCLEROSIS WITH LACUMIN AND PLACEBO (LACUMIN P)

Subjective effect	Lacumin	Lacumin P
Only side effects	8	
Better	13	35
Worse	47	2
No effect	15	18
Total	83	55

TABLE II—RESULTS OF TREATMENT OF 48 PATIENTS WITH DISSEMINATED SCLEROSIS WITH LACUMIN AND PLACEBO (LACUMIN P)

Subjective effect	Lacumin	Lacumin P	Total
Better	8	32	40
Worse	34	2	36
No effect	6	14	20
Total	48	48	96

$\chi^2 = 45.6 \quad P < 0.001$

Lacumin P in most cases gave a feeling of improvement (increased euphoria, strength, and agility) 4 patients considered lacumin P to be indispensable Only 2 said they were worse (buzzing in the ears, increased tiredness, nausea, impaired sense of balance, increased frequency of micturition, and pricking sensation all over the body)

The results in the 48 patients who received both lacumin and the placebo are shown in table II The placebo gave a better result than lacumin, and this tendency was statistically highly significant

We must be especially critical when estimating the therapeutic effect of a drug in patients with disseminated sclerosis Spontaneous variations are common, and most of them must not be interpreted as the effect of the treatment The results of this investigation show that lacumin helped in few cases and the improvement could not be objectively verified As a rule, the side effects of the drug were pronounced, in many cases the drug had to be stopped In most cases, however, a small dose of lacumin had a favourable, slight sedative effect

The results show in a convincing way that subjective improvement can be obtained by treatment with a substance which is, pharmacologically, completely inactive This was probably because the patients strongly believed in the new treatment, and it could easily be believed that the placebo tablets were better than lacumin as they had no side effects The patients belonged to a society and many kept in touch w each other, which may have led to suggestive in

Neurological Clinic,
University of Gothenburg, Sweden LARS H BLOMBE

Parliament

The Exchequer and the Local Authorities

ON Feb 12 Mr HENRY BROOKE, Minister of Hous and Local Government, announced that the Governm had completed their review of local-government fin and outlined the conclusions which they now prop to put before the local authorities

The Government's proposals, he said, were desig strengthen the local-government system In doing it was essential to improve the financial relatio between the central Government and local author The ratio between Exchequer grants to local autho and their revenue from local rates, which thirty y ago was 1 to 2 was now 6 to 5 Not only had th remarkable shift reduced the financial independence local authorities and their degree of direct responsib to their own ratepayers, in addition, much of th Exchequer aid was on a percentage basis towards t expenditure incurred on specific services Percent grants, whatever their merits, carried two disadvanta First, there might be danger of excessively det central supervision over spending, secondly, there w no certainty from year to year what the Excheq might be asked to contribute He was sure that th greater the independence of local authorities in the r and the spending of their money, the better for the g health of local government The Government, afte thorough investigation, did not think it practicable devise a satisfactory new source of local revenue N did they believe it right to earmark for the direct bene of local authorities any tax that was now levied nati ally Rates were in this country a well establish instrument of local taxation There were still som difficulties to be overcome in the rate system, but i provided a sound basis for local finance, and no bett system of local taxation has been propounded

After describing the proposed changes in the rate t be paid by industry and freight transport, Mr Brook went on to discuss the financial relationship between th Exchequer and local authorities Here a major reconstru was intended which would entail a radical revision of the structure of Exchequer grants, as well as some reduction of the grants to take account of the new rate income With a few exceptions, specific grants wou be replaced by a general grant of an amount fixed in advance for a short period of years, though not necessarily at the same level for each year of the period The general grant would be distributed to all county and coun borough councils in England and Wales, and to county and town councils in Scotland, by reference to objective factors (mainly of weighted population) which w readily ascertainable and afforded a fair and reasonabl measure of the relative needs of each authority

With this change, local authorities would acqu a great increase of responsibility in determining the s to be spent on the various services, in accordance with local needs Local government would become more truly local The Government's aim was to foster and stimulate a vigorous and independent local government and to give members of councils a greater incentive to take a lively interest in their local expenditure by placing much more of it under their own control Under the proposal the Government had in mind, the amount of general grant-in-aid, not tied in any way to individual services, would, at present levels of expenditure, rise from less than one sixth to close on two-thirds of the total Exchequer grants to local authorities

A Chance to Reconsider Retirement

One of the provisions of the National Insurance Bill the text of which was published on Feb 15, allows retirement pensioners (men under 70, women under 65) who decide to go back to work to revoke their declarations of retirement They will then be eligible to earn pension increases against their final retirement

QUESTION TIME

Onset of Surtax

Mr John Hall asked the Chancellor of the Exchequer what s his estimate of the gross salary which in 1938 would ve given a married man with two children the same purasing value after tax as he received today from a gross ary of £2000 —Mr J Enoch Powell replied For a rried man with two children a gross salary of about £620 1938–39 would have given about the same purchasing-power, er tax, as a salary of £2000 at the present time Mr Hall es the Minister think that a level of purchasing power of 20 is the right level at which to start surtax? Is he aware at it is because we in this country have the highest taxation the Commonwealth on brains that so many of our able ung men and women are thinking of emigration?—Mr well The starting level for surtax is a matter for the dget which I cannot anticipate

Prescriptions in Dermatological Clinics

Mr Philips Price asked the Minister of Health whether was aware that in dermatological clinics throughout the untry the average prescription requiring more than one eparation is higher than any other type of clinic, and hether, in view of the heavy burden that this puts on atients suffering from skin trouble in comparison with other pes of cases, he would abolish making a charge of 1s on l items in excess of a certain figure —Mr Dennis Vosper plied My information is that there is some tendency for e average number of items for these prescriptions to be gher than the general average, but I am not satisfied that ny special action is needed in addition to the existing rangements to give assistance when it is required

Prescription Charges

Mr H E Randall asked the Minister of Pensions and ational Insurance how much of the Supplementary Estimate f the National Assistance Board is due to National Health rescription charges —Mr J A Boyd Carpenter replied bout £150,000

Composite Packs

Mr Ness Edwards asked the Minister what were the omposite packages now issued on one prescription —Mr osper replied The undermentioned sets of apparatus or ressings, each of which includes two or more articles, may e ordered as one prescription

Atomiser
Colostomy apparatus
Douche
Hypodermic syringe
Smog mask
Multiple pack dressing
Perfusion fittings
Suprapubic belt
Higginson's enema syringe
Urine sugar analysis set
Vaporiser

Dental Students

Mr M R Kimball asked the Minister how many dental tudents began their training in 1954, 1955, and 1956, and o what extent the number of students fell short of the future eeds of the profession?—Mr Vosper replied The numbers who started the first year of their professional course at English dental schools in the academic years 1954–55, 1955–56, nd 1956–57 were 381, 494, and 509 respectively, the Committee on Recruitment to the Dental Profession estimated that reat Britain needed 800 new dentists each year, of which, n the basis of present distribution, the share of England and Wales would be about 700

Dental Hygienists

Mr D K Freeth asked the Minister what progress had been made with the training of ancillary dental workers —Mr Vosper replied More than 200 dental hygienists have been trained for employment in the Forces and in the public dental service and hold my certificate of efficiency, further arrangements for the training of dental hygienists are held up until the General Dental Council have made regulations to widen the scope of their employment

Foreign Dentists

Mr N A Pannell asked the Minister when regulations would be introduced which would make it possible for those foreign dentists whose degrees or diplomas are not as yet accepted as sufficient qualification for registration to qualify by special examination —Mr Vosper replied The General Dental Council has submitted regulations to the Privy Council for approval An amendment of the regulations to accord with the views of Parliament that the examination might be mainly practical has been suggested to the council for consideration at its next meeting on March 27 and I hope it will then be possible for the regulations to be approved and introduced

Increases for War-disabled Pensioners

Mr Henry Hynd asked the Minister if he was aware that the recent award of special age allowance to war pensioners is being deducted from their National Assistance payments, and whether this is done by his authority —Mr Boyd-Carpenter replied In the case of war disability pensioners receiving National Assistance who qualify for the special age-allowance, 20s of the pension will already be disregarded in the assessment of their resources for National Assistance purposes The amount by which a pension exceeds 20s is taken into account by the National Assistance Board in accordance with the National Assistance Act

Institutional Confinements

During 1955 the number of institutional confinements in England and Wales was 440,857, which was 64 75% of the total

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Obituary

PERCIVAL HARTLEY

Kt C B E, M C, D.Sc Lond, F R S

Sir Percival Hartley, who died in London on Feb 16 at the age of 75, had been associated with medicine from the time he joined the Lister Institute in 1906, and had made substantial contributions to the work of the profession

A Yorkshire man, he graduated with first-class honours in chemistry at the University of Leeds in 1904 From Leeds he went to the Lister Institute, on a Grocers Company research scholarship, and there obtained his introduction to biological research After two years he was appointed to the staff of the Imperial Bacteriological Laboratory at Muktesar in India, but he returned to the Lister in 1913 During the 1914–18 war he served in France with the Royal Army Medical Corps and was awarded the Military Cross

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Although Hartley's work on diphtheria was perhaps his outstanding contribution to medicine, he was also actively involved as director of the Standards Department, in many other fields, and in 1943 and 1949 we published interesting observations by him and his colleagues on the relation of such factors as shock, infection, cold, and restriction of diet to the body's capacity to produce antibody in response to an antigenic stimulus His department was responsible for preparing and maintaining many of the international biological standards and he worked untiringly in bringing these standards into effective operation on the widest possible basis He was a member of the British Pharmacopœia Commission from 1933 to 1948 and of the Medical Research Council from 1949 to 1953 After his formal retirement he worked for several years at the London School of Hygiene and Tropical Medicine and at the William Dunn School of Pathology at Oxford

Those privileged to have known Hartley will always remember him by his friendliness, courtesy, and modesty, as well as by his fervent devotion to his work He was a most valuable colleague, easy of approach and always ready to give what help he could

He married, in 1920, Olga Parnell, she died in 1950 He leaves two daughters

HARRY COOPER

Mr Cooper was the official reporter of the *British Medical Journal* and of many medical and scientific societies Many doctors who had never met him appreciated his skill, accuracy, and conscientiousness Those who had met him appreciated also his modesty, friendliness, and unfailing helpfulness

He was born at Boston, Lincolnshire, and learnt shorthand while he was still a child, for his father was an enthusiast and used it for all his business records Harry Cooper came to London at the beginning of the century to work with the Amalgamated Press, and his first job was to report the funeral of Queen Victoria In his spare time he did free lance work, and one of his first clients was a small camera club This contact led to his doing some reporting for the Royal Photographic Society, and this in turn led to his becoming reporter to the Röntgen Society (now the British Institute of Radiology) This appointment was his introduction to the medical profession In 1907 he attended his first annual representative meeting of the British Medical Association, in the next fifty years he missed only one

From then on much of his work was for the medical profession He was reporter for the Royal Society of Medicine, Medical Society of London, Hunterian Society Royal Medico Psychological Association, Medical Society for the Study of Venereal Diseases, Ophthalmological Society of the United Kingdom, Oxford Ophthalmological Congress, and Research Defence Society But he also reported for other scientific societies, for half a dozen friendly societies and in the law-courts The scope of his practice reflected the reputation he had won as a reliable reporter of technical matter and as the writer of workmanlike reports in lucid English

Though his health had been failing for several years, he carried on with his work The last meeting he reported was the session of the General Medical Services Committee in November He died on Feb 14 at the age of 76 He leaves a widow and a daughter

Appointments

EDWARDS J R G, M B Lond, F R C S assistant plastic surgeon, Royal Victoria Infirmary and plastic surgeon with the Newcastle Regional Hospital Board

EVANS MARGARET M B Dubl, D P H senior M O for mental health Derbyshire

GORRIE G McL M B Glasg, D P H deputy M O H and school M O Hastings

MURRAY, B T A M B N U I D C H, D P H assistant M O H and assistant school M O Oldham

SHERRATT T W M R C S, L D S assistant M O H and assistant school M O Oldham

WATT JOYCE D M B Lond, D OBST D C H assistant M O H, and assistant school M O, West Bromwich

The Hospital for Sick Children, Great Ormond Street, London

COTTOM D G M A B M Oxfd M R C P resident assistant physician

LAIRATT, I D M R C P part time senior registrar skin department

HAYNES JOHN I M B Leeds assistant resident M O, Tadworth

HOWITT R G B M Oxfd M R C P part time senior registrar, skin department

STROUD C J M B Wales M R C P D C H medical registrar and pathologist

Colonial Appointments

ARNAUD J D M B D C P superintending M O bacteriological laboratory health department Trinidad

BEECHER J L L M S S A resident M O, Kenya

BISHOP H S A M B Edin M O (grade B), health department (institutions) Trinidad

BOOTS MARY M M B N U I assistant bacteriologist, Barbados

BOYD P I M D Lond D P H D D M S British Guiana

GRAY A M B Durh deputy chairman of the silicosis medical bureau Northern Rhodesia

HETREED A W J M B Lond T D D senior specialist Federation of Nigeria

McDONALD W R M B E M B Lond D T M & H deputy director of medical services Fiji

MORGAN R C M R C S assistant M O Princess Margaret Hospital Bahamas

SIVAM K L M S D P H senior port health officer Singapore

TELFER J M B Glasg M O Northern Nigeria

WALCOTT J I M B Glasg D T M & H bacteriologist and pathologist Barbados

Diary of the Week

FEB 24 TO MARCH 2

Monday, 25th

UNIVERSITY COLLEGE LONDON, Gower Street, W C 1
5 30 P M Mr T S Work, D SC Biochemical Approach to the Problems of Protein Synthesis (Second of two lectures)

POSTGRADUATE MEDICAL SCHOOL OF LONDON, Ducane Road W 12
4 P M Prof M L Rosenheim Pyelonephritis

MANCHESTER MEDICAL SOCIETY
8 P M (Medical School, University of Manchester) *General Practice* Dr J S Johnston, Dr Raymond Jud Evils and Benefits of Sea Transport on Disease

Tuesday, 26th

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields W C 2
5 P M Prof D F E Nash Congenital Spinal Palsy—the Management of Incontinence (Hunterian lecture)

ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W 1
8 P M *Medicine* Prof J H Burn F R S Dr Richard Doll Dr Neville Oswald Pharmacological and Medical Aspects of Smoking

ST MARY'S HOSPITAL MEDICAL SCHOOL, Paddington, W 2
5 P M Dr Peter Bishop Problems of Intersex

BRITISH POSTGRADUATE MEDICAL FEDERATION
5 30 P M (London School of Hygiene and Tropical Medicine, Keppel Street, W C 1) Prof J B Duguid Arterial Occlusion

ROYAL ARMY MEDICAL COLLEGE, Millbank, S W 1
5 P M Prof W Melville Arnott Physiological Features of Emphysema

INSTITUTE OF DERMATOLOGY Lisle Street W C 2
5 30 P M Mr B E D Cooke Disorder of Buccal Mucosa

ROYAL STATISTICAL SOCIETY
5 30 P M (Westminster Medical School, Horseferry Road S W 1) *Medical Section* Mr D J Newell, Dr A T Ilde Provision of Hospital Beds

Wednesday, 27th

ROYAL SOCIETY OF MEDICINE
5 P M *Endocrinology* Dr E B Astwood, Dr L T Samuels, Dr M Sonnenberg, Prof C J O R Morris Hormones in Blood

POSTGRADUATE MEDICAL SCHOOL OF LONDON
2 P M Dr J H Humphrey Biochemical Mechanisms Underlying Hypersensitivity Reactions (Second of two lectures)

INSTITUTE OF DISEASES OF THE CHEST, Brompton S W 3
5 P M Mr Vernon Thompson Surgery of Mitral Stenosis

INSTITUTE OF DERMATOLOGY
5 30 P M Dr Phyllis Wade Radiation Treatment of Skin Cancer (Second of two lectures)

BIRMINGHAM MEDICAL INSTITUTE 154 Great Charles Street
8 P M *Psychiatry* Dr Stephen Taylor Psychiatry and Politics

MANCHESTER MEDICAL SOCIETY
4 30 P M *Medicine* Prof Wilfrid Gaisford Future of Pe (Presidential address)

Thursday, 28th

ROYAL COLLEGE OF SURGEONS OF ENGLAND
5 30 P M Dr D B Fry Speech and Language

ROYAL SOCIETY OF MEDICINE
8 P M *Urology* Mr W M Borthwick, Dr W G Wimsett, Mr Arthur Jacobs Mr H G Hanley Modern Trend in Treatment of Genito-urinary Tuberculosis

BRITISH POSTGRADUATE MEDICAL FEDERATION
5 30 P M (London School of Hygiene and Tropical Medicine) Prof Hans Grüneberg, F R S *Localisation of Inherited Diseases in the Body*

INSTITUTE OF DERMATOLOGY
5 30 P M Dr Henry Hobbs Cutaneous Manifestations of Syphilis

NUFFIELD ORTHOPAEDIC CENTRE
8 30 P M (Wingfield Morris Orthopaedic Hospital, Oxford) Mr O J Vaughan Jackson Surgical Aspects of the Rheumatoid Hand

LIVERPOOL MEDICAL INSTITUTION 114 Mount Pleasant, Liverpool 3
8 P M Dr A B Christie Prof A W Downie F R S Mr G J Thomas Dr J R Esplen Poliomyelitis

UNIVERSITY OF ST ANDREWS Queen's College Small's Wynd Dundee
5 P M Prof C A Wells Diaphragmatic Hernia and Related Conditions

Friday, 1st

ROYAL SOCIETY OF MEDICINE
10 30 A M *Otology* Mr T E Cawthorne Some Points on the Technique of Temporal Bone Surgery Dr C A Hutchinson Interdependence of the Lar Dr
2 30 P M *Laryngology* Mr A Young, Dr C S Hall Dr Lionel Wolman Larynx in Rheumatoid Arthritis Dr C P Wilson Choanal Atresia
5 30 P M *Anaesthetics* Dr Andrew Doughty Mr Keith Rotter Anaesthesia for Adenotonsillectomy

POSTGRADUATE MEDICAL SCHOOL OF LONDON
10 A M Mr A Dickson Wright Intestinal Obstruction
4 P M Dr J N Morris Epidemiology of Coronary Heart Disease

ST MARY ABBOTS HOSPITAL Marloes Road Kensington W 8
6 P M Mr Simson Hall Mobilisation Operation in the Treatment of Otosclerosis (James Yearsley lecture)

BRITISH TUBERCULOSIS ASSOCIATION
4 30 P M (26 Portland Place London W 1) Dr Thor Simpson Mr N R Barrett Mr T Holmes Sellors Acute Emergencies in Chest Medicine

ROYAL MEDICO-CHIRURGICAL SOCIETY OF GLASGOW
8 30 P M (Royal Faculty of Physicians and Surgeons of Glasgow) Dr A T Doig Prevention of Industrial Diseases

Notes and News

A BIRTHDAY TRIBUTE

On Feb 22 Sir Gordon Holmes consulting physician to the National Hospital, Queen Square, is 80 In opening the celebrations at the unveiling of his portrait on Feb 7 Dr Macdonald Critchley said that the physicians at Queen Square had felt that the reissue of some of Sir Gordon's work in a monograph[1] was not enough to mark the occasion, and Mr Harold Knight, R A, had been commissioned to paint a portrait to hang in the medical school of the National Hospital Former residents and students from all over the world had contributed The artist unhappily could not be at the unveiling, though Dr Critchley welcomed his wife, Dame Laura

Sir Francis Walshe described Sir Gordon as "the greatest teacher of clinical neurology of our time," and congratulated Mr Knight, who had "so cunningly and beautifully captured and put on canvas for us the inward spirit and the outward seeming of Gordon Holmes" Describing himself as one of Sir Gordon's oldest pupils, and a friend of nearly fifty years' standing, he paid tribute to his lessons in accurate observation and faithful and methodical recording Many distinguished neurologists in North America were proud to recall how they had striven and suffered on his ward rounds while serving as his clerks, for to suffer and to strive were among the necessary conditions for the acquisition of knowledge

Sir Francis then unveiled the portrait, and Sir Ernest Gowers, chairman of the committee of management, accepted it on behalf of the medical school

UNIVERSITIES AND PARLIAMENT

The House of Commons' Committee of Public Accounts have repeatedly declared their uneasiness at the degree of freedom allowed to the University Grants Committee in its allocation of the funds put at its disposal by Parliament The Treasury, to its credit, has long resisted additional control of the U G C,[2,3] and it has now refused its concurrence in the recommendation that papers and records relating to non recurrent grants should be open to inspection by the Auditor General[4]

The Exchequer's subvention (the Treasury points out) would fail in its object if the independence of the universities were damaged by the imposition of Government control over academic policy or academic standards This unique relation between the Government and the universities calls for financial arrangements which are also unique 'It is clear that if the Government and Parliament are to abstain from the sort of control which would normally follow from the grant of such considerable sums of public money, while at the same time being unwilling to make grants without any condition as to their allocation and use, there must be a devolution of some of the functions of Government to some body standing between the Government and the Universities, and enjoying the confidence of both" The U G C has been appointed to this rôle and the Treasury has complete confidence in the U G C 's determination and ability to discharge its functions with a full sense of responsibility both to the Government and to the universities

At the same time, the U G C and the universities recognise that the obligation to observe the strictest canons of economy and financial propriety apply with even more than ordinary force to bodies spending public money without being subject to the ordinary processes of financial control on behalf of the Government and Parliament To go some way towards the objectives of the Public Accounts Committee, the universities have agreed that in future each university and university college shall (1) formally notify its auditor of every non recurrent grant received and the purpose for which it was made and (2) ask its auditor to give a certificate in general terms to the effect that every such grant received during the accounting period was duly applied to the purpose for which it was made The Treasury expresses a hope—which will be widely shared—that the Committee of Public Accounts will be satisfied with this procedure

COST OF HOME CARE FOR THE ELDERLY

It is often said to be cheaper to keep old people in their own homes than under any form of communal care The National Corporation for the Care of Old People[1] had doubts about this, and, since no figures had apparently been published, they decided to look for a reasonable basis for estimating the actual cost of domiciliary services Details were examined in 21 cases where different services had been provided in varying amounts for old people at home The cost of each service was estimated with the help of figures given by the appropriate authorities in the area or from Ministerial statements in Parliament To make possible a direct comparison with the cost of institutional care, a figure of £2 5*s* a week representing items such as maintenance of building rent rates, fuel, provisions, and clothing, was added to the cost of the services This figure, the Corporation s report adds, may seem arbitrary but ' it can, it is thought, be justified

Estimated in this way, the cost of home care varied enormously For example, for a patient of 93 who, but for the night attendance provided, might have been in hospital, the weekly average was £9 15*s* 10*d*, for an old lady of 80, who should have been in hospital but refused to go, the cost was £8 5*s* 7*d* per week, and for 4 old ladies, described as "persons who might otherwise require part-III accommodation," the figures were £6 15*s* 6*d*, £4 7*s* £4 6*s*, and £2 14*s* The hospital costing returns for England and Wales in 1954–55 gave the weekly average inpatient cost (adjusted by the vacant bed factor) as £6 12*s* 8*d* for chronic sick hospitals and £12 6*s* for mainly general hospitals The average weekly cost of all sizes of local authority homes in the area concerned was £4 9*s* 8*d*

The governors of the Corporation do not claim that these figures finally prove the case one way or the other, but they think they do show that it is not necessarily cheaper for old people to remain at home with the help of the domiciliary services The cost and the call on available man power may be such that, on these grounds alone, institutional care would be preferable The governors hope that the publication of these figures will encourage others to make similar estimates

ATARAXICS IN NEW YORK

The Commissioner of Health of New York City asked the committee on public health of the New York Academy of Medicine to ascertain whether the present widespread use of tranquillisers was a menace to public health At present 5–10% of all prescriptions in the city are for these drugs and the proportion is increasing The committee has reported that there is no proof at present that they are a menace to public health, but it recognises the many dangers of their being taken without competent medical supervision It recommends that the sanitary code of New York city be revised to make it accord more fully with Federal rules Prescriptions for potentially harmful drugs (including tranquillisers) could then be refilled only on the order of the prescriber, which is not the case now Physicians, says the report, may be dangerously misled by the extravagant claims in the advertising of certain manufacturers, who propose far too many indications for tranquillisers and ignore their harmful effects The committee advises the city board of health to survey the advertising literature "as the first step toward bringing about improvement in it"

University of Cambridge

On Feb 9 the degree of M B was conferred on Terry Buchan and, by proxy, on A C Fernando

University of London

On Jan 30 the degree of M.D was conferred on P H Connell and J G P Hutchison

Royal College of Surgeons in Ireland

At the charter day dinner the honorary fellowship of the college was conferred on Mr T J D Lane

Bill to Restrict Sale of Alcohol in France

On Feb 13 the National Assembly voted in favour of a Bill to forbid the sale to children under 12 years old, in bars and other public places, of drinks containing more than three degrees of alcohol The Bill would also forbid the distribution or dispatch to people less than 20 years old of matter advertising any alcoholic drink

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[1] Selected Papers of Sir Gordon Holmes Edited by F M R Walshe London 1956

[2] See *Lancet* 1954 i 423

[3] *Ibid*, 1956 ii 420

[4] Committee of Public Accounts Treasury Minute H M Stationery Office 1957 Pp 20 1*s*

[1] The National Corporation for the Care of Old People Nuffield Lodge Regent's Park London N W 1 9th annual report of the Board of Governors, for the year ended Sept 30 1956

Queen's University, Belfast

Dr O L Wade, senior lecturer in medicine in the University of Birmingham, has been appointed to the chair of therapeutics and pharmacology in the university The duties of the post include charge of beds in the teaching hospital

Dr Wade, who is 35, was a scholar of Emanuel College Cambridge, and gained a double first in the natural sciences tripos At University College Hospital he was Acheson scholar and after qualifying in 1945 he held house appointments there and at Addenbrooke's Hospital Cambridge Later he was for a short time in the Medical Research Council pneumoconiosis unit at Cardiff Since 1951 he has been in the medical professorial unit at the Queen Elizabeth Hospital Birmingham *In 1954 he held a Rockefeller travelling* fellowship in medicine which he spent with Dr Robert Loeb and Dr Stanley Bradley at the Columbia Medical Center Dr Wade's *investigations have been into the hæmodynamics of the pulmonary* and hepatic circulations

Royal College of Surgeons of England

At a meeting of the council on Feb 14, with Sir Harry Platt, the president, in the chair, Sir Henry Dale, O M, was admitted as a member of the court of patrons The honorary medal of the college was presented to Lady Webb Johnson

Mr A L d'Abreu (Birmingham) and Mr E G Muir (King's College Hospital) were elected to the court of examiners for three years Mr A C McEachern (Adelaide) was elected a member of the court of examiners for one year Sir Harry Platt was appointed visitor to the first primary fellowship examination of the College of Physicians and Surgeons of South Africa The Hallett prize was awarded to Darrel Felix Weinman, of Ceylon The college agreed to a request from the University of Ceylon for a primary F R C S examination to be held in Colombo in *January, 1958*

A licence to practise was conferred on J R Anthony

Fellowships were granted in the Faculty of Anæsthetists to the following

J K Trotter, T R Bomonji, H M C Corfield, Peter Dinmore, Alan Thorogood, Morag J R Bastable, June E Brett, J B Montgomery J D Holdsworth D I Chisholm, Cecil Moss, R H Bolton Wendy A Clark Michael Rosen Frank Wilson Azmy Ragheb Boutros, T D W Davies W J Glover R P Holmes R T Pettigrew, H G Saunders, K B Holloway, James Moore R G Waterhouse, I E Purkis

At the Hunterian Festival dinner on Feb 14, Sir Harry Platt, president of the college, reported that the Nuffield College of Surgical Sciences now had eighty postgraduate students in residence, and it was to be officially opened by Lord Freyberg on April 5 By September, the third and final phase of reconstruction would be completed as a shell Two years ago hopes had been high, but now a halt would have to be called until the country came to realise that the college must be restored, extended, and maintained in order that it might fulfil its destiny as an international academy of surgery Sir Harry was responding to the toast of The College proposed by Sir Albert Richardson, past president of the Royal Academy, who spoke of that body's debt to John Hunter's brother, William, who in 1768 became the Academy's first professor of anatomy As a patron of the arts, William Hunter set an example which Sir *Albert Richardson enjoined* his hearers to follow His speech ranged widely and wittily, and the Archbishop *of* Canterbury, when he rose to reply for The Guests to Mr Lawrence Abel's toast, complained that the sermon had already been preached, for Sir Albert's observations had been marked by the exhortation, denunciation, and salesmanship which were the proper functions of any sermon More seriously, the Archbishop declared that doctors and others should think of themselves as concerned with persons—not with problems or cases Regarding people as problems led to the formulation of principles, principles must be related to people, for dehumanised principles led to slogans, and slogans were the work of the Devil Sir Ernest Finch, as Hunterian Orator, responded to Sir Russell Brock's toast

St *George's Hospital London*

Owing to rebuilding in the medical school, the postgraduate lectures in neurology and psychiatry have been cancelled until further notice

Institute of Dermatology, London

A semi permanent exhibition by Dr C D Calnan on cosmetic dermatitis, will be held at this institute, Lisle Street, W C 2 from March 4 to 25

Royal Society of Health

A sessional meeting of this society will be held on Thursday, Feb 28, at 10 A M in the Town Hall, West Bromwich, when the programme will include a paper by Dr J F Skone on the coloured worker

Army Appointment

Dr R Bodley Scott has been appointed honorary consultant in hæmatology to the Army at home, *in succession to the late* Sir Lionel Whitby

Council of Europe Medical Fellowships

The council has allocated 9 million French francs for medical *fellowships for 1957* This sum will provide for 100 "fellowship months" The duration of each fellowship will be at least 3 *months, and it* will cover subsistence, travel, and incidental expenses British applicants may obtain further information *from Mr W H Boucher, Ministry of Health,* Savile Row London, W 1 The closing date for applications is March 1

Royal Society of Medicine

Leverhulme Associates—The council of this society, through the Leverhulme Trust Fund, is able to appoint 100 of these associates each year who, without payment of any subscription, enjoy nearly all the privileges of fellows

Men and women are eligible provided that they are not already *fellows of the society, that they hold a full time clinical or* pre-clinical teaching or research appointment in a medical dental or veterinary department of a British university, and that their total income from academic or professional sources does not exceed £1500 p a Forms of application may be had from the deans of medical schools or from the secretary of the society, 1, Wimpole Street London, W 1 Applications may be made at any time but most vacancies are filled each year during the last week in March *For this reason it is advisable to apply between March 1 and 15*

Rockefeller Foundation Grants

During the last quarter of 1956 the Foundation distributed over $8 million Grants for medical education and public health amounted *to $1,064,709*, and for biological and medical research, $1,147,260

For the support of its field services in medical education and public health in 1957, the Foundation has appropriated *$371,625, an increase of more than $50,000 over* the amount appropriated for 1956 For the promotion of medical education *and public health throughout the world*, the Foundation maintains regional offices in Brazil, Chile, and India, and it is planned to open *one* in the Middle East this year if political conditions permit

Hunterian *Society*

At the Society's annual dinner, held in London on Feb 14 *Lord Luke confessed himself* a *new recruit to the* admirers of John Hunter He was proposing the toast of The Society and, *in preparation, he had* been *reading* the life of Hunter which the society's officers had thoughtfully provided for him It was a fascinating story if anyone had made a mark on his age it was John Hunter, *he* was a rebel, and there was a great affinity between rebels and pioneers The essence of research, Lord Luke thought, was not to be satisfied, and though research in industry was more in his line than medical research he had a feeling that in both campaigns the enemies were the same the war was being waged against waste, inefficiency, and high costs (or should it be high blood pressure ?) One of the common denominators of this work was a certain amount of vision John Hunter had had a lot of vision, and that was an attribute which Lord Luke would like to see more in evidence today In his reply Dr C D Coyle, president of the society, referred warmly to the work done on its behalf by Mr A *E Mortimer* Woolf Mr C R Rudolf, Mr R S Murley, and Dr C W Keson This year, *Dr Coyle recalled, was the 50th* anniversary of the first attendance of the Lord Mayor of London at the *society's annual dinner, and the toast of* The Lord Mayor and Corporation, dashingly proposed by Dr Macdonald Critchley, was drunk with enthusiasm Dr Critchley thanked the Lord Mayor, Colonel Sir Cullum Welch, for bringing zest and buoyancy to all his duties and for making so many gay and good natured contributions to our morale In his friendly remarks about the society, Sir Cullum said he was delighted that the Hunterian Oration was to be delivered in his home, the Mansion House A reference to the Whittington Hospital then brought him to the stone on *Highgate Hill* associated with his distinguished predecessor and he pointed out that it was wrong on three points *Dick* Whittington was Mayor (the office of Lord Mayor came later), he occupied *the civic chair four not three times, and there was no evidence* that he was ever knighted Mr Ian Robin dealt adroitly *and courteously with The Guests,* who were in the fortunate position of having Miss Rose Heilbron, Q C, to reply for them

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Prof W W Mushin is to address the New York State Medical Society at its sesquicentennial celebrations in February In March he is to be a visiting professor of surgery (anæsthetics) in the University of California Medical Center in Los Angeles

HYPERTENSIVE STROKES

A W D LEISHMAN
MA, DM Oxfd, F R C P
CONSULTING PHYSICIAN,
UNITED SHEFFIELD HOSPITALS

IF a patient is fated to die from hypertension, the chances are that he will do so from heart failure, uræmia, cardiac infarction, or stroke Heart-failure and uræmia can usually be forecast appreciably in advance of the event, and the risk of a cardiac infarct can only be accepted philosophically as a hazard of middle life inevitably greater in a hypertensive person A stroke, the most dreaded of all these disasters, seems to offer little or no chance of prediction, and even the cause of cerebral hæmorrhage in hypertension remains to a large extent speculative

Apart from the observation of Pickering (1955) that "cerebral hæmorrhage seems to be more common in subjects with very high pressure," the patient who has the stroke seems to have received remarkably little attention, but this perhaps is not altogether surprising, for *it* is unusual for much to be known about a hypertensive patient before he has his stroke A group of hypertensive patients under regular observation since 1946 has, however, now provided an opportunity to study, at least on a modest scale, the clinical antecedents of cerebral vascular accidents

The total number of patients in this group was 234, of whom 95 (40 6%) were men and 139 (59 4%) women The present status or fate of all of these is known, and the survivors have been regularly re examined at least annually None of the patients was aged more than 60 when first examined, only 44 exceeded this age at their last examination or at the time of their death, and in every case the diastolic pressure exceeded 100 mm Hg on the occasion of their first examination No patient in this group received effective hypotensive treatment, but this is not so reprehensible as it may seem, for during much of the time covered by these observations modern drug treatment was far from established and none of the patients was considered suitable for, or was willing to undergo, surgical treatment

During the ten years covered by this study 97 (41 4%) of the 234 patients died as a consequence of hypertension,* and stroke, which accounted for 41, was easily the commonest cause of death In addition to these 28 other patients had strokes which they survived Since, however, the particular concern of this investigation was with cerebral vascular accidents, which occur at a relatively early age, this report is confined to an analysis of the 56 patients who had a stroke before the age of 60, 31 cases in which the stroke was fatal (group I) being considered separately from 25 cases where it was survived (group II) The clinical state of all these patients having been subject to regular review up to the time of their having a stroke, it was hoped that it might thus be possible to recognise among them a common clinical pattern which would be useful in future prediction of these catastrophes

It was, however, obviously desirable that the clinical features of these two groups should be further contrasted with a "control" series of patients who had survived appreciably longer without experiencing a stroke, but, to be of any value, it was clear that this must consist as far as possible of hypertensive cases of comparable severity Accordingly the control group (group III) was limited to 32 patients with diastolic pressure of 130 mm Hg or higher who had survived unscathed an average of seven years beyond the average age at which strokes developed in the first two groups Thus three groups of patients have been compared in fig 1, which records the percentage incidence in each group of clinical features which normally provide a basis for assessing the severity of hypertensive disease

The somewhat meticulous grading of diastolic pressure seems to have been justified by events, but any classification of hypertensive patients according to blood-pressure has limitations because of the notorious instability of blood-pressure, especially in the higher ranges, though this source of error can be reduced if records are made only under "basal" conditions However, readings obtained in this way appear somewhat unrealistic and are likely to bear little resemblance to blood-pressure during hours of normal activity Consequently, throughout this study, measurements have been taken under standardised conditions of rest alone, being recorded as the average pressure in both arms, in lying and standing positions Since the influence of high blood-pressure is likely to be related to "peaks" rather than "troughs" of blood-pressure, the individual blood-pressures which form the basis of comparison in fig 1 represent the highest readings of systolic and diastolic pressure among those obtained in this manner at the first and last routine examinations of each patient

In fig 1 hearts are described as enlarged when the cardio/thoracic ratio is greater than 1 2, comparison of electrocardiograms is based on the appearance of "strain pattern", and ophthalmoscopic examinations report only the incidence of papillœdema, on the one hand, and of retinal exudates and hæmorrhages, on the other, since clinical records have not allowed more accurate differentiation of the retinal appearances The remaining points of comparison scarcely need clarification, except that the criterion for "fixed specific gravity" was failure to concentrate urine after twelve hours' deprivation of fluid, and that "family history" refers to the occurrence before the age of 70 of a stroke in a parent, a brother, or a sister Apart from records of blood-pressure the comparison is invariably based on the clinical findings either at the patient's last examination before the stroke or at the most recent routine examination in the case of the patients in group III

Results

Possibly the first impression gained from this survey is that there appears to have been justification for considering fatal and non-fatal strokes as distinct clinical entities, because analyses of these two groups of patients differ appreciably However, the main purpose in presenting fig 1 is to compare each of these groups individually with the controls, because if enlightenment is forthcoming at all it should emerge from these comparisons

Comparison of Group I with Group III (fig 1)

The following five features in particular appeared with notably greater frequency among patients in group I than in the controls

	Prevalence	
	Group I	*Group III*
Diastolic pressure exceeding 149 mm Hg	68%	18%
Gross albuminuria	29%	3%
Diminished urea-clearance	30%	9%
Papillœdema	22%	0%
Urea retention	10%	0%

Figuring also more prominently in this group were higher systolic pressures, slight albuminuria, retinal exudates and hæmorrhages, abnormal electrocardiograms, and patients of normal weight, but in all these instances the difference in prevalence was considerably less impressive It is improbable also that the higher male representation (39%) in group I has any significance, for among the total of 426 hypertensive patients attending the clinic the proportion of men was very similar to this (42%), and the dearth of men eligible for the control group was entirely due to their greater mortality from hypertensive causes other than stroke Since, however, it thus appears probable that fatal strokes at this age are equally common in both sexes, the considerable preponderance of women should not affect the validity of the control group

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* Stroke 41 uræmia 29 congestive failure 13 cardiac infarction 12 ruptured aorta 2

Although these figures unquestionably support the view *that there is an important association between very high blood-pressure and the development of a fatal cerebral vascular accident* and, in particular, have suggested that diastolic pressure of 150 mm Hg is in this respect a critical level, it is equally plain that this is not the exclusive influence, for a third of the patients have blood-pressure consistently below this level Searching therefore for other sign posts, we naturally notice the frequent appearance in these cases of signs of severe renal damage, a category which does not include loss of renal concentrating power (This is not unexpected, for this particular measure of renal impairment appears to have little prognostic importance in hypertensive disease) *It therefore seemed desirable to explore the possibility* that renal damage might be an influential factor in the absence of excessively high blood-pressure by considering first the individual renal status of the 10 patients with diastolic pressures below 150 mm Hg who died from strokes (table I)

TABLE I—RENAL STATUS OF 10 PATIENTS WITH DIASTOLIC PRESSURES LESS THAN 150 MM HG WHO DIED FROM STROKES

Case no	Diastolic pressure (mm Hg)	Albumin	Blood urea	Urea clearance	Remarks
1	149	+	Normal	Normal	
2	146	+	Normal	Normal	
3	144	+	Normal	Normal	
4	140	++	88 mg per 100 ml	25 %	
5	139	++	Normal	40 %	
6	132	+	Normal	Normal	Recurrent heart failure
7	130	–	Normal	Normal	Survived previous stroke
8	128	++	60 mg per 100 ml	30 %	
9	122	–	Normal	Normal	Survived previous stroke
10	120	–	Normal	Normal	Survived previous stroke

From the table it will be seen first that 3 patients (cases 7, 9, and 10), who were exceptional in showing the features of mild and benign hypertension, had each survived a previous stroke It seems, however, much more likely that, in these circumstances, the fatal stroke was determined by local cerebral vascular changes following infarction than that it was an expression of advanced general vascular disease If this view is *accepted, these cases should clearly constitute a category* of their own Of the remainder, cases 4, 5, and 8 were undoubtedly in renal failure when they succumbed to strokes, and the first 3 patients, each of whom retained fair renal function, showed, on the other hand, a degree of hypertension only slightly less severe than the level which has been judged rather arbitrarily to be critical. Thus there remains only 1 patient (case 6) who fails altogether to be accounted for in terms of particularly high blood-pressure or serious renal involvement There is, however, a strong suspicion that, in his case, the fatal stroke was due to massive cerebral infarction rather than to cerebral hæmorrhage, since for several years he had been an invalid with recurring attacks of hypertensive heart failure

Nevertheless, before any weight can be attached to this concept, it must clearly be tested also in relation to the control group, for, if it were found that an appreciable proportion of these patients, who, despite very high levels of blood pressure, escaped strokes also showed signs of substantial renal damage, this association would cease to have any significance However, in this respect the patients in the control group (table III) have provided a satisfying contrast, because only 1 of the 11 cases with the highest diastolic pressure in the group showed at most a noticeable degree of albuminuria Since this particular patient died at the age of 61 from cardiac infarction, one may perhaps speculate about the fate which otherwise might have overtaken him

There does therefore appear to be considerable support for the belief that signs of renal damage are second in importance only to very high blood pressure in distinguishing the hyper-

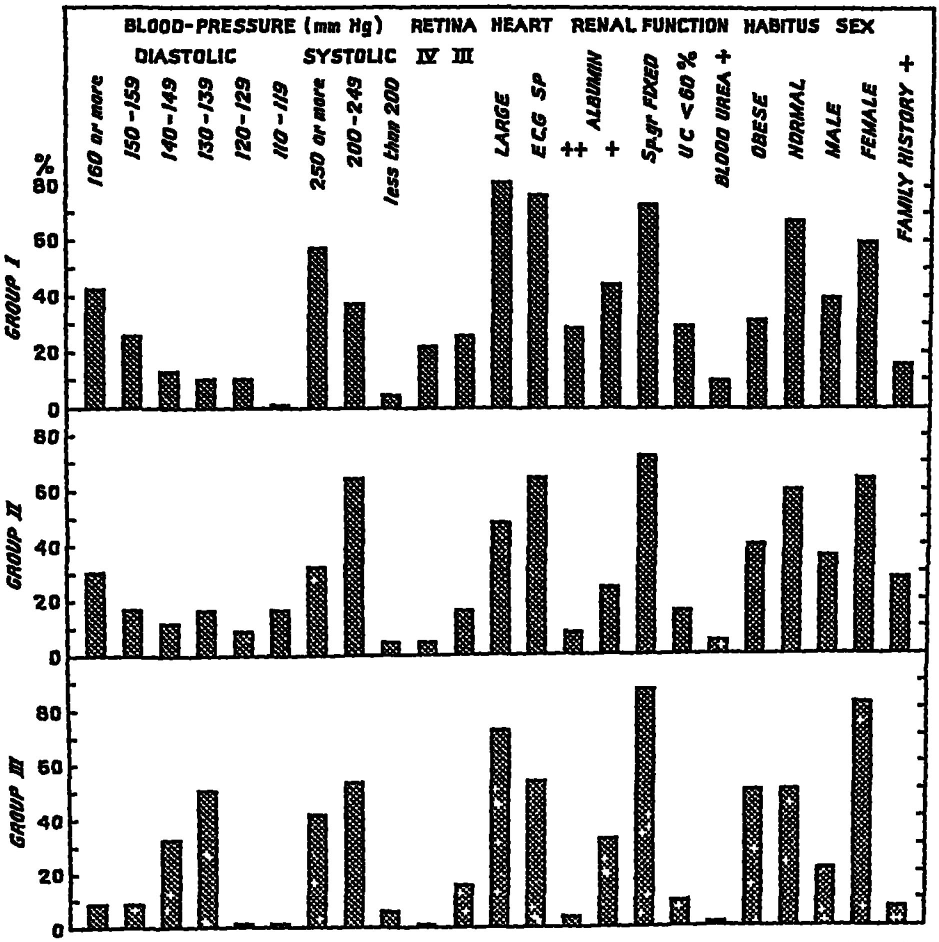

Fig 1—Analysis of clinical findings in hypertensive patients group I, fatal strokes in 31 patients (av age 50½) group II 25 patients (av age 52) who survived strokes, group III, 32 (av age 59) who had no strokes U C., urea-clearance

ensive patient who is in particular hazard of a fatal cerebral vascular accident

Apart, however, from papillœdema being seen only in patients destined to die from stroke, comparison of these two groups has revealed no other distinguishing feature, and it is important to note that, in agreement with the observations of Soloff and Bello (1948), the development of retinopathy has not appeared to have particularly sinister implications

Therefore I suggest that it is reasonable to conclude from this clinical study that (1) a fatal stroke is likely in any patient with exceptionally high blood-pressure (i e, diastolic pressure which consistently exceeds 150 mm Hg), (2) a fatal stroke may also occur when blood-pressure is somewhat lower than this if there is severe renal damage (i e, an appreciable degree of albuminuria with or without decreased urea-clearance or urea retention), and (3) there is risk of a fatal stroke at any level of blood-pressure when a patient has previously survived a stroke

TABLE II—RENAL STATUS OF 11 PATIENTS WITH DIASTOLIC PRESSURE IN EXCESS OF 140 MM HG WHO ESCAPED STROKES

Case no	Diastolic pressure (mm Hg)	Albumin	Blood urea	Urea-clearance
1	165	–	Normal	Normal
2	160	±	Normal	Normal
3	160	–	Normal	Normal
4	156	–	Normal	Normal
5	156	–	Normal	Normal
6	150	–	Normal	Normal
7	148	+	Normal	Normal
8	145	–	Normal	Normal
9	145	–	Normal	Normal
10	144	–	Normal	Normal
11	142	–	Normal	Normal

Comparison of Group II with Group III (fig 1)

In contrast to the previous comparison there appears to have been remarkably little difference in the clinical character of these two groups of patients The incidence of severe diastolic pressure (150 mm Hg or higher) was again notably higher in group II (46% compared with 18%), but no real significance can be attached to this, because the remainder of the cases in this group were evenly distributed throughout the lower ranges of blood pressure and a quarter of these patients had a diastolic pressure lower than that of any of the controls Since the highest grades of systolic pressure also were more prevalent among the controls, it must be concluded that the occurrence of this type of stroke is uninfluenced by blood-pressure

Signs of renal damage were no more evident in group II than among the controls, nor at any other point of clinical comparison was there any real difference between these groups However, patients who subsequently had a stroke provided a family history of such occurrences four times more often than did those who had so far escaped

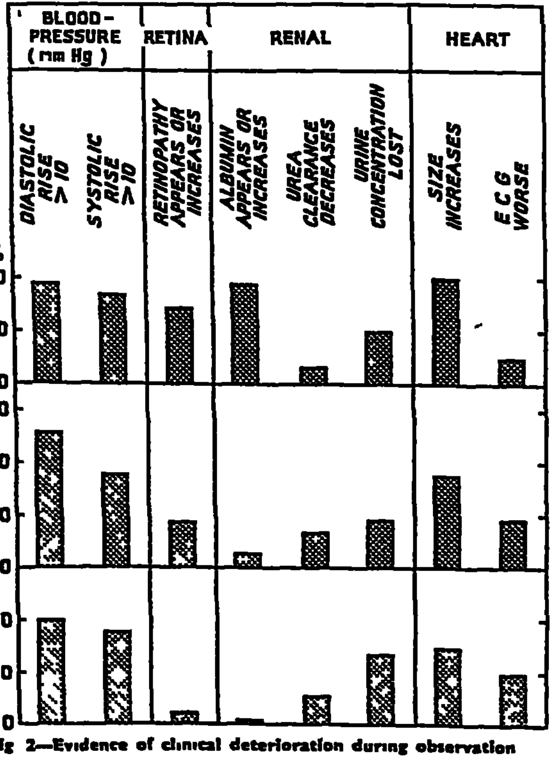

Fig 2—Evidence of clinical deterioration during observation

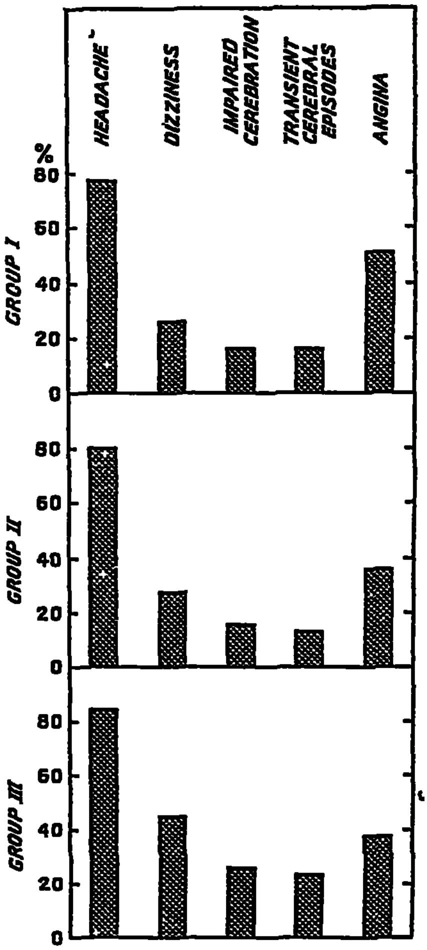

Fig 3—Comparison of symptoms

Thus the hypertensive patient destined for a stroke of this character appears to carry no special mark of identity, and it must be assumed that, apart from the undoubted influence of a family propensity, the risk of this is one that is evenly shared

The possibility that patients who have strokes may have an especially progressive form of hypertensive disease was also considered In fig 2 the three groups of patients have been further compared as regards rise of blood-pressure and other signs of clinical deterioration during observation This comparison, however, is inevitably of rather limited value because the frequency with which adverse features were recorded as appearing during observation was influenced by their previous prevalence in that group Also in this instance the number of patients in the first two groups was slightly smaller than usual owing to lack of opportunity to re-examine every patient before the stroke Nevertheless, in view of the emphasis earlier placed on this association, it is of some interest to see that patients destined to die from strokes were the only ones to show a tendency to progressive albuminuria Retinal hæmorrhages and exudates developed rather more frequently among the patients in groups I and II, but increase in blood-pressure seemed to be uniformly distributed and in all other respects the behaviour of the three groups differed very little

Finally, the incidence of certain symptoms, particularly those which may be ascribed to disturbances of cerebral circulation, is recorded in fig 3 The remarkable similarity of the three groups in this respect makes it clear, however, that such symptoms are no guide to future cerebral disaster In particular, the transient cerebral episode or "little stroke" so commonly regarded as sinister has occurred no more frequently among patients destined for strokes than among the remainder Although the nature of these attacks continues to be debated, the evidence here seems scarcely to support Pickering's (1948) contention that arterial thrombosis rather than spasm is invariably their basis

Discussion

It can be assumed that thrombosis developing in an atherosclerotic cerebral artery accounts, if not for all, at least for most strokes which have not proved fatal It is therefore no surprise that these occurrences have appeared to be uninfluenced by the severity or character of the hypertensive disease, nor is the conclusion unexpected that it is no easier to predict the development of thrombosis in a cerebral artery than its occurrence in a coronary or peripheral limb artery

Where fatal strokes are concerned, however, clinical analysis has proved more helpful, and the characteristics which appear to distinguish this group of hypertensive patients from the remainder were sufficiently prevalent to suggest that some pathological condition other than atherosclerosis may be involved here

As the constant use of the non-committal term "fatal stroke" will have suggested, the cause of these strokes unfortunately can only be inferred, because necropsy appears only to have been done in 3 cases, in each of which intracerebral hæmorrhage was found Nevertheless, except in 2 cases described as "cerebral thrombosis" and 2 further cases where this information was unobtainable, the cause of death was in every case certified by the patient's doctor as "cerebral hæmorrhage," and from the almost invariable description of rapid progressive coma there is little reason to doubt the accuracy of the certification The great majority of such patients appear to have survived only a few hours, in no case longer than twenty-four hours, thus following closely the course reported by Rose (1948) in his account of over 200 proved cases of cerebral hæmorrhage

Both subarachnoid hæmorrhage and massive cerebral infarction may be mistaken for intracerebral hæmorrhage Nevertheless, on the evidence available, it seems fair to conclude that, for practical purposes, the term "fatal stroke" can here be regarded as virtually synonymous with death from intracerebral hæmorrhage

The exact mechanism of hypertensive cerebral hæmorrhage is still largely conjectural, since objective studies have invariably been defeated by the extent of the accompanying brain damage Apart from Scheinker (1945), who suggested that bleeding might originate in cerebral veins which had become thin-walled from long-standing congestion, it has been generally assumed that the hæmorrhage is arterial, but further than this lies difficulty, for the pathological changes of arteriosclerosis lend themselves more convincingly to explanations of thrombosis than of hæmorrhage

This difficulty at least was avoided by Globus and Epstein (1953), who suggested that artery walls might become weakened in areas of ischæmic cerebral softening through lack of supporting brain substance, but it is nevertheless in terms of arteriosclerosis that an explanation of the hæmorrhage has usually been sought Eros (1951), for example, drew attention to an essentially degenerative and therefore potentially vulnerable form of arteriosclerotic change affecting cerebral arteries which constitutionally had a hypoplastic elastica Russell (1954), on the other hand, considers that the replacement of medial muscle by fibrous tissue, which she finds a characteristic of arteriosclerotic perforating cerebral arteries, adequately explains the prevalence of capsular hæmorrhages in benign hypertension

Earlier in this review it was suggested that, in a few cases where hypertension appeared surprisingly mild and benign, cerebral hæmorrhage was probably a sequel to previous cerebral thrombosis This sequence of events may logically be related to the development of arteriolar necrosis, which is not uncommonly seen in the marginal area of a cerebral infarct (Pickering 1955) In older hypertensives (excluded from this analysis) cerebral hæmorrhage has often appeared to develop upon this background, but below the age of 60 this has been exceptional, and the two features which consistently have distinguished these cases have been very high diastolic pressure (exceeding 150 mm Hg) and rather lower pressure associated with signs of renal damage, both of these features being characteristic of the "accelerated" form of hypertensive disease (The term "malignant" hypertension is traditionally reserved for such cases when papillœdema is also present)

Only 2 of the 31 patients with cerebral hæmorrhage who provide the basis for this discussion were considered likely to have had primary renal disease, and, apart from 5 patients in whom hypertension followed pregnancy toxæmia, the remainder were all regarded as having primary hypertension Thus, with few exceptions, any renal changes present were likely to be the consequence rather than the cause of the hypertension

Castleman (1951), from renal biopsy during lumbodorsal sympathectomy, established that the degree of impairment of renal function shown by a hypertensive patient was fairly closely related to the grade of arterial change found in the kidneys, and that the latter bore an even closer relationship to the height of the diastolic pressure

In a small but similar study of biopsy material from hypertensive cases of rather exceptional severity Heptinstall (1954) confirmed these findings Of especial interest for this discussion is his observation that fibrinoid necrosis of renal arterioles seemed to appear with increasing frequency as the diastolic pressure exceeded 150 mm Hg Although it is not to be expected that in every case arteries will show a precisely similar reaction to a certain level of blood pressure, the identity of this figure with the blood pressure level clinically considered particularly critical in the development of cerebral hæmorrhage seems more than a coincidence Inevitably this prompts the suggestion that fibrinoid necrosis in cerebral arterioles offers the most likely explanation for most cases of cerebral hæmorrhage in hypertensive patients, at least before the age of 60

If this explanation is correct—on a pathological basis it has been accepted by Russell (1954) as explaining the prevalence of pontine and brain stem hæmorrhages in malignant hypertension—it is likely to be of more than academic interest

It is generally believed that, unlike any other form of degenerative arterial disease, fibrinoid necrosis is a direct result of excessively high arterial blood pressure Byrom (1954) has offered the attractive theory that necrosis is a consequence of local anoxæmia of the arteriolar wall when spasm is provoked by the stimulus of high intra-arteriolar pressure, the summated effect of innumerable foci of reflex arteriolar spasm producing the characteristic pattern of accelerated or malignant hypertension

It is, however now firmly established that the malignant form of hypertension is at least potentially reversible by measures which successfully, though intermittently, lower the diastolic pressure to "safe" level By implication this also suggests that arteriolar necrosis is reversible and even more certainly is preventable Thus with increasing awareness of the absolute necessity of reducing blood pressure which approaches the critical level before irreparable kidney damage renders the impracticable, and with anticipated improvements in the drugs which will achieve this, it does not seem too much to expect that, in the future, this particular form of cerebral vascular hazard may be largely eliminated. There is indeed already a distinct impression that cerebral hæmorrhage uncommonly causes the death of a hypertensive patient who has been treated even with partial success by either sympathectomy or ganglion-blocking drugs.

Summary

A group of 234 hypertensive patients under observation for ten years provided an opportunity for studying the clinical background of cerebral vascular accidents.

During this time 97 patients died as a *consequence of* hypertension, and stroke, which accounted for 41 cases was the commonest cause of death.

The present review is concerned only with strokes which occurred before the age of 60 and is based on the study of 31 cases in which the stroke was fatal and 25 cases where it was survived. No necropsies were done, but there is reason to believe that, with very few exceptions, the fatal strokes were due to intracerebral hæmorrhage, and the non-fatal strokes mostly to cerebral thrombosis.

Since the clinical status of every patient had been fully assessed before the stroke, it was hoped that study of these cases might offer some guidance in predicting these catastrophes.

From comparison of the clinical characteristics of these cases with those of a control group of hypertensive patients who have remained free from strokes, it appears that cerebral hæmorrhage is liable to occur in any case where the diastolic pressure is excessively high (150 mm. Hg or higher) but is also likely when blood-pressure rather lower than this is accompanied by signs of severe renal damage.

Cerebral hæmorrhage, which occasionally develops as a late sequel to cerebral infarction, appears to be uninfluenced by either the severity or the character of the hypertensive condition and cannot therefore be foreseen.

The study failed to reveal any special features by which a patient destined to develop cerebral thrombosis may be identified in advance.

Cerebral symptoms were equally prevalent in the three groups of hypertensive patients studied and thus gave no indication of prognosis.

Cerebral hæmorrhage due to hypertension is not easily explained in terms of atherosclerosis, and the clinical character of the cases studied suggests that fibrinoid necrosis is likely to be mainly responsible for cerebral hæmorrhage before the age of 60.

Since fibrinoid necrosis is potentially a reversible condition and almost certainly preventable timely and effective hypotensive treatment should substantially reduce its incidence.

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"Freud came upon a world that was naively sober and earnest. Truth, it held, was truth and fact—fact. Relationships were patent, or were to be made so. Reality was reality and neither ever was nor ever could be anything else. Into this all too cock certain world Freud threw the bombshell of symbolism. Reality, he asserted, stood not monolithically by itself, but in a series of relatednesses, and was in effect but the latest symbolic representation of that relatedness. Dreams spoke in symbols but so also do we, waking, for words have meaning and representations far above and behind their explicit conveyance."—Dr. I. GALDSTON, *Bull. N.Y. Acad. Med.* 1956, 32, 908.

PAGET'S DISEASE OF BONE ASSOCIATED WITH HASHIMOTO'S STRUMA LYMPHOMATOSA

A CLUE TO THE PATHOGENESIS OF PAGET'S DISEASE *

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THIS paper describes the concomitance of Paget's disease of bone with Hashimoto's struma lymphomatosa in a group of patients. The association appears to be frequent enough to warrant a wider clinical and radiological study of both disorders and, if confirmed, may provide a clue to the ætiology of Paget's disease. In the present series of 35 patients with Hashimoto's disease, histological examination *of the thyroid gland was made* in 32. Of the 3 cases not so examined, 2 showed hypothyroidism, a firm goitre, and grossly abnormal serum-flocculation reactions (Luxton and Cooke 1956), and 1 had hypothyroidism with a firm goitre. Of the 35 patients with struma lymphomatosa, clinical Paget's disease (confirmed radiologically) was present in 3, and Paget's disease was discovered radiologically in 4 others. The thyroid gland was examined histologically in all the patients with Paget's disease: all showed the features typical of Hashimoto's disease.

Case-reports

Case 1.—A woman, aged 42, presented as a case of Graves's disease and was treated for four months with average doses of methyl thiouracil. The goitre became very hard and thyroid biopsy showed Hashimoto's disease (Dr. J. Davson). An X ray *of the pelvis revealed Paget's disease of bone (Dr. J. B.* Fawcitt). Serum flocculation tests, at first grossly abnormal, returned to normal twenty-three months after the start of treatment with dried thyroid gland. The serum alkaline-phosphatase, initially normal, has gradually increased to 25 King-Armstrong units per 100 ml.

Case 2.—A euthyroid woman, aged 42, presented with a large goitre of fairly soft consistence and apparently recent in origin. Paget's disease had been discovered in her right tibia five years before (Dr. J. Blair Hartley). The serum alkaline phosphatase was normal but serum flocculation tests were abnormal. The thyroid histology was that of definite but early Hashimoto's disease (Dr. Davson).

Case 3.—A woman, aged 68, had radical mastectomy for scirrhous carcinoma in 1949. In a routine follow-up chest X ray in January, 1950, the radiologist (Dr. Blair Hartley) noted Paget's disease of the right clavicle. A hard goitre was first noticed in November, 1954, its microscopic picture being that of 'lymphadenoid goitre' (Dr. Helen Russell). Radiologically the right clavicle showed no alteration during a period of five years and nine months. The patient had not had endocrine treatment for secondary carcinomatosis and there is no reasonable doubt about the diagnosis of Paget's disease.

Case 4.—A woman, aged 78, had a goitre of twelve months' duration which clinically appeared to be malignant, but which, on microscopy, showed Hashimoto's disease (Dr. Russell). Clinically there were no bone lesions, but X rays showed well-marked Paget's disease in pelvis and skull (Dr. Fawcitt). Abnormalities were present in the serum proteins, shown by electrophoresis and flocculation tests.

Case 5.—A woman, aged 55, first noticed a goitre in 1946 which was removed nine months later, its histology being typical of Hashimoto's disease (Dr. Russell). In 1955 clinical examination showed mild hypothyroidism and Paget's disease of the right tibia. The serum flocculation tests were negative. Radiologically Paget's disease was found in other bones (Dr. Fawcitt) and the diagnosis was confirmed by bone biopsy (Dr. Davson).

Case 6.—A woman, aged 69, had a hemithyroidectomy for a goitre which histologically showed Hashimoto's disease (Dr. Russell). Subsequently she was treated with dried thyroid gland Five years later the patient was euthyroid and the serum flocculation tests and serum protein electrophoretic pattern were normal Radiographs of the skull showed advanced Paget's disease (Dr Blair Hartley)

Case 7 —A woman, aged 48, had a small firm diffuse goitre, hypothyroidism, and abnormal flocculation tests Histologically, the goitre showed Hashimoto's disease (Dr Dawson) For the previous four years she had had clinical and radiological signs of what was thought to be polyostotic fibrous dysplasia affecting the left tibia, right great trochanter, and one metacarpal A second biopsy of the tibia revealed histologically that the bone lesion was, undoubtedly, Paget's disease (Dr Dawson)

Biochemical Features

In 5 of the 7 cases existing plasma-protein disturbance was revealed by abnormal serum flocculation tests or by serum-electrophoresis (Similar changes in serum-proteins had probably been present in the remaining 2 patients before treatment of the thyroid disorder, the one by partial thyroidectomy and the other by dried thyroid gland [Luxton and Cooke 1956, Roitt et al 1956]) The serum-alkaline phosphatase was within the normal range in 1 case, slightly raised (11–15 K -A units per 100 ml) in 2 cases, and persistently high in 4 cases Serum-calcium and inorganic phosphate levels were normal in the 6 cases examined

Discussion

Prevalence of Paget's Disease

The prevalence of Paget's disease in the general population may be assessed by necropsy studies and by radiological field surveys Schmorl (1932), performing 4614 necropsies on unselected persons aged over 40, found 138 with Paget's disease—a rate of 3% A recent necropsy study, comparable in its method, was made by Collins (1956) who examined in detail the skeleton of 650 unselected persons aged over 40 who died in general hospitals in Leeds and Sheffield Paget's disease was found in 24 of these cases—a rate of 3 7% Collins states that " this study was mainly concerned with the recognition of minor, localised or early lesions " and " regeneration of bone in Paget's disease always leads to an abnormal trabecular pattern, as easily recognised by the pathologist in the sawn bone as by the radiologist in the living skeleton " He observes that only a third of all cases of Paget's disease are diagnosable clinically, and that the disease is commoner in men than in women, probably in the proportion of four men to three women The prevalence figures are greatly influenced by age Collins divided his cases into 15-year groups and found Paget's disease in 1 8% of persons aged between 40 and 54 years, 3 6% between 55 and 69 years, 5% between 70 and 84 years, and 9 1% between 85 and 94 years

Paget's disease of bone is a fairly common incidental finding in radiological examinations To obtain accurate figures of its incidence, radiological surveys of the general population would need to cover the whole skeleton of each individual, for the disease may be localised to a single bone or part of one bone So far as I can ascertain, no extensive field survey of this nature has been made However, Kellgren and Lawrence (personal communication) in a study in Leigh, Lancashire, made radiological examinations of 173 unselected men in the decade 55–64 years and found 8 cases of Paget's disease ($4^1/_2$%), and of 208 women in the same age group of whom 1 showed Paget's disease ($^1/_2$%)—an over all incidence in both sexes of 2 4% The X-ray examination in each person was limited to the cervical spine, lumbar spine, pelvis, knees, hands, feet, and lateral aspect of the skull (partial) In all such studies, the criteria for making a radiological or histological diagnosis must vary slightly from one examiner to another and the factor of " observer error " must always be remembered

It is probable that the prevalence-rate of Paget's disease found by Schmorl and by Collins is reasonably accurate For assessing the presence of Paget's disease Collins's method of examination of the skeleton would seem comparable in accuracy with the limited radiological bone survey made in the patients with struma lymphomatosa Lacking precise radiological studies of the incidence of Paget's disease in the general population, I have therefore taken Collins's figures as a basis The rising prevalence of Paget's disease with increasing age is, of course, important statistically

TABLE I—DISTRIBUTION IN AGE GROUPS OF PAGET'S DISEASE AND HASHIMOTO'S DISEASE

—	Age group (years)		
	40–54	55–69	70–84
Collins's figure of prevalence of Paget's disease in the general population	1 8%	3 6%	5 0%
No of cases of Hashimoto's disease	17	14	4
No of cases of Hashimoto's disease with Paget's disease associated	3	2	2

Statistical Evaluation of Present Group of Patients

Table I shows the numbers of cases of Hashimoto's disease and of Paget's disease in the different age groups, alongside Collins's estimation of the incidence of Paget's disease in the general population Statistically the following may be deduced

1 The higher proportion of patients with Paget's disease in the whole group of 35 patients with Hashimoto's disease is statistically highly significant (P=0 0004 when tested by χ^2 with Yates's correction)

2 Although the actual number of cases of Paget's disease is small and breakdown into age-groups makes the individual statistical values less significant, tests on this basis give the following results

40–54 age group		0 006< P <0 005
55–69	„ „	P = 0 2
70–84	„ „	P = 0 01

In calculating figures for the purpose of applying statistical tests of significance, corrections have been incorporated to allow for two features which would otherwise introduce bias

(*a*) All the patients with Paget's disease in this series are women In the 1951 census population of North West England, which has been used for providing denominators, 55% in the age-group 40–84 are women, whilst in the individual age-groups enumerated above, the proportions of women are 52%, 57%, and 61% respectively

TABLE II—TIME RELATIONS BETWEEN PAGET'S DISEASE AND GOITRE

Case	Age (years) when Paget's disease first diagnosed	Time relations between diagnosis of Paget's disease and discovery of goitre	Thyroid activity before thyroid operation
1	43	Goitre 18 months before Paget's disease	Hypothyroid
2	37	Paget's disease 5 years before goitre	Euthyroid
3	69	Paget's disease 58 months before goitre	„
4	79	Goitre 18 months before Paget's disease	„
5	64	Goitre 9 years before Paget's disease	„
6	74	Goitre 5 years before Paget's disease	„
7	45	Paget's disease 46 months before goitre	Hypothyroid

(b) The prevalence of Paget's disease in the general population is in the ratio of 4 men to 3 women

Relationship between Hashimoto's Disease and Paget's Disease

Hyperthyroidism and hypothyroidism do not appear to be factors in the genesis of Paget's disease Of the patients with Paget's disease in this series, 1 was originally hyperthyroid, 1 euthyroid, and 1 hypothyroid (Preoperative observations on the state of thyroid activity were inadequate in 4 patients, neoplastic goitre being suspected)

There are three main ways in which an association between struma lymphomatosa and Paget's disease could arise struma lymphomatosa may predispose to Paget's disease, Paget's disease may predispose to struma lymphomatosa, or there could be a predisposing factor common to both diseases Table II shows the time relations between the discovery of Paget's disease and the first observation of the goitre in this group of patients It must be emphasised that in a slowly evolving disease such as Paget's, the actual time of onset is hard to assess even in terms of years A similar comment applies to struma lymphomatosa, for not only may the disease antedate the goitre, but the goitre may long remain undiscovered Table II indicates that in 4 cases an observed goitre preceded the discovery of Paget's disease by periods up to nine years, and in 3 cases known Paget's disease preceded discovery of the goitre by periods up to five years For what these figures are worth, they do not support the suggestion that either disease predisposes to the other

Summary

Of 35 patients with Hashimoto's struma lymphomatosa, 3 patients showed clinical signs of Paget's disease of bone A radiological bone survey of the 35 patients, limited in most cases to skull, lumbar spine, pelvis and upper femora, and one tibia, revealed that 7 out of the 35 patients had Paget's disease The diagnosis was confirmed by bone biopsy in 2 patients

Accurate assessment of the prevalence of Paget's disease in the general population has been attempted by others from careful necropsy examination on large series of unselected persons, and to a lesser extent, by radiological field surveys It is considered that such necropsy studies give figures of incidence of Paget's disease in the general population comparable in accuracy with the limited radiological bone survey made in the 35 cases of struma lymphomatosa

Statistical analysis shows that the prevalence rate of Paget's disease in this series of patients with struma lymphomatosa is highly significant

The pathogenesis of Paget's disease seems to be unrelated to hyperthyroidism or to hypothyroidism

The evidence available suggests that Paget's disease does not predispose to Hashimoto's disease, nor does Hashimoto's disease predispose to Paget's disease There may be some predisposing factor common to both disorders

I am indebted to several pathologists and their staffs—to Dr Helen Russell of the Christie Hospital and Holt Radium Institute, to Dr James Davson and Mr H V Street of Crumpsall Hospital, and to Dr Lois Stent and Mr David Moss of Withington Hospital The radiological bone surveys were made by Dr J Blair Hartley (at the Christie Hospital) and Dr J B Fawcitt and Dr J Cowen (at Crumpsall Hospital) Medical and surgical colleagues at Crumpsall Hospital and the Christie Hospital and Holt Radium Institute have been most helpful For expert statistical help I thank Miss Marion H Russell of the Christie Hospital and Holt Radium Institute Prof J H Kellgren and Dr J S Lawrence kindly allowed me to quote their unpublished field studies I am especially grateful to Professor Kellgren and to Prof S L Baker for their interest and advice

References at foot of next column

A METHOD OF HYPOTHERMIA FOR OPEN HEART SURGERY

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THE value of hypothermia during open heart surgery is now well recognised The pioneer work of Bigelow in Toronto has paved the way for the use of hypothermic techniques in both cardiovascular surgery and neuro surgery He showed (Bigelow et al 1950a, b, and c) that the reduction in oxygen consumption that accompanies a fall in body temperature would permit the safe interruption of circulation to vital tissues for far longer than at normal temperatures Recent reports (Stone et al 1956) show that oxygen consumption in the human brain is reduced by two thirds at 30°C and by three quarters at 28°C A reduction of body-temperature to these levels can be expected to give an operating-time of ten minutes within the open heart without cerebral damage

Two main methods of inducing hypothermia are currently in use—extracorporeal cooling of the bloodstream and surface cooling of the body Extracorporeal cooling of the blood (Delorme 1953, Ross 1954) has the advantage that it can be initiated after surgery has begun and the exact nature of the lesion has been determined, but it has the disadvantage of complexity, of causing considerable biochemical disturbances (Brewin et al 1956), and of provoking cardiac irregularities more often (Graham 1955) Surface cooling has as its great merits simplicity and lack of gross physiological disturbance

I describe here the method of surface cooling used for open heart surgery at the Middlesex Hospital So far 32 patients have been subjected to open cardiac surgery 26 for the repair of atrial septal defects and 6 for the relief of pulmonary stenosis There have been no deaths and few complications

We have followed closely the method developed by Swan et al (1955) at the University of Colorado School of Medicine, and it is a pleasure to acknowledge their valuable help and guidance during a visit to Denver We have modified their technique as regards temperature level and rapid surface rewarming This rewarming, together with close surgical cooperation and effective "dovetailing" of the several stages of the procedure, has reduced to three hours the time from induction of anæsthesia to the return of the rewarmed patient to the ward The time factor is of some importance in view of the number of cases awaiting surgery and the need to avoid disruption of ward and operating-theatre routine

Ours has been a team project and I am indebted to my surgical, cardiological, and anæsthetist colleagues and to theatre, ward, and technical staff, who have all contributed to making the method practical The salient features of this method are

(1) Minimal anæsthesia using ether and muscle relaxants
(2) Surface cooling by blanket and cold bath
(3) A deep tissue temperature of 30°C during circulatory arrest
(4) Immediate rapid surface rewarming by blanket during surgery and by warm bath subsequently

These features are well illustrated in the chart (fig 1) of the operation *for an atrial* septal defect in a child of 6 years

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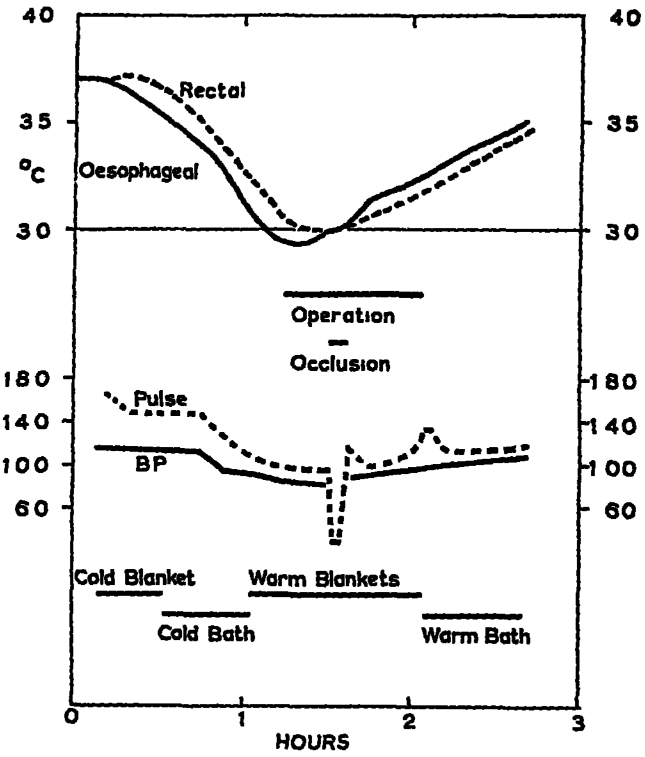

Fig 1—Repair of atrial septum under hypothermia in a child aged 6 years and weighing 40 lb

The Method

Anæsthesia

An hour after premedication with promethazine, pethidine, and scopolamine, anæsthesia is induced with thiopentone This is immediately followed by administration of succinylcholine and by oral intubation Anæsthesia is continued with nitrous oxide, oxygen, and ether Tubocurarine (' Tubarine ') is given to secure complete relaxation, and respiration is controlled throughout the entire procedure

Ether is used because it is less irritant to the cooling myocardium than are many other anæsthetic agents It causes vasodilatation and thus assists heat exchange When the patient has been cooled to the required temperature, ether is discontinued and most of what remains in the body is removed by vigorous ventilation This ensures that during the period of circulatory arrest the tissues—particularly the brain—are as free as possible from drugs During the operation anæsthesia is maintained by a sum of the depressant effects of hypothermia and its potentiation of the residue of the drugs not yet eliminated—the so-called " hypothermic anæsthesia " (Virtue 1955)

Cooling

As soon as induction of anæsthesia is completed, the patient is placed between plastic blankets through which water at 15°C is circulated Electric thermometers are placed in the œsophagus (to the level of the nipple line), *in the nasopharynx,* and in the rectum Intravenous drips are set up, and electrocardiographic leads and a blood pressure cuff are attached to the patient During this time some superficial cooling takes place, which helps to shorten the procedure

When these preliminaries are completed, the patient is immersed in a bath of water at 15–17°C, and shortly afterwards ice is added to keep the temperature of the water between 8°C and 10°C throughout the rest of the cooling

The gradual introduction to the cold environment is deliberate, so that the temperature of the venous blood returning to the heart shall not drop suddenly Immersion of a patient with dilated vessels in freezing water may well precipitate ventricular fibrillation It was the ease with which this catastrophe could occur in venous cooling in dogs that caused us to abandon this method in the experimental stages, when it was found that the temperature of the myocardium could rapidly become 6 or even 10°C cooler than the other tissues of the body

In the bath the patient's head and hands are supported above water After twenty minutes the toes are also lifted out to prevent undue chilling of the digits A towel soaked in cold water is placed over the patient so that the chest and knees, which tend to float above water, are effectively cooled and the maximum surface area is offered for heat exchange This towel also serves to satisfy those who criticise the method on æsthetic grounds The water is repeatedly stirred, and the superficial tissues of the patient are frequently massaged and kneaded to prevent stagnation of cold blood and to speed up heat exchange When the temperature of the bath water is maintained at about 10°C, there is no undue venospasm and circulation to the periphery remains reasonably good; thus heat exchange keeps pace with the superficial cooling and no large volume of cold superficial tissues is built up which might cause a profound drop in temperature after the patient has been removed from the bath

Temperatures are recorded every five minutes, and after a lag of from five to fifteen minutes they are found *to fall progressively, the rate of descent depending* on the relations of surface area to body weight Should the fall become retarded, or the patient shiver or develop excessive goose pimples, further ether and tubarine are given to overcome the body's attempts to increase heat production

As the body-temperature drops so does the heart rate, and by the time the operation is in progress it may be as low as 35–40 a minute The systolic blood pressure, which is low immediately after induction, rises on immersion in the bath, as a result of vasoconstriction, but it falls later to 80–90 mm Hg and remains at that level, except during circulatory arrest, until it rises again on completion of rewarming The radial pulse is palpable without difficulty during cooling Another sign of cooling is the gradual increase in the size of the pupils, which become widely dilated at temperatures below 30°C As cooling progresses, a distinctive pink coloration of the immersed skin is seen it is thought to be due to a combination of capillary stasis or paralysis and reduced metabolism in the skin The patient is removed from the bath when the œsophageal temperature reaches 31°C in children or 32°C in adults The time in the bath varies from about thirty minutes in a child weighing 40 lb to seventy minutes in a plump woman weighing 120 lb

Immediate Rewarming

The patient is removed from the bath, dried, and placed between plastic blankets through which water at a temperature of 40°C is now circulating The chest is exposed, and the arms are abducted to 90° and placed on arm rests angled upwards slightly to prevent damage to the brachial plexus

After drop

With hypothermia induced as thus described the after drop or drift in œsophageal temperature is about 2°C in adults and $1^1/_2$°C in children This drift takes place despite immediate rewarming with water blankets at 40°C The drift in nasopharyngeal temperature is usually 1°C more, but, as there is a lag of 1°C in the nasopharyngeal behind the œsophageal temperature, equilibrium is reached at or just below 30°C The after drift reaches its maximum in about twenty five minutes in children and forty minutes in adults

Operation

Ether is discontinued when the patient is removed from the bath Nitrous oxide is discontinued when the

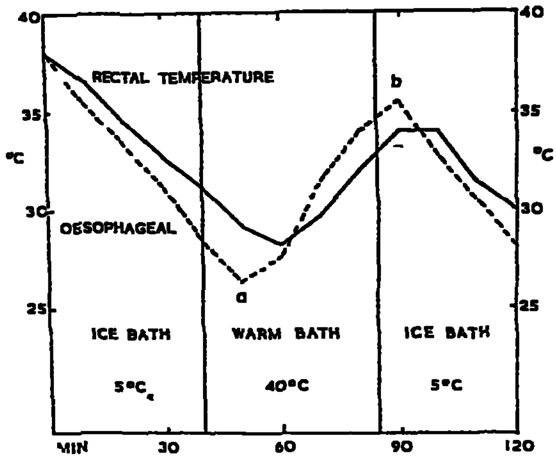

Fig 2—Experimental hypothermia in a dog weighing 34 lb

ncision is made, and vigorous controlled respiration is iaintained with pure oxygen until after the period of irculatory arrest This rapidly eliminates ether and llows diathermy to be used throughout the operation lood is given to replace that lost during exposure of the eart through the bilateral anterior incision, and an ttempt is made to reach optimum circulatory and espiratory conditions immediately before circulation is rrested Tourniquets are placed round the venæ cavæ, nd a clamp is placed through the transverse sinus ready o occlude the aorta and the pulmonary artery The ncision is made into the heart with a controlling clamp n place so that no unnecessary manœuvre should waste aluable seconds during the period of occlusion

After occlusion of the venæ cavæ, from ten to fifteen econds is allowed for the heart to empty, when neostigmine 0 03 mg per stone of body-weight is injected roximal to the aortic clamp (Prevedel et al 1954, Sellick 955) This reaches the coronary circulation and almost immediately slows the heart The controlling clamp is emoved, the heart is opened, residual blood is aspirated, nd the defect is repaired under direct vision During the eriod of circulatory arrest the lungs are kept gently nflated so that time is not lost in reinflating them when he circulation is restarted At the completion of closure f an atrial septal defect an increase in pressure on the bag nflating the lungs drives remaining blood from the lung nto the left atrium, excludes air, and demonstrates the atisfactory closure of the defect

The Time of Circulatory Arrest

The period of occlusion that can safely be tolerated by he brain and myocardium at 30°C is about ten minutes ew of our cases have taken longer than eight minutes he average has been five and a half minutes

In one case, in a man aged 26, after an occlusion of even and a half minutes, a tear was found in the inferior vena cava, and an immediate reocclusion of four minutes was needed to repair it Later in the operation a third occlusion, of two and a half minutes, was required to correct the venous return from the inferior vena cava into the right atrium This man showed no delay in recovering consciousness and no evidence of any cerebral damage and made an uneventful recovery

Subsequent Rewarming

After restoration of the circulation the blanket temperature is raised to 43°C, and, when a rising temperature shows that rewarming of the deep tissues has begun, 50% nitrous oxide is added to the oxygen When surgery is complete, a watertight dressing is applied to the wound, and the patient is returned to the bath and immersed at a temperature of 40°C By this time some rewarming has taken place from the water blankets In children the temperature may have reached 32°C and in adults 31°C by the completion of the surgery The warm bath is maintained at 40°C, and the same stirring and kneading technique is used as during the cooling The patient remains in the bath until an œsophageal temperature of 35°C is reached Spontaneous respiration is re-established, and residual curare is counteracted with atropine and neostigmine

After rise

A phenomenon similar to the after-drop occurs when the patient is removed from the warm bath and an after-rise in temperature is seen (fig 2, b) This after-rise is usually of the same order as the after-drop, and within an hour of return to the ward the patient is at normal temperature Consciousness is regained within an hour of removal from the bath As rewarming takes place, the size of the pupils returns to normal and is a good indication of the return of normothermic cerebral activity

Postoperative Care

The patient goes back to the ward with an oxygen mask and is then placed in an oxygen tent and nursed flat for eight hours Gentle suction is applied continuously to the thoracic drains to prevent pneumothorax After eight hours the patient is helped to sit up, by stages, and is taken out of the oxygen tent Methadone is used as an analgesic, and physiotherapy is begun as soon as possible

Results

In 32 cases open cardiotomy has been performed with circulatory arrest using this method of hypothermia 26 of the operations have been for the repair of an atrial septal defect (1 of these having an associated pulmonary valvular stenosis which was also corrected under direct vision at the same time, and 1 an associated mitral stenosis which was split digitally via the atrial defect), and 6 have been for the division of pulmonary stenosis (1 of these had a preoperative hæmoglobin of 188%)

Complications

There were no deaths During the operation auricular fibrillation and flutter often occurred when the body-temperature was at or below 30°C, but normal rhythm returned on rewarming Only 1 patient developed ventricular fibrillation, this happened at the onset of manipulation of the heart and coincided with a sudden change in pH due to replacement of a faulty soda lime canister in the anæsthetic circuit One shock from the electric defibrillator restored normal rhythm, and no further dangerous arrhythmia was observed There were no complications during cooling or during rewarming in the bath

After operation 2 patients developed pneumothorax despite intrathoracic drains One patient had a transient hemiplegia twelve hours after operation and a phlebothrombosis of the leg it was found later that his inferior vena cava drained partly into his left atrium, which probably explains his systemic embolism 2 patients sustained trivial superficial burns, both due to overheating in the rewarming blanket before a satisfactory thermostatic control was fitted

Discussion

Hypothermia is not a physiological condition, and our aim has been to keep its duration and depth to the minimum compatible with the proposed length of circulatory arrest Cooling in the bath is by far the most efficient means of heat exchange because the greatest possible surface area is exposed to the cooling medium On the other hand, excessively cold water, though possibly it cools the body more rapidly, produces vasospasm which delays transference of heat from the deep to the superficial tissues, with the result that a large volume of cold tissue is built up and the temperature may later fall unpredictably and often profoundly

Immediate surface rewarming made little difference to the degree of after drop in temperature after removal from the bath (fig 2, a), but it significantly shortened the hypothermia With skilled surgical coöperation it is possible to manipulate the heart during the period of maximum cooling of deep tissues—i e, at the lowest part of the curve (fig 1) The bilateral thoracotomy exposure of the front of the heart and the placing of tourniquets round the venæ cavæ are surprisingly speedy, and often the tourniquets have been in position before the lowest temperature was reached

Surface rewarming from deep hypothermia is said to be dangerous (Bigelow et al 1952), but our experience—after being disappointed with diathermy rewarming in the earlier cases—has been that rapid surface rewarming from 28°C does nothing but good, and we have seen no cardiovascular disturbances during it

Œsophageal temperatures have been taken as the criterion of the deep tissue temperatures The rectal temperatures were very unreliable and could indeed be dangerous if taken alone, for the lag that occurs if the rectal thermometer is insulated by fæces may well lead to excessive cooling In later cases nasopharyngeal temperatures were also recorded these followed more closely the œsophageal temperatures and can probably be taken as representing the temperature of the brain (Lucas 1956)

We think it unnecessary to lower the temperature below 30°C to provide a period of five to ten minutes' circulatory arrest At this temperature the risk of ventricular fibrillation is very slight, even in grossly enlarged hearts When hypothermia was first used, its dangers were undoubtedly magnified because temperatures as low as 26°C were considered necessary

Summary

A method of hypothermia for open heart surgery is described and discussed Its salient features are minimal anæsthesia using ether and relaxants, surface cooling by blanket and cold bath, deep-tissue temperature of 30°C during circulatory arrest, and immediate surface rewarming by blanket during operation and by warm bath subsequently

The results of 32 cases without mortality are reported

The integration of the effects of hypothermia and anæsthetic drugs make it convenient for the anæsthetist to be in over-all control of surface hypothermia and to report on the method used, but successful major cardiac surgery is the result of the work of a team which includes members from almost all departments of a large hospital

The method of hypothermic anæsthesia used at the Middlesex Hospital has been developed for open cardiac surgery in particular for the closure of atrial septal defects This project has involved close coöperation between cardiologists, surgeons, and anæsthetists

I am therefore particularly indebted to Dr D Evan Bedford and Mr T Holmes Sellors for their help and advice, and also to many other members of the team—surgical, medical, nursing, physiotherapy, and technical Facilities for experimental work on hypothermia were given me by the Institute of Clinical Research of the Middlesex Hospital

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THE HEAT RESISTANCE OF DRIED SMALLPOX VACCINE

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DURING recent years there has been increasing inter in the development of stable dried smallpox vacci in which the living virus could be preserved for lo periods at tropical temperatures Glycerinated vaccir lymph deteriorates rapidly at room temperature a thus has always been a major difficulty in the contr of smallpox in hot countries with poor transport facilit and inadequate refrigeration A stable dry vacc could, moreover, be stored with confidence as a reserve and thus ensure adequate supplies during an epidemi when immediate mass vaccination was essential Th ability to preserve virus preparations of known potenc in a dry state would also make it possible to mainta standards for international use and facilitate the com parison of strains of vaccinia virus from differe countries

This increasing interest is reflected in the extensive laboratory and field trials of dried smallpox vacci produced in several countries that have been carried out under the auspices of the World Health Organisation The results of these trials (1957) have shown that dried vaccines are available which are much more resistant to heat than any glycerinated vaccine lymph

The combined laboratory and field trials on the dried smallpox vaccine prepared at the Lister Institute have been continued over a longer period Since this advance in vaccine production is of great importance to tho responsible for vaccination campaigns in hot climate a summary of the results obtained in these trials i presented here

Materials and Methods

Preparation of Vaccine

This has been fully described by *Collier* (1955) Briefly, the vaccine consists of a suspension of vaccinia virus, partially purified by differential centrifugation and by exposure to phenol, in a solution of 5% peptone in distilled water The suspension is dried in a centrifugal freeze-drier and sealed under vacuum in phials of neutral glass These are dispensed together with the require amounts of reconstituting fluid in 25 dose and 100 do outfits Because of the small amounts of dried materi and the very small amounts of reconstituting fl required, it is not practicable to issue this vacc in single-dose tubes

The dried vaccine is of much greater purity than ordinary vaccine lymph, it is free from contaminating bacteria and tissue debris and in consequence produce less local secondary reaction Storage tests have shown that the virus is better preserved when sealed unde vacuum than in nitrogen, even when precautions are taken to remove traces of moisture and oxygen from the gas The reconstituting fluid is 40% glycerol in McIlvaine's buffer at pH 7 2 This is supplied in phials designed to obviate the need for sterilised syringes in transferrin the fluid to the dried vaccine The risk of contamination is thus reduced

Storage of Vaccine

Samples of the dried vaccine were stored at –10°C, 37°C, and 45°C. A batch of glycerinated vaccine lymph was also maintained at –10°C throughout the experiment to control the susceptibility to vaccination of the rabbits used in potency titrations and of the people on whom the vaccine samples were tested.

Samples of the vaccine stored at –10°C were tested at the beginning and end of the trial. Samples stored at 37°C and 45°C were removed at intervals from 4 weeks to 106 weeks (approximately 2 years) for titration in the laboratory and trials in primary vaccination in man. Samples are still being maintained at the higher temperatures to detect any future deterioration.

In addition, samples from some other batches of vaccine selected at random were stored at 37°C and 45°C for 8 weeks and then tested in the same way to ensure that the batch used in the trial was not exceptional in its resistance to heat.

Titration of Stored Samples

All potency titrations were duplicated in the department of bacteriology of the University of Liverpool and in the Lister Institute, Elstree. At the start of the trial, titrations were done on the dried vaccine and the glycerinated lymph held at –10°C and subsequently on the dried vaccine stored at 37°C and 45°C. Thus each sample was titrated in the laboratory at the time of issue for clinical trial. Finally, at the end of the trial, samples of the dried vaccine and the control lymph held at –10°C were again titrated to ensure that there had been no deterioration at that temperature.

Titrations by scarification in rabbit skin.—These were duplicated on the clipped backs of two rabbits in each laboratory. Dilutions of vaccines were made in McIlvaine buffer, 0.01 M phosphate at pH 7.4. Volumes of 0.1 ml. of the appropriate dilution were spread over areas of about 5 sq. cm., and the skin was lightly scarified through the fluid. Threefold dilutions from 1:1000 to 1:27,000 were tested, and the glycerinated lymph was titrated on each rabbit to control its susceptibility to vaccinia virus. The lesions were recorded on the 5th and, if necessary, 6th days.

Titrations on chick chorio-allantoic membrane.—The technique of this test has been described in detail in the report on the W.H.O. trials in the *Bulletin of the World Health Organisation* (1957). Here it is only necessary to state that 0.1 ml. amounts of the appropriate dilutions of vaccine were inoculated on the dropped chorio-allantoic membranes of groups of five or six 12-day chick embryos for every dilution tested. After 48 hours' incubation at 35°C the dropped areas of the membranes were removed and washed, and the lesions were counted. Titres were expressed as infectious units per ml. of undiluted vaccine (i.u. per ml.) and were computed from the mean pock count at the lowest dilution giving discrete countable pocks.

Vaccinations

Thanks to the cooperation of the directorate of hygiene and research of the Royal Air Force and of the Headquarters Technical Training Command, in particular of the Principal Medical Officer there, Air Commodore J. Hill, sufficient volunteers were available for vaccination.

Young men with no history of previous vaccination and without scars on their arms were selected for vaccination with the samples under test. In the first instance groups of men were vaccinated with the dried vaccine and with the glycerinated lymph held at –10°C to ensure that both vaccines produced 100% of successes. Thereafter the dried vaccines stored at 37°C and 45°C were each tested in groups of about a hundred men up to 78 weeks' storage. The size of the control group vaccinated with lymph was reduced to about fifty after the earlier tests and, in view of the successful results already obtained, the size of the groups tested with dried vaccines at 106 weeks was also reduced to about eighty.

All the vaccinations were made by one of us (R. M. C.) by a uniform technique—a single linear scratch $^1/_4$ inch long. Arms were inspected on the 7th day and the results recorded as "vesiculation" or "no vesiculation". No other distinction was made.

Results

Resistance at 37°C and 45°C

The results of the laboratory titrations and of the vaccinations after storage for 32, 64, and 106 weeks are shown in the accompanying table. Samples were in fact withdrawn for test after storage for 4, 8, 16, 32, and 78 weeks, but, in view of the uniformly satisfactory results obtained at the later tests, it is unnecessary to include all the earlier ones in the table.

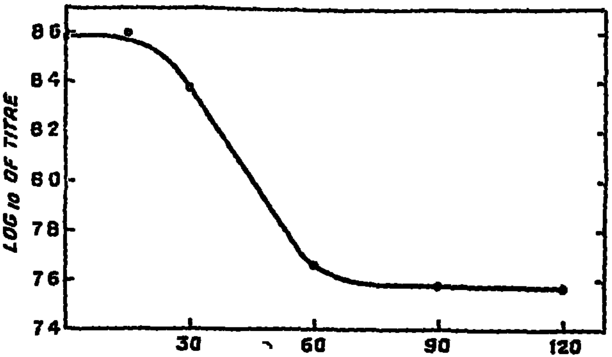
It will be seen that there was no detectable deterioration either by pock counting or scarification tests after 32 weeks' storage at 37°C and 45°C. Vaccination with these samples also produced 100% of successes. After 64 weeks' storage there was no detectable deterioration by pock counting in the sample stored at 37°C, though there might have been a slight decrease in the potency measured on the rabbit. The sample stored at 45°C showed a slight but possibly significant decrease in potency by both pock counting and rabbit titration. Both samples still produced 100% of successful vaccinations.

After 2 years (106 weeks) there was still no detectable decrease in the pock count of the sample stored at 37°C, though there was some apparent decrease in the potency measured in rabbits. The sample stored at 45°C showed a slight further decrease in pock count measured in one laboratory but not in the other. The samples stored at both temperatures still produced 100% of successful

STORAGE OF DRIED SMALLPOX VACCINE

Period of storage (weeks)	Where titrated	Titre on chorio-allantoic membrane (i.u. per ml.)	Rabbit scarification titre				No. of men vaccinated	Vaccination success rate (% successful)
			1/1000	1/3000	1/9000	1/27,000		
At –10°C								
	A	3.5 × 10^8	c	c	c	sc+	50	100
			c	c	c	sc+		
	B	4.9 × 10^8	c	c	sc	3		
			c	sc	sc	4		
At 37°C								
32	A	3.6 × 10^8	c	sc+	sc+	1	100	100
			c	c	sc+	1		
	B	1.8 × 10^8	c	c	sc+	8		
			c	c	sc	7		
64	A	2.5 × 10^8	sc+	sc−	9	3	100	100
			c	c	sc−	6		
	B	3.8 × 10^8	c	c	9	2		
106	A	1.8 × 10^8	c	c	sc+	sc−	88	100
			c	sc+	sc	4		
	B	1.8 × 10^8	c	sc	8	4		
			sc	sc	2	4		
At 45°C								
32	A	1.8 × 10^8	c	c	sc+	7	114	100
			c	c	sc+	0		
	B	1.3 × 10^8	c	c	sc−	3		
			c	c	sc	8		
64	A	1.1 × 10^8	sc+	sc−	5	1	100	100
			c	sc+	sc	3		
	B	1.8 × 10^8	c	c	5	2		
106	A	3.4 × 10^7	c	sc+	6	0	87	100
			c	sc+	3	1		
	B	1.8 × 10^8	c	c	8	12		
			c	sc	1	1		

i.u. per ml. = infective units per ml. by pock count on chorio-allantoic membrane
c = confluent lesion 100% of area
sc+ = semiconfluent lesion 70–80% of area
sc = semiconfluent lesion 50–70% of area
sc− = semiconfluent lesion <50% of area
numbers = discrete vesicles
A = samples titrated in Lister Institute
B = samples titrated in Liverpool



Survival of dried smallpox vaccine in water at 100°C

vaccinations, there was no evidence of any modification of the vesicular lesions obtained and no difference between the reactions produced by the samples stored at the higher temperatures and by those kept at –10°C

Resistance at 100°C

Phials of dried vaccine from two different batches were immersed in boiling water Two phials were removed at each sampling-time after exposure to this temperature for periods of from 30 up to 120 minutes and titrated separately by pock counting The results are shown in the accompanying figure Each point on the graph is the arithmetic mean of the titres of surviving virus in the pair of phials

The initial titre of the virus was 6 0 × 10^8 p u per ml After 30 minutes the titre had fallen to 3 0 × 10^8 p u per ml and after 60 minutes to 6 0 × 10^7 p u per ml Thereafter there was no further detectable fall in titre up to 120 minutes Thus the vaccine from these two batches after 2 hours' exposure to 100°C contains sufficient living virus for 100% of successful vaccinations Since the dried material was in direct contact with the glass of the phial, it can be assumed that during the heating its temperature was not far short of the surrounding boiling water

Heat Resistance of Other Batches

Samples from seven other batches of dried vaccine selected at random were stored at 37°C and 45°C for 8 weeks After this period the samples stored at 45°C were each tested on groups of at least twenty five men and produced 100% of successful vaccinations Although when titrated by pock counting some of these batches showed slight deterioration at this temperature, the result of this test shows that the batch of vaccine used in the main storage test was not exceptionally heat-resistant

Comment

Public health authorities responsible for vaccination programmes involving the transport and storage of smallpox vaccine in hot climates with inadequate refrigeration will be relieved to know that a stable vaccine is available which will resist tropical temperatures for many months They will also be able to maintain reserves available for immediate distribution in epidemics, if these reserves are held in refrigerators they should have a very long life indeed So far we have not been able to detect any deterioration in refrigerated dried vaccine during periods of up to 2 years

Summary

The results of tests on a dried smallpox vaccine stored at 37°C and 45°C for up to 2 years are recorded

At the end of this period the vaccine stored at the higher temperature still produced 100% of successful vaccinations in man and showed only a slight decrease in potency by laboratory titration

A dried smallpox vaccine with such resistance to heat should solve the major difficulty in carrying out vaccination programmes in hot countries with poor transport and inadequate refrigerating facilities It would also enable adequate reserves to be held in these countries against epidemics.

The coöperation of Prof A W Downie, F R S, and Dr K R Dumbell, of the department of bacteriology, University of Liverpool, in the laboratory titrations of the vaccine is gratefully acknowledged

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PARTIAL MEGALOBLASTIC ERYTHROPOIESIS

IN ELDERLY ACHLORHYDRIC PATIENTS WITH MILD ANÆMIA

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DURING 1955 we tried to estimate the incidence of vitamin B_{12} deficiency in mainly elderly patients with histamine refractory achlorhydria This group was selected as being likely to contain cases with vitamin B_{12} deficiency because pernicious anæmia is associated with histamine refractory achlorhydria and is most common in the elderly

The primary diagnostic criteria of vitamin B_{12} deficiency were typical (Ehrlich) megaloblasts in the sternal bone-marrow and a typical response to treatment with vitamin B_{12} Supplementary investigations, including estimation of the level of vitamin B_{12} in the blood plasma, were also made

In this way we discovered quite a high frequency of patients with incipient or partial megaloblastic erythropoiesis and mild anæmia This group was compared with a group of achlorhydric patients with complete megaloblastic erythropoiesis (typical pernicious anæmia) Deficiency of iron and of vitamin C was common in both groups, especially the women—a finding which is of particular interest, because it makes the diagnosis of vitamin B_{12} deficiency more difficult

Material

The "*incidence material*" came from Medical Department E of the Frederiksberg Hospital, Copenhagen, and comprised all the cases diagnosed in 1955 as histamine refractory achlorhydria and subjected to a study of the bone marrow (which was done in as many of the patients as was practicable) These cases were compared with achlorhydric patients seen in 1954 (table I)

The "*compared material*" consisted of 13 achlorhydric patients with megaloblastic erythropoiesis observed in 1954 and 1955, supplemented by similar cases seen in 1956 to get two equally large groups of consecutively studied patients, one including 10 patients with total megaloblastic and the other 10 patients with partial, megaloblastic erythropoiesis

TABLE I—FREQUENCY OF STERNAL MARROW STUDIES AND INCIDENCE OF MEGALOBLASTIC ERYTHROPOIESIS IN PATIENTS WITH HISTAMINE-REFRACTORY ACHLORHYDRIA

Year	No. of patients admitted			No. examined for histamine refractory achlorhydria	No. with histamine refractory achlorhydria	No. submitted to sternal puncture	No. with megaloblastic erythropoiesis
	M	F	Total				
1954	907	1147	2054	384 (*18·5%*)	72 (*18·7%*)	30 (*41·7%*)	6 (*20·0%*)
1955	940	1228	2168	389 (*17·8%*)	93 (*23·9%*)	63 (*67·7%*)	13 (*20·6%*)

In addition, there were the patients with achlorhydria, ormoblastic erythropoiesis, and mild anæmia whose itamin-B$_{12}$ level in the plasma had been determined nd two control series of "healthy" elderly persons in one f which serum-vitamin-B$_{12}$ levels and in the other serum-ron levels had been determined.

Diagnosis and Treatment

Methods

The indications for examining a patient for achlorhydria were those ordinarily used in the department, especially astro intestinal complaints and anæmia. When histamine-efractory achlorhydria (fractional withdrawal of gastric uice for 60 minutes after subcutaneous injection of histamine ydrochloride 0·5 mg.) was found, we did a sternal puncture nd examined the blood in the ordinary way—hæmoglobin evel (100% = 14·8 g. of Hb per 100 ml.), red cell count, olour index $\frac{\text{Hb}\%}{(\text{erythrocytes (mill.)} \times 21)}$ total and differential hite cell counts, reticulocyte counts, and determination of he serum iron level by the method of Hoyer (1950) and of he ascorbic acid level (dichlorphenolindophenol method). If egaloblastic erythropoiesis was found, the level of vitamin B$_{12}$ in the plasma was determined by one of us (H. P. O. K.) using the *Lactobacillus leichmannii* 313 (Kristensen 1956).

The sternal marrow was examined (by A. S. O.) partly in sections after coagulation and mounting and partly in smears stained by the method of May Grünwald-Giemsa. Megaloblasts and promegaloblasts were counted and recorded per 400 white cells. Total megaloblastic erythropoiesis is taken to mean that the only red cells were promegaloblasts and megaloblasts, whereas in partial megaloblastic erythropoiesis there were both normoblasts and megaloblasts. Megaloblastic erythropoiesis was diagnosed only when megaloblasts and promegaloblasts of the classical Ehrlich type were found. The discovery of maturation disturbances of the granulocytes with pernicious anæmia neutrophils" without typical changes in the erythroblasts—interpreted during recent years as a mild deficiency of antimegaloblastic substances (Jones 1943, Fox et al. 1950, Bastrup Madsen 1954, Jewesbury 1954)—indicated the need for repeated examination, often after energetic treatment with iron. The same applies to the discovery of megaloblast like cells" "intermediary megaloblasts" and macronormoblasts."

Other tests included examination of the fæces for blood, kidney function tests, radiography of the stomach and intestines to detect cancer, sprue, strictures, &c., determination of the excretion of fat in the stools, and (in most cases) Coombs's test.

Many patients were treated first with iron and ascorbic acid, partly because of low serum iron levels and partly to accelerate, if possible, a megaloblastic alteration of the bone-marrow, which did not initially satisfy our criteria of megaloblastic erythropoiesis. When the diagnosis of megaloblastic erythropoiesis had been established, we administered vitamin B$_{12}$ parenterally (cyanocobalamin 30–60 µg. daily for ten days). Treatment was continued with liver preparations ('Hepsol Fortior') or an oral combined preparation ('Cycoplex' capsules, each containing dried pyloric mucosa 50 mg. and vitamin B$_{12}$ 5 µg.), as well as iron and ascorbic acid. The patients were kept in hospital as long as necessary and were followed up after discharge. Their blood and bone marrow were repeatedly examined to ascertain whether the erythropoiesis had returned to normal, the hæmoglobin level and erythrocyte count had satisfactorily increased, and the levels of iron, ascorbic acid, and vitamin B$_{12}$ had become normal.

Criteria

The diagnosis of *iron deficiency* was established by an increase in the reticulocytes and the colour index during iron medication (either oral or parenteral) before antimegaloblastic treatment. Since the effect of iron was not specially investigated in all the cases, other criteria were also used (see below).

The diagnosis of *vitamin-C deficiency* was established by a serum ascorbic acid level of 180 µg. or less per 100 ml., followed by an increase to normal after treatment with ascorbic acid.

The diagnosis of *vitamin-B$_{12}$ deficiency* was established by a decrease in the megaloblastic erythropoiesis in direct time relation to treatment with pure cyanocobalamin accompanied by a typical fall of the serum iron level and an increase in the reticulocytes followed by an increase in the red cells to 4,500,000 per c.mm. in uncomplicated cases.

The diagnosis of *nephrogenous hæmolytic anæmia* was established by a spontaneous reticulocytosis of at least 4% after an abrupt decrease in the hæmoglobin and the red cells or persistent spontaneous reticulocytosis of at least 2% in patients with impaired renal function.

Results and Comments

"INCIDENCE MATERIAL"

In table I the material of 1955 is compared with that of 1954. Twice as many achlorhydric patients had their bone-marrow examined in 1955, and twice as many cases of megaloblastic erythropoiesis were found, as in 1954. The frequency with which the erythropoiesis of the cases submitted to bone marrow study was interpreted as megaloblastic (20%) was unchanged from 1954 to 1955. Moreover the frequency with which the patients were examined for achlorhydria was the same (18%). Since, furthermore, achlorhydria was found only slightly more often in 1955, the findings indicate that technique, indications, and interpretation had not changed in 1955 except for the more frequent examination of the bone-marrow.

The frequent bone-marrow studies in achlorhydric patients in 1955 seem to be the main reason why the number of patients with newly diagnosed megaloblastic erythropoiesis was doubled.

Of the 93 patients (30 men and 63 women) in 1955 with histamine refractory achlorhydria 7 had incipient or partial megaloblastic erythropoiesis. These patients belonged to the group of 51 who satisfied the criteria of mild anæmia (Hb 51–84%), age over 50, and no definite signs of pernicious anæmia. Of these 51 patients 5 did not have their bone-marrow studied, but, since they did not differ in other respects from the remaining 46

TABLE II—AVERAGE FINDINGS IN 51 ACHLORHYDRIC PATIENTS SEEN IN 1955, AGED 50 OR MORE, WITH MILD ANÆMIA BUT WITHOUT MANIFEST PERNICIOUS ANÆMIA (TOTAL MEGALOBLASTIC ERYTHROPOIESIS)

—	Erythropoiesis (sternal marrow)			
	Normoblastic	Partially megaloblastic	Total	Not examined
Total number	39	7	46	5
Men	8	0	8	1
Women	31	7	38	4
Age (yr.)	69	66	68	67
Hb (%)	68	71	68	70
Red cells (millions per c.mm.)	3·10	3·13	3·30	3·40
Colour index	0·95	1·05	0·96	0·98
Serum iron level (µg. per 100 ml.)	54	56	51	43

TABLE III—FINDINGS IN 10 PATIENTS (7 FEMALES AND 3 MALES) WITH TOTAL AND 10 (8 FEMALES AND 2 MALES) WITH PARTIAL MEGALOBLASTIC ERYTHROPOIESIS BEFORE AND AFTER TREATMENT

Finding	Megaloblastic erythropoiesis			
	Before treatment		After treatment	
	Total	Partial	Total	Partial
Age (yr.)	41–81 (av. 66)	53–87 (av. 69)		
Promegaloblasts and megaloblasts in bone marrow				
Per 100 "white" cells	678–177 (av. 310)	101–11 (av. 55)		
Per 100 "red" cells	100 (av. 100)	91–11 (av. 43)		
Hæmoglobin (%)	33–63 (av. 45)	51–83 (av. 71)	88–111 (av. 100)	85–100 (av. 9
Red cells (millions per c.mm.)	1·13–2·21 (av. 1·65)	2·15–4·62 (av. 3·11)	1·62–5·17 (av. 4·98)	4·02–4·56 (av. 4·
Colour index	1·16–1·56 (av. 1·30)	0·96–1·11 (av. 1·09)	0·85–1·07 (av. 0·96)	0·91–1·07 (av. 1·
Serum iron (µg. per 100 ml.)	15–200 (av. 120)	7–109 (av. 76)		
Plasma level of vitamin B_{12} (µµg. per ml.)	10–85 (av. 52)	55–205 (av. 127)		
Serum ascorbic acid (µg. per 100 ml.)	90–180 (av. 143)	20–160 (av. 144)		
Highest reticulocyte count after vitamin B_{12} therapy (per 1000 red cells)			62–276 (av. 115)	20–200 (av.

(table II), the incidence of partial megaloblastic erythropoiesis was very probably the same, therefore we can disregard these 5 in computing the incidence. The 46 patients thus make up a series in which the incidence of partial megaloblastic erythropoiesis can be computed. The result is as follows: in 46 consecutive patients, aged more than 50, with histamine-refractory achlorhydria and mild anæmia but no definite signs of pernicious anæmia, the bone marrow showed that 7 had incipient or partial megaloblastic erythropoiesis.

Table II shows that the sex-distribution in the series is so unequal that the incidence of partial megaloblastic erythropoiesis seems to be about 20% for women (7/38) and is unknown for men (0/8). The same table shows that the difference between the 7 patients with partial megaloblastic erythropoiesis and the others as regards age, hæmoglobin level, red-cell count, colour index, and serum iron level is so slight that the true nature of the erythropoiesis will very easily escape detection if the bone marrow is not examined (see also discussion below).

"COMPARED MATERIAL"

Table III gives average data for 10 cases of total and 10 cases of partial megaloblastic erythropoiesis. The data for the 10 patients with partial megaloblastic erythropoiesis have already been reported by Pedersen et al. (1957b).

Sex and Age

The distribution is the same in both groups.

Bone marrow

As might be expected, the greatest changes were found in patients with total megaloblastic erythropoiesis. In partial megaloblastic erythropoiesis about 10–90% (average 43%) of the erythroblasts were megaloblastic. In 3 cases definite Ehrlich megaloblasts did not develop until intensive treatment with iron had been given, and in 2 cases macroforms in the granulocytes (e.g., giant metamyelocytes) were seen when typical megaloblasts were not yet present.

Hæmoglobin, Erythrocyte count, and Colour index

In the 10 patients with total megaloblastic erythropoiesis these factors were typical of pernicious anæmia. All the patients with partial megaloblastic erythropoiesis had mild anæmia, but a few were at the limit of normal. Later we had occasion to diagnose partial megaloblastic erythropoiesis in non-anæmic patients, as might be expected. The colour index was surprisingly low in this group (average 1·09). Only 3 of the 10 had a colour index above normal (≧1·15), and in 2 cases the colour index was <1·00. In the patients with partial megaloblastic erythropoiesis the blood smears showed some macrocytosis of the red cells, but the variations in their size were not thoroughly examined. Like the erythrocyte counts, the average leucocyte and thrombocyte counts were decreased, mostly in patients with total megaloblastic erythropoiesis. Lymphocytosis too was more pronounced and macropolycytes were more commonly seen in total megaloblastic erythropoiesis.

Serum iron Level

On the average, the levels were only 120 and 76 µg. per 100 ml. in total and in partial megaloblastic erythropoiesis respectively. In the 5 men it was 150 µg. per 100 ml. and in the 15 women 81 µg. per 100 ml. In comparison, in 9 men and 9 women aged more than 50 (average 65) without anæmia and with normal gastric secretion the serum iron levels were 107 and 103 µg. per 100 ml. respectively (Pedersen et al. 1957a). Thus, whereas the men had a raised serum iron level, as might be expected in pernicious anæmia, the women, both those with total and those with partial megaloblastic erythropoiesis, had a lower serum iron level than normal. Without doubt the main cause of this low initial serum iron level was iron deficiency (Pedersen et al. 1957a). In 5 patients with an initial serum-iron level of 100 µg. per 100 ml. at the most we observed a reticulocytosis, and an increase in the colour index and sometimes in the hæmoglobin during intensive treatment with iron before antimegaloblastic treatment was instituted. Afterwards, the latter caused a second typical reticulocytosis and a fall in the serum-iron level.

In addition, the following facts gave indirect proof of iron deficiency:

(1) Some initial serum iron levels were so low (≦8 µg. per 100 ml.) that they were only explicable by iron deficiency.

(2) When the initial serum iron levels were somewhat higher (up to 100 µg. per 100 ml.) we found such low values (≦30 µg. per 100 ml.) immediately after the institution of antimegaloblastic therapy that iron deficiency must be considered proved.

(3) As mentioned above, iron and ascorbic acid were often administered before antimegaloblastic therapy was started. Lately we routinely continued or instituted this treatment with iron and ascorbic acid at the same time as specific therapy. Despite this iron medication we found serum iron levels of ≦10 µg. per 100 ml. in several patients after having administered specific therapy for some time. In some of the

cases it was necessary to give an intravenous injection of about 2–3 g of iron before the iron deficiency was overcome

In the present series 16 of the 20 patients appear to have had iron deficiency which was demonstrable, in most of the cases, at the time when megaloblastic erythropoiesis was diagnosed Both groups of patients with megaloblastic erythropoiesis, particularly the women, characteristically had vitamin-B_{12} deficiency and iron-deficiency anæmia It seems characteristic also that the iron deficiency was traced back to hæmorrhage in only 2 cases

Plasma-vitamin-B_{12} Level

In 19 cases the vitamin-B_{12} level in the blood-plasma was determined on one to three occasions before anti-megaloblastic therapy was instituted In the patients with total megaloblastic erythropoiesis the vitamin-B_{12} level was, as expected, very low (average 52 μμg per ml) In the patients with partial megaloblastic erythropoiesis the corresponding value was 127 μμg per ml (in 4 cases <100, in 3 cases 100–150, and in another 3 >150 μμg per ml) Table IV, which also gives the intra-individual variation, compares these two groups with a group of patients with achlorhydria but without megaloblastic changes in the bone marrow (from the "incidence material") and with a group of "healthy" persons in whom the gastric secretion and sternal bone marrow were not examined In the last two groups the average values were 275 and 395 μμg per ml respectively The average values conform to the degree of megaloblastic alteration in the bone marrow in the three achlorhydric groups In addition, the table makes clear the far from surprising fact that pernicious anæmia does not comply with an all or nothing law Although the four groups overlap, the agreement between the bone marrow findings and the vitamin B_{12} levels in the plasma is so good that determination of the latter can apparently restrict the number of patients who need a bone marrow examination or other tests, when a deficiency of vitamin B_{12} is suspected

TABLE IV—PLASMA LEVEL OF VITAMIN B_{12} IN ANÆMIC PATIENTS WITH HISTAMINE REFRACTORY ACHLORHYDRIA AND IN HEALTHY NON ANÆMIC PEOPLE

Group	Age (yr)	No of persons	Histamine refractory achlorhydria	Megaloblastic erythropoiesis	Plasma level of vitamin B_{12} (μμg per ml)
Severe anæmia (Hb 45 %)	44–84	10	+	Total	10–100 (av 52)
Mild anæmia (Hb 71 %)	53–87	10	+	Partial	(40) 70–220 (av 127)
Mild anæmia (Hb 70 %)	50–86	26	+	None	88–725 (av 275)
Healthy people* (Hb ≧ 85 %)	67–88	29	Not examined	Not examined	190–770 (av 395)

* Kristensen's (1956) series

Serum ascorbic acid Level

The initial serum ascorbic acid level was estimated in 15 of 20 patients and found to be low in 12 (extremely low in some of them) There was no difference between the two groups, hence the vitamin-C deficiency may be added to the iron deficiency and the vitamin-B_{12} deficiency as a characteristic of both groups

Tongue Signs and Neurological Signs

Of the patients with total megaloblastic erythropoiesis 7 presented objective tongue signs and 3 loss of reflexes, whereas of those with partial megaloblastic erythropoiesis 5 had objective tongue signs and 3 paresis or loss of reflexes

Clinical Types with Partial Megaloblastic Erythropoiesis

The patients in this group appear to fall into two clinical types

(1) An ordinary pernicious anæmia type (in our series 4 elderly grey haired blue eyed women in a good nutritional state—e g , case 1)

(2) The other type—represented by 4 or 5 cases—was characterised by its complications and by the multiple origin of the anæmia Patients in the second category might present—in addition to anæmia with deficiencies of iron, vitamin C, and vitamin B_{12}—nephrogenic, more or less hæmolytic, anæmia as well as infectious and/or toxic anæmia—e g , case 3

Case 2 represents a transition between these two types

Illustrative Case reports

Case 1 *sideropenic anæmia + megaloblastic anæmia* —A woman, aged 74, somewhat arteriosclerotic but otherwise well preserved, was admitted in 1953 with degenerative osteo arthritis of the knees and Hb 91%, and readmitted in 1954 with the same condition and Hb 85%, red cells 4,040,000 per c mm , and colour-index 1 00 In 1955 she was admitted complaining of intermittent diarrhœa She had Hb 72%, red cells 3,520,000 per c mm , colour index 0 90, serum iron level 37 μg per 100 ml , and serum ascorbic acid level 122 μg per 100 ml Histamine test showed achlorhydria, and plasma vitamin-B_{12} level was 120 μμg per ml Sternal puncture revealed normoblastic erythropoiesis, but the granulocytes showed large neutrophil forms with hypersegmented nuclei After intensive iron medication the Hb increased to 85% and the colour index to 1 10, and there was a simultaneous increase in the reticulocytes A month later there was unequivocal partial megaloblastic erythropoiesis, and the plasma-vitamin B_{12} level was 135 μμg per ml Administration of vitamin B_{12} produced a renewed increase and decrease in the reticulocytes and a return of the bone marrow to normal The other usual hæmatological data did not become normal, however, until intensive treatment with iron, vitamin C, and hepsol had been continued for ten months The only reasons that could be suggested were arteriosclerosis and old age , there were no radiological changes in the stomach and intestines and no increased excretion of fat in the fæces

Case 2 *sideropenic anæmia + megaloblastic anæmia + mild nephrogenic anæmia* —A woman, aged 53 who for the past twenty-three years had noticed burning of the tongue and had been receiving "acid tablets" for many years, had been admitted many times to other hospitals with migraine, muscle pain, and nervousness During the past six months she had been getting ever more tired and nervous A month before admission she entered the psychiatric department of our hospital with the diagnosis of mental depression and hysteria During her stay there her Hb decreased from 89 to 74%, red cells from 3,950,000 per c mm to 3,500,000 per c mm , and colour-index from 1 08 to 1 00 Sternal marrow showed incipient megaloblastic erythropoiesis The serum iron level was 68 μg per 100 ml , the ascorbic acid level 120 μg per 100 ml , and the plasma vitamin B_{12} level 85 μμg per ml Treatment, first with iron and vitamin C and later with vitamin B_{12} produced an increase and decrease of the reticulocytes on both occasions and a return of the sternal bone marrow to normal after vitamin B_{12} therapy It was not until the treatment had been given for six months however, that the blood values became satisfactory In addition to iron deficiency and vitamin B_{12} deficiency the patient had chronic pyelonephritis with occasional albuminuria and colipyuria (treated with various antibiotics) and slightly impaired renal function After treatment she felt "completely transformed", her tongue signs and fatigue had disappeared

Case 3 *sideropenic anæmia + megaloblastic anæmia + nephrogenic anæmia with hæmolytic component + toxic infectious anæmia* —A woman, aged 55, had been admitted several times during the past ten years with various muscle pains, colitis, pyelitis (*Esch coli*) and poisoning with phenacetin A month before admission to our department her Hb was 80%, red cell count 3,340,000 per c mm , and colour index 0 94 She had previously been energetic and efficient but during the past few years things had gone wrong She had not been out of doors for the past eighteen months and had been confined to bed for the past nine months (partly because of a fracture of the spine). She was known as a phenacetin addict and often had to be given injections of morphine by the night doctor. She was transferred from the psychiatric department because of pain in her abdomen and loin, malaise, nausea, and vomiting. She had flaccid muscles and was anæmic, yawning, sleepy, grey cyanosed like "tablet eaters," and looking more debilitated at first glance than later. Her Hb was 67%, colour index 1.20, serum iron level 52 µg per 100 ml., ascorbic acid level 130 µg per 100 ml., and plasma vitamin B_{12} 203 µµg per ml. Sternal marrow showed partial but severe megaloblastic erythropoiesis. During the first few days her temperature rose, and on the sixth day colibacillæmia was found. Blood-transfusion, iron, ascorbic acid, and vitamin B_{12} produced a striking increase in reticulocytes (20%) on the seventh day after the start of vitamin-B_{12} therapy, but at the same time the Hb decreased to 43% and the colour index to 1.07. This was no doubt because of a hæmolytic crisis due to the colisepsis in connection with kidney disease (albuminuria 0.8 g. per 100 ml., impaired power of concentration), and methæmoglobinæmia (0.8 per 100 ml.). However, on the fourteenth day of vitamin B_{12} therapy the erythropoiesis was normoblastic. The infection was treated with penicillin, streptomycin, and erythromycin and eventually responded after four weeks' treatment. Thereupon the blood values rapidly increased. Provocative doses of phenacetin and sulphathiazole did not produce any reticulocytosis or decrease in Hb. By energetic training and continued treatment of the anæmia we got the patient out of bed. She put on 7 kg in weight, her erythrocyte sedimentation rate fell, and she was "feeling better than in the past fifteen years." After her discharge the blood values tended to fall slightly when she began "tablet eating" again (methæmoglobinæmia 0.5 per 100 ml.).

Response to Treatment

In the patients with total megaloblastic erythropoiesis the reticulocytes and other blood values increased appropriately in a reasonable time (table III). On the treatment used, the levels of vitamin B_{12}, iron, and ascorbic acid in the serum were fairly easy to keep normal.

In the patients with partial megaloblastic erythropoiesis the increase in reticulocytes after treatment with iron + ascorbic acid and with vitamin B_{12} was also appropriate in view of the high initial values of Hb and red cells (table III). The bone-marrow was immediately rendered normoblastic by vitamin B_{12} therapy, and the ascorbic acid and vitamin-B_{12} levels in the serum rapidly returned to normal. On the other hand, it was difficult to keep the serum iron levels normal in some patients, who required 2–3 g. intravenously for a few months before this was accomplished. It was also difficult to obtain a sufficient increase in the Hb and red cells in these patients. This was explained partly by the presence of anæmia of multiple origin, but often six months' intensive treatment with iron, ascorbic acid, and vitamin B_{12} was necessary, also in the ordinary pernicious anæmia type. In 3 patients no explanation other than arteriosclerosis was found. The most intensive therapy was necessary in the patients with partial megaloblastic erythropoiesis, but it was extremely successful when the complications were not too disabling.

Discussion

Incidence of Partial Megaloblastic Erythropoiesis

So far as we know, no other study on partial megaloblastic erythropoiesis, confirmed by sternal puncture, in achlorhydric people has been published; but its incidence, as found by us, fits in with recent studies on the incidence of gastric atrophy and reduced absorption of radioactive vitamin B_{12} in achlorhydric people.

From biopsies of gastric mucosa in 42 cases of hypochromic anæmia Davidson and Markson (1955) concluded that anæmia might coexist with a normal stomach, with atrophic gastritis, and with gastric atrophy. There were no specific changes of the gastric mucosa in hypochromic anæmia, although abnormalities were more common than in a control series of 31 non-anæmic patients. Gastric atrophy was equally common in both groups—10% and 13% respectively. From their data it can be calculated that 24 patients (20 with secondary anæmia and 4 without anæmia) had histamine-refractory achlorhydria, and that 7 of them had gastric atrophy either equal to or approaching that which is typical of pernicious anæmia.

Badenoch (1954), examining biopsy specimens from 24 patients with hypochromic anæmia and achlorhydria, found severe gastric atrophy in 7. In 1 of them the changes were indistinguishable from the atrophy of pernicious anæmia, and in 6 the changes approached this form of atrophy. In 4 of the patients the absorption of radioactive vitamin B_{12} was decreased.

Finally, Schilling et al. (1955), studying 31 patients with various diseases but all with histamine-refractory achlorhydria without "laboratory evidence of pernicious anæmia," found decreased absorption of vitamin B_{12} in 8.

We have added figures from the above studies to those derived from the present study. The results are as follows: of 48 patients with histamine-refractory achlorhydria with or without anæmia 14 had gastric atrophy (in other words, they ran a great risk of developing pernicious anæmia); in 12 of 55 such patients the quantity of intrinsic factor was reduced (i.e., they were already developing pernicious anæmia); and 7 of 46 such patients had unequivocal megaloblastic erythropoiesis, probably due to incipient pernicious anæmia in most cases.

If we disregard the number of patients, their age distribution, diseases, &c., the trend of these figures suggests that the incidence of partial megaloblastic erythropoiesis found by us is probably not too high. Moreover Davies (1931), in a careful study of the peripheral blood of 15 patients with histamine-refractory achlorhydria and secondary anæmia, found indubitable "dimorphous anæmia" in 2.

Iron Deficiency Combined with Vitamin B_{12} Deficiency

Most of the patients in the "compared material" had anæmia due to iron deficiency and vitamin B_{12} deficiency. The frequent coexistence of these two deficiencies, especially in women, has been emphasised by Whitby and Britton (1953), and Trowell (1943, 1944) used the designation dimorphous anæmia for this combination in African Negroes.

Iron deficiency is severe both in patients with total and in patients with partial megaloblastic erythropoiesis, but the vitamin B_{12} deficiency is considerably more severe in patients with total megaloblastic erythropoiesis. As a result patients with total megaloblastic erythropoiesis appear clinically to have pernicious anæmia complicated by iron deficiency, and the usual diagnostic criteria of pernicious anæmia are not obscured thereby, except that there is no initial increase in the serum iron level. Since patients with pernicious anæmia are usually under thorough hæmatological supervision the iron deficiency is nearly always diagnosed, usually when the blood ceases to improve despite continued anti-megaloblastic treatment—a phenomenon well known to clinicians.

With patients who have partial megaloblastic erythropoiesis this is not so. The anæmia presents the characteristics of iron deficiency or other form of simple anæmia and the complicating vitamin B_{12} deficiency may easily escape diagnosis for a very long time. The primary diagnostic difficulties may be seen from tables II and III. There is a negligible difference between the average data for patients with normoblastic (sideropenic) anæmia and patients who also have partial megaloblastic erythropoiesis. The typical effects of the two deficiencies proceed in opposite directions and may neutralise each other in some hæmatological data, which therefore give a false impression, the colour-index and the serum iron, for instance, not being increased (tables II and III). In 1 of our patients (with 55 µµg of vitamin B_{12} per ml. of plasma) the colour index was 0.95 and the serum iron level 46 µµg per 100 ml.; this does not immediately suggest megaloblastic erythropoiesis.

When the mild anæmia has been treated and perhaps partly remedied with, for example, iron, the complicating vitamin-B_{12} deficiency is seldom diagnosed, because such patients are usually not submitted to thorough hæmatological control. This very time, however, would be good for discovering vitamin-B_{12} deficiency because it seems that when one deficiency is relieved another is unmasked. Although perhaps the causal relationship has not been strictly proved, iron therapy seems to promote the signs of deficiency of antimegaloblastic substances. Heath (1932), Miller and Dameshek (1941), and Trowell (1943, 1944) reported cases of pronounced normoblastic iron-deficiency anæmia which bone-marrow studies showed to have become megaloblastic when treated with iron—to the great surprise of the investigators. In obscure cases we have, as mentioned above, systematically used intensive iron therapy to this end and have thereby induced typically megaloblastic erythropoiesis.

Partial is more interesting than total megaloblastic erythropoiesis with iron deficiency because in this condition it is more difficult to diagnose vitamin-B_{12} deficiency and iron deficiency. This difficulty, however, has probably not prevented correct treatment in some cases in spite of an incorrect diagnosis—e.g., when liver therapy has been successful in dealing with the anæmia of achlorhydric patients after iron has proved ineffective.

Since vitamin-B_{12} deficiency is not uncommon in achlorhydric patients with mild anæmia and is often complicated by iron deficiency and/or anæmia of multiple origin, a closer examination of the peripheral blood picture and a more frequent use of sternal bone-marrow are essential if this condition is to be diagnosed more often. Besides, determination of the vitamin-B_{12} content of the blood and repeated examination of the bone-marrow after intensive treatment with iron seem to be important diagnostic procedures.

Vitamin C Deficiency

This condition was found in nearly all the patients in both groups. Since vitamin C increases the uptake of dietary iron (Moore 1955), vitamin C deficiency may be expected to contribute to the iron deficiency. Vitamin-C deficiency may play a part in the development of megaloblastic erythropoiesis because vitamin C takes part in the metabolism of folic acid; but we have not observed any decrease of megaloblastic erythropoiesis or of reticulocytosis after the administration of large doses of ascorbic acid, even though the serum ascorbic-acid level has been brought back to normal by this treatment.

Deficient Diet of Aged Persons with Achlorhydria

Since cancer and hæmorrhage were found only in exceptional cases, the main cause of iron deficiency must be a decrease in absorption and/or administration of iron. The absorption of iron must have been greatly reduced in those patients in whom only intravenous administration could deal with the iron deficiency. But the diet may also have been poor, qualitatively and/or quantitatively. Although a purely nutritional iron deficiency anæmia in men and postmenopausal women is often considered merely a theoretical possibility, a diet which per se is not particularly poor may become so insufficient for an achlorhydric person with little appetite, dyspepsia, and poor absorption that a previously acquired iron deficiency persists. However, the pronounced vitamin C deficiency indicates that the diet would have been faulty even for healthy people, because we have so far seen only 1 patient who could not absorb vitamin C given by mouth. We have found that lonely old people often take incredibly little and of a very poor diet. This agrees with more elaborate geriatric studies (Eckerström and Geill 1955, Lyons and Trulson 1956). It therefore seems probable that the iron deficiency is due not exclusively to a reduced capacity to absorb iron but also to insufficient nutrition. Achlorhydric and other dyspeptic patients—especially elderly women—appear to be particularly exposed to such faulty nutrition.

Possibly some of our cases of vitamin-B_{12} deficiency were partly due to inadequate diet (cf. Harrison et al. 1956). To investigate this question further studies with labelled vitamin B_{12} and gastric biopsies would be necessary.

Summary

Serial studies of the sternal marrow in 46 patients, aged 50 or more, with histamine-refractory achlorhydria and mild anæmia but no manifest pernicious anæmia showed that 7 had partial or incipient megaloblastic erythropoiesis. This incidence agrees with recent studies on the incidence of gastric atrophy and reduced absorption of vitamin B_{12} in achlorhydric people.

Partial megaloblastic erythropoiesis in patients with mild anæmia is too seldom diagnosed because mild vitamin-B_{12} deficiency is often masked by more or less severe iron deficiency (dimorphous anæmia) and vitamin-C deficiency and/or anæmia of a different pathogenesis; hence some ordinary hæmatological studies (colour-index, serum-iron level) may be misleading. Studies of the sternal marrow are therefore of the utmost diagnostic significance. Determination of the vitamin-B_{12} level in the blood may also acquire importance, and it is emphasised that relief of iron deficiency may accelerate the signs of vitamin-B_{12} deficiency in the erythropoiesis.

Two clinical types with partial megaloblastic erythropoiesis are described: one is characterised by incipient ordinary pernicious anæmia complicated by iron-deficiency anæmia, and the other by anæmia of multiple origin.

Treatment with iron and vitamins B_{12} and C is rewarding but has to be intensive and prolonged (this applies particularly to the iron medication) before the blood returns to normal.

As the vitamin-B_{12} level in the blood-plasma falls, we can recognise four categories: (1) apparently healthy people, (2) histamine-refractory achlorhydric people with normoblastic erythropoiesis, (3) partial megaloblastic erythropoiesis, and (4) total megaloblastic erythropoiesis. The transition between the groups appears to be fairly even, as might be expected.

Unlike the vitamin-B_{12} deficiency, the incidence of iron and vitamin-C deficiencies appears to be equal in patients with total and in patients with partial megaloblastic erythropoiesis. Vitamin-C deficiency is due to a faulty diet, and iron deficiency to insufficient absorption and, probably, a poor diet as well.

Elderly achlorhydric people, especially women, probably often receive a diet which is very poor both qualitatively and quantitatively.

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TRACHEOTOMY FOR FLAIL CHEST

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INJURIES to the thorax, with fracture of one or more ribs or costal cartilages, are very common and are quite simply and satisfactorily treated in most cases, but the crush injury causing multiple fracture of ribs and costal cartilages, producing "stove-in" or "flail" chest, with its paradoxical movement, is surprisingly rare Proctor and London (1955) collected only 8 recorded cases of stove-in chest, with paradoxical respiration requiring surgical treatment in 344,000 injured persons treated at the Birmingham Accident Hospital in 1944–52, only 1 of the 8 patients survived The gravity of this condition and its high mortality are emphasised by many workers—e g, Cameron et al (1949), Coope (1948), Elkin and Cooper (1943), Gardner (1946), Heroy and Eggleston (1951), and Rives and Kahle (1939)

Results of Flail Chest

The pain on breathing limits the respiratory excursion of the chest, and the paradoxical movement of the unstable part of the chest wall reduces still further the tidal volume—i e, the breathing is shallow and inefficient, and aeration of the lungs is poor

More rapid and vigorous respiratory efforts result, involving the accessory muscles of respiration, with accompanying exhaustion and increased pain

There is loss of effective cough, with accumulation in the tracheobronchial tree of secretions which increase the resistance to inspiration and expiration The intrapleural negative pressure on inspiration is greatly increased and on expiration is decreased or may become positive This increases paradoxical movement The deterioration in the patient's condition at this stage is often striking and alarming

Considerable anxiety is caused by a sense of suffocation (Heroy and Eggleston 1951)

Treatment

In the mild case adhesive strapping may suffice, for the more severe injuries most workers suggest skeletal traction applied to the ribs, costal cartilages, or sternum (Bailey and Matheson 1953, Butler 1938, Davis 1956, DeBakey 1942, Dolley and Brewer 1942, Wise 1942)

Jaslow (1946) describes the use of towel clips and screw-hooks Jones and Richardson (1926) the use of cervical forceps, and Proctor and London (1955) the use of cup hooks, applied to the sternum in each case Heroy and Eggleston (1951) used a sharp clamp designed originally for reducing Bennett's fracture Williams (1948) used pericostal traction with towel clips

McKim (1943) treated a case by open operation and reduction of the displacement, inserting Kirschner wires across the fracture sites, and Sweet (1954) advises open operation and fixation of each fracture with stainless steel wire Coleman and Coleman (1950) advise wiring each fracture, sometimes with the addition of an intramedullary peg, in their cases the average number of ribs so treated was 6, but in one case 16 ribs were wired

Belsey (1953) and Bonnin (1951) advise a plaster of paris cuirass to immobilise the floating segment

Hagen (1945) described an interesting case in which he used a Drinker respirator and Brooks (1942) found the Nuffield respirator satisfactory for this purpose Gray (1942) and Watson Jones (1955) also advise the use of a mechanical respirator

In all these instances apparatus is required which may not be at hand and requires careful and continuous surveillance Skeletal traction also entails the risk of infection which it is so important to avoid in this condition Skeletal traction appears to have little effect in preventing the ultimate deformity of the thorax (Jones and Richardson 1926, Proctor and London 1955)

Treatment of flail chest by tracheotomy has been described by Carter and Giuseffi (1953), who have used the method since 1949, and the treatment in the two cases described here was based on their method

In a survey of the indications for tracheotomy in modern medicine and surgery (Pitman and Wilson 1955) flail chest was not mentioned, nor was it included in the discussion on the value of tracheotomy in acutely ill surgical patients by Colvin and Morrison (1953), who emphasise, however, the importance of prophylactic tracheotomy in very ill post operative patients in whom the cough is expected to be ineffective

Rationale of Tracheotomy

1 The tracheobronchial tree can be aspirated easily and quickly by the nurses to remove the secretions which accumulate owing to the lack of effective cough and tend to produce the "wet lung" syndrome described by Brewer et al (1946) The removal of bronchial secretions reduces the resistance to air movements in the tracheobronchial tree and removes the sense of suffocation

Aspiration through the tracheotomy tube is far simpler and less exhausting to the patient than the repeated bronchoscopic aspiration advised by most workers

2 Dead space is reduced by about 60–75 c cm, the volume of the mouth, nose, and pharynx in anæsthetised patients (Guedel and Waters 1928) Carter and Giuseffi (1953), working on necropsy specimens, found the average volume to be 117 c cm, but one would expect the dead space to be less in the living, owing to the tone of the pharyngeal constrictors Tidal volume is much reduced when paradoxical movement of a segment of the thoracic wall takes place, and the reduction in dead space brought about by tracheotomy, and the equivalent increase in *effective* tidal volume, are probably of clinical importance in the efficacy of tracheotomy

3 The resistance to air movements imposed by the upper air passages, chiefly owing to the small cross section area of the glottis, and caused by the turbulence of air currents in the pharynx, nose, and mouth, is removed, hence respiratory movements can take place more freely The range of negative pressure in the thorax between the limits of the respiratory cycle is reduced, and there is thus less tendency for the "floating segment" of the thoracic cage to be sucked in on inspiration and blown out on expiration (Carter and Giuseffi 1951) Clinically this is apparent in the visibly decreased amplitude of the paradoxical movement Again this favours an increased effective tidal volume, with the expenditure of less energy and causing less pain

4 Oxygen consumption is decreased because of the diminished muscular exertion needed to provide satisfactory ventilation

Each of these four factors contribute something to break a vicious circle and to change laboured, rapid, and shallow into easier, deeper, and slower breathing

With the relief of dyspnœa and pain the patient becomes less frightened and can relax and sleep

One must anticipate the complications of hæmothorax, which occurs frequently after chest injuries (Butler 1938) and may become manifest some days after injury (Cato and Norman 1940), and perhaps pneumothorax, either of which will reduce the patient's vital capacity and increase dyspnœa or accelerate its onset

Tracheotomy is easy to effect under local anæsthesia, but the patient has to lie supine and quite still for a few minutes As indicated in case 2, the onset of complications causes dyspnœa and extreme discomfort when the patient is supine For these reasons it is suggested that tracheotomy should be seriously considered in all cases of flail chest immediately on admission

Case-reports

Case 1—A lorry driver, aged 45, was admitted to the Pontefract General Infirmary on March 5, 1955 He had been leaning over the chassis of his tipping lorry doing maintenance work, with the body of the lorry in the raised position, when the hydraulic mechanism failed and the body descended He sustained a crush injury to the thorax and minor abrasions

On examination he had traumatic asphyxia with exophthalmos, hæmorrhages into the conjunctivæ, petechiæ into the facial skin, and paradoxical sternal movement grotesque in its amplitude He was very anxious, restless, and slightly cyanotic and complained of severe pain in his chest His respirations were only slightly increased in rate but were very laboured, involving the accessory muscles of respiration Radiography showed anterior fractures of ribs 2–7 on the right side and clinically there were also fractures of the costal cartilages or separation at the costochondral junctions 2–6 on the left side

Treatment and Progress—Strapping was applied to the front of thorax, but this did little to diminish the paradoxical movement or to ease the pain Penethamate hydriodide ('Estopen') 500,000 units b d was given prophylactically During the night the patient's chest became wet, and by next morning his respirations were 50 a minute, and his inability to cough, due to both pain and lack of tussive force, caused great distress Tracheotomy was done, under local anæsthesia (2% lignocaine), through a vertical incision, the isthmus of the thyroid gland being divided to give access to the second tracheal ring A Jaques's catheter inserted through the tracheotomy tube and attached to an anæsthetic suction pump removed a large amount of slightly bloodstained mucoid secretion from the trachea and main bronchi The patient was at once less distressed He was nursed in an almost sitting position in a steam tent, aspiration being done every fifteen minutes By the next day his respirations had decreased to 30 a minute, and thereafter they remained 24–30 a minute On the following day radiography showed partial collapse of the lower left lobe with elevation of the left diaphragm and slight surgical emphysema 'Alevaire' was then administered as a mist by attaching an oxygen cylinder to a nebuliser containing the detergent liquid This loosened the mucoid secretion and enabled it to be removed by the suction catheter, which was used as often as required The patient remarked on the efficacy of alevaire, and the treatment was given for a few minutes every hour On March 12 the patient was allowed up for bed making, and on March 14 the tracheotomy tube was removed At that time the paradoxical movement had almost ceased, the patient had no pain, and he had been able to expectorate for two or three days despite the presence of the tracheotomy tube He continued to expectorate large quantities of sputum but had a little dyspnœa at night for some time Serial radiographs showed gradual improvement and expansion of the left lower lobe The patient was discharged from hospital on March 22, 1955, to a convalescent hospital and was finally discharged on April 9, 1955

Follow up—Twenty months after the injury he had no disability, no depression of the sternum, and his chest expansion was $2^1/_2$ inches He had returned to his original work

Case 2—An electrician, aged 31, was admitted to the Pontefract General Infirmary on Nov 10, 1956, having been in a head on collision while driving a motor car He had the typical "steering-wheel" injury, with a very obvious paradoxical movement of the anterior part of the upper left chest He was rather shocked, his respirations were 40 a minute, and breathing was very laboured Radiography confirmed the clinical impression that the upper five left ribs were fractured, each at two sites anteriorly It was surprising that there was no damage to the subclavian vessels

Treatment and Progress—Zinc oxide strapping applied to the upper left chest did not improve the paradoxical movement or the pain Ten hours after the injury the patient was very distressed Moist sounds in his chest were audible without the use of a stethoscope There was now much cyanosis, and tracheotomy was done under local anæsthesia with 2% lignocaine The supine position was extremely distressing to the patient and the operation was done with some difficulty because of his restless movements As soon as the tracheotomy tube was inserted, a large amount of bloodstained mucoid secretion was aspirated with the suction catheter The patient was nursed in the sitting position in a steam tent, with intermittent inhalations of alevaire provided through a nebuliser Next day his cyanosis had disappeared, he was breathing easily, and, although paradoxical movement was still present, the excursion of the floating segment was much less Radiography on Nov 12 showed increased shadowing in the lower half of the left lung field and a pneumothorax estimated at 15% On Nov 13 there was an obvious collection of fluid in the left side of the chest, confirmed radiologically, and aspiration through the eighth intercostal space removed 300 ml of almost pure blood Next day a further 450 ml of blood was aspirated, and on the following morning 40 ml. of bloodstained fluid was removed, this latter with some difficulty Radiography on Nov 15 showed the upper half of the left chest to be occupied by pneumothorax and the lower half by collapsed lung and effusion The apex of the lung, however, showed aeration No further aspirations were done, and serial radiographs showed a rapid re-expansion of the lung and absorption of the pneumothorax and the remaining effusion By Nov 23 the paradoxical movement had completely ceased, the respiratory movements were free and painless, and there was good air entry at the left apex More vigorous breathing exercises were begun On Nov 28 the tracheotomy tube was removed without any following discomfort The patient was discharged from hospital on Dec 4 symptomless, with a slight depression of the anterior upper left chest but no other physical signs

At follow up he had no symptoms, a chest expansion of $3^1/_2$ inches, and had started work

Summary

Immediate tracheotomy is advocated for crush injuries of the chest causing flail chest

Physiological arguments, supported by clinical observations, indicate that tracheotomy breaks a vicious circle and produces less paradoxical movement, better pulmonary aeration, less pain, less expenditure of energy and ease in aspiration of the tracheobronchial tree

I wish to thank Mr J A Rhind, under whose care these cases were admitted and who advocated this method of treatment, for permission to publish and for advice and encouragement at all times

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ENDOCARDIAL FIBROSIS OF UNKNOWN ORIGIN

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ENDOCARDIAL fibrosis can occur in both infants and adults

In infancy, there is gross thickening of both fibrous and elastic elements in the endocardium, with little or no inflammation or involvement of the myocardium The condition is known as fibroelastosis or fœtal endocarditis, and, though its origin is obscure, Still and Boult (1956), using electron microscopy, have recently demonstrated superficial deposition of fibrin

In adults idiopathic endocardial or endomyocardial fibrosis is generally rare, but may be common in Africa (Ball et al 1954) It differs from infantile fibroelastosis in appearance and does not seem to be so well-defined Descriptions vary, but there is usually an increase in fibrous tissue in the endocardium and to a varying extent in the neighbouring myocardium The elastic tissue is ordinarily unaffected, and there is little or no inflammatory reaction

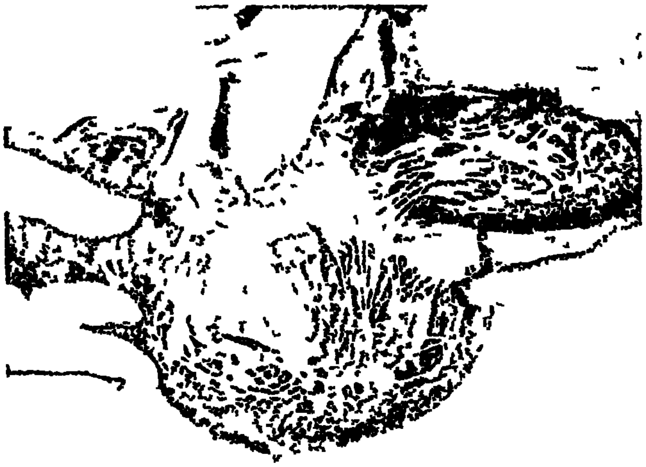

Fig 1—Interior of ventricles showing patchy endocardial fibrosis The myocardium is not involved

In the following case of the adult type, the notable features were the history of possible injury to the heart, the patchiness of the fibrosis, and the absence of elastosis and of involvement of the myocardium

Case-report

Mr A, a journalist aged 67, was admitted in March, 1956 with increasing breathlessness for two months

In 1914, whilst playing cricket abroad, he was hit on the heart ’ by the ball He immediately fell unconscious to the ground and lay there for five minutes Spectators thought he was dead A foreign doctor who saw him diagnosed ‘ concussion of the heart ” and treated him with an electric instrument over the precordium

He served in the Middle East and Gallipoli in the 1914–18 war, and apart from an attack of “ malaria ten years after his return home, he was well until October, 1954 At that time he had a “ strained heart ” and nocturnal frequency, and was admitted to hospital The heart appeared slightly enlarged, pulse rate 84, blood pressure (B.P) 160/95 mm Hg The heart sounds were normal and there was no dyspnœa or œdema Urinary investigations showed an enlarged prostate and a slight left hydronephrosis

In January, 1955, he had another attack of “ heart strain, but he was not admitted to hospital

Last Illness

History—Three months before admission he had become increasingly breathless During the previous three weeks his ankles had swollen and he had had an occasional hæmoptysis, for two days he had been cyanosed and very breathless, and had vomited frequently

He ate a normal diet and had no allergy He had never been to Africa, apart from war service in Egypt

Examination—He was a well nourished man with severe congestive heart-failure He had auricular fibrillation with a ventricular rate of 120 a minute A harsh systolic murmur was heard over the whole cardiac area The apex beat was 5 in from the midline in the 6th space, B P 110/80 A blood count showed a slight polymorphonuclear leucocytosis Total white cell count 14,600 per c mm (polymorphs 82% eosinophils nil)

Congestive heart-failure of unknown origin was diagnosed He died eight days after admission with increasing failure

Necropsy

Nourishment—Good

Cardiovascular ystem—Signs of congestive failure were present The heart was enlarged (weight 405 g), mainly because the ventricles were dilated The aorta and coronary arteries were singularly free of atheroma The pericardium, myocardium, and valves appeared normal, but there were several small mural antemortem thrombi in the right auricle There was a patchy irregular superficial thickening of the endocardium of the left ventricle The myocardium was not involved (fig 1)

A small infarct was found in the lower lobe of the left lung, with an embolus or possibly a thrombus in the appropriate branch of the pulmonary artery There were a few small acute ulcers on the lesser curve of the stomach near the pylorus, with 3 oz of free fresh blood in the lumen An old infarct (2 × 1 × 1 in) was present in the *spleen* Benign enlargement of the *prostate gland*, a large thin-walled *bladder*, and bilateral hydronephroses were found

Histology

There was a thick patchy fibrous deposit in the endocardium containing fine fatty granules, but with little or no proliferation of elastic tissue The myocardium was normal except for some large nuclei (fig 2)

Discussion

Fibrosis of the parietal endocardium of obscure origin can occur in infancy, childhood, and adult life The

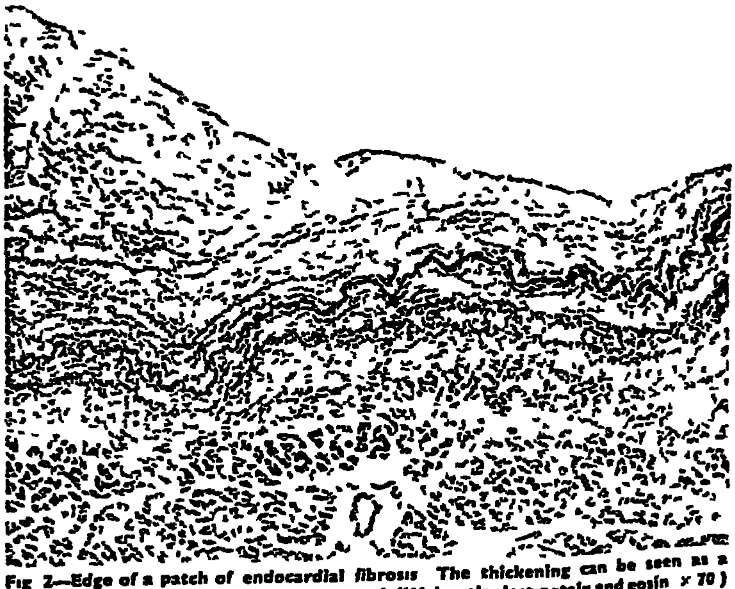

Fig 2—Edge of a patch of endocardial fibrosis The thickening can be seen as a fibrosis as the elastic layer is not increased (Weigert's elastic stain and eosin × 70)

fibroelastosis of infancy is probably distinct from the fibrosis of childhood and adult life, but Thomas et al (1954) suggest that they have a common ætiology. Using Verhoeff's elastic tissue stain they found in their adult cases that the thickening of the endocardium was a fibroelastosis They also tested some of the endocardia from the adult cases reported by Davies and Ball (1955) from Uganda, and found only a few broken elastic fibres, they suggested that each of the two series had a different ætiology The question whether the adult type is a fibrosis or a fibroelastosis is important ætiologically In the case reported here there appeared to be a pure fibrosis of the endocardium, with no increase in elastic tissue and little or no involvement of the myocardium

Despite a long search, no reports of adult endocardial or endomyocardial fibrosis in Britain have been found, but recently Watt and Lynch (1956) described a case of endomyocardial fibroelastosis in a boy of 12 Lennox (1948) reported a case in which a woman had a parietal endocarditis with swollen and pyknotic endothelial cells and infiltration of lymphocytes and polymorphs, the myocardium was œdematous She had status asthmaticus and eosinophilia, and Lennox suggested that the condition might have proceeded to fibrosis had she lived

Adult endocardial and endomyocardial fibrosis though uncommon, has been known for many years, particularly to the German and Swiss pathologists It was reported briefly as early as 1883 (Nauwerk) and at intervals up to 1936—e g, Kockel 1897, Nagayo 1909, Dewitzky 1911–12, Hertel 1921, Boger 1929 In 1936 Loffler described 2 cases as endocarditis parietalis fibroplastica with eosinophilia Since then three large series have been reported from Africa—40 cases by Bedford and Konstam (1946), 40 by Becker et al (1953), and 31 by Davies and Ball (1955), who gave an excellent detailed description of the pathology of the condition On the whole the evidence favours a nutritional cause for the African cases, but Becker et al (1953) suggested it was a collagen disease Gray (1951) described 2 cases in Englishmen living in Nigeria and advanced the idea that as there was no nutritional deficiency in his cases and it was commonest in Africa, it might be due to a tropical infection A similar case in an Englishman resident in Africa who had syphilis was reported by Edge (1946)

Apart from the African series, small numbers have been reported from Switzerland, Germany, Austria (e g, Mumme 1940, Büchler 1941–42, Fossel 1942, Egger 1944, Roulet 1944, Berblinger 1948) and America (e g Comeau 1937, McKusick and Cochran 1952, Smith and Furth 1943, Thomas et al 1954)

The pathological picture in the cases reported is by no means uniform, but a general composite picture can be made up

The patient is usually a man young or middle-aged rather than old (though the condition has been described in a man aged 71) The heart is usually normal in size but it is occasionally enlarged with dilatation of the ventricles rather than hypertrophy Very occasionally the enlargement is massive The pericardium and coronary arteries are normal The mural endocardium is thickened either in a sheet-like manner or in plaques It is usually white or greyish-white The thickness varies but can be up to 4 mm or rarely so great that the lumen of the chamber is largely obliterated The left ventricle is most often affected then the right ventricle, and only occasionally the auricles The commonest site seems to be the posterior wall and the least common the interventricular septum The mitral and tricuspid valves are sometimes involved probably by extension from the walls but the semilunar valves are always free The nature of the thickening is still not clear

The majority of reports describe the condition as a fibrosis others as a fibroelastosis Commonly there is no inflammatory reaction, but in many of the African cases there is a deep layer resembling granulation tissue In the myocardium adjacent to the endocardium there is commonly muscular degeneration and an extension of the fibrosis, more rarely these changes are seen throughout the myocardium In many cases, possibly those of milder type, only the endocardium is affected Inflammatory reaction in the myocardium is uncommon but occasionally small collections of small round cells are seen Polymorphs are noticeably absent

Thrombus formation on the endocardial fibrosis is very common and embolism is rarer than would be expected Other lesions found at different times elsewhere in the body include infarcts, signs of malnutrition allergic and collagen disorders, and eosinophilia in the peripheral blood Loffler (1936) first described the eosinophilia and suggested that it died out as the disease progressed The case presented here showed only some of these features, as do the majority of cases The full picture is rare

The ætiology is obscure, but there have been many suggested causes, such as malnutrition or defective absorption (Smith and Furth 1943), allergy (Loffler 1936, Lennox 1948), Fiedler's myocarditis (Bedford and Konstam 1946), tropical infection (Gray 1951), syphilis or antisyphilitic treatment (Edge 1946), extension of the infantile type to adult life (Thomas et al 1954) collagen disease (Becker et al 1953, Watt and Lynch 1956), pulmonary disease (Lenegre and Gerbaux 1952), stretching of endocardium in cardiac hypertrophy (Hertel 1921), and initial myocardial disease, virus myocarditis, or direct injury (Davies and Ball 1955) It is generally agreed that rheumatism and ischæmia do not cause this disease The only obvious cause in my patient was a presumed injury to the heart, when he was struck in the precordial region by a cricket-ball I should like to advance the view, apparently so far unexpressed, that endocardial fibrosis is the end-result of damage to the endocardium irrespective of the nature of the damage Endomyocardial fibrosis might then be regarded as the final result of more severe damage or as the end stage where both the myocardium and endocardium have been damaged

The nature of the process is still obscure, but if the above hypothesis is accepted, the course of the disease might follow lines similar to those put forward by Duguid (1946, 1949) for the formation of atherosclerosis

Briefly, Duguid's hypothesis is that fibrin deposits are laid down on the arterial intima and that these are incorporated in the intima by organisation with a final covering of endothelium The recent paper by Still and Boult (1956) suggests that a similar process may occur in infantile fibroelastosis

The sequence of events in adult endocardial fibrosis would then be (*a*) damage to the endocardium by one of many possible factors, (*b*) deposition of fibrin on the affected areas, and (*c*) organisation of the thrombi and incorporation in the endocardium as an apparent fibrosis

Summary

A case of adult mural endocardial fibrosis is presented with the necropsy findings Its pathology, ætiology, and nature is discussed It is suggested that it is the end-result of any damage to the endocardium and that the mechanism might accord with Duguid's hypothesis on the formation of atheroma

My thanks are due to Dr S A Propert for permission to publish the case, to Dr P G Seear for details of the patient's history, to Dr L W Proger for his help and advice, and to Dr J W Nicholas for the photograph of the specimen

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SERUM-POTASSIUM LEVELS AS AN INDEX OF BODY CONTENT

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In acute experimental depletion of potassium the serum-potassium level may show a relationship to the extent of the depletion (Black 1953) In clinical practice, however, *not all depletion arises acutely* *Moreover* a rise in the serum-potassium level at a time of acute loss of potassium has been reported (Moore et al 1955)

We present here the results of 110 simultaneous observations of total exchangeable body-potassium and serum potassium levels in patients with various complaints, mostly either congestive heart failure or steatorrhœa

Methods

The methods used for determining exchangeable body-potassium have been detailed elsewhere (Blainey et al 1954, Flear et al 1957) The serum-potassium levels were determined with the 'Eel' direct reading flame photometer

Results

Table I shows the distribution of the observations and diagnoses Only the patients with congestive heart-failure clinically were œdematous In the accompanying figure the serum potassium levels are plotted against the amounts of total exchangeable potassium in absolute terms and in relation to weight and to height In each case the values are expressed as percentages of the mean normal values computed from published reports (Flear et al 1957)

Discussion

The method used estimates the amount of potassium in the body which has exchanged with its radioactive isotope ^{42}K from twenty four to thirty two hours after its injection Thus total exchangeable mass of potassium (K_e) may be the whole of the body potassium (Corsa et al 1950), but Rundo and Sagild (1955) have considered it to be significantly less They estimated the total body potassium from the total gamma count emitted by the body In people not exposed to radioactive materials this has been attributed solely to the naturally occurring isotope ^{40}K, and the total body-potassium can be computed from the ratio in which ^{40}K is found to ^{39}K Total body-potassium was about 15% more than K_e Theoretically this potassium might be either completely unexchangeable or might exchange at a much slower rate We did not detect any further exchange during the eight hours following the first twenty four after injection of ^{42}K (Flear et al 1957), nor did we detect any further exchange during this period between the body sodium and ^{24}Na, though studies using the longer life isotope ^{22}Na (Veall et al 1955) have revealed a slow further exchange requiring several days for completion Whether a similar slow exchange exists with potassium is unknown However, whichever possibility is correct, K_e probably represents the fraction of body-potassium more readily available for metabolic interchanges

The amount of potassium present in the extracellular fluid of the body constitutes only about 2% of the value obtained for K_e Effectively, then, changes in K_e will reflect changes in intracellular potassium The exchangeable mass of potassium has therefore been used to assess the state of the body-potassium, more particularly the extent of any intracellular depletion Its use is, however, open to certain criticisms Firstly, there is the practical difficulty of the variation in K_e which occurs from individual to individual and from day to day within any individual This variability between individuals to some extent may be mitigated by the separate consideration of males and females and by reference to body weight or to height, on the general principles that the sexes reasonably may be expected to show differences of body content, and that the size of the individual may be a factor involved Sagild (1956) has shown that K_e per kg of body-weight varies with age

Change in K_e may take place from a reduction in the amount of potassium within cells or from a reduction in the number of cells The former constitutes cellular depletion of potassium, and the latter represents loss of tissue mass *Loss of potassium from cells* causes a fall in K_e per kg , whereas loss of lean tissue does not However, these two factors may not be wholly independent It is known, for instance, that experimental depletion of potassium leads to a secondary loss of lean tissue The value of K_e per kg may therefore not fully represent the real depletion of potassium Furthermore, the value for K_e per kg of body weight is altered by change in body composition other than loss of potassium

TABLE I—DISTRIBUTION BY DIAGNOSIS OF PAIRED OBSERVATIONS OF TOTAL EXCHANGEABLE MASS OF POTASSIUM (K_e) AND SERUM POTASSIUM LEVELS

Diagnosis	No of patients	No of observations
Steatorrhœa		
Idiopathic	21	31
Whipple's	2	7
Crohn's	3	4
Pancreatogenous	3	4
Ileo colitis	2	2
Postgastrectomy	2	2
Reticulosis	1	1
Gastrocolic fistula	1	1
Colostomy	1	1
Ileocolostomy	1	1
Peptic ulcer	4	4
Congestive heart failure with œdema	21	20
Addison's disease	1	3
Chronic bronchitis	2	3
Healed pulmonary tuberculosis	2	2
Carcinoma of bronchus	1	2
Alkalosis	1	2
Cirrhosis	2	2
Macrocytic anæmia	1	1
Anxiety state	1	1
Headaches	1	1
Nephrocalcinosis	1	1
Arteriosclerosis	1	1
Hypertension	1	1
Bronchiectasis	1	1
Idiopathic hypoproteinæmia	1	1
Chronic ulcer of leg	1	1

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from cells It cannot, therefore, be relied on by itself to afford a clear index of the normality of intracellular potassium It is necessary also to consider the absolute value for K_e and the value for K_e per cm of body-height

Among changes in body composition influencing the value for K_e per kg may be listed gain or loss of body-fat and gain or loss of extracellular and intracellular fluids in œdematous states and dehydration respectively The qualitative consequence of such changes in composition on K_e (absolute and when referred to body-weight and height) are detailed in table II Such changes in composition may arise singly or in combination Table II focuses attention on the difficulties which arise in interpreting the value for K_e in any one individual, even when all three parameters are used

There is a further complicating factor, at least theoretically possible—i e, the proportion of body-potassium not exchangeable with ^{42}K within twenty-four hours might vary This possibility is raised by the observation reported by Rundo and Sagild (1955) but will not be considered further here

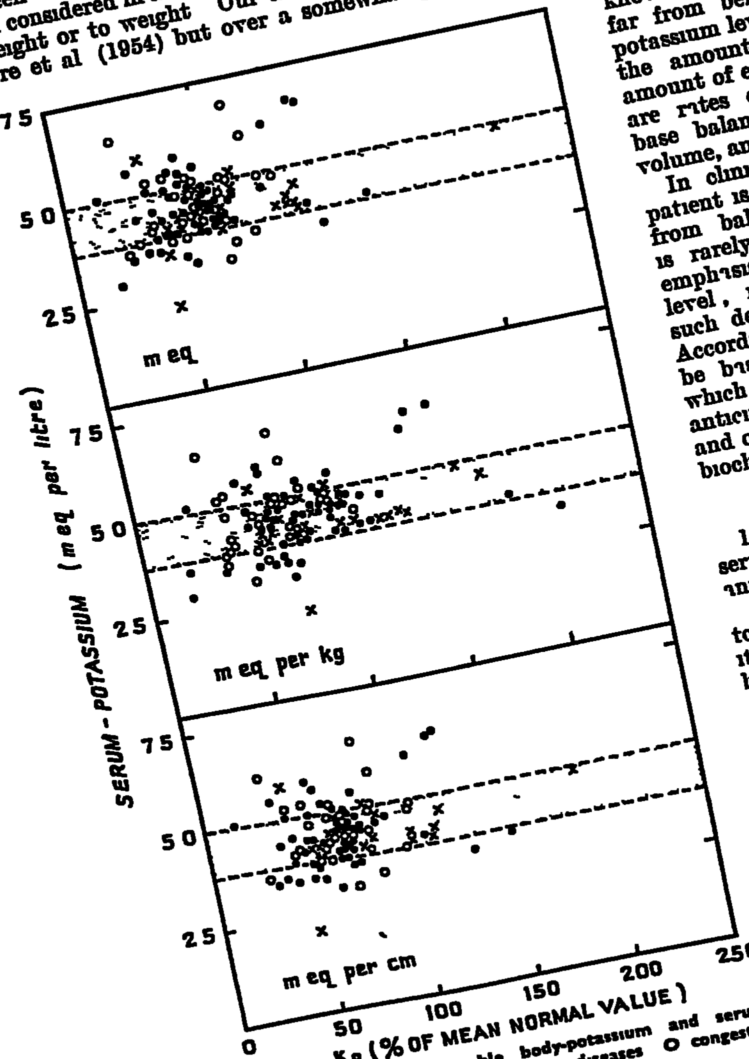
Using K_e as an index of depletion of body-potassium one can say that our data do not reveal any relation between it and the serum potassium level This is so when considered in absolute terms and when standardised to height or to weight Our data thus confirm those of Moore et al (1954) but over a somewhat greater range of variation in K_e (Our range of variation was K_e 16–123%, K_e per kg 27–142%, and K_e per cm 16–123% Their range was K_e 39–101% and K_e per kg 50–102%) The observations of these workers were made on patients with either renal, alimentary-tract, or cardiovascular disease High potassium levels may be found in the presence of low values for K_e showing that such high levels do not imply a normal or raised amount of body-potassium Conversely, a low serum-potassium level need not imply depletion of potassium

TABLE II—EFFECT OF SOME CHANGES IN BODY COMPOSITION ON ABSOLUTE VALUES FOR TOTAL EXCHANGEABLE MASS OF POTASSIUM AND VALUES REFERRED TO HEIGHT AND WEIGHT

Changes in body composition	Changes in total exchangeable mass of potassium		
	m eq	m eq per kg	m eq per cm
Loss of potassium from cells	Decrease	Decrease	Decrease
Gain of intracellular and/or extracellular water—œdema	No change	Decrease	No change
Loss of intracellular and/or extracellular water and salts			
Including potassium	Decrease	No change	Decrease
Excluding potassium	No change	Increase	No change
Loss of lean tissue	Decrease	No change	Decrease
Loss of fat	No change	Increase	No change
Gain of fat	No change	Decrease	No change

These findings are not surprising, because it is well known that the amount of intracellular potassium is far from being a passive consequence of the serum-potassium level Conversely, many factors other than the amount of intracellular potassium influence the amount of extracellular potassium Among these factors are rates of tissue katabolism, renal function, acid/base balance, intake of potassium, extracellular fluid volume, and cellular metabolism

In clinical practice the question whether or not a patient is deficient in potassium often arises Evidence from balance data, muscle biopsy, or radio-isotopes is rarely available Our data clearly indicate that emphasis should not be placed on the serum-potassium level, moreover the symptoms which may accompany such depletion are not pathognomonic and may vary Accordingly the diagnosis of potassium depletion should be based firstly upon a recognition of circumstances which, from experimental and clinical studies, may be anticipated to lead to a loss of potassium from the body, and only secondly upon clinical signs and symptoms and biochemical findings consistent with its presence



Distribution of total exchangeable body-potassium and serum-potassium levels in 110 patients with various diseases O congestive heart failure ●, steatorrhœa X, miscellaneous

Summary

110 observations of exchangeable body-potassium and serum potassium levels are presented which do not show any correlation between them

Clinical awareness of the circumstances likely to lead to potassium depletion is the most important factor in its diagnosis Clinical symptoms and signs and serum-biochemical findings are of secondary importance

We wish to thank the physicians at the Queen Elizabeth and General Hospitals for allowing us to investigate patients under their care, and the ward sisters for their coöperation in these studies

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Medical Societies

ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE

Disorders due to Heat

At a meeting of this society on Feb 21, Dr W S S Ladell, who was recently in charge of the Hot Climates Physiological Research Unit, Lagos, Nigeria, read a paper on Disorders due to Heat

He divided these into four parts skin disorders (sunburn and prickly heat), circulatory disorders (heat syncope), disorders of water and electrolyte metabolism (heat exhaustion, heat cramps), failures of heat regulation (tropical anidrotic asthenia, hyperpyrexia)

Heat exhaustion and heat cramps are probably due to the strain of extra effort in a person chronically slightly short of water At one time salt deficiency was thought to be the major factor, but Ladell now thinks that water debt—in people who consistently do not drink enough—is the predisposing cause Extracellular fluid is lost in the heat, and about 2 litres can be lost before the intracellular water is affected, but the loss of much of the extracellular water renders the person susceptible to heat exhaustion, depletion of intracellular water is dangerous

The rôle of salt is complex In the state of water debt, if water is taken but no salt the intracellular fluid is maintained, and any deficit falls on the extracellular fluid, if salt is taken, particularly in the absence of enough water, the intracellular fluid volume falls, and the extracellular fluid volume is maintained at the expense of the intracellular fluid This intracellular dehydration leads to collapse Treatment consists of plenty of water and a controlled supply of salt, excess of salt will deplete the intracellular fluid and make the patient worse Therefore, in persons in chronic slight water debt, unless there is a sudden emergency calling for an extra output of sweat, extra salt should not be taken, and if any extra salt is taken ample water should be drunk Extra salt may also depress aldosterone secretion, and this may be dangerous Ladell thinks that man has become addicted to salt as a habit, not as a necessity in the amounts normally consumed

Tropical anidrotic asthenia is seen at the end of the hot season, there is no collapse but there is lack of energy, failure to sweat properly, and polyuria The symptoms may be explained first by failure of the renal tubules to respond to antidiuretic hormone, which leads to excessive production of that hormone, and this may suppress sweating Secondly, there is diminished activity by the adrenal cortex, which leads to electrolyte imbalance and asthenia The condition is often associated with prickly heat or lichen tropicalis The only satisfactory treatment is prolonged rest in the cool

Ladell's conception of heat hyperpyrexia is that it is essentially a physiological, not a pathological, process Its ætiology is not clearly known, but it may have an affinity with "sweat gland fatigue" (which, being reversible is not true fatigue) Experiments have shown that the response of the sweat glands in the healthy person becomes progressively less as the rectal temperature rises, and a critical point can be reached (for instance, after hard work in the heat or if physiological cooling is prevented as by the wearing of too much clothing or lack of ventilation) at which sweating stops and cooling ceases with rapid—and without treatment, fatal—results Treatment consists in cooling by means of tepid sponging wrapping the patient in wet towels, and the use of fans for evaporation

Lieut-Colonel J H Walters cited a series of cases of heat hyperpyrexia seen in Iraq and Kuwait Some of the patients were middle aged pilgrims or fat cooks, subject to great heat stress, and some were men with arsenical dermatitis after treatment for syphilis, in the latter sweating was inhibited There may be an element of acute anoxia in heat hyperpyrexia, which may indicate the use of oxygen in treatment In some patients who recovered there was evidence of serious damage to the nervous system

Major-General A Sachs recalled the pathological findings in hyperpyrexia, with hæmorrhages into the suprarenals and cerebellum and circulatory collapse

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Reviews of Books

The Nature of Brucellosis

Wesley W Spink, M D, D SC, professor of medicine at the University of Minnesota Minneapolis Minnesota University Press London Oxford University Press 1956 Pp 464 63s

This book gives an up-to-date account of brucella infection ("undulant fever") in man, founded upon a series of 244 cases seen at the University of Minnesota Hospitals

The first part gives a good summary of the history of brucella infection in animals and man, the characters and methods of differentiating the three varieties of brucella, and the natural history of the disease in the animal hosts The author has made a special study of this disease over the past seventeen years, and his cases, each of which he summarises, were thoroughly investigated and carefully treated His handling of the difficult problem of so called "chronic brucellosis" is particularly good, though more attention might have been paid to those cases in which a very short and sometimes afebrile acute attack, which is usually regarded at the time as a "cold," is followed by chronic ill health that is eventually shown by culture or blood agglutination to be due to brucella infection Greater emphasis might have been placed on the value of a negative intradermal test in excluding brucellosis The clinical picture of the Minnesota cases differs considerably (and rather unexpectedly, as they were all due to the abortus variety of the organism) from the English cases reported by Dalrymple Champneys In the Minnesota cases rigors were much commoner, spondylitis was the commonest complication, which was not so in the English series, and unlike the English cases, a majority were occupational infections, 55% of the patients being employed in a local meat packing plant

This is a most valuable work

Modern Trends in Geriatrics

Edited by William Hobson, B SC, M D, D P H, professor of social and industrial medicine, University of Sheffield London Butterworth 1956 Pp 422 72s 6d

This is a welcome addition to British accounts of the care of the elderly Professor Hobson and his eighteen fellow authors have written a textbook with some outstanding merits By careful selection of material, proper emphasis has been placed on aspects where principle and practice differ from those in the care of younger people many of the contributors are not geriatricians but specialists who realise that geriatrics involves problems that concern many different specialties As the title implies, this work is not intended to cover the whole field of geriatric medicine but it could be made the foundation of a reference volume comparable to the well-known American books edited by E J Stieglitz and by A I Lansing

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Pathological Histology (5th ed Edinburgh F & S Livingstone 1957 Pp 468 32s 6d)—This work by Dr R F Ogilvie has established itself as a standard textbook For the new edition many photomicrographs have been replaced and the text has been rewritten and amplified but the over all length has been reduced

THE LANCET

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Government and Profession

INDIGNATION was justified In the twelve months since National Health Service doctors outlined their case for a rise of pay,[1] the Government had refused to discuss its merits but had kept the negotiations in play Then, without any kind of warning or consultation, they announced that the whole subject of medical and dental remuneration is to go to a Royal Commission—a form of inquiry which takes a very long time Members of our profession who would not wish to press their claim at a moment of special economic difficulty were affronted by a decision which postponed that claim indefinitely and looked as though it were intended to absolve this particular Government of any further responsibility for action—except on the pay of junior hospital doctors Happily the PRIME MINISTER's reply on Monday to SIR RUSSELL BRAIN and DR TALBOT ROGERS' implies that the need for an interim settlement is now recognised

The Government, of course, have their own point of view In this country recovery from the war has not gone far enough to make everyone better off than before, and the attempt to create a more healthy society, without gross poverty, has necessitated a redistribution of real income which has hit many people very hard Among those now less well-to do are most of the professional classes (unless attached to industry), for their earnings have seldom risen enough to make up for the fall in the value of money, and the full force of taxation hits them at a level of purchasing-power which gets lower and lower Responsible elements in both political parties regret the narrowing and impoverishment of professional life thus caused Labour, with its special concern for the success of the nationalised industries and services, should have no wish to drive good brains abroad, while the Conservatives obviously think that redistribution of wealth has gone too far But the remedies, though easy to prescribe, are difficult to apply The three means by which the professional lot could be alleviated are reduction of taxation, increase in pay, and halting of inflation Nobody can doubt that MR MACMILLAN's Government will reduce direct taxation as soon as they dare, but they cannot yet look to much relief on Defence, and meanwhile they have to provide for higher expenditure elsewhere—this year's estimate for the National Health Service, for example, being £49 million more than last year's[2] Though members of some professions could certainly be helped by giving more to those on the public pay-roll, a Chancellor of the Exchequer who wants to reduce taxes is understandably loth to add, for instance, £20 million to the £550 million which taxpayers will have to find for the N H S next year—especially perhaps when he is still under fire for raising only twice that sum by adding 10*d* to the National Insurance contribution Thirdly, a Government can undertake more radical but painful treatment to stop the inflation which is responsible for so many of our symptoms, and if they can show that they are really trying to do this they are entitled to ask for the patient's cooperation Having incurred, to this end, the unpopularity of the credit squeeze, the present Government will naturally be inclined to turn its deafer ear to any small group which is not only asking for a lot of money but also (it may seem) for a privileged economic position

Granted, however, that a Government's duty is to govern—that they deserve no respect unless they can say "No" to their friends—strength of purpose does not excuse unfairness What has been unfair about the attitude of successive Governments is that in seeking economies they have expected a special contribution from people who get their livelihood from public funds When the Civil Servant or the person working in some national undertaking is denied the proper rate for the job because the Government "cannot afford it," he is in fact being forced to make an additional contribution to the Exchequer, supplementary to what he pays in taxes and the same is true of the doctor who is asked to accept uncompensated depreciation of his income when (even in the National Health Service itself) the need for compensation of other groups is freely recognised[3] What is unjust is also in the long run unwise, and grave damage to the service will be averted only if the Government demonstrate that they are not as uninterested or as cynical as they appeared Particularly in a new service such as the N H S, confidence is vitally important, and we trust they will be able to restore it quickly by immediate concessions which reasonable people will find acceptable Thereafter it might be possible for the Royal Commission to plan its work with a view to a fairly early interim report on the general level of medical and dental remuneration and how this should be maintained

What, it is asked, should be the profession's attitude towards the Royal Commission? Apart altogether from delay, two objections to its appointment have been raised First there is the "melting-pot" objection everything (it is rightly said) will have to be considered afresh—from mileage to merit awards—and Spens will be superseded by a report carrying higher authority We admit that in this melting process something may be lost, but we think it at least equally likely that something will be gained—including, possibly, improvements on some of the present methods of remuneration Good though they were, the Spens reports were incomplete and not entirely consistent, and for our part we have long wished to see them reconsidered so that N H S remuneration should be set on a properly agreed base[4] When it comes to the point no responsible inquiry can ignore the terms on which doctors entered the service, and the case for preserving the doctor's accustomed place in the community seems to us so strong that it can safely be entrusted to the judgment of sensible people such as usually sit on Royal Commissions After all at worst, when the commission has reported the profession will be entitled, if it wishes, to hold to the letter of the bargains it reached with the Government in 1946 and 1948. It will be uncommitted by what the commission says. So too, of course, will be the Government; and it is the Government's freedom to pay no attention to the commission's report that is the other big objection raised to the present plan. The outcome here, we believe, depends largely on public opinion. Even among other professional people, the response to the present medical claim has been distinctly ambivalent; and, so far from being thanked for giving a lead, our profession is often held to be taking a selfish line. One reason for this is that, *intent on their present wrongs*, doctors have sometimes seemed to underestimate the difficulties of many other professional people, which may be at least as serious. According to the *Financial Times*,[5] the "average" practitioner with a wife and two children, earning £938 in 1938 and £2222 in 1956, has sustained a loss of real income (after paying taxes) of 27%. But the university professor (arts) runs him close at 24%, and the estimated loss of the headmaster of a large grammar school and of the assistant secretary in the Civil Service are higher at 32% and 43% respectively. As for the general public—many of whom still think that the whole of their weekly National Insurance contribution goes straight into their family physician's pocket—they do not readily understand how doctors justify an average "wage claim" for an additional £10 a week, which is more than many of them earn altogether. They would feel differently perhaps if they saw the calculation[6] that for consultation or visit the doctor now gets an average of half a crown. Perhaps no completely satisfactory arrangements can be made until the public, as well as the Government, understand that they cannot continue to have really good doctors unless they are prepared to pay for really good doctors.

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[1] *Lancet* 1956 i 277
[2] See p 474
[3] See *Lancet*, Feb 2, 1957, p 258
[4] *Ibid*, 1951, i, 1277

But we would add that the future of the profession ultimately depends not on what the public think, or on what the Government say, but on what the profession itself does; and, since the immediate outlook remains uncertain, we must state our opinion of the current proposal that professional action should take the form of pressure on the Government through an undertaking by practitioners to withdraw from the National Health Service. In our view this proposal is wrong: we think that even if it were 100% successful such action would still do great harm to the profession—more harm than could be done by any Government. In offering this opinion we do not mean that doctors need remain in a service in which they lose confidence: we think that those who, now or later, want to leave the N.H.S. should certainly do so; and we agree that if any substantial exodus were in prospect the professional organisations would need to do all they could to help both their members and the public to overcome the difficulties thus arising. But a genuine decision by individual doctors to return to private practice would be quite different from a withdrawal, or the threat of a withdrawal, organised for political ends. This we regard as an alien procedure, out of keeping with the character of any profession, and especially that of medicine.

Hypophosphatasia

IN 1948 RATHBUN[1] drew attention to an osteodystrophy in infants which resembled severe rickets in many respects, but in which there was a great reduction in the level of serum-alkaline-phosphatase activity: he called the syndrome hypophosphatasia. Further reports have appeared of what appears to be the same disorder, and a clearer picture of this remarkable new bone disease is beginning to emerge.

The disorder may be clinically apparent at birth or soon afterwards. RATHBUN's patient was 3 weeks old when first admitted to hospital, with multiple abnormalities and defective mineralisation of the skeleton; and MCCANCE et al.[2] have lately described an infant who was certainly affected at birth and who had indeed been recognised as abnormal in utero by X-ray examination. At birth the bony cranium was very poorly developed and there were widely patent and communicating fontanelles. The chest was flattened at the sides, and beading of the costochondral junctions could be felt. The lower ends of the forearms were much widened, and the long bones were soft and easily bent. An older sister had been shown to have the same condition, from which she had died at 14 weeks. But by no means all cases are apparent as early as this. ENGFELDT and ZETTERSTRÖM's patient[3] seemed to have developed quite satisfactorily until she was 3 months old; then a failure to thrive and the generalised skeletal disorder resembling rickets first became apparent. SOBEL et al.'s patient[4] had evidently progressed well during the first year of life and medical advice was not sought till she was 19 months old. During the preceding 2 months several teeth had been shed, and increasing rickety deformities of the limbs had developed. A similar variation in the age of apparent onset is seen in the three hypophosphatasic children described by SCHLESINGER et al.[5] Two brothers, aged 10 and 13, were admitted to hospital for orthopædic correction of genu valgum and were found to have very low levels of serum alkaline phosphatase[6]; they probably had an even milder form of the condition. When the disease appears in infancy the outstanding features are failure to thrive, early rachitic type bone deformities, and very poor calcification of the skeleton. The fontanelle is often tense and bulging, though the cause of this sign is obscure. The teeth are hypoplastic and are commonly shed prematurely. Very often there is hypercalcæmia and sometimes consequent renal damage. It is possible that these infants are hypersensitive to vitamin D and that even relatively low doses may raise the serum-calcium level.

The prognosis seems poor when the disorder is clearly manifest at birth or soon afterwards, but otherwise it is more hopeful, and the bones slowly calcify, symptoms abate, and growth advances, though varying degrees of bony deformity persist. A surprising complication in some patients is premature craniostenosis which may necessitate cranio

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[5] *Financial Times*, Feb. 22, 1957, pp. 1 and 6.
[6] Cardew, B. *Times*, Feb. 16, 1957.

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[1] Rathbun, J. C. *Amer. J. Dis. Child.* 1948, 75, 822.
[2] McCance, R. A., Fairweather, D. V. I., Barrett, A. M., Morrison, A. B. *Quart. J. Med.* 1956, 25, 523.
[3] Engfeldt, B., Zetterström, R. *J. Pediat.* 1954, 45, 125.
[4] Sobel, E. H., Clark, L. C., jun., Fox, R. P., Robinow, M. *Pediatrics*, 1953, 11, 309.
[5] Schlesinger, B., Luder, J., Bodian, M. *Arch. Dis. Childh.* 1955, 30, 265.
[6] Schneider, R. W., Corcoran, A. C. *J. Lab. clin. Med.* 1950, 36, 985.

tomy[5] Despite the apparent spontaneous healing, the low serum-alkaline-phosphatase level persists, and this may enable the disease to be diagnosed later in life, when the survivors may be first seen because of skeletal abnormalities and spontaneous fractures[7]

Alkaline-phosphatase activity can normally be demonstrated in serum, and also in many different tissues, especially in calcifying bone, small-intestine mucosa, renal cortex, and lactating breast tissue It seems certain that it plays an important part in normal bone formation but its function in other situations remains obscure Probably several different specific enzymes with alkaline phosphatase activity exist, but they cannot as yet, be identified with confidence In mature bone, phosphatase activity is found mainly in the periosteal and endosteal regions In developing embryos it is found in those condensations of mesenchyme destined to form membranous bones, but not those which will form cartilage and it does not appear in cartilage until just before ossification begins The enzyme activity may be demonstrated in the cartilage cells as they begin to hypertrophy, and it then spreads to the matrix Evidently calcification takes place only in the presence of extracellular phosphatase It has been generally believed that, in bone formation, the enzyme was mainly concerned with the production in the matrix of high concentrations of inorganic phosphate and the consequent precipitation of insoluble calcium phosphate More recent work, however suggests that phosphatase has more to do with the actual formation of the organic matrix[8]

In hypophosphatasia, examination of material from liver, kidney small intestine and bone obtained at necropsy[1,2] and from bone and liver by biopsy,[4] have shown that alkaline-phosphatase activity is deficient in all these tissues It seems that the low serum-alkaline-phosphatase in these patients reflects a generalised defect in the formation of at least one of this group of enzymes throughout the body The abnormal bone development which is characteristic of the disease may be reasonably regarded as a consequence of this failure in enzyme formation, and detailed studies of bone formation in hypophosphatasia may well throw new light on the normal rôle of phosphatase in this process Similarly, we may hope that inquiry into the biochemistry of other tissues in hypophosphatasia will help to explain what phosphatase does in their normal metabolism

One interesting biochemical finding is likely to be significant the urine of patients with hypophosphatasia contains unusually large amounts of phosphoethanolamine,[7,9,10] a phosphate ester widely distributed in the cells of many different tissues[11] Its metabolic rôle is unknown, but the increased amounts in the urine of patients deficient in tissue alkaline-phosphatase suggest that it may be one of the natural substrates for this enzyme[7] and that it accumulates and is excreted in excess when the enzyme is deficient

Hypophosphatasia in more than one member of a family of brothers and sisters is not rare Since no environmental cause has been found to account for this familial incidence, or to explain why only some children in the same family are affected i seems probable that the condition is genetical determined This view is supported by the comm finding that some of the apparently healthy parer and other relatives of affected children have unusually low levels of serum-alkaline-phosphatase[2,4] In at least one instance the parents of the patient were consanguineous[12] The known data are consistent with the hypothesis that the patients with clinically apparent hypophosphatasia are homozygous for a rare abnormal gene, which in heterozygotes results in only minor biochemical abnormalities, leaving the individual clinically unaffected But much more detailed family studies are needed to confirm this hypothesis, and other possible explanations of the familial distribution must be examined Should the genetic hypothesis be confirmed and should the essential metabolic lesion turn out to be defective synthesis of a specific enzyme with alkaline-phosphatase activity then the condition will fall into the classical pattern of an ' inborn error of metabolism '

Annotations

MAN AND RADIATION

In more ways than one, mankind is at an important and possibly decisive point in its history on the one hand, there is the probability, and for Britain the necessity, of a new social and industrial revolution based on nuclear power, on the other, there is the louring threat of a war fought with nuclear weapons and of a hitherto unprecedented and unimagined biological disaster The wider the understanding of what the exploitation of atomic energy can mean (and the dangers it can bring) the more likely is it to be used wisely and the medical profession has a vital part to play in the appreciation of what is happening and in the dissemination of the knowledge necessary for that appreciation

We welcome therefore the statement from the United Nations Scientific Committee on the Effects of Atomic Radiation which we publish on p 467 and which makes several very important points In some countries at least radiological methods now provide the most important source of artificial radiation to which man is exposed In the words of the committee, " irradiation of human beings, and especially of their germinal tissue, has certain undesirable effects ", and artificial irradiation, administered in the course of medical practice, is already, in a few countries at any rate, quantitatively equal to the natural radiation background—a fact which makes plain the gravity of the present situation

The weighing of the balance between the risk and the benefit of medical radiology must remain a responsibility of the medical profession But we know very little about radiation doses and their effects and it is therefore an important duty of every doctor, so far as lies in his power, to cooperate fully with the organisations and the individuals who are at work on these matters, so that all possible information may be sent to the United Nations committee through appropriate Government channels It is already clear that we must urgently seek ways of reducing the radiation dose administered by diagnostic methods without diminishing their efficiency And fuller understanding of the biological action of radiation is necessary for the more accurate assessment of tolerable

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Dent C E In Bone Structure and Metabolism Edited by G E W Wolstenholme and C O Connor London 1956 p 266

8 Bourne G H The Biochemistry and Physiology of Bone New York 1956

9 Fraser D Yendt E R Christie F H E Lancet 1955 i 286

10 McCance R A Morrison A B Dent C E Ibid p 131

11 Tallan H H Moore S Stein W H J biol Chem 1954 211 927

12 Ulstrom R Amer J Dis Child 1955 90 551

exposure levels. There are several difficulties in the study of the effects of low doses of radiation on man: the two main ones are those of measuring in retrospect individual and population dose, and recognising radiobiological effects and correlating them with their true causes. The prevailing uncertainty means constant reassessment and reduction of the recommended "safe" levels of radiation.

In this country machinery now exists, in the form of the committee lately appointed by the Minister of Health under the chairmanship of Lord Adrian,[1] for the collection of relevant information and for reviewing radiological practice. This committee and other bodies, such as the International Commission on Radiological Protection and the Medical Research Council, will be asking for detailed information on radiation dosages and their effects; and we hope they will receive immediate and energetic support from everyone who can help in these crucial inquiries.

LYMPHOGRANULOMA VENEREUM

THE virus infection, lymphogranuloma venereum, which can be a distressing and crippling disease, is fortunately rare in this country and when it appears it is usually in seaport areas. The infection is thought to be imported by coloured immigrants. In recent years there has been an undoubted increase in the number of cases which have been discovered: the chief medical officer of the Ministry of Health reported 63 patients with lymphogranuloma venereum in this country in 1954, and in 1955 the number had increased to 86. The rise in the prevalence of the disease may well have continued in 1956 though no official figures are yet available. It must be remembered too that, from the nature of the disease, particularly in its early stages, many cases remain undiagnosed and are therefore not recorded in the official figures; and it may be that the infection is much commoner than is generally recognised. The recent rise in the figures for lymphogranuloma venereum may be due to the increased entry of Negroes into this country, but there is no proof of this. At all events, it is clear that improvements in present methods of prevention and diagnosis would be welcome.

King et al.[2] examined 1317 patients attending the venereal-diseases clinic at the London Hospital with a view to demonstrating the incidence of lymphogranuloma venereum among this type of patient. After a full clinical history had been taken, the patient was examined and an intradermal test was performed using a yolk-sac culture of the J.H. strain of lymphogranuloma-venereum virus. The sera of all positive skin reactors were then tested for the virus by complement-fixation: fixation of complement at a serum dilution of 1 in 32 or more was regarded as confirmation of the diagnosis. The examinations of 1119 patients were completed. Of the 206 patients (18%) who reacted to the intradermal test, 23 (2%) had strongly positive complement-fixation tests. The sera of 157 (14%) patients reacted in the complement test but not at a level high enough to be taken as diagnostic. Thus, though King et al. believe that 2% of the patients were undoubtedly suffering from lymphogranuloma venereum, 14% presumably required further or longer investigation. Negroes yielded a higher proportion of skin reactors and proven disease than did whites; but there was no evidence to support the suggestion that the recent increase in lymphogranuloma venereum in this country was due to a greater influx of Negroes. Further work on similar lines in different seaport areas seems indicated.

To combat lymphogranuloma venereum, doctors, particularly those practising in and around ports, must be more alert to the possibility of this infection. The opportunity of identifying the transient painless primary lesion is rare, but ulceration of the genital area accompanied by enlarged tender inguinal glands or a bubo should arouse suspicion. The inguinal mass, consisting of many discrete enlarged lymph-nodes held together by a plastic periadenitis, is characteristic and is followed by irregular breakdown of lymph-node tissue, with fistula formation. Suspect cases should be referred to a venereal disease clinic where skin and serological tests can be applied. Further investigation into methods of increasing the specificity and sensitivity of the complement-fixation test for lymphogranuloma venereum might help to determine more precisely the value of the test, and give a clearer picture of the present position.

STABLE SMALLPOX VACCINES

THE dried smallpox vaccines which have now been fully tested under the auspices of the World Health Organisation[1] should do much to improve control of a disease which is still a major menace. In the hot countries chiefly afflicted by smallpox, efficient vaccination has been difficult because ordinary vaccine lymph quickly deteriorates unless kept cool, and the vaccinators seldom have rapid transport or efficient refrigeration at their disposal. Often the population will not come to the large centres where stocks of lymph can be held in refrigerators; and when vaccinators go to the villages, which may be many days' journey from urban centres, their lymph is liable to lose its virtue on the way. For the same reason it may be difficult to hold adequate reserves of lymph at local centres, and the immediate control of epidemics has thus been hampered. But every country can now have dried smallpox vaccine which will withstand many weeks' exposure to tropical temperatures and which will last indefinitely in an ordinary refrigerator working at the usual domestic temperature.

The W.H.O. trials, which started in 1952, were carried out in two stages. The first was a purely laboratory study of the keeping qualities of dried and wet (glycerinated) vaccines produced by laboratories in four different countries. They were tested for heat resistance and bacterial purity in laboratories in Elstree (England), Copenhagen, and Paris after storage at 0°, 22°, 37°, and 45°C for periods varying up to 2 years. The results of these studies have not been published, but by courtesy of W.H.O. it may be said that, though the dried vaccines from all four laboratories were definitely more resistant to heat than the corresponding wet vaccines, there was much variation and one dried vaccine was outstandingly better than the others.

A second batch of this vaccine and another vaccine which had given promising results in a similar study were therefore included in the second stage of the trials. This was a combined field and laboratory study of the two dried vaccines after periods of storage at 37° and 45°C. The dried vaccines selected for this trial were another batch from the laboratory whose vaccine had come out best in the first trial and a vaccine from another laboratory which had given encouraging results in another trial. The dried vaccines were held at 37° and 45°C for periods of 4, 8, 16, 32, and 64 weeks, after which they were tested for potency in the laboratory and for vaccination success rates on volunteers in the Royal Air Force. The laboratory tests were done in duplicate in the department of bacteriology of the University of Liverpool and at the Lister Institute, Elstree, and the potency of all the vaccines was assessed by counting pocks on the membranes of the chick embryo, in addition to the usual test on the skin of the rabbit. The test vaccinations were on groups of 100 recruits with no history of previous vaccination and no scars. For the first time, it was possible to investigate the relative accuracy of the two laboratory methods of test and to assess their relation to success-rates in the field

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[1] See Lancet, Feb. 16, 1957, p. 381.

[2] King, A. J., Barwell, C. F., Catterall, R. D. Brit. J. vener. Dis. 1956, 32, 209.

[1] Cockburn, W. C., Cross, R. M., Downie, A. W., Dumbell, K. R., Kaplan, C., McClean, D., Payne, A. M. M. Bull. World Hlth Org. 1957, 16, 63.

In this trial one dried vaccine resisted heat better than the other The less successful vaccine, however, still produced a 47% vaccination-success rate after 4 weeks at 45°C (a very severe test), 96% successes after 8 weeks at 37°C, and 72% after 16 weeks at 37°C Though the more successful vaccine showed a slight but significant drop in potency after storage at 45°C for 64 weeks, it still produced 100% vaccination successes in the field, as it had at all the earlier tests This indicates that after long exposure in hot climates it would still produce the maximum possible number of successful vaccinations The potency tests revealed the superiority of titration by pock-counting on the membranes of the developing chick -the results obtained by this method showed a satisfactory correlation with the vaccination success rates in the field

On p 446 we publish an article on the heat resistance of a dried smallpox vaccine, prepared at the Lister Institute of Preventive Medicine, which resisted heat very well, as judged both by laboratory titration and by clinical trial We may add that dried vaccine produced by this method has been in use by the Armed Forces for the last two years with uniform success and is also being prepared for the reserves maintained in this country against an epidemic The fact that stable smallpox vaccine is now to be had should enable public-health authorities in hot climates to review their arrangements for the control of smallpox by prophylactic vaccination and to hold reserves of vaccine in many localities for use as soon as smallpox breaks out

DIABETES MELLITUS AND ANÆSTHESIA

IN the preparation of diabetic patients for general anæsthesia, glucose is often given by mouth It is of the greatest importance to prevent both hypoglycæmia and ketosis in these patients, but it is equally imperative not to overlook the potential dangers of *regurgitation* and vomiting when glucose is given shortly before anæsthesia is induced During the past few years, these events have achieved some notoriety as causes of death and other complications in *all* patients given a general anæsthetic, including some with diabetes mellitus

The normal emptying time of the stomach after a solid meal is about four hours, and up to two hours after fluid Thus preoperative oral carbohydrate if it is to serve any useful purpose, must be given so close to the time of anæsthesia that it becomes a potential hazard unless the stomach empties quickly In fact, it may well empty slowly because of fear, premedication, and the glucose itself

King[1] has lately confirmed that the hazard is a real one 200 ml of water, containing phenol red and 50 g glucose, was given to each of a group of fasting healthy young adults and the stomach was completely aspirated at intervals varying from fifteen minutes to two hours It was found that, on the average, the meal was diluted to about twice its volume, but that after two hours only 46 ml of fluid, containing 0 3 g glucose, remained A similar solution, but containing no phenol red was given to each of 20 diabetic and non diabetic patients two hours before operation the stomach was aspirated two hours later Previous investigations had shown that gastric function was normal in all these patients, yet in 10 of them volumes ranging from 100 to 265 ml (average 146 ml), containing 2–10 2 g glucose were removed from the stomach Thus, there seems little doubt that pre operative glucose solutions given by mouth are potentially dangerous and unlikely to prevent hypoglycæmia

The answer is to give the glucose intravenously or not at all A single intravenous injection of glucose given not more than an hour before the induction of anæsthesia may be enough for a minor operation on some diabetic patients, but in most cases King recommends continuous intravenous glucose over a number of hours, including the postoperative period, when there may be nausea and vomiting Soluble insulin should be given in divided doses every four or six hours King believes that this method is the safest and most effective means of ensuring good control for all diabetic patients undergoing emergency or major operations, and for patients with severe diabetes whatever the operation Many mild diabetics need no glucose preparation for a small operation, provided it is carried out early in the morning and an adequate intake of carbohydrate is ensured after operation

King has clarified a subject which is often an irritation to anæsthetists, but he adds a wise reminder that dogma has no place in the control of diabetic patients treated by surgery each case must be considered individually

OPERATING ON EMPHYSEMATOUS BULLÆ

AN emphysematous bulla may become very big and give rise to respiratory distress by compressing adjacent lung If the cause of the trouble is a localised defect of the bronchial tree acting as a check-valve,[1] treatment is straightforward—removal of the affected lobe or segment will liberate the compressed healthy lung and allow it to function But most emphysematous bullæ are associated with generalised respiratory disease, and then the outcome of operation is more problematical These bullæ are usually found in patients with chronic bron chitis, and are merely gross examples of widespread emphysematous lesions caused by air-trapping But routine radiography occasionally discloses large air spaces traversed by filmy strands of tissue in the lungs of people who give no history of respiratory trouble and in whom no evidence of bronchospasm can be detected such lesions may be due to degeneration of the pulmonary elastic tissue and they produce respiratory insufficiency only if the degenerative process extends, if spontaneous pneumothorax occurs, or if air trapping (due to bron chial distortion) causes enlargement of the space with compression of adjacent lung

Surgeons have tried to treat these bullæ in various ways Thoracoplasty has been used in an attempt to obliterate them by external compression, but the results have been poor More success has been claimed for Monaldi drain age[2] (continuous intra cavitatory suction applied by means of a catheter inserted through the chest wall), but this is a laborious procedure involving preliminary pleurodesis to prevent leakage of air or infection from the bulla into the pleural space, and it has won few adherents Resection of the lobe or segment is probably the most widely used operation, and, though it seems undesirable that the remaining part of the lung should have to over expand to fill the hemithorax, Deterling[3] considers that the consequent straightening of the bronchi may bring about a useful improvement in air flow He advises against such space filling measures as plombage, which may have the opposite effect Massie and Welchons[4] point out, however, that resection of a bullous pulmonary unit may entail the sacrifice of functioning lung tissue which can ill be spared, they recommend local excision, even of multiple bullæ, where this will conserve useful lung

Stringer and Burnett[5] now go further and condemn excision altogether They advocate the more economical technique of obliterating the bulla by removing its pleural roof and approximating the pleura and the parenchyma which forms its walls with a continuous suture of fine chromic catgut, each bite including the least possible

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[1] King R C *Anæsthesia* 1957, 12, 30

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[1] Allison P R *Thorax* 1947, 2, 169
[2] Head, J R, Avery E F *J thorac Surg* 1949, 18, 761
[3] Deterling R A jun In Pulmonary Emphysema London 1956 p 133
[4] Massie J F jun, Welchons, G A *Ann Surg* 1954, 139, 244
[5] Stringer C J Burnett, C A *Amer Rev Tuberc* 1956, 74,

depth of parenchyma. This type of operation gave good results in 18 patients, all of whom had obvious respiratory insufficiency due to compression of lung tissue by the emphysematous bullæ themselves or by spontaneous pneumothorax resulting from the rupture of such bullæ. *Postoperative complications* were few: in 2 cases intercostal suction for a fortnight was needed to re-expand the lung, and in a 3rd patient (who had presented as a spontaneous pneumothorax) thoracoplasty had to be performed because the lung did not re-expand fully. There were no deaths, and all the patients, some of whom had been respiratory cripples, were able to return to work. Pulmonary reserve has remained good for periods ranging from six months to four years since operation.

The scope of surgery in the treatment of generalised pulmonary emphysema is severely limited even when the pressure effects of large bullæ contribute significantly to the impairment of respiratory function; but these results indicate that surgery has sometimes much to offer.

ESSENTIAL HYPERTENSION IN CHILDHOOD

THE *measurement of blood pressure in infants and* children is fraught with potential errors. Restlessness or crying may raise the systolic blood-pressure by 20–30 mm. Hg in infants,[1] and a sphygmomanometer cuff that is not wide enough may give readings that are too high. It is also important to recognise the physiological increase in systolic and diastolic pressures which takes place throughout the growth period, so that normal standards may be available[2] against which abnormally high readings may be measured. A persistent reading of more than two standard deviations above the normal for age is generally regarded as representing hypertension.

Hypertension is less common in childhood than it is in adult life, and when it is found it is usually associated with renal disease, coarctation of the aorta, endocrine disturbances, or diseases of the central nervous system. Essential hypertension seems to be rare in childhood,[2 3] but it is a condition which must be considered when the more usual causes of a raised blood pressure have been ruled out. (Clearly, such operable conditions as unilateral renal disease, coarctation of the aorta, and phæochromocytoma must be carefully excluded before a diagnosis of essential hypertension is made.) Haggerty et al.[2] have recently described 9 children under the age of 14 years in whom they made this diagnosis, the youngest being discovered at the age of 7 months. They took as their criterion of hypertension at all ages a blood-pressure which was persistently above 130/90 mm. Hg. In 5 children the blood pressure was more than 160/110 mm. Hg and in all of them headaches and changes in the retinal blood-vessels were present; 2 also had convulsions and hemiplegia, and 1 of them died. Essential hypertension was diagnosed when exhaustive clinical and laboratory investigation failed to reveal any well defined cause for the raised blood pressure; and the search included surgical exploration of the abdomen in all 5 children with serious hypertension. In 5 cases, 4 of them mild, there was a family history of hypertension.

Treatment follows much the same pattern as in adults. Sedation and weight reduction when necessary are important; but restriction of activity and a low sodium diet have not proved practicable in children and they were not therefore adopted by Haggerty. Of the hypotensive drugs, they found rauwolfia, hydrallazine hydrochloride ('Apresoline'), and hexamethonium were all of some value in the milder cases. For the treatment of hypertensive encephalopathy, they were impressed by the efficacy of the ganglion-blocking agent trimetaphan camphorsulphonate ('Arfonad'). In 4 of the most severely affected children, sympathectomy was carried out, with benefit to 2 of them.

Though permanent elevation of the blood pressure is rare in children, a transient rise is quite common. The significance of this finding is not fully understood, but there is some evidence to suggest that children whose blood-pressure behaves in this way may develop essential hypertension in adult life.[3] Hines[4] studied 1522 adults, who were divided into two groups and re-examined ten and twenty years after they had first had their blood pressures measured. Of those in whom the initial reading was 140/85 mm. Hg or less only just under 4% had persistent hypertension twenty years later; on the other hand, in a similar group in whom the first reading was over 140/85 mm. Hg as many as 82% had persistent hypertension twenty years later. Levy et al.[5] found similar but less striking differences among some army officers in a five-year follow-up. Thus, children who show transient rises in blood pressure may grow into adults with essential hypertension; but further investigation is needed before such a conclusion can be drawn.

DISLOCATIONS OF THE LUNATE

INJURIES of the carpal bones are not uncommon but they often escape detection. The increasing awareness of the difficulties in the diagnosis of the scaphoid fracture has not, on the whole, been accompanied by better recognition of the more extensive injuries of the scaphoid and lunate. Provided the possibility of a carpal dislocation is borne in mind, its diagnosis from standard wrist films should present no difficulty.

It is customary to separate injuries about the lunate into two groups—dislocation of the bone and dislocation of the carpus about it. Dislocation of the carpus is commonly associated with a scaphoid fracture, and injuries of the radial and ulnar styloids may also be present. A simple dislocation of the lunate in the early stages can almost always be reduced by local pressure over the lunate, assisted by traction on the fingers, at first in extension of the wrist, and then in flexion. The results of this manœuvre are good, and aseptic necrosis rarely follows. Operative reduction, on the other hand, is seldom satisfactory, and it is probably better to excise the lunate, though the wrist may not recover full function. A recent perilunar dislocation of the carpus, if the scaphoid is not fractured, can also be reduced manually, and if this fails, open reduction gives a fair result. When the injury is associated with a scaphoid fracture, however, the problem is much more difficult. If adequate reduction of the fracture-dislocation can be achieved, then the scaphoid may well unite, although immobilisation for five or six months is often necessary, and the incidence of avascular necrosis of the proximal fragment of the scaphoid may be as high as 50%.[6] Excision of the avascular proximal fragment of the scaphoid allows partial dislocation of the capitate and produces a very poor wrist. It is for these patients, and for those in whom accurate reduction is not possible, that Wagner[7] favours immediate wrist fusion. Such an approach may well shorten the total period of disability.

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[1] Woodbury, R. A., Robinow, M., Hamilton, W. F. *Amer. J. Physiol.* 1938, 122, 472.
[2] Haggerty, R. J., Maroney, M. W., Nadas, A. S. *Amer. J. Dis. Child.* 1956, 92, 535.
[3] Sobel, I. P. *Ibid*, 1941, 61, 280.
[4] Hines, E. A. *J. Amer. med. Ass.* 1940, 115, 271.
[5] Levy, R. L., Hillman, C. C., Stroud, W. D., White, P. D. *Ibid*, 1944, 126, 829.
[6] Russell, T. B. *J. Bone Jt Surg.* 1949, 31B, 524.
[7] Wagner, C. J. *Ibid*, 1956, 38A, 1108.

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THE INDEX and title-page to Vol. II, 1956, which was completed with THE LANCET of Dec. 29, is published with our present issue. A copy will be sent gratis to subscribers on receipt of a postcard addressed to the Manager of THE LANCET, 7, Adam Street, Adelphi, W.C.2. Subscribers who have not already indicated their desire to receive indexes regularly as published should do so now.

Special Articles

THE RESPONSIBILITIES OF THE MEDICAL PROFESSION IN THE USE OF X RAYS AND OTHER IONISING RADIATION

Statement by the United Nations Scientific Committee on the Effects of Atomic Radiation

I INTRODUCTION

(1) The United Nations General Assembly, being aware of the problems in public health that are created by the developments of atomic energy, established a Scientific Committee on the Effects of Atomic Radiation This committee has considered that one of its most urgent tasks was to collect as much information as possible on the amount of radiation to which man is exposed today, and on the effects of this radiation Since it has become evident that radiation due to diagnostic radiology and to radiotherapy constitutes a substantial proportion of the total radiation received by the human race, the committee considers it desirable to draw attention to information that has been obtained on this subject

(2) Modern medicine has contributed to the control of many diseases and has substantially prolonged the span of human life These results have depended in part on the use of radiation in ,the detection, diagnosis, and treatment of disease There are, however, few examples of scientific progress that are not attended by some disadvantages, however slight It is desirable therefore to review objectively the possible present or future consequences of increased irradiation of populations which result from these medical applications of radiation

II GENERAL SURVEY OF THE IRRADIATION OF HUMAN BEINGS

(3) Man has always been exposed to some irradiation from natural sources To this has now been added, as a result of modern discoveries and the applications of ionising radiation and radioactivity, certain forms of artificial irradiation

(4) *Natural irradiation* is due to

(1) Cosmic radiation,
(2) " Background gamma radiation from radioactive substances present locally in the earth, rock, or building materials, and from disintegration products of radon in air,
(3) Radiations emitted from natural radio elements such as potassium 40, radium, radon, and carbon 14 which are incorporated in the body

(5) The amount of this natural radiation varies with locality, but has been estimated as usually delivering between 70 and 170 mrems per year to the gonads Of this total, the major contributions are of about 45% from local gamma radiations, 30% from cosmic rays, and 20% from body potassium 40[1]

(6) *Artificial irradiation* is derived from

(1) The contamination of the environment, the atmosphere or water by radioactive waste from atomic industries or from users of radio elements
(2) The radioactive fall out, at greater or lesser distances from the source, or radioactivity resulting from the explosion of nuclear devices
(3) The occupational exposure of certain groups of workers medical practitioners, radiologists, dentists, nurses, atomic energy workers, uranium or thorium miners and the industrial or scientific users of radiation generators or radioactive isotopes
(4) The medical use of X rays, other ionising radiations, and radio elements in the detection diagnosis, investigation, and treatment of human diseases,
(5) The use of certain devices which emit radiation, such as television receivers, watches with luminous dials, and the X ray generators used for the purpose of fitting shoes

(7) The amount of artificial radiation must vary considerably in different countries and we have inadequate information as to the over all significance of these factors In certain countries where estimates have been made, it appears that the greatest gonad irradiation of the population is due to diagnostic radiological procedures, the amount from this source about equalling that from all natural sources in certain instances The total present contribution from occupational exposure, from the products of atomic industries, from radiotherapy, and from the radiating devices mentioned above (paragraph 6, sub-paragraph 5) is likely to be very considerably smaller That from radioactive fall out to the gonads appears at present to be in the region of 1% of the natural gonad irradiation in most areas[2]

(8) Both the magnitude and the significance of these various sources are under review by the committee Since medical irradiation accounts for a substantial if not the major proportion of all artificial exposure, it is important that its magnitude should be known accurately for different countries and circumstances The possibility of making such an assessment depends upon the help of the medical profession, and particularly on the adequacy and availability of records kept by doctors, dentists, and organisations responsible for the use of ionising radiation

III RADIATION HAZARDS

(9) The medical use of radiation is clearly of the utmost value in the prevention, diagnosis, investigation, and treatment of human disease, but the possible effects of this irradiation of individuals require examination

(10) Generally speaking, the irradiation of living beings may produce radiobiological effects either on the irradiated individual himself or, through him, on his descendants , the former being termed somatic and the latter genetic effects Somatic effects vary according to the different organs or tissues affected, and range from slight and reversible disturbances such as cutaneous erythema to the induction of leukæmia or of other malignant diseases The possible reversibility of the somatic effects of radiation received in small doses or at low dose rates encourages the belief that there are permissible doses of radiation which will not cause completely irreversible or significant somatic damage The threshold for occasional somatic damage may, however, prove to be low In the case of genetic effects, on the other hand, there may be no threshold These effects increase with a frequency corresponding to the total amount of radiation received by the germinal tissues, and in the great majority of cases, are adverse

(11) Many other factors complicate the interpretation of radiobiological effects The differences between whole and partial body radiation, between a single exposure and continuous irradiation, or between the effects of different types of radiation are still imperfectly understood Biological differences in the radiosensitivity of various tissues, or of the tissues of people of different age or sex, obviously influence the nature of radiation hazards It is clear, however, that any radiation of gonads, and any substantial irradiation of other tissues, involve a chance of significant damage which requires assessment

IV GENERAL RECOMMENDATIONS REGARDING THE MEDICAL AND OCCUPATIONAL IRRADIATION OF HUMAN BEINGS

(12) The radiological profession, through the International Commission on Radiological Protection,[3] has

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[1] From reports sent by India Sweden the United Kingdom, and the United States of America

[2] According to the reports sent by the United Kingdom and the United States of America

[3] Report of the International Commission on Radiological Protection. *Brit J Radiol* December, 1954, suppl no 6 *J franç electro radiol* October, 1955, no 10, &c

undertaken a valuable and responsible duty in defining maximum permissible limits of exposure for the main radiation hazards

(13) The establishment of these maximum permissible levels for those who are occupationally exposed to radiation depends on the view that there are doses which, in the light of our present knowledge, do not cause detectable somatic injury in the individual irradiated, and on the consideration that the number of individuals concerned is small enough for the genetic effects on the whole population to be negligible For the gonads, or for irradiation of the whole body, the levels are such as to exclude doses greater than 0 3 rem in any week or 3 0 rem in any 13 weeks, or a sustained irradiation rate greater than 5 rem per year These values imply that no total dose of over 50 rem will have been received by the gonads by the age of 30, or of over 200 rem by the whole body by the age of 60, in any occupationally exposed person [3]

As regards irradiation of the whole population, it is considered prudent to limit the average dose to germinal tissues from artificial sources to the order of magnitude of that received from all natural sources

(14) In considering the extent to which the population is irradiated for medical purposes, it is essentially the genetic hazard which is involved although it seems possible that in certain circumstances somatic injury may occur occasionally after low doses of radiation arise Otherwise, the relevant dose is that indicating the mean gonad irradiation among the population as a whole up to the end of the average reproductive period

(15) The extent of such genetic irradiation from diagnostic procedures has been found to be equal to at least 100% of all natural radiation in two countries,[4] and that from a third equalled at least 22% of this figure [5] Even before obtaining more exact values for these and other countries, it is clear that the exposure can be substantial in countries with extensive medical facilities, and that it is essential to consider any ways in which this exposure could be reduced without detriment to the existing or developing value of medical radiology

(16) The committee is therefore anxious to obtain the help of radiologists in suggesting through appropriate governmental channels any methods by which this total exposure could be reduced and in estimating the amount of reduction that might be expected from any such methods In particular it would be valuable to know how much the radiation to the gonads could be reduced

(a) by improved design or shielding of equipment,
(b) by fuller training of any individuals using radiographic or fluoroscopic equipment,
(c) by any local shielding of the gonads that is practicable, especially during abdominal or pelvic examination,
(d) by the use of techniques involving radiography rather than fluoroscopy when full information can be obtained by this means,
(e) by improvement of administrative arrangements designed to obviate unnecessary repetition of identical examinations of the same subject,
(f) by a general study of certain medical conditions such as that of peptic ulcers to identify the circumstances in which the establishment of a radiological diagnosis has or has not a definite influence upon the treatment or prognosis given

V SUMMARY

(1) The Scientific Committee on the Effects of Atomic Radiation established by the United Nations General Assembly accepts the view that the irradiation of human beings, and especially of their germinal tissue, has certain undesirable effects

(2) Information received so far indicates that, in certain countries (Sweden, United Kingdom, United States of America), by far the most important artificial source of such irradiation is the use of radiological methods of diagnosis and that this may be equal in importance to radiation from all natural sources It is possible that such radiation may be having a significant genetic effect on the population as a whole

(3) The committee is fully aware of the importance and value of the medical use of radiations but wishes to draw the attention of the medical profession to these facts and to the need for a more accurate estimate of the amount of exposure from this source The help of the medical profession would be most valuable to make it possible to obtain fuller information on this subject

(4) The committee would be particularly grateful for information through appropriate governmental channels on ways in which the medical irradiation of the population can be reduced without diminishing the true value of radiology in diagnosis or treatment

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[4] Sweden United States of America
[5] United Kingdom

MALTA MEDICINE

EARLY last year a dispute arose between the government of Malta and the Medical Officers' Union As part of the settlement of this dispute a commission was appointed to review the medical services of Malta and Gozo and make recommendations for their future organisation Mr John Cronin, M P, had previously submitted a short report on the services [1] The chairman of the commission was Mr Leslie Farrer-Brown, director of the Nuffield Foundation, who was nominated by the Colonial Secretary The other members were Sir Harold Boldero and Mr J Bagot Oldham, nominated respectively by the Royal Colleges of Physicians and Surgeons They have now made their report,[2] in which they endorse the view that "Malta is midway in the modernisation of its medical and health service"

The report commends the progress already made, but says that much remains to be done Development has so far been piecemeal with no general plan There is still much suspicion and ill-will between the government and the doctors, and the commission hopes that the government will set about healing the breach by giving a clear indication of its good intentions The following is a summary of the findings and advice given in the report

ADMINISTRATION

At present the health services are controlled by the minister of health, the chief government medical officer, the senior medical officer (who is in charge of hospital and specialist services, district medical services, and the School for Nurses), and the senior health officer (who is in charge of public health services) There are certain statutory bodies such as the Council of Health (which recommends legislation and investigations), the Medical Board (which has various duties including the issue of licences to practise), and the Board of the Hospital for Mental Diseases (which is concerned with certifying insane persons but not with administering the hospital), as well as the non statutory Hospital Board, which was formed in 1935 to advise on the running of the hospitals, has met few times, and is regarded as a failure

Comment —Control is over centralised and the senior officers have not enough staff There is no established machinery for consultation between government and doctors The disciplinary machinery is faulty The implied distinction between medicine and health is unfortunate

Proposals —Three bodies should be created

(1) A Medical Council, with functions similar to those of the General Medical Council in Britain The chairman would be a judge and the members include some appointed

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[1] See *Lancet* 1956 ii 1271
[2] Farrer Brown L Boldero H Oldham J B Report of the Medical Services Commission London 1957

by the government and the university and some elected by doctors and dentists.

(2) An Advisory and Executive Board, whose members would be in part appointed by the government and the hospital management committees and in part elected by doctors and nurses. It would advise the Minister on various topics, keep a register of professions, and review the terms of service of medical appointments. It should have several standing committees.

(3) Four hospital management committees, to ease the administrative load on the headquarters staff and improve the running of the hospitals. On each about a third should be active staff in the hospitals and a third laymen, with a lay chairman. The mental hospitals in Malta and Gozo would come under one committee and all other hospitals in Gozo under another, which could with advantage be made the standing committee for Gozo on the Advisory and Executive Board.

HOSPITALS

The existing hospitals are reviewed in detail.

St Luke's is the main general hospital with over 500 beds, and there is room for expansion in the present buildings. It has consultants in various specialties, and the physician, surgeon, and accoucheur are professors in the university. There are three anæsthetists, often one is working in two operating theatres simultaneously. There is a large but ill-equipped and ill staffed laboratory. The female nurses are controlled by a mother superior and the male nurses by a wardmaster, neither of whom is State registered. Most ward-sisters are State registered and most nursing is done by hospital attendants.

The Central Hospital has a few beds for venereal disease, dermatology, and ophthalmology, most of it is used as a police headquarters. There are an ophthalmic clinic, which is too small, and antiquated radiotherapy apparatus. The other hospitals house mental patients, the infirm and chronic sick, the diminishing number of lepers, and patients with tuberculosis, tinea capitis, and infectious diseases.

In Gozo is an adequate general hospital of 94 beds, a mental hospital, and a home for the infirm.

Comments and Proposals.—The basic specialties are well established, but there are no units for such sub-specialties as neurology or plastic surgery. Such units are not needed, in view of arrangements with hospitals abroad and the possibility of each of the present consultants developing a special interest.

More and better accommodation is required for the chronic sick, with more segregation—e.g., the young from the old. More doctors, and especially more administrative assistants, are wanted. All the hospitals were spotlessly clean, but on the whole cheerless and ill-provided with amenities. The internal and external surroundings should be made more cheerful and occupational therapy should be provided.

There is little or no shortage of beds, but more consultants, more residents, and many more nurses, technicians, and clerks are needed. Some consultants seem to have insufficient qualifications and experience, and either a scheme for much more postgraduate teaching overseas should be started at once, or the conditions should be improved enough to attract trained specialists from abroad. Selected laboratory assistants should also be sent abroad for training.

Each medical superintendent should be responsible to the hospital management committee, and in St Luke's Hospital his load of responsibility should be shared by a medical staff committee including all the consultants. There should be a lay secretary and a fully qualified matron, and a records officer trained in Britain.

More beds (including an admission block for men) are urgently needed at the mental hospital, and new accommodation at St Luke's is needed for the units now at the Central and isolation hospitals. But there is no need for a new general hospital, for St Luke's would be big enough if fuller use was made of existing beds. The only waiting lists are a short one for ear, nose, and throat cases and one for minor surgical cases. The demand for children's beds is generally falling and home care schemes would help to reduce it even further.

NURSING

Working on the two islands are 87 State registered nurses, and 646 hospital attendants most of whom have had no proper training. There is a school for nurses at St Luke's Hospital, but very few apply for training. This is partly because nursing as a profession is not held high in public esteem and partly because conditions and pay for student nurses are poor, especially compared with those of hospital attendants. A proposed training-course for attendants has been delayed because of a dispute over lecture fees.

Most ward sisters are members of the order of Sisters of Charity, to whom Malta "has reason to be grateful." But few are State registered, though the mother provincial of the order intends to send more to Britain for training.

Recommendations.—Every hospital should have a matron who is a State registered nurse and who must be an equal partner with the medical superintendent. She should be responsible for the nursing and welfare of patients, for the recruitment, training, and welfare of nurses, and for ward equipment, but not for catering. There should be higher pay for students and State registered nurses and a fully residential school, and the present ward sisters should be encouraged to train for State registration.

DISTRICT SERVICES

Malta is divided into three areas, each with its medical officer of health. He has a staff of sanitary inspectors and health visitors. There is a public-health laboratory and antenatal, child-health, school, and tuberculosis services. The district nursing is done by a small voluntary organisation.

Proposals.—The responsibilities of the M.O.H. should be enlarged and he should be given clerical help and an assistant chief sanitary inspector. The health visitors need better training. The obstetric services should be more unified. The family doctor who is to conduct the delivery should give antenatal care, and the antenatal clinics be replaced by consultative clinics staffed by obstetric specialists. Similarly, hospital and district care for babies and children should be part of one comprehensive service, whose staff should consist in family doctors rather than full time clinic officers. The care of mentally deficient children needs great expansion.

A campaign to make the public aware of the importance of dental health should be begun. As it succeeds more dentists will be needed.

The government should grant the district nursing association enough money to expand its services to cover the island. The industrial health service should be part of the general medical service.

At present, prescriptions for free drugs for the needy are scrutinised centrally with much delay. This scrutiny should be abolished or made locally.

INSURANCE CERTIFICATION AND NEEDY PATIENTS

Whole time doctors are employed to investigate claims under the National Insurance Act. There is little justification for this unsatisfactory system, and certificates from the doctor treating the patient should be accepted.

Few patients pay hospital fees, and even fewer pay the maximum fees, but even these do not cover the cost of treatment. The needy can also get aid for drugs, appliances, special diets, &c., and there are district medical officers to care for them. This last system is unsatisfactory in many ways, not least because the patient has no choice of doctor. Poor patients should be allowed to consult a family doctor in the ordinary way, and he should be paid by the government for such services—preferably on a capitation rather than a fee for service basis. The present district medical officers hold pension rights which would have to be honoured.

TERMS OF EMPLOYMENT OF DOCTORS

The present arrangements are full of anomalies The doctors in government service should be divided into

(*a*) Professional Civil Servants, including the chief government medical officer (whose salary should be £2000 a year, i e , the equal of the highest ranking Civil Servant), medical officers of health, and port medical officers

(*b*) Clinicians having no relationship to the Civil Service

The appointments of the clinicians should be whole-time (without private practice), or part-time and paid on a sessional basis

Those holding conjoint posts (with government and university) would be reckoned as part time clinicians Specialist posts should carry superannuation rights The payment recommended for each weekly session is £175 per annum for the senior consultants and £120–170, according to seniority, for the other consultants A medical superintendent engaged mainly in administration should be paid £1250 and given free board and lodging The junior posts would carry proportionately smaller salaries

There should be scholarships for study abroad free from any legal restriction about future service

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THE PRIME MINISTER TO THE NEGOTIATING COMMITTEE

On Feb 26 the Prime Minister published his reply to a letter sent to him by Sir Russell Brain and Dr A Talbot Rogers, joint chairmen of the Negotiating Committee, in which they expressed the committee's dissatisfaction at the Government's decision to appoint a Royal Commission to consider the profession's remuneration claim In the committee's view

"The Government has refused to honour its obligation to apply the terms of the Spens Committee's reports, as interpreted by the Danckwerts award It has thus broken its agreement with the doctors when they entered the health service It has been made clear that the Government does not recognise this obligation, but the late Minister of Health, Mr Turton, said that it would not be right for him to be judge in his own cause"

The committee agreed, however, that the method of adjusting medical remuneration to changing circumstances might usefully be considered They added

"If that stood by itself we should welcome the opportunity of assisting the Government in every way possible But a Royal Commission is no answer to the present claim, and it is manifestly unfair that doctors who have had no compensation for the rise in the cost-of-living for six years should await the result of the slow deliberations of a Royal Commission, and meanwhile be expected to go on loyally and ungrudgingly maintaining the health service though their real incomes remain grievously depressed We therefore ask that the present dispute between us should be submitted to an independent arbitrator without delay"

The text of the Prime Minister's reply is as follows

"Dear Sir Russell Brain I have to acknowledge the letter of February 21 signed by yourself and Dr Talbot Rogers regarding the difficult situation that has arisen in connexion with the remuneration of doctors in the health service

"Naturally I am very sorry that it has not been possible to arrive at an agreed solution of this problem The Government feels that the Royal Commission is the only way in which a permanent system can be devised which will stand the test of time I want to assure you that the purpose of the Royal Commission is not to waste time On the contrary, I shall certainly urge its chairman to proceed without delay Moreover, the work of the Royal Commission would not preclude some interim adjustment

"I must also repeat the Government's offer to deal with certain classes, that is hospital officers up to senior registrars, immediately

"While I realize the disappointment of your members at any delay I am convinced that in the long run this procedure is likely to improve the relations of the medical profession with the State and the public whom they serve so loyally"

Public Health

HOUSEHOLD INFECTION IN POLIOMYELITIS

C C Spicer
M R C S , Dip Bact
BACTERIOLOGIST

J C McDonald
M D Lond , D P H , D I H
EPIDEMIOLOGIST

CENTRAL PUBLIC HEALTH LABORATORY, LONDON

The investigation reported here is concerned with some of the facts known about poliomyelitis patients in households where there have been 2 or more cases The data relate to all such cases notified in England and Wales during the years 1951–54 Similar studies have been published abroad, but no comparable figures have appeared for this country

TABLE I—DISTRIBUTION OF MULTIPLE CASES OF POLIOMYELITIS IN HOUSEHOLDS

No of cases in household	No of households			
	Paralytic cases only	Non paralytic cases only	Paralytic and non paralytic cases	All cases
1	7603	3731	0	11,334
2	72	72	88	232
3	3	8	15*	26
4	0	2	1†	3
Total	7678	3813	104	11,595

* 6 households with 2 paralytic cases and 9 with 2 non paralytic case
† 2 paralytic and 2 non paralytic cases

MATERIAL AND METHOD

The information used was available from an investigation (Medical Research Council 1956) on inoculation procedures and neurological lesions, and comprised records of cases of poliomyelitis notified between April 1, 1951, and Dec 31, 1954 Cards existed for each patient giving the following information (*a*) age and sex, (*b*) whether paralytic or non-paralytic, (*c*) date of onset of illness, (*d*) address, and (*e*) history of tonsillectomy or inoculation within twelve weeks of onset

These records were examined to identify all cards which showed the same address All cards that related

TABLE II—AGE AND SEX DISTRIBUTION OF PRIMARY AND SECONDARY CASES OF POLIOMYELITIS IN HOUSEHOLDS WHERE MULTIPLE CASES HAVE ARISEN PRIMARY CASES INCLUDE ALL DOUBLE PRIMARIES WITH ONSETS ON THE SAME DAY

Age (yr)	Primary cases			Secondary cases			All multiple cases		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
0–5	66	60	126	36	46	82	102	106	208
6–10	61	26	87	39	24	63	100	50	150
11–15	16	10	26	15	17	32	31	27	58
16–20	7	7	14	8	8	16	15	15	30
> 20	22	23	45	24	35	59	46	58	104
	172	126	298	122	130	252	294	256	550

to institutions such as schools, barracks, and places other than ordinary households—about 10% in all—were then eliminated. The remaining cards were taken to refer to individual households. This process may appear rather arbitrary, but there was in fact little difficulty in classifying the institutional cases, and the remainder were nearly all people of the same name living at the same address.

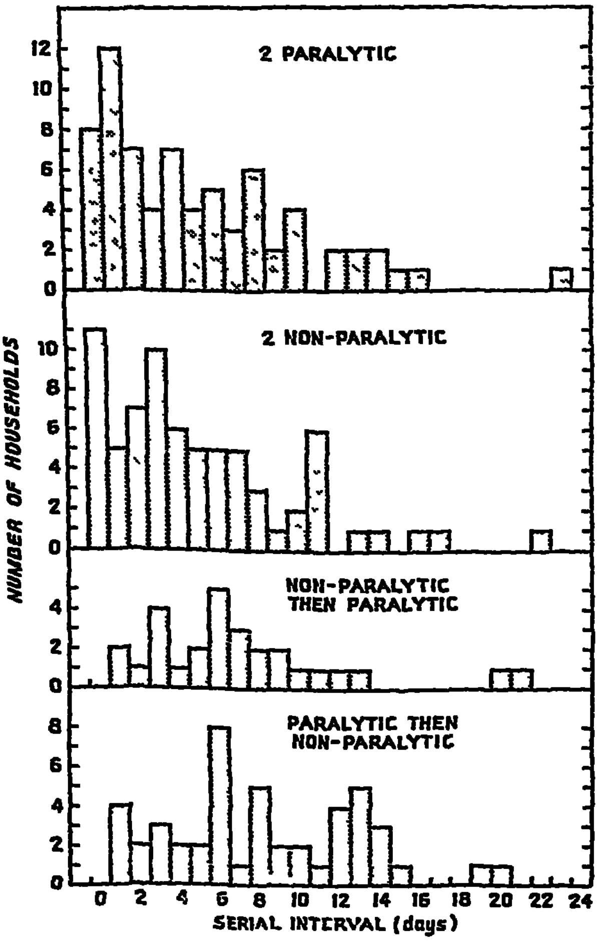
The records were complete in almost every instance, but in one or two the exact age was not given or the date of notification was given instead of the date of onset. There were 5 households in which the dates of onset of illness were more than sixty days apart; these were excluded from further study.

RESULTS

Household Distribution

Table I shows the number of households with various numbers of paralytic and non-paralytic cases. The number of households with single cases is slightly overestimated, since multiple cases in institutions were eliminated but single cases were not.

The proportion of households with multiple cases was about 2·3%—rather less than the 3·6% reported by Siegel and Greenberg (1953) for New York. In only 82 out of 7782 households in which there was a patient with paralytic poliomyelitis was there a second paralytic case. The difference between the numbers for houses with paralytic cases only, and for those which included non-paralytic cases, is not unexpected, in view of the uncertainties of diagnosis of non-paralytic poliomyelitis and the lesser likelihood of it being notified.



Distribution of serial intervals in households with 2 cases of poliomyelitis classified according to type of cases.

TABLE III—DISTRIBUTION OF SERIAL INTERVALS IN HOUSEHOLDS WITH 2 CASES OF POLIOMYELITIS, CLASSIFIED ACCORDING TO TYPE OF CASE

Serial interval (days)	No of households				
	2 paralytic cases	2 non paralytic case	Non paralytic, then paralytic case	Paralytic, then non-paralytic case	Total
0	8	11	→ 8 ←		27
1	12	5	2	4	23
2	7	7	1	2	17
3	4	10	4	3	21
4	7	6	1	2	16
5	4	5	2	2	13
6	5	5	5	8	23
7	3	5	3	1	12
8	6	3	2	5	16
9	2	1	2	2	7
10	4	2	1	2	9
11	0	6	1	1	8
12	2	0	1	4	7
13	2	1	1	5	9
14	2	1		3	6
15	1			1	2
16	1	1			2
17		1			1
18					0
19				1	1
20			1	1	2
21			1		1
22		1			1
23	1				1
>23	0	1	2	2	5
Unknown	1	0	0	1	2
Total	72	72	31	57	232

Age and Sex Distribution

In table II the age and sex distribution of multiple cases is given, classified as to whether they were primary or secondary. The primary cases include double and triple primaries. It will be seen that there is a curious deficiency of girls aged 6–10 years, which is especially noticeable among the primary cases and for which there is no obvious explanation. This is counterbalanced to some extent by an excess of female adults among the secondary cases. It is reasonable to explain the latter finding as due to infection of mothers by their children. Secondary cases are commoner in females than in males.

Serial Intervals

The distribution of serial intervals among various types of household with 2 cases is given in table III. In character it is very similar in households with 2 paralytic and those with 2 non-paralytic cases, but there seem to be differences between these and the mixed ones. In houses with 2 paralytic cases the 2nd case usually followed the 1st in a short time—about two thirds of them within a week.

Twins

Investigations of twin cases made by Herndon and Jennings (1951) and of consanguinity in parents of paralytic cases by Wintrop Oostenrijk (1955), have suggested the existence of a genetic factor influencing susceptibility to paralysis. Addair and Snyder (1942) have even claimed that susceptibility may be determined by a recessive gene. On the other hand, the work of Borgstrom (1939) and Masini (1953) does not support this possibility. We examined our data for the frequency of twin cases to see whether they were present in sufficient numbers to support the hypothesis of a genetic factor. A rough calculation based on the Registrar General's statistics of household size indicated that about 2·5% of twins might be expected by random sampling alone. It was found that, in 145 households with 2 cases aged less than 16, there were 10 in which the 2 patients had the same name and date of birth. Of 39 paralytic pairs 5 (13%) were twins, while the incidence in mixed and non-paralytic pairs was 1 in 53 (2%) and 4 in 53 (8%) respectively. The excess of twins in the paralytic pairs though suggestive, is not statistically significant.

TERMS OF EMPLOYMENT OF DOCTORS

The present arrangements are full of anomalies The *doctors in government service should* be divided into

(*a*) Professional Civil Servants, including the chief government medical officer (whose salary should be £2000 a year, i e, the equal of the highest ranking Civil Servant), medical officers of health, and port medical officers

(*b*) Clinicians having no relationship to the Civil Service

The appointments of the clinicians should be whole-time (without private practice), or part time and paid on a sessional basis

Those holding conjoint posts (with government and university) would be reckoned as part time clinicians Specialist posts should carry superannuation rights The payment recommended for each weekly session is £175 per annum for the senior consultants and £120–170, according to seniority, for the other consultants A medical superintendent engaged mainly in administration should be paid £1250 and given free board and lodging The junior posts would carry proportionately smaller salaries

There should be scholarships for study abroad free from any legal restriction about future service

THE PRIME MINISTER TO THE NEGOTIATING COMMITTEE

On Feb 26 the Prime Minister published his reply to a letter sent to him by Sir Russell Brain and Dr A Talbot Rogers, joint chairmen of the Negotiating Committee, in which they expressed the committee's dissatisfaction at the Government's decision to appoint a Royal Commission to consider the profession's remuneration claim In the committee's view

" The Government has refused to honour its obligation to apply the terms of the Spens Committee's reports, as interpreted by the Danckwerts award It has thus broken its agreement with the doctors when they entered the health service It has been made clear that the Government does not recognise this obligation, but the late Minister of Health, Mr Turton, said that it would not be right for him to be judge in his own cause "

The committee agreed, however, that the method of adjusting medical remuneration to changing circumstances might usefully be considered They added

" If that stood by itself we should welcome the opportunity of assisting the Government in every way possible But a Royal Commission is no answer to the present claim, and it is manifestly unfair that doctors who have had no compensation for the rise in the cost-of-living for six years should await the result of the slow deliberations of a Royal Commission, and meanwhile be expected to go on loyally and ungrudgingly maintaining the health service though their real incomes remain grievously depressed We therefore ask that the present dispute between us should be submitted to an independent arbitrator without delay "

The text of the Prime Minister's reply is as follows

" Dear Sir Russell Brain I have to acknowledge the letter of February 21 signed by yourself and Dr Talbot Rogers regarding the difficult situation that has arisen in connexion with the remuneration of doctors in the health service

" Naturally I am very sorry that it has not been possible to arrive at an agreed solution of this problem The Government feels that the Royal Commission is the only way in which a permanent system can be devised which will stand the test of time I want to assure you that the purpose of the Royal Commission is not to waste time On the contrary, I shall certainly urge its chairman to proceed without delay Moreover, the work of the Royal Commission would not preclude some interim adjustment

" I must also repeat the Government's offer to deal with *certain classes*, that is hospital officers up to senior registrars immediately

" While I realize the disappointment of your members at any delay I am convinced that in the long run this procedure is likely to improve the relations of the medical profession with the State and the public whom they serve so loyally "

Public Health

HOUSEHOLD INFECTION IN POLIOMYELITIS

C C Spicer
M R C S, Dip Bact
BACTERIOLOGIST

J C McDonald
M D Lond, D P H, D I H
EPIDEMIOLOGIST

CENTRAL PUBLIC HEALTH LABORATORY, LONDON

The investigation *reported here is concerned* with some of the facts known about poliomyelitis patients in households where there have been 2 or more cases The data relate to all such cases notified in England and Wales during the years 1951–54 Similar studies have been published abroad, but no comparable figures have appeared for this country

TABLE I—DISTRIBUTION OF MULTIPLE CASES OF POLIOMYELITIS IN HOUSEHOLDS

No of cases in household	No of households			
	Paralytic cases only	Non paralytic cases only	Paralytic and non paralytic cases	All cases
1	7603	3731	0	11,334
2	72	72	88	232
3	3	8	15*	26
4	0	2	1†	3
Total	*7678*	*3813*	*104*	*11,595*

* 6 households with 2 paralytic cases and 9 with 2 non paralytic cases
† 2 paralytic and 2 non paralytic cases

MATERIAL AND METHOD

The information used was available from an investigation (Medical Research Council 1956) on inoculation procedures and neurological lesions, and comprised records of cases of poliomyelitis notified between April 1, 1951, and Dec 31, 1954 Cards existed for each patient giving the following information (*a*) age and sex, (*b*) whether paralytic or non-paralytic, (*c*) date of onset of illness, (*d*) address, and (*e*) history of tonsillectomy or inoculation within twelve weeks of onset

These records were examined to identify all cards which showed the same address *All cards that related*

TABLE II—AGE AND SEX DISTRIBUTION OF PRIMARY AND SECONDARY CASES OF POLIOMYELITIS IN HOUSEHOLDS WHERE MULTIPLE CASES HAVE ARISEN PRIMARY CASES INCLUDE ALL DOUBLE PRIMARIES WITH ONSETS ON THE SAME DAY

Age (yr)	*Primary cases*			*Secondary cases*			*All multiple cases*		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
0–5	66	60	126	36	46	82	102	106	208
6–10	61	26	87	39	24	63	100	50	150
11–15	16	10	26	15	17	32	31	27	58
16–20	7	7	14	8	8	16	15	15	30
> 20	22	23	45	24	35	59	46	58	104
	172	*126*	*298*	*122*	*130*	*252*	*294*	*256*	*550*

to institutions such as schools, barracks, and places other than ordinary households—about 10% in all—were then eliminated The remaining cards were taken to refer to individual households This process may appear rather arbitrary, but there was in fact little difficulty in classifying the institutional cases, and the remainder were nearly all people of the same name living at the same address

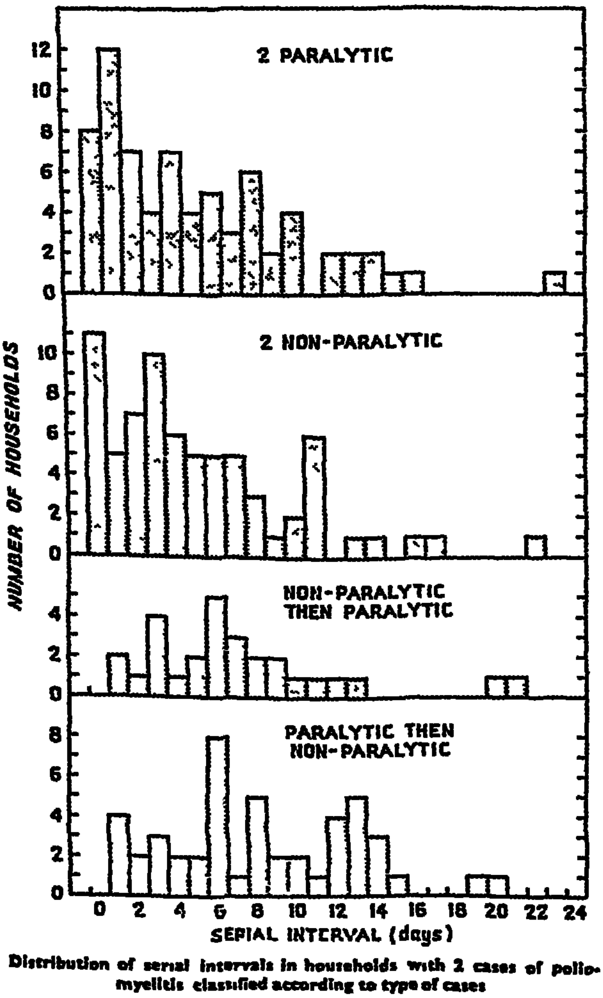
The records were complete in almost every instance, but in one or two the exact age was not given or the date of notification was given instead of the date of onset There were 5 households in which the dates of onset of illness were more than sixty days apart, these were excluded from further study

RESULTS

Household Distribution

Table I shows the number of households with various numbers of paralytic and non-paralytic cases The number of households with single cases is slightly overestimated, since multiple cases in institutions were eliminated but single cases were not

The proportion of households with multiple cases was about 2 3%—rather less than the 3 6% reported by Siegel and Greenberg (1953) for New York In only 82 out of 7782 households in which there was a patient with paralytic poliomyelitis was there a second paralytic case The difference between the numbers for houses with paralytic cases only, and for those which included non-paralytic cases, is not unexpected, in view of the uncertainties of diagnosis of non-paralytic poliomyelitis and the lesser likelihood of it being notified



Distribution of serial intervals in households with 2 cases of poliomyelitis classified according to type of cases

TABLE III—DISTRIBUTION OF SERIAL INTERVALS IN HOUSEHOLDS WITH 2 CASES OF POLIOMYELITIS, CLASSIFIED ACCORDING TO TYPE OF CASE

Serial interval (days)	No of households				
	2 paralytic cases	2 non-paralytic case	Non paralytic, then paralytic case	Paralytic, then non paralytic case	Total
0	8	11	→ 8 ←		27
1	12	5	2	4	23
2	7	7	1	2	17
3	4	10	4	3	21
4	7	6	1	2	16
5	4	5	2	2	13
6	5	5	5	8	23
7	3	5	3	1	12
8	6	3	2	5	16
9	2	1	2	2	7
10	4	2	1	2	9
11	0	6	1	1	8
12	2	0	1	4	7
13	2	1	1	5	9
14	2	1		3	6
15	1			1	2
16	1	1			2
17		1			1
18					0
19				1	1
20			1	1	2
21			1		1
22		1			1
23	1				1
>23	0	1	2	2	5
Unknown	1	0	0	1	2
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Investigations of twin cases made by Herndon and Jennings (1951), and of consanguinity in parents of paralytic cases by Wintrop-Oostenrijk (1955), have suggested the existence of a genetic factor influencing susceptibility to paralysis Addair and Snyder (1942) have even claimed that susceptibility may be determined by a recessive gene On the other hand, the work of Borgstrom (1939) and Masini (1953) does not support this possibility We examined our data for the frequency of twin cases to see whether they were present in sufficient numbers to support the hypothesis of a genetic factor A rough calculation based on the Registrar-General's statistics of household size indicated that about 2–5% of twins might be expected by random sampling alone It was found that, in 145 households with 2 cases aged less than 16, there were 10 in which the 2 patients had the same name and date of birth Of 39 paralytic pairs 5 (13%) were twins, while the incidence in mixed and non-paralytic pairs was 1 in 53 (2%) and 4 in 53 (8%) respectively The excess of twins in the paralytic pairs, though suggestive, is not statistically significant

Other Characteristics

The general characteristics of multiple cases, apart from certain features of the age and sex distribution mentioned above, were similar to those of single cases There was no peculiarity of their seasonal distribution, nor were there any obvious changes in the frequency of multiple cases during the four years over which the present data were collected A recent history of inoculation or tonsillectomy was no commoner than in single cases Multiple cases were slightly commoner in rural areas, 30% being found instead of the 22% expected from the Registrar-General's statistics

DISCUSSION

The present study provides little evidence that paralytic cases tend to be associated with one another in households In the whole of England and Wales during four years, there were only 82 households in which 2 or more paralytic cases of poliomyelitis were reported In table IV the observed distribution of multiple cases is compared with that which would have been expected if there had been no association between the cases at all and they were random events in a uniform population of households In these circumstances they would follow a Poisson distribution, and it can be seen that the observed and calculated distributions agree remarkably well There is a significant discrepancy as measured by the χ^2 test, but this could easily be ascribed to the roughness of the hypothesis, which ignores variation in household size and other complications, in any case the χ^2 test is not reliable with distributions of this kind where the major discrepancies are found between very small expectations and their observed counterparts

TABLE IV—COMPARISON OF OBSERVED DISTRIBUTION OF MULTIPLE PARALYTIC CASES IN HOUSEHOLDS WITH THEIR EXPECTED VALUES FROM THE POISSON DISTRIBUTION HOUSEHOLDS WITH NON PARALYTIC CASES EXCLUDED

No of cases in household	No of households	
	Observed	Calculated
0		
1	7603	7600·6
2	72	77·0
3	3	0·4

The distribution of serial intervals is also difficult to reconcile with the existence of a strong association between paralytic cases The distributions in table III relating to pairs of paralytic cases or pairs of non-paralytics are very similar to those that would have been obtained if the members of the pairs had been infected simultaneously by some common source There is no evidence of the existence of a group of cases arising from the primary at about the time of the usual incubation *period* *This finding has also been reported by* Littell and Smith (1955) on the basis of other data on the serial interval, and they have suggested that it could be explained if patients became infectious early enough in the incubation period The work of Casey (1942) does not support this explanation, since it indicates that the infectious period is most commonly from three days before till three days after the onset of symptoms

From a practical aspect the information given above suggests that, so far as a patient's home contacts are concerned, there is little value in quarantine measures or passive immunisation with γ globulin These could not prevent more than about 1% of all paralytic cases even if they were universally applied and completely effective, and every secondary case arose by infection from the primary Furthermore, most secondary cases arise so soon that it would be difficult to take any action in time

SUMMARY

Multiple cases of poliomyelitis, in households in England and Wales from 1951 to 1954, have been studied

In 82 out of 7782 houses in which there was a case of paralytic poliomyelitis, there were 1 *or more* secondary cases This distribution is similar to what would have been expected by chance alone

About two-thirds of the secondary cases arose within a week of the primary

Apparently there was no strong association between paralytic cases

We are indebted to the Medical Research Council committee on inoculation procedures and neurological lesions for permission to use their records We should like to thank Miss Eileen Bebb for her great assistance in the analysis, Dr J Knowelden for his help, and Dr P Armitage for advice and criticism

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Poliomyelitis Vaccination

It was hoped that the distribution of poliomyelitis vaccine would start again this week and a batch sufficient to vaccinate 200,000 children with two injections was being made ready But the Ministry of Health announces that information has been received from the manufacturers that signs of possible deterioration during storage have been detected in a few of the phials of vaccine that were ready for issue It has been decided to defer distribution pending investigation During the first phase of the programme last year some 200,000 children between the ages of 2 and 9 were vaccinated, leaving about 1,500,000 children in England and Wales still registered These children are now to be given priority In Scotland about 35,000 children were vaccinated last year, leaving 265,000 children still registered

Medicine and the Law

Negligence Claim Fails

A SCOTTISH jury has unanimously rejected a claim against a doctor for alleged negligence in the injection of an anæsthetic[1] The pursuer (plaintiff) was a Mrs Sutherland She alleged that, in giving her an injection of thiopentone ('Pentothal') before an operation, the doctor negligently caused the point of the needle to enter the median nerve of the left arm It was alleged that as a consequence the patient suffered considerable pain in her left arm and hand from time to time, and that she had difficulty in raising her left arm to the height of her shoulder She also contended that she had defective sensation in the tips of her left thumb and fingers and general clumsiness in her left hand

The defence did not admit that the needle had in fact entered the median nerve, and it does not appear to have been proved that this happened It was admitted, in view of the injury sustained by the patient, that some penetration of the nerve may have taken place, but it was contended that this was not due to any negligence on the part of the doctor Two anæsthetists gave evidence to the effect that any piercing of the nerve could have been due to a completely involuntary muscular movement within the arm which the doctor could not have foreseen or have seen happening

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[1] *Glasgow Herald* Feb 16 1957

Coma Mistaken for Death

A Mrs L, aged 78, decided apparently to end her life by taking an overdose of drugs[2] Her daughter found her in bed, and believed her to be dead She sent for a doctor who was also of opinion that Mrs L was dead The body was removed to a mortuary, no sign of life being observed during the journey to the mortuary As the undertaker and a police officer were leaving the mortuary, however, the officer noticed that some cotton-wool which had been placed on the woman's face had slipped The undertaker returned and saw that she was breathing Resuscitation apparatus was called for and applied while she was taken to hospital She died later at the hospital

Giving evidence at the inquest, Prof J M Webster said that death was caused by hypostatic pneumonia due to acute narcotic poisoning Mrs L had taken about three times the lethal dose In thirty years' experience, it was only the third case he had known where coma had been mistaken for death and the patient removed to a mortuary

Professor Webster said that the case was a particularly difficult one, because it was in an old lady and the narcotic drugs depressed the vital nerve centres, particularly the respiratory senses In the coma Mrs L had been almost dead, with no pulse at all, and it was a perfectly reasonable mistake to say she was dead The case was almost hopeless from the start owing to the amount of drug absorbed

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Parliament

Royal Commission on Remuneration

ON Feb 20, in the House of Commons, Mr HAROLD MACMILLAN, the Prime Minister, announced the appointment of a Royal Commission to review the remuneration of doctors and dentists He said

> The House will know that a claim has been submitted for an increase of 24% in the remuneration of all doctors in the National Health Service The extra cost to the country would be about £20 million a year. In present circumstances, the Government do not feel able to admit this claim, and representatives of the profession have been so informed
>
> This does not mean that the Government have reached any conclusion as to the merits of the claim Indeed, they have decided that the time is opportune for a full review of medical remuneration through an independent inquiry which would take into account the position of the medical profession in relation to other professional classes in the community, and would suggest how the matter could be kept under review
>
> Within the last few days a claim, similar to that of the doctors, has been received on behalf of the dental profession, and the dental profession will be included in the review to be conducted by the Royal Commission The question whether the remuneration of doctors and dentists employed by local authorities should be included in the terms of reference is under consideration
>
> I will announce at a later date the names of the chairman and members of the Royal Commission, together with the terms of reference

Mr HUGH GAITSKELL Would the Prime Minister clarify the position ? How long does he expect it will be before the Royal Commission reports ? Is it to be in the nature of an arbitration tribunal which is to pronounce upon the claim ? If so, are we to understand that the Government bind themselves in advance to accept whatever recommendations are made by the Royal Commission ? Will the terms of reference include specialists as well as general practitioners ? Finally, will it be within the terms of reference of the Commission and within its powers to recommend back-dating the award, if there is an award ? The PRIME MINISTER It will of course, be in the power of the Royal Commission to recommend that any award or any proposal should be made retrospective, but we must await the recommendations of the Royal Commission on that point The terms of reference will include the specialists I believe that the character of the Royal Commission will be best set out in detail when I am able to present both the names of the members and the precise terms of reference, but I think it is generally agreed that it would be a good thing if the relation of this profession with other professions could be established and if a satisfactory system could be laid down by which future reviews could be carried out from time to time I think it would be to everybody's benefit if that resulted from the Royal Commission

Sir IAN FRASER While welcoming this proposal, may I ask whether the remuneration of medical auxiliaries such as physiotherapists, radiographers and others who work so closely with the medical and dental profession, could be included in the Commission s considerations ? The PRIME MINISTER. I should prefer not to answer that today, but to take it into account when the terms of reference are settled

Mr HERBERT MORRISON. Does not the Prime Minister think that this is a very doubtful way of seeking to settle wages, salaries, and remuneration ? Does it not take negotiation, from the taxpayer's point of view, out of the hands of Ministers who are responsible to the House and put it in the hands of an outside body ? Is it not unlikely to lead to coördinated responsible decisions ? Does the Prime Minister recall—I admit that this happened under the Labour Government—that the Spens Committee, dealing with somewhat similar circumstances, landed the country into an expenditure and into repercussions which were very embarrassing ? The PRIME MINISTER This is a very difficult problem, but I feel that the work of the Royal Commission on the Civil Service, which is not quite similar but is somewhat parallel has been an advantage Again, it was a question in which Ministers were finally responsible, as they will be in this matter, but I think that it has been an advantage in the general life of the Civil Service. If some equally good results followed from this Royal Commission, I think it would be generally acceptable

Mr G D NABARRO May I ask the Prime Minister to make it perfectly clear, in framing the terms of reference for the Royal Commission, that a primary purpose should be to endeavour to eliminate all the legal and other uncertainties which have arisen during the past few years from the Spens report and the Danckwerts award made under it, all of which are responsible for the present difficult position with the doctor ? The PRIME MINISTER One of the purposes of the Royal Commission will be to clear up this situation and to lay down a system which, through the years, will be more workable and more acceptable

Dr EDITH SUMMERSKILL· As this is virtually a repudiation of the recommendations of the Spens report, could the Prime Minister say what was the reaction of the professional organisations towards this new suggestion ? The PRIME MINISTER The discussions between the representatives of the profession and the Minister of Health are another matter Today, I have simply preferred to confine myself to stating that I have recommended the appointment of the Commission, that Her Majesty has been pleased to accept the recommendation, and that the terms of reference and the membership will be announced I think that all the detailed questions had better be put to the Minister responsible

The appointment of the Royal Commission was announced in the House of Lords by the MARQUESS OF SALISBURY In receiving the statement for the Opposition VISCOUNT ALEXANDER OF HILLSBOROUGH admitted that the statement's first impressions on him were not very cheerful

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[2] *Birmingham Post*, Feb 19, 1957

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[1] *Glasgow Herald*, Feb 16 1957

Pension Adjustment

On Feb 25, Mr H A MARQUAND called on the Government in their next Budget to increase retirement and old-age pensions and adjust the scales of National Assistance One of the recognised criteria of the adequacy of pensions and benefits was the number of people dependent on them who were obliged to draw National Assistance At the end of last year, he said, this figure stood at 927,000, which in his view justified an increase Another reason for an increase was the continuous rise in the cost of living Since April, 1955, it had risen by 9% He believed that in future there must be a much closer relation between pensions and the level of wages "Means must be found to protect pensions from erosion by inflation He reminded those who said that an immediate improvement in pensions and benefits would throw too heavy a burden on the Exchequer that State support for privately financed superannuation was about £175 million against £137 million for National Assistance

In all, 2½ million people were now dependent on National Assistance and he was uneasy about their standard of living For instance, he did not see how the present rate of *18s* for a child between eleven and sixteen could be fair when a foster parent received *32s* He thought that we should have an authoritative commission to lay down minimum physical standards and set up a cost-of-living index based on these findings

Miss EDITH PITT, joint parliamentary secretary to the Ministry of Pensions and National Insurance, maintained that, though the cost of living had risen, pensions had a better purchasing power today than at any time for the past seven years National Insurance benefits, including pensions, were not, she continued, payments according to needs or means They were paid as a right in return for contribution, and if we were to increase benefits we must also consider increased contributions The Government had no money except what was raised from taxation or contributions Not only must we consider what we could afford but also the burden we were placing on succeeding generations There were today about 4,600,000 retirement pensioners, by the end of 1980 there would be 7½ million To give a £3 pension now would cost an extra £220 million a year, which was equal to *4s* on the joint contribution In twenty-five years it would amount to £370 million or *7s* on the contribution

Turning to the question of nutrition she said that many old people who were found to be lacking food were not short of money but had no friends or relatives to help them According to the National Food Survey for April to June, 1956, the old-age pensioner spent *25s 5d* a week on food compared with *28s 4d* per person in all households She did not think that the allowance paid for a foster child could fairly be compared with an allowance for a child living with its family The boarded-out child went to strangers and some payment was made to them for their care She believed that the Government had protected pensions and benefits and would continue to protect them

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In his way, he was a great naturalist His favourite resting-place lay under the bridge by the river, and in time even the records department came to recognise this as his official residence He lived with the birds and the trees and suffered with the elements In the summer he had sunstroke, in the winter frostbite, the spring showers brought crippling arthritis, while November would bring him cyanosed and gasping feebly, as the fog seeped through his lungs One icy Christmas day, he slipped and broke his wrist The nurses did a wonderful job disinfesting his beard, and he was the best Father Christmas the hospital has ever known

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In our outpost of Empire the cinemas of the town are out of bounds, film shows therefore come to us Our cinema, at other times the company dining-hall, is formed by the end-to-end anastomosis of a series of Nissen huts, internally it is reminiscent of the Bakerloo or prophetic of the airliner of the Future We were agreeably surprised to find one day before Christmas that a film so recent as *Rock around the Clock* was to be our fare The shambles reported in towns in England was not for us, the presence of N C O s in force and the extremely durable furniture militated against this, still, there was nothing half-hearted in our rendering of "See you later, alligator"

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"How's your back?" our orthopod asked solicitously as he got into the lift with me And well he might, for, but for his present girth, he would have stood in my place on the stage during our Christmas show

It is not easy for the tyro to wait for the laugh of recognition, or a sympathetic titter, after the long pause when he has sucked his teeth slowly, flexed and extended his knees that inch or so from the stand-at-ease to the stand easy I was clad only in white paint, plenty of black eye-shadow, and short-sleeved long woollen combinations, and it seemed to me an age before our orthopod

Having regard, he continued, to the long, outstanding application of the great profession of medical men and women to the State service, I feel it is extraordinary that, after this length of time, the question of their remuneration should be referred to a Royal Commission Here we are dealing with something which is urgent, outstanding, and necessary to retain the good will of the medical profession in maintaining a great national service to the people To me, it seems like cowardice on the part of the Government for them not to deal with, and decide their policy upon, what is an urgent matter

There was no such reference to a Royal Commission, no such delay, before the Government made the statement in the other place the other day about the increased costs of welfare milk and the weekly contribution of the worker to the health service as there is going to be in regard to the remuneration of the doctors But here it looks as if the medical profession may be "got at" with a view to putting up with a Royal Commission Having regard to his former association with the great medical profession, no doubt the Chancellor of the Duchy of Lancaster will be busy trying to spin the necessary story of glamour to his professional colleagues

The MARQUESS OF SALISBURY This is a very wide and complex question It is no good the noble Viscount and others saying that the medical profession can be *dealt with entirely in isolation, it cannot be done* This is one of the most complicated questions that exist, as I know from my connections with the research bodies in this country, and it is an eminently suitable question to be dealt with by a Royal Commission

VISCOUNT ALEXANDER OF HILLSBOROUGH How long did it take the Government to discover that this was so complicated a question in comparison with others? For months and months this matter has been under discussion with the medical profession, and it has certainly been within the knowledge of the Ministry of Health from the moment that the State scheme was launched Now, at this stage, when the doctors are in a very poor position—at least, some of them are—in relation to the increasing cost of living, that they should be dealt with by means of a Royal Commission seems to me almost unthinkable Will the noble Marquess say whether, while the Royal Commission is sitting, any adjustment is going to be made to ease the position of the doctors? The MARQUESS OF SALISBURY I understand that my right honourable friends the Minister of Health and the Secretary of State for Scotland have told the doctors and dentists that they are willing to agree to the granting of an interim increase to the junior hospital medical and dental staff This is on the basis that they can justifiably be regarded as underpaid at present The offer will be negotiated through the established Whitley machinery It will not be extended beyond this limited class to, for example, the lower-paid general-practitioner doctors or dentists, it is meant to apply to those who are in most need at the present time

LORD AMULREE I must agree that the questions raised by the medical profession have been going on for a long time and I hope that the Royal Commission will now settle them quickly I very much hope that the position of local-authority doctors and dentists will come under the terms of reference of the Royal Commission This is a matter of some urgency, and I trust that this Royal Commission will report in six months and not a longer period The MARQUESS OF SALISBURY My Lords, the period which the Royal Commission will take is a matter for the Commission The Government desire that it shall be as rapid and efficient as possible in its work

LORD CONESFORD May I ask my noble friend whether, in settling the terms of reference of the Royal Commission, he will consider the advisability of making them wide enough to enable the Royal Commission to compare, not only professional earnings as between different professions, but professional earnings with non-professional earnings? The MARQUESS OF SALISBURY I have said that there must be some limitation of the terms of reference, even of a Royal Commission

⁂ This matter is carried further in correspondence reproduced on p 470 —ED L

Paying for the Welfare State

On Feb 19, on the eve of the publication of the Civil Estimates for 1957–58, Mr PETER THORNEYCROFT, Chancellor of the Exchequer, said that its total was £2654 million, an increase of £110 million over this year Large items in the increase were for education (£63 million) and the National Health Service (£49 million) As a whole the social services showed an increase of £146 million over the original Estimates for this year This was largely due to higher prices, salaries, and wages, but in part it was due to there being more children to be educated and to the increasing use being made of the National Health Service The large and continuing increase in our total expenditure, he continued, imposed a burden on the economy which the Government could not ignore

It would not be right to meet our difficulties by making changes in defence policy alone, and there must also be changes of policy on the civil side Changes in local government finance had been announced The Government had also decided to reduce the subsidies for welfare milk and school meals The price of welfare milk would be increased to *4d* a pint—that is, roughly half price This would leave the subsidy at about the amount per pint at which it was first introduced in 1940 With a corresponding increase in the price of National dried milk, the saving in 1957–58 would be £14 million The charge for school meals would be increased by *2d* to *1s*, saving £3½ million Both these changes would take effect from the beginning of April The existing arrangements for hardship exemptions would continue

Turning to the National Health Service, he said that the Government had given anxious consideration to its growing cost When the service was introduced it was expected to cost a total of £175 million a year By 1949–50, this had risen to £450 million In 1950 a ceiling of £400 million was imposed on Exchequer expenditure, below which the cost of improvements and extensions to the service had to be contained In 1957–58, the total cost of the service would be £690 million Towards this, as things stood now, £40 million would come from the contribution made from the National Insurance Fund, which was *10d* a week for the adult man and lesser sums for other contributors, £100 million would come from other receipts (including charges to patients), and the whole of the balance of £550 million—£49 million above the estimate for last year—would be provided by general taxation

The alternatives to this increase in the charge on the Exchequer were to reduce the scope of the service, to charge more to patients, or to increase the contribution It was widely believed that the National Health Service was paid for by weekly contributions He wished to make it clear that this was not so The contribution had never paid for more than a small proportion of the cost of the service, and this proportion had steadily declined each year When the original National Health Service Bills were before Parliament, it was expected that contributions would provide about a fifth of the gross cost of the service Today, they provided only about a seventeenth The Government, therefore, proposed to increase the contribution by *10d* for an adult man, and by smaller sums for adult women and juveniles The employer would pay the same proportionate share as at present The Government's purpose was to establish a separate National Health Service contribution towards the cost of the service Next year, the contributory element would rise from a seventeenth to about a ninth of the gross cost of the service Separate legislation for this purpose would be introduced as soon as possible The change would provide an additional £10 million for the Exchequer in a full year In view of the rise in the cost of the service he did not think it unreasonable to go back to what was a traditional arrangement—for people to contribute a little when they were well in order that they might be looked after when ill

Members suggested that the increases would fall heaviest on families with small children but the SPEAKER reminded them that these matters would be debated on the Estimates Mr THORNEYCROFT added that the Government had given careful thought to these points, but the worst damage that could be done to the social services would be to allow their cost to rise to unmanageable proportions

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I had been told to slow up my movements even more if I found the audience "dead," which I did Also as a face-saver to turn my back ("Show your gorgeous trapezii, old boy") on the audience and still with arms bent do a slight gyration with the hips Many years ago this had gained a coarse guffaw from the rear of the hall when the orthopod had saved the same turn from going sour He assured me it would start a laugh riot and panic the audience Unfortunately, without benefit of rehearsals or stagecraft, it was I who panicked, and without waiting any longer I started, with a quick nod to the pianist a too quick rendering of *You too can have a body like mine* At the third line I had lost the artificial quavering croak which had taken a lot of bathroom practice and I searched my vocal chords to resuscitate it without success Leaving the pianist behind, I now gained speed and forgot to gaze in meditation at my navel for the long pause after *make your liver shiver and your kidneys quiver*

In the corner of my eye I noted restlessness in the wings as well as in the audience, and I started on the deep-breathing exercise ("It has to be done very, very slowly, old boy, it's the punch moment of the whole item"), which our orthopod said would tie everybody in knots providing I gained the audience's confidence Neither I nor the audience had any confidence, and the deep breathing degenerated into short pants Once more I hurried into the refrain and began to sense escape was near

I shuffled to the cunningly dispensary-painted "plaster-of paris" bar-bell weights which had been placed front centre-stage only to find that the orthopædic department had left a genuine 60 lb on each end of the bar As I swore and tore to raise it for the "snatch, clean and jerk" I felt the ominous click and the sharp pain in my back Bent double I made my exit holding up one end 18 in from the floor

The gratifying roar that resounded on my disappearance was due, I was told later, to the beaming genial aplomb of our orthopod, who, exhaling good cheer and sparing me the insult of the desultory clap, swung with a crash of opening bars straight into *I'm the man who found The Lost Chord*

* * *

The B B C News Service had just told of last month's earth tremors A professor of geology from the Midlands was reported to have said that the shock wave was so severe that it "nearly threw him from his chair" A colleague commented that if this was the usual effect of earthquakes then our little university town might well benefit by a series of seismic shocks

* * *

The dominant gene, the dominant gene
Is the happiest creature that ever was seen,
We mortals can only admire at a distance
The joys of a chromosomatic existence—
Or marvel how Nature determines the sexes
By cunningly mixing the Y's and the X's
(For as Mendel has proved, it is only statistics
That settle our primary characteristics)
Just imagine the life of ineffable bliss you
Could spend as a speck in the nuclear tissue!
Fraternally twinned with a charming recessive—
Your relationship tender, but firmly possessive,
Dictating the pigment, the shape of the nose,
Or whether your host shall have suckers for toes
Do you find immortality's promise seductive?
Make your home in a cell that is marked "Reproductive"
A short life, but merry? You dread being static?
Your calling is plain—you are clearly Somatic—
For you cannot grow stale, with your every ambition
Fulfilled by perpetual cellular fission
So banish your doubts, your neuroses, and revel
In life as it's lived at molecular level!

Envoi

Princess! You'll discover the key to my riddle
By shuffling two chromosomes—split down the middle

Letters to the Editor

BRONCHIAL CARCINOMA

SIR,—Mr Thompson, in his letter last week, draws attention once more to the delay in referring patients with cancer of the lung to the surgeon One reason for this delay will be appreciated by all whose task it is to recognise cancer of the lung among other diseases with identical presenting symptoms and radiological findings They see many patients with persistent cough due to a respiratory infection, pulmonary consolidation resolving slowly but permanently under treatment, and blood in the sputum the source of which is an acutely inflamed bronchial mucosa Any one of them may be suspected for a time of having cancer If they were all sent to a thoracic surgical department without preliminary sorting the surgeons would soon find themselves overwhelmed Mr Thompson's figures, illustrating the slow progress of his patients from the general practitioner to the surgeon, cannot therefore be seen in perspective unless we know the size of the sick population from which they were drawn For every one of his 135 patients with carcinoma of the lung there must have been many others who did not go beyond the general practitioner or the chest physician, because they were found to have some less serious disease during the seemingly long period of observation

Just over a year ago a group of six general practitioners agreed to refer to me every man aged 45–70 years who had been a heavy smoker as soon as he reported one of a previously defined set of symptoms suggesting the possibility of bronchial carcinoma The number of patients referred to me under this arrangement in 1956 was 56 Amongst these I found 2 with bronchial carcinoma, only 1 of whom was in a fit state to be referred to the surgeon It was often impossible to settle the diagnosis at the first consultation, and many patients were seen several times before being dismissed from observation If Mr Thompson's suggestion had been adopted, he and his colleagues would have examined over 7500 patients, many of them more than once, in order to find 135 cases of cancer of the lung This conservative estimate is based on the assumption that his patients were also selected from a similar age group of men at special risk

The special techniques available to thoracic surgeons, by which Mr Thompson probably means facilities for bronchoscopy and thoracotomy, are readily accessible everywhere The difficulty is to know when to use them Most patients find bronchoscopy too unsettling an experience for it to be used on the large scale necessary for efficient case finding Nobody would wish to rely on thoracotomy as a means of diagnosis except as a last resort There is no such objection to a search for malignant cells in the sputum, but this examination demands great skill and is time consuming It remains to be seen whether it is economical to provide such a service on the scale required for general use

It would be unprofitable to discuss whether this or that class of doctor is better qualified to recognise cancer of the lung in its early stages If the arrangements we are testing on a small scale were extended to the whole population, the work involved would overstrain the resources of any one specialty

Queen Mary's Hospital
Sidcup

PAUL FORGACS

SIR,—It is extraordinary to find such a distinguished surgeon as Mr Vernon Thompson blaming the medical profession for the failure to diagnose lung cancer earlier and making the misleading suggestion that the present tendency "to refer chest cases to chest clinics, which have evolved from the old tuberculosis dispensary, in order to get an X ray, has contributed largely to the delay."

It is surely common knowledge that when patients complain of respiratory symptoms, elucidation of their condition requires a chest X ray. Indeed, as Mr Thompson himself says, "radiology is now an essential part of clinical examination," and today the overwhelming majority of general practitioners know this and refer their patients liberally to the most convenient centre. All over the country efficient chest clinics are now in existence doing this work, and, owing to the recognition of the importance of radiology, enormous strides have been made toward the earlier and effective diagnosis of all pulmonary conditions.

Mr Thompson cannot be serious when he suggests that "general practitioners who suspect that their patients have carcinoma of the lung should be encouraged to send them direct to surgical centres. There are enough fully trained thoracic surgeons to deal with the problem." Does Mr Thompson really suggest that general practitioners should send all their patients with cough or sputum or hæmoptysis or dyspnœa or chest pain to such thoracic surgical centres for investigation? There are less than one hundred consultant thoracic surgeons in England and Wales. It is quite certain that every consultant thoracic surgeon would be so swamped with such diagnostic work that he would at once cease to have any time to operate. At this clinic, a general practitioner can obtain an X-ray report on any patient within twenty-four hours without making a special appointment. In 1955, over 2000 patients were referred to this clinic complaining of respiratory symptoms. A large proportion of these had symptoms which are common to lung cancer and to other lung diseases.

Unfortunately Mr. Thompson bases his illogical argument on 135 selected cases of lung cancer which had found their way to a single teaching hospital in 1954. It is well known that patients who find their way to teaching hospitals commonly do so because they are not straightforward cases, and the conclusions to be drawn from such a series must be interpreted with that in mind. It is astonishing that Mr Thompson quoted 3·8 months as the average interval between a patient seeing a chest physician and coming to his department. We find it difficult to believe that such a state of affairs in any way represents common clinical practice in England today. If any one of us had a patient who could not be bronchoscoped at any thoracic centre within a fortnight on our recommendation, that patient would straight away be referred elsewhere for bronchoscopy, but in practice we enjoy the closest cooperation with the thoracic surgeons with whom we are associated.

The earlier diagnosis of lung cancer, as of pulmonary tuberculosis, is to be achieved by the wholehearted coöperation of every branch of the medical profession together with highly efficient hospital organisation in regard to outpatient appointments and inpatient investigation.

Bournemouth Chest Clinic.

W H TATTERSALL
D J APSIMON
A T HENDRY

SIR,—Mr Thompson's strictures about procrastination by chest physicians when diagnosing carcinoma of the bronchus have led us to examine from this angle all our cases diagnosed in 1956.

We serve a population of about 300,000 from which general practitioners have free access to our X-ray-only service. 8605 patients were sent up of whom we recalled 381 for clinical examination and 43 were finally diagnosed as carcinoma of the bronchus (this includes cases referred direct for appointment). In these 43 cases the average time from initial X ray until bronchoscopy was 2½ weeks and the further interval until thoracotomy was 2½ weeks. Much of the credit for these figures is due to our surgical colleagues for their close coöperation.

There can be little room for criticism of delay in these figures, and in fact about half the delay before operation is the time awaiting a surgical bed once bronchoscopy has confirmed the diagnosis. It would be interesting if Mr Thompson's figures could be completed by giving the average interval from diagnosis until thoracotomy, as in our experience this even if unavoidable, is not always negligible.

While we feel justified in doubting whether any other method would reduce delay still further, we must admit that 2 of our cases had previous films at the clinic about a year and two years before, and on looking back we had obviously missed the small original lesion. We are aiming to avoid this in future by independent double reading of all new films, but do not feel it affects the present argument.

We would, however, be very willing to have instruction from the character who apparently in Mr Thompson's estimation could have picked out on one small postero-anterior film the 20 cases which should be referred for surgery out of the 381 recalled for examination. It took us much time with further radiological, clinical, and pathological examination, not to mention about 80 bronchoscopies, to weed out these 20 apparently operable cases. Any shortening of the process would be welcome.

We understand that each thoracic surgeon serves about half a million of the population, and it is quite unrealistic to suggest he could tackle this preliminary sifting of cases as well as perform the surgery.

Thoracic surgeons are peculiarly fortunate among their surgical brethren in having most of their cases presented to them already worked out by physicians. This leads to a rather Olympian outlook, and we would warn them that a descent to primary contact with the patient might lead to humiliation; they too might be subject to observer error.

Isolation Hospital,
Norwich

P H SUTTON
A H C COUCH

SIR,—Every thoracic surgeon in this country will sympathise with Mr Frank Nicholson (Feb. 9) and Mr Vernon Thompson in their anxiety to improve the diagnosis of this dread and relentlessly increasing disease.

There still seems to be a proportion of family doctors who regard bronchial carcinoma as a sufficiently uncommon disease not to consider it in patients presenting with an acute respiratory illness for the first time in their lives, or in those complaining of a cough or wheeze, hæmoptysis, "tightness of the chest," or even frank dyspnœa. I have purposely excluded pain from my list of important symptoms, for I have come to regard it as a late and sinister feature indicating inoperability in many cases.

It is interesting to notice how many patients are becoming aware of facilities available to them, and after a period of treatment from their own physician have themselves requested a radiograph only for an inoperable growth to be discovered.

Admittedly there is a risk that a tuberculosis-minded physician may lose time watching the effect of antituberculous drugs on a radiological shadow, perhaps caught off his guard by the finding of tubercle bacilli in the sputum, whereas a simple inspection through the bronchoscope would have revealed an unsuspected concomitent tumour. I would hesitate, however, to throw the weight of diagnostic responsibility on to the radiologist on whose report the family physician may have to depend. Very few radiologists have the time or the facilities to conduct a careful appraisal of the patient's history and symptoms, and still less to examine him clinically—steps which may be of critical importance, and are, therefore, tempted to fall back on the formula of a "follow up examination in 4–6 weeks"—a process which, if two or three radiologists are each reading films in a busy department, may add several months to the diagnostic time

What is the answer? Some years ago Sir Russell Brock advised that any patient over the age of 40 suffering from an attack of pneumonia ought to have a chest X-ray before returning to work I venture to suggest that over the age of 30 would be even better Furthermore, one notices nowadays that the astute physician seeing a patient who is presenting with symptoms referable to the chest for the first time, or with a change in his respiratory history, now arranges for a radiograph, and if an abnormal shadow is visible on the films he then refers his patient to a thoracic surgeon for an opinion This course of action does, I believe, conform with Mr Thompson's criteria of making the full range of diagnostic facilities, by bronchoscopy, bronchography, and if necessary thoracotomy, immediately available to the patient and may save a great deal of valuable time in treating a disease which manifests itself with unpleasant frequency at a distressingly late stage

Victoria Hospital,
Blackpool
P JEWSBURY

UNMARRIED PARENTHOOD

SIR,—Dr Comfort's letter (Jan 26) was most welcome The problem of unmarried motherhood is, however, part of a larger problem—that of the unwanted child The desirable situation is that every child should be positively desired Ignorance of contraception not only causes undesired extramarital pregnancies, it also causes many unwanted children to be born in wedlock And while it is probably true that most mothers come to accept these pregnancies in the end (only a minority of the babies so conceived come to be classed as rejected children), yet there is a world of difference between such acceptance and the joyful welcome of a child whose conception was positively desired

Furthermore security in the matter of contraception extends a beneficial effect far beyond the question of desired or undesired pregnancies, for it provides the basis for a sexual life freed from such anxieties Family doctors of discernment have known many cases where family life has been disrupted by pregnancy anxiety with its attendant destruction of sexual fulfilment, and a high proportion of the illnesses which stem from anxiety can be traced to this same pregnancy anxiety Coitus interruptus has long been known to exert a baleful effect upon those who practise it, yet the prevalence of this crude method is itself an indication of the ignorance regarding more rational and æsthetic techniques

The field of medicine in which knowledge of reliable contraceptive techniques can be of profound help is therefore enormous The family physician is the obvious person to disseminate information and create a healthy attitude, but he is severely handicapped by the fact that the teaching hospitals do not regard it as their responsibility to give any guidance to students about contraception (as far as I know, University College Hospital is the only London teaching hospital to have a contraception clinic) Even today it is not unusual for women to be advised by gynæcological clinics against further child bearing without any advice being added as to how pregnancy is to be avoided This has happened several times in my practice despite the existence of an excellent birth control clinic in the district The training of doctors in contraceptive techniques is undertaken by the Family Planning Association, but it is left entirely to individual doctors to discover the usefulness of such knowledge, and to decide to acquire it Here is a field in preventive medicine which is largely unrealised, but which can yield rich results in helping to prevent unhappy homes, and the bringing into the world of unwanted or only half-wanted children It is to be hoped that those in charge of medical education will soon realise their responsibilities in this matter

London, S E 1
JOHN HEWETSON

BIRTHDAYS OF SPASTICS

SIR,—Dr R T Bevan's letter of Feb 16 prompted me to review the birth dates of 227 known spastics born in the years 1940 to 1953 in the County of Stafford

The monthly incidence from January to December was 17, 20, 21, 18, 27, 26, 21, 12, 15, 15, 17, 18 These figures do not show the distribution recorded by Dr Bevan, for in the period December to March 76 cases had their birthdays whilst the period June to August accounted for 59 cases The lowest incidence in this series was in the months July to September—42 cases

Wolverhampton
C SIMPSON SMITH

PRACTITIONER AND LOCAL AUTHORITY

SIR,—I was somewhat puzzled by a phrase in your leading article of Feb 2 "And, if one can judge by the correspondence in our columns, most doctors think " One would accept this level of reasoning in The Widdicombe File but not in your editorial columns

I believe the number contributing to the correspondence was 26 What proportion of 26 supported the original anonymous contributor is evidently a matter of opinion I thought the balance was remarkably evenly held, even without allowing for the relative numbers of general practitioners and of local authority medical officers in the profession

My quarrel with your phraseology is that neither the total of 26 nor any part of it constitutes a significant proportion of the medical profession It could be that "most doctors" did not think an anonymous gibe was worth powder and shot

Ethics have been mentioned What of the ethics of blackguarding, under a nom-de-plume, a section of the profession of which the writer admittedly knew little All in fun? Perhaps, but from the young man's final contribution he evidently expected to be taken seriously If, in the course of his professional career, he never comes across anything more unethical than clinic services he will be fortunate

Galleywood, Essex
HILDA MENZIES

THE Rh BLOOD-GROUPS

SIR,—I am sorry to prolong this correspondence, but Dr Wiener (Feb 16) has so grossly misquoted me as to require an answer

I did not say that the use of "most likely genotypes" leads to paradoxes—far from it My complaint was that he had interpreted one of his tables as if each genotype were a certainty *instead of being one of several possibilities as the words* "most likely" surely imply There is in fact *no* paradox in either table presented in either notation *All that* can be said is that two of the tables are less complete than the other two (a fact clearly *indicated* in their headings) *It* requires neither legal *nor scientific* acumen to realise that they are unsuitable for paternity work where interest lies in impossibilities and not probabilities, however high

I find it difficult to reconcile the beginning and the end of Dr Wiener's second paragraph He says that workers use the CDE system because they understand no other, but that they would find it easy to change because they already use the "shorthand" symbols and, therefore, have nothing fresh to learn Really, Sir, he cannot have it both ways

Dr Wiener's third paragraph proposes an odd use for his nomenclature He seems to be suggesting that it should be used to impress (and presumably baffle) lawyers, who, he thinks, might suspect that a CDE user did not understand his subject The reaction of an English barrister to evidence in Wiener's notation is easy to predict "Thank you, Doctor Now would you mind explaining to My Lord and the Jury in simple English just what you mean?"

Pathology Laboratory,
Essex County Hospital,
Colchester

J W NICHOLAS

REMUNERATION IN HOSPITAL SERVICE

SIR,—Your correspondence columns have recently included letters in connection with the status and remuneration of pharmacists, laboratory technicians, and radiographers, and Mr David White (Feb 16) indicated that the discontent embraced the whole field of medical auxiliaries

The medical profession itself is seething with discontent regarding its conditions and remuneration Recent letters to the *Times* indicate that there are similar causes for concern over the remuneration of catering officers and chefs Administrative workers are equally dissatisfied with conditions and rewards

It is clear, therefore, that all who are working in the hospital branch of the National Health Service are dissatisfied with the rewards available for ability and effort, and I suggest that there is a great need for representatives of all branches of the professions engaged in the health service to meet with a view to presenting a general demand to the Minister for an early review of the whole question of remuneration to hospital service staffs, particularly with reference to the methods of negotiation

Aylesbury Bucks

RONALD MACDONALD

THE DISINTEGRATIVE ACTION OF THE NERVOUS SYSTEM

SIR,—The Bradshaw lecture of Dr William Phillips, published in your issue of Feb 9, is a fine contribution to that holistic or integrative medicine which dominates contemporary thought and practice We must be grateful to him for having again stressed the importance of the psychological factors in disease and of the consideration of the patient as a person, in a true Hippocratic spirit

There is, however, a certain danger of swinging the pendulum too far, and this was pointed out at the Third International Congress of Neohippocratic Medicine Even psychiatrists are beginning to return patients referred to them to the hospital departments from whence they came The only way to avoid this danger is to insist on an accurate nosological diagnosis We have to start our medical handling by labelling the patient and placing him under one of the morbid categories of nosology The famous slogan of Peter "There are no diseases, but only patients" ought to change into "There are diseases *and* patients" History has shown that neglect of this first step in diagnosis renders all our subsequent individual consideration of the patient often useless The failure of the German "physiological" school of the 19th century, so well described by Sir Francis Walshe in his Gowers lecture,[1] is a recent demonstration of that historical law It is after an accurate nosological diagnosis that personalistic investigation, psychological, physical and environmental has to be considered

I am astonished, however, to note in Dr Phillips's fine lecture that he is amazed that intelligent people consider that a classical education trains the mind in some unique fashion and that "the old ways of thought inherited from the Greeks and Hebrews, and modified at the Renaissance, will gradually change" Is not our integrated holistic medicine of today based on our Greek classic, Hippocrates? Do we not find in Plato the principle that physicians to cure a local disease have to treat the whole body and mind? Do we not encounter in all ancient Greek medical observations the stress on social environmental factors, including worry about the payment of the fees? Can we find a better insight into the human mind than in the Greek tragedians, *The Bible*, and Shakespeare? Dr Phillips accepts the opinion of Putman that a thorough preliminary course in psychology and philosophy, following close on chemistry and physics, is the best preparation for medical practice The philosophy that has not been inherited from the Greeks and Hebrews is that of crossword puzzles that delights dons far removed from active life, and that which leads to inhuman totalitarianism and universal extermination The philosophy necessary for us physicians is that inherited from the Greek thinkers, who were essentially men of action, in daily contact with the rough and tumble of life, and from the great Hebrew prophets, who opened our eyes to the transcendent and spiritual value of life We have, of course, to augment that heritage, but we cannot do away with it if we do not wish our civilisation to be buried in the sands, like all those ancient civilisations that had done away with their spiritual values

London W 1

A P CAWADIAS

OBSTETRIC FLYING-SQUADS

SIR,—In the light of your annotation last week reporting the 21st anniversary of the Newcastle Obstetric Emergency Service, may I mention what, as far as I am aware, was the first "flying-squad" to be set up in the County of London?

In 1938, Prof F J Browne, on behalf of the University College Obstetric Hospital, agreed to provide a hospital flying squad for mothers in this borough The staff of the unit comprised a physician of consultant standing, with three alternative consultants to act as deputies, one medical officer to act as assistant to the consultant, and one qualified nurse The borough council also agreed to pay the hospital a fee of seven guineas for each occasion upon which the unit was called out A report from the doctor or midwife calling out the unit was asked for as soon as possible, and the cooperation of the police was also obtained to cope with any possible difficulty in calling the unit

The number of calls upon the unit was few at first, but increased as time went on, and there were nine emergency calls in 1946, and ten in 1947 The following two cases, taken from my 1947 annual report, are typical

CASE 1—The flying squad was called at 11 20 P M The patient, aged 22, had been delivered of her first baby and immediately after delivery of the placenta there had been a very severe postpartum hæmorrhage with the loss of 80 oz of blood The patient was found to be in a state of collapse with a pulse rate of 140 and blood pressure of 80/50 Patient was given plasma and blood transfusion one pint of each, and morphine, and with this treatment she made a very satisfactory improvement and the flying squad left the house at 1 A M

CASE 2—The flying squad was called at 10 A M and the unit arrived at the house at 10 20 A M The patient was found to be in a state of obstetric shock suffering from postpartum hæmorrhage Her blood pressure was 80/50 and her pulse rate about 100 An immediate transfusion (group O, Rh negative) was put up and manual removal of the placenta was carried out under chloroform anæsthesia The transfusion was completed and the patient received a total of 420 ml of blood and 300 ml human serum A course of penicillin and sulphathiazole was ordered At 11 30 A M the patient s condition showed a great improvement, there being no further bleeding, the blood pressure was 130/70 and the pulse rate 110 The patient s general condition was satisfactory when the unit left the house at 11 40

The borough council's arrangement for the flying-squad was terminated on July 5, 1948, when responsibility for the personal health services passed to the London County Council as the local health authority under the National Health Service Act, 1946

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[1] *Lancet* 1956 ii 1059

Public Health Department,
Metropolitan Borough of Islington,
London, N 1

V FREEMAN
Medical Officer of Health

TOWARDS PREVENTING SUICIDE

SIR,—We should like to thank correspondents who have written concerning our paper "Towards Preventing Suicide" We set out to establish that more common admission to hospital is one effective answer to the increasing total mortality from suicide To achieve this we concluded that changes must be brought about in public attitude and professional awareness It was not our purpose in a short article to discuss either the ætiology or the prevention of suicide in a comprehensive way, and it was not suggested that admission to a mental hospital is the only worth-while preventive measure If our figures are representative of what happens in the country as a whole, it means that of an annual total of about 5000 suicides, 2650 are not under medical care at the critical time, but 2000 are under medical care including 500 who have been seen by a psychiatrist but not admitted to hospital Admission may have been advised and refused, and it may be the right decision in individual cases, after full assessment, not to advise admission to hospital But these figures suggest that admission is not achieved sufficiently often, and either the patient or perhaps the doctor too often contracts out of the best proven method of preventing suicide

R W PARNELL
IAN SKOTTOWE

Warneford Hospital, Oxford

DEPOT TUBERCULIN

SIR,—Last May Dr James and Dr Pepys described a technique for giving purified protein derivative of tuberculin (P P D) in an emulsion of light liquid paraffin and anhydrous lanolin, as a tuberculin test[1] This "depot tuberculin" remained in the skin for two or three months and became "positive" as the patient's allergy developed, or, if the patient was a positive reactor, it gave a reaction in forty eight hours The method seemed to have an important bearing on B C G work, and indeed Dr James and Dr Pepys had used it in conjunction with B C G in 9 cases If depot tuberculin were given at the same time as B C G vaccination, the result could be read at the same time as the vaccination was inspected, thereby simplifying procedure The authors had seen no non-specific oily reactions, and said that the positive result disappeared within three months

This has not been our experience at Great Ormond Street Between May and November, 1956, we gave depot P.P D to 200 people (142 newborns, 38 older children, and 20 adults) with the following results

Uncontrolled	
P P D in vehicle negative, Mantoux positive (10 units)	40
P P D in vehicle positive Mantoux negative (10 units)	1
P P D in vehicle positive, no Mantoux test	88
Controlled against Vehicle	
P P D in vehicle positive, vehicle negative	23
P P D in vehicle positive vehicle positive	17
(But P P D reactions larger than control reactions)	
P P D in vehicle negative, vehicle negative, Mantoux positive	7
Equal reaction to P P D in vehicle and to vehicle alone	2
Reaction to vehicle greater than reaction to P P D in vehicle	1
All tests negative	2
Failed to return for reading	19

Thus no fewer than 47 cases out of 200 were negative to P P D in the oily vehicle, although positive Mantoux reactions demonstrated that the patients had developed sensitivity to tuberculin For this reason alone we would not regard this test as reliable

Secondly, in several cases there was no difference—or very little difference—between the reaction to P P D and the reaction to the vehicle alone, indeed, in one case the latter was the greater!

Thirdly, after six months some patients still have a dusky red indurated area about half an inch in diameter which shows no signs of disappearing Although painless, this is æsthetically very unpopular and is probably the greatest disadvantage of depot tuberculin

I am drawing attention to our results because others may encounter the same difficulties We do not feel we can recommend this technique at present

B C G Clinic, Hospital for Sick Children,
Great Ormond Street, London, W C 1

MARCIA HALL

THE FUTURE OF NURSING

SIR,—Dr Thomas Anderson's latest letter (Feb 9) spurs against my laziness in not writing before The majority of student nurses do not possess the intellectual capacity for university training and few receive financial support from their parents after leaving school They are anxious to engage in practical nursing as soon as possible without lengthy preliminary academic training, for such, the present State training is perfectly adequate and they rapidly realise their prime ambition, which is the emotional satisfaction of nursing the sick patient There would be a severe drop in the general entry to nursing if a university-trained cadre was available, the simple S R N would feel hopeless of ever attaining high rank in her calling and no longer would a matron's baton be present in any probationer's knapsack Already an excessive theoretical knowledge is demanded my lectures in surgery to nurses are up to Conjoint diploma level No one can decide a nurse's future quality at the age of 18, and her outlook and possible late mental development may make her a very different person at 21 The advanced course of training should be available after general training has been completed—at the stage of being about to take a ward sister's post when such a course would be of great value

A nurse will always be subordinate to the doctor because he will always dictate the main line of treatment and take the major responsibility If a nurse finds her work intellectually unsatisfying then she should (as many have) embark on medicine At all costs let us avoid the appalling hybrid of nurse cum doctor as envisaged by one of your correspondents of senior nursing rank, though Miss Edwards's wise letter was a reassuring counterbalance

Wolverhampton

ERIC DOLTON

SIR,—One month after my 18th birthday I entered the preliminary training school of a large teaching hospital in Cape Town. Six weeks later I was sent to a surgical ward as its most junior nurse and spent by far the greater part of my time making beds, giving out bedpans, keeping the sluiceroom clean, and washing dirty bed linen We were also required to do a certain amount of purely domestic work, such as dusting and washing up

After two months of this I still felt exhausted every evening (one was almost never off duty dead on time), but as the atmosphere of the ward was cheerful and few of the cases chronic I had no doubts about carrying on I was then sent on night duty as an extra relief—a job which involved moving round from ward to ward wherever additional help was needed, and one which usually went to the most junior nurse on duty During my first three weeks of this I nursed the following cases a two and a half year old girl dying of tuberculous meningitis, a young man in the terminal stages of laryngeal carcinoma whom I specialled for three nights until he died, and a case of advanced pemphigus who smelt so appalling that joss sticks were burnt in the room Every morning I was required to change and sluice his linen and every morning

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[1] James D G Pepys J Lancet 1956 i 602

I was sick. What made things a great deal worse was that there was virtually nothing I could do to help any of the three.

At the end of the three weeks I went to my family doctor who was the only person with whom I felt I could discuss things and told him what I had been doing and that I felt I could not carry on Other girls might be able to cope but I had had too much. He told me that if I could stick it I should as I would never come across anything worse I took his advice, found that what he had said was true, and finished my training

One does not wish to give too gloomy a picture During those three and a half years I enjoyed myself a great deal both on and off duty, and made many friends. I never regretted for long my decision to stay But during that first on the whole very unhappy year I worked under only one ward sister who tried to help me as an individual and who taught me what nursing could be at all levels.

Now I have a very small daughter and if she should wish to become a nurse I shall try to dissuade her from starting until she is 21—that is unless all the people, matrons, sisters. tutors and particularly doctors. who are concerned with the training of student nurses have made a real and sympathetic attempt to understand the special problems they are called upon to face

Lincoln **CLODAGH WILKINSON.**

"REGISTRARS"

SIR,—Since hospital registrars no longer compile the register could they not revert to the title of assistant—first, chief, senior, junior, medical surgical, or what you will?

St Mary s Hospital
London, W.2

A J HARROLD

MULTIPLE PRIMARY GROWTHS

SIR,—For a patient to have three primary growths removed from different organs all in one year must be uncommon

A woman, aged 62, was admitted to Hackney Hospital on Jan 19 1956, with a two-month history suggestive of pyloric stenosis Barium meal examination confirmed this, and at laparotomy on Jan 27 a mobile carcinoma of the pyloric antrum was found with no apparent local or distal spread. In addition there was a mobile carcinoma of the cæcum Partial gastrectomy was undertaken but owing to the patient s poor general condition it was decided to remove the cæcal growth later

Convalescence was protracted and it was not until March that she was regarded as fit for further operation On March 9 right hemicolectomy was undertaken and bowel continuity was restored by an end to side anastomosis. On this occasion, as previously no abnormality was found in the pelvis. Convalescence was uneventful and she was discharged on April 25

On Aug 23 she attended the surgical outpatient clinic complaining of slight loss of blood per vaginam twice during the past three months On examination there were no abnormal physical signs but dilatation and curettage on Sept. 14 showed a well differentiated adenocarcinoma. On Sept. 28 total hysterectomy and bilateral salpingo-oöphorectomy was undertaken The uterus showed a raised ulcerated area $^1/_2$ × $^1/_2$ in on the posterior wall of the fundus with no extension to the peritoneum or myometrium

The patient s convalescence was uneventful and she was discharged on Oct 22 When last seen as an outpatient on Nov 15 she appeared quite well having no trouble with her bowels and an excellent appetite

The relevant pathological reports were as follows

Stomach—An irregular prepyloric ulcer 9 × 6 cm. with hard edges, microscopically a moderately well differentiated adenocarcinoma with few mitoses.

Cæcum—An ulcerating growth 3 × 4 cm reaching the serosal surface apparently involving no glands: microscopically a poorly differentiated adenocarcinoma not extending to the serosal surface in the portion examined

Uterus—A thickened area of endometrium near the fundus 1 5 cm in diameter, microscopically, a well-differentiated adenocarcinoma

Hackney Hospital London E.9 **R F READ**

"DOCTOR"

SIR,—Your leading article of Feb 16 does not do justice to the spirit of the quotation with which it closes. Whether a man "thinketh in his heart" that he is a doctor or a physician and surgeon or a medical officer will not I think, be likely to affect what he is The surgeon who prefers to be called "Mister" may recognise. in his heart that he can assume no higher title than that of a man

Enfield, Middlesex **C M SMALL.**

ACUTE POLYNEURITIS TREATED WITH CORTISONE

SIR—Following upon the report by Dr. Graveson (Feb 16) of the successful use of cortisone in acute polyneuritis, it may be of interest to record an example of serum neuritis which quickly resolved following prednisone therapy.

The patient, a man aged 37, injured his thumb and was given an injection of anti-tetanus serum on the next day Eight days after the inoculation he had an acute systemic reaction with fever, generalised body pains, and a diffuse erythematous macular rash which lasted twenty-four hours. The generalised body pains cleared in two days but severe pain persisted in the right shoulder, and the musculature of the shoulder girdle especially the deltoid was very weak The C.S.F obtained by lumbar puncture showed: cells 17 per c.mm protein 90 mg per 100 ml, globulin ——, and Lange 1223330000 Oral prednisone 5 mg six-hourly was prescribed Within a day the pain had cleared Muscular power returned to almost normal in ten days. The dosage of prednisone was tapered off and discontinued after three weeks. A repeat of the C.S.F examination ten days after the original lumbar puncture revealed: cells 5 per c.mm, protein 50 mg per 100 ml globulin —, and Lange 1110000000

The concept of acute polyneuritis as an allergic manifestation and the general agreement that neurological sequels of serum therapy have a similar basis[1] suggest that steroid therapy promptly administered may prevent irreversible damage in serum neuropathy.

Victoria Hospital
Burnley, Lancs.

J SHAFAR

HEAD INJURIES

SIR,—Mr. T G. Lowden (Jan 12), writing about patients with head injuries admitted to peripheral hospitals asks "what should guide us in deciding whether to send on a case, to ask a neurosurgeon out to see it, or to get on with it ourselves" May I suggest that there is one kind of case which the local surgeon *should* get on with himself It is the patient who sustains a head injury without impairment of consciousness or with only momentary impairment who is apparently well for an hour or so, and who then complains of headache *or* vomits *or* becomes drowsy *or* exhibits any neurological sign Such a sequence must suggest an extradural hæmorrhage and there is no time to transfer the patient or to summon a neurosurgeon Many fruitless journeys into the country have convinced me that the local surgeon must assume responsibility for such cases. He may be diffident in tackling them for two reasons (1) he feels that he has not enough neurological experience to be sure of the diagnosis (2) he is unfamiliar with the operative technique May I point out that the clinical diagnosis is certain only when the patient is near death The only way to make certain before that stage is to make an exploratory burr-hole The rule is a burr hole on suspicion an operation when the suspicion is confirmed If the surgeon looks on a burr-hole as a purely diagnostic procedure not as an operation he will be much more likely to tackle these cases early The surgical technique necessary for dealing with a middle meningeal hæmorrhage could be acquired by any general surgeon who takes a week off to loiter in a neurosurgical centre When

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[1] *Brit med J* 1956 i 972

patients who were unconscious on admission develop signs of compression of the brain, urgency calls for the local surgeon rather than the consultant

Dublin A A McCONNELL

DIHYDROCODEINE

SIR,—Respiratory depression has long been considered an unfortunate but inevitable effect of potent narcotics The recent report by Beecher and his colleagues[1] that *dihydrocodeine bitartrate produces full analgesia* while sparing the respiratory exchange has therefore aroused considerable interest

Having recently studied the effects of pethidine on the respiration in anæsthetised patients,[2] I decided to investigate dihydrocodeine under similar conditions Using the standards of equivalency of Gravenstein et al[1] and Nathan,[3] dihydrocodeine 0 25 mg per kg body-weight has been taken as approximately equivalent to the pethidine 0 6 mg per kg body weight used in the previous (control) study[2] There is no previous report of the intravenous use of dihydrocodeine, and in view of its pronounced acidity a dilute solution has been employed and the injection made slowly

First Study

The first investigation was carried out on twenty patients who were about to undergo surgical operation As in the pethidine series the patients were all in good general condition and were aged 20–50 The preparation of the patient and experimental technique have been reported elsewhere[4]

Briefly, anæsthesia was induced with 5% sodium thiopentone 8 mg per kg body-weight injected intravenously in 45 seconds, and nitrous oxide and oxygen (3 1) was then administered throughout the experiment via a closed circuit Respiratory rate and minute volume (M V) were measured 5 minutes after starting the thiopentone injection At the end of this (control) reading—i e , at 0+6 minutes—dihydrocodeine in standard dilution (25 mg per 10 ml) and standard dosage (0 25 mg per kg body weight) was injected intravenously in 30 seconds The respiratory rate and M V were measured 3, 5, 7, and 9 minutes after the administration of dihydrocodeine

About 1 minute after the injection of dihydrocodeine four patients began to move either one or both arms and/or legs, sometimes quite forcibly This movement continued for ½–2 minutes after which the patient became settled This phenomenon never occurred in the pethidine series In two patients there was localised reddening and wealing at the site of injection Neither of these effects was noted by Gravenstein et al[1] No other side effects were seen

Table I shows that dihydrocodeine produced, in mild degree, the typical effects of a narcotic analgesic Comparing its effects with those of pethidine (after checking with the F test of variance that the two groups come from a homogeneous population) the difference between the respiratory rates at corresponding times is significant at $p<0\ 005$, and the difference between corresponding M V s is significant at $p<0\ 005$ (except at 7 min $p<0\ 01$) In five patients there was virtually no depression of M V , in three there was a fall of more than twice the group average M V depression

TABLE I—RESPIRATORY CHANGES AFTER PETHIDINE 0 6 MG PER KG AND DIHYDROCODEINE 0 25 MG PER KG

Feature	Series	Control	3 min	5 min	7 min	9 min
Respiratory rate (min)	Pethidine (S E ±)	10 1 *(0 8)*	10 6 *(1 0)*	9 9 *(1 1)*	10 1 *(1 0)*	9 2 *(0 6)*
	Dihydrocodeine (S E ±)	18 3 *(0 7)*	15 2 *(0 7)*	14 4 *(0 7)*	14 0 *(0 7)*	13 8 *(0 7)*
Minute volume (ml)	Pethidine (S E ±)	5361 *(400)*	3260 *(353)*	3318 *(409)*	3618 *(414)*	3129 *(327)*
	Dihydrocodeine (S E ±)	5129 *(311)*	4075 *(307)*	4985 *(295)*	5081 *(232)*	4912 *(263)*
% change in minute alveolar ventilation	Pethidine		−32 4	−20 7	−0 7	−2 1
	Dihydrocodeine		−0 6	+7 3	+11 0	−7 5

Second Study

This superiority of dihydrocodeine over pethidine in respect of respiratory depression may be intrinsic, but it could be because this dose of the drug is not, in fact, equipotent with pethidine 0 6 mg per kg body weight Accordingly the experiment was repeated in a further twenty patients using twice the dose of dihydrocodeine, the solution was of twice the concentration Furthermore it was decided to try the antagonistic effect of levallorphan tartrate in any cases where appreciable respiratory depression occurred

The "stimulating" effect mentioned above was seen in three cases Local wealing and reddening occurred in five patients Linear wealing along part or the whole length of the injected vein was noted in six cases

Table II gives the respiratory changes in this group of patients Statistical comparison with the pethidine series shows that the mean *fall* in respiratory rate is significantly less ($p<0\ 025$) and the mean M V significantly greater ($p<0\ 05$) in the dihydrocodeine group In three cases there was virtually no fall in M V , in two the M V depression was more than twice the group average

TABLE II—RESPIRATORY CHANGES AFTER DIHYDROCODEINE 0 5 MG PER KG

Feature	Control	3 min	5 min	7 min	9 min
Respiratory rate (min) (S E ±)	15 5 *(0 9)*	14 6 *(1 0)*	13 6 *(1 0)*	13 4 *(0 8)*	13 0 *(0 8)*
Minute volume (ml) (S E ±)	5141 *(305)*	4644 *(355)*	4470 *(286)*	4613 *(308)*	4601 *(293)*
% change in minute alveolar ventilation		−3 8	−3 0	+5 3	+7 2

Levallorphan was injected intravenously 10 minutes after the dihydrocodeine and readings of the respiratory rate and volume were taken 1, 3, and 5 minutes later As in two patients a 1 100 ratio of the two drugs proved ineffective, a 1 50 ratio was tried This has been employed in nine cases and has been found consistently to produce an immediate and pronounced increase in M V and some increase in rate

Comment

Investigation of dihydrocodeine under the present conditions will exaggerate the drug's respiratory depressant effect because of an additive effect with thiopentone[5] However, comparison with the effects of pethidine under identical conditions shows that dihydrocodeine depresses respiration considerably less even in apparently more than equipotent dosage

The results suggest that further clinical studies of dihydrocodeine's analgesic potency would be worth while Although this drug does not appear to produce appreciable respiratory depression in clinical dosage it is valuable to have an antidote available, and it seems likely that levallorphan will fill this need The initial "stimulating" and the histamine releasing properties of dihydrocodeine will require investigation

I am grateful to my surgical colleagues and to the theatre staffs of Salford Royal and Hope Hospitals for their cooperation, Mr Kenneth Spencer and Dr Randolph White for undertaking the statistical analysis, and Duncan, Flockhart & Co Ltd for providing the dihydrocodeine bitartrate

Salford Royal Hospital
Manchester

MARK SWERDLOW

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[1] Gravenstein J S Smith G M Sphire R D Isaacs J P, Beecher H K *New Engl J Med* 1956 254 877

[2] Swerdlow M *Anæsthesia* (in the press)

[3] Nathan P W *Brit med J* 1952 ii 903

[4] Swerdlow M *Brit J Anæsth* 1957 29 21

[5] Swerdlow, M *Anæsthesia*, 1956 12, 42

OLD PEOPLE IN HOSPITAL

SIR,—The articles in your last issue by Dr DeLargy and by Dr Rang raise an important question What principle should guide us in admitting elderly patients to hospital? The waiting list of most geriatric units contains the names of some who are likely to respond to medical treatment but of many others who are not Dr DeLargy's scheme of a six-week stay in hospital is a valiant attempt to meet the needs of the latter My own survey in Croydon[1] demonstrated that the majority of elderly patients have some social problem complicating their medical condition Even though they may recover from the illness which precipitated admission to hospital, they may not be able to return whence they came Yet there are many others anxiously awaiting the use of the bed they occupy

I have found that in such cases transfer to a "halfway house" is helpful The frail ambulant can here continue with some treatment and rehabilitation while a solution to their social problems is sought I am somewhat disturbed, therefore, to read that the average length of stay in the "halfway house" for Dr Rang's unit is measured in years rather than weeks My own turnover has been 3 per week (out of a total of 24 beds) for several years past

My greatest perplexity arises over the mass of incurable patients who tend to silt up the beds in my hospital wards Some have been transferred from general hospitals to free acute beds there, some have been admitted as social emergencies to prevent further suffering in unsuitable surroundings, and some are simply unlikely to respond to medical treatment It is these patients, not those in the "halfway house," whose length of stay tends to be measured in years rather than weeks It is these whose relatives have so far been unwilling to take them home to nurse them there It is these cases whose mere existence prolongs the waiting-list and delays admissions

The number of aged sick, increasing year by year, grows faster than the number of staffed hospital beds available for their treatment, care, or custody Hence Dr DeLargy's scheme has a great deal to commend it for trial For, if there is delay in admitting patients with social complications, a state of urgency is likely to arise Yet, if such cases are given priority, the length of the waiting list and average duration of stay in hospital increases Let us hope that the Langthorne procedure will be the via media out of this impasse

London S W 16 TREVOR H HOWELL

MUNCHAUSEN'S SYNDROME

SIR,—It may be useful to report another case of Munchausen's syndrome who has been turning up at London hospitals over the past few years

Usually he simulates meningitis or subarachnoid hæmorrhage, but his repertoire has also included tetanic spasms as well as the usual abdominal components of the syndrome Our first record of him dates from December, 1953, when he was admitted to Guy's Hospital with abdominal pain and hæmatemesis, but laparotomy showed no abnormality He has five abdominal scars in all The following year he was admitted to both Putney Hospital and Guy's Hospital with symptoms suggesting tetanus In 1955 he apparently attended many hospitals, including Guy's, St Thomas's St Bartholomew's, St George's, St Pancras, Poplar General, North Middlesex and this hospital He was seen in several psychiatric outpatient departments but never kept his further appointments His symptoms included abdominal pain, suicidal impulses and neck stiffness In December, 1956 he attended Guy's Hospital with neck stiffness, photophobia and headache, he was admitted but discharged when nothing abnormal was found A week later he was admitted to the West London Hospital again with feigned meningitis He discharged himself on Jan 16 and the same afternoon was admitted to St Mary's Hospital complaining of the sudden onset of headache, stiff neck, and photophobia Lumbar puncture yielded normal cerebrospinal fluid, and after two days he began to have spasms of opisthotonos with flexion of one arm and leg On being confronted with the evidence of his previous hospital admissions, and with the news that his father was coming to see him, he immediately recovered and was discharged

It seems highly probable that he will turn up at other hospitals over the next few years, and this information may help to identify him

St Mary's Hospital,
London, W 2 P H SANDERSON

ALLOXAN AS A POSSIBLE THERAPEUTIC AGENT FOR PRIMARY CARCINOMA OF THE LIVER

SIR,—Laboratory observations by others that alloxan-diabetic rats are either totally resistant to the experimental induction of hepatomas by feeding azo dyes, or can suppress the growth of tumour implants, prompted Professor Gillman and his colleagues (Jan 12) to administer alloxan to patients with advanced hepatomas in an attempt to induce diabetes and to influence the tumour Although their results in 4 cases were rather doubtful in regard to the effect of alloxan on the blood sugar and on the course of the malignant disease, they conclude that the "findings provide some basis for recommending further and more extensive investigation of the significance and interactions of alloxan injections on cancers "

The authors are apparently unaware that such investigations were carried out more than ten years ago shortly after the discovery of the diabetogenic action of alloxan[1–3] They were terminated because of rather deleterious results In a small group of patients with far-advanced carcinoma of various organs with and without liver metastases, alloxan failed to induce diabetes but precipitated severe hepatorenal damage with jaundice and hepatic coma Also, in insulinomas no satisfactory control of the hypoglycæmia could be obtained but severe liver damage occurred Histological examinations in these cases demonstrated no significant effect on either the pancreatic beta cells or the tumour tissue but destruction of renal and hepatic parenchyma It appeared that in man, unlike most laboratory animals, the hepatotoxic and nephrotoxic dose of alloxan is smaller than the diabetogenic dose

While Professor Gillman and his colleagues observed no aggravation of the liver disease, they too failed to obtain hyperglycæmia and glycosuria I would feel negligent if I did not recall these earlier observations and caution against the use of alloxan in man even in conditions which are presently incurable and usually fatal

Jewish Chronic Disease Hospital,
Brooklyn 3, New York MARTIN G GOLDNER

RADIOACTIVE VITAMIN B_{12} IN THE DIAGNOSIS OF NEUROLOGICAL DISORDERS

SIR,—The informed comments of Dr Booth and Dr Mollin relating to radioactive vitamin B_{12} (Feb 16) are most welcome in underlining important theoretical points relating to physiological and pathological aspects of vitamin B_{12} utilisation

May we re-emphasise the practical clinical importance of the excretion test and in particular of the second part of the test in establishing a diagnosis of subacute combined degeneration of the spinal cord? If with the Schilling excretion test a normal result is obtained after

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[1] Howell T H *J Amer geriat Soc* 1956 4 221

[1] Brunschwig A Goldner, M G, Allen, J G Gomori, G *J Amer med Ass* 1943 122 966

[2] Brunschwig A Allen J G Owens, F M, Thornton, Th F *Ibid* 1944 124 212

[3] Goldner, M G, *Proc Amer Diabetes Ass* 1946, 6, 392

RESOLUTIONS BY JUNIOR HOSPITAL STAFF

ON Feb 11 at a meeting of the junior medical staff of the Edgware General Hospital, the following resolutions were passed unanimously

We shall support to our utmost every effort to secure the 24% increase in remuneration being sought by the Negotiating Committee At the same time we wish to draw especial attention to the urgent needs of full time junior hospital staff, whose salaries are entirely inadequate and who need more than a 24% increase on their present salaries to bring them to a reasonable standard of remuneration

Further it is agreed that the present claim and past increase in salary in no way detract from our belief that the Spens report concerning the remuneration of hospital staff must finally be implemented, as this has not hitherto been done

It is also resolved that a mere increase in salary is not sufficient nd that prospects of promotion must also be improved. At present he prospects of promotion for those wishing to specialise are irtually non-existent, and to this end a complete revision of the taffing of hospitals is urgently required

CHILDREN'S INSTITUTIONS

TODAY it is widely accepted that an institution is one of the less satisfactory places in which to bring up a child But unfortunately there will always be some children who, usually for unhappy reasons, must spend a shorter or longer part of their childhood in an institution It is therefore important that the place should not be as forbidding as the name and that the care it offers should be the best that can be arranged. A report to the Social Commission of the United Nations[1] reviews institutions and new work in countries all over the world A global survey of only 70 pages must be selective, but this one makes clear that, though the diversity of their practice sensibly reflects local customs and conditions, the nations share a common concern for these vulnerable children

MALARIA CONTROL

LAST November delegates from many countries in Africa and islands in the Indian Ocean met in Nairobi under the auspices of the World Health Organisation, to discuss malaria control South Africa, Mauritius and the higher parts of Southern Rhodesia and Madagascar are now (it was reported) virtually free of the disease the control campaigns will be continued till malaria has become a curiosity—which is already true in Mauritius In West Africa success is described by Dr M T Gillies as only occasionally great enough to justify the large sums of money spent on it, "The fact that it is only partially successful," he says, "means that the spraying must be continued indefinitely It is here that the danger lies In Northern Nigeria a trial project was carried out using one of the newer insecticides The results were so encouraging the first year that plans were made for a very large scale extension of the scheme so as to protect eventually up to two and a half million people But during the second year the mosquitoes began to come back again into the houses, and it was soon discovered that they had become resistant to the insecticide and were no longer being killed by it When I was there in July 1956 the position was so bad, and the mosquitoes so numerous, that in the evenings the toads would gather about the verandah floor and pick off the *Anopheles* from our shoes and ankles as they settled there to bite In fact it was perfectly clear that control with this insecticide had completely broken down and the whole campaign had to be switched to another insecticide which remains, for the moment, moderately successful This unhappy experience has up till now only been repeated in one other area, also in Northern Nigeria But its occurrence is the writing on the wall. It is now realised that in regions where resistance is likely to occur, we have only a few years in which to eliminate malaria before the weapons become blunted in our hands We do not know at present how widespread the tendency to develop resistance is but it is encouraging that it has not appeared in South Africa despite the use of insecticides for up to ten years"

Air-conditioning for Bronchitis

A scheme is being prepared for air conditioning two wards at the Liverpool Chest Hospital so that the effect of nursing chronic bronchitics in such accommodation during severe winter weather and fog can be studied.

University of Leeds

Dr G H. Lathe has been appointed professor and head of the department of chemical pathology

Dr Lathe who is 43 years of age graduated B.Sc in 1934 from McGill University, Montreal, and M D four years later After holding research appointments in the department of physiology he served from 1941 to 1945 as a regimental medical officer and later as a biochemist in the Royal Canadian Army Medical Corps In 1946 he came to England and held an I C I research fellowship at the University of Oxford and at the Postgraduate Medical School of London. In 1947 he was awarded the degree of PH D of McGill University Since 1949 he has held the post of biochemist in the Bernhard Baron Chemical Research Laboratories of Queen Charlotte's Maternity Hospital, London, and he is a member of the academic board of the Institute of Obstetrics and Gynaecology He has published articles on absorption from the alimentary tract, the physiological and metabolic consequences of wounds, and the biochemistry of the bile pigments and their production in the liver

Dr J M Roberts has been appointed lecturer in the department of psychiatry.

University of Otago

Dr J R Robinson, assistant director of research in the department of experimental medicine of the University of Cambridge, has been appointed associate professor of physiology in the university

Dr Robinson, who is 42 was educated at Ulverston Grammar School and Emmanuel College, Cambridge He took a double first in the natural sciences tripos and after graduating spent some years while holding the research scholarship of his college, in the departments of biochemistry and colloid science studying the shapes of protein particles in solution. In 1938 he took the degree of PH D and in 1940 he went to the London Hospital Medical College with an open entrance scholarship After qualifying in 1943 he held house appointments at the London and in 1944 he joined the R.A.M.C and served in India, where he was in charge of the biochemical department of the central military pathological laboratory at Poona In 1947, after he returned to civilian life, he was appointed college lecturer and director of studies in medicine at Emmanuel College and was elected to a supernumerary fellowship He was appointed to his present post in the department of experimental medicine in 1949, and since 1951 he has also been secretary to the faculty board of medicine He received the degree of M D in 1952 He spent 1954–55 in New Zealand as a senior visiting lecturer in the department of physiology of the University of Otago His published work includes papers on electrolytes and renal function.

University College of the West Indies

Dr R J Gourlay, assistant senior medical officer of the North West Metropolitan Regional Hospital Board, has been appointed senior lecturer in preventive medicine

Harveian Society of London

Sir Russell Brain, P R C P, will deliver the Harveian lecture to this society on Wednesday, March 27, at 8 15 P.M, at 11, Chandos Street, London, W 1 He is to speak on disorders of the cerebral circulation

British Diabetic Association

The Banting memorial meeting of this association will be held in Oxford on July 12 and 13 The speakers will include Prof H A Krebs, F R.S, and Prof C H Best, F.R S Further particulars may be had from the association, 152, Harley Street, London, W 1

Association of Surgeons of Great Britain and Ireland

The annual general meeting of this association will be held at Newcastle upon Tyne from April 25 to 27 Prof Alexander Haddow will give the Rutherford Morison lecture on the present trends of cancer research, and the programme will also include discussions on prevention of sepsis in operating-theatres (opening speakers Mr D R Davies Dr R Blowers, and Dr R A Shooter), minor complaints of the rectum and anus (Mr T McW Millar, Mr A G Parks, Mr H T Simmons, and Mr H R Thompson), early treatment of burns (Mr A B Wallace), and thyrotoxicosis (Dr W R Trotter and Mr K Paterson-Brown)

A Comprehensive Nursing Course

In September an experimental course is to be started by the Postgraduate Medical School of London, the Battersea College of Technology, and the Queen's Institute of District Nursing which will enable a student in 4 years, instead of the present 5 years or more, to qualify as a State registered nurse, a health visitor, and a Queen's district nurse She will be able to take a part I Central Midwives Board certificate, so that with only 6 months' further training she can also become a fully qualified S C M Previously the course for each of these examinations has had to be taken separately

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[1] Institutional Care of Children (United Nations Department of Economic and Social Affairs 1956 Obtainable from H.M Stationery Office Pp 70 3s 6d)

Newcastle Flying Squad

The 21st birthday of the Newcastle Obstetric Emergency Service, whose work was described in an annotation last week, was celebrated on Feb 21 when a party was given at the Princess Mary Maternity Hospital by the board of governors of the United Newcastle upon Tyne Hospitals Viscountess Ridley, chairman of the committee of management of the Princess Mary Maternity Hospital, presented a portrait to Prof E Farquhar Murray, who was largely responsible for the inauguration of the service

Nutrition Society

This society is holding a symposium at 1, Wimpole Street, London, W 1, on Saturday, March 23, on Man's Need for Water Prof R A McCance, F R S, will be in the chair and the speakers will include Mr H W Cremer, F R I C, Dr J R Robinson, Dr J Russell Elkinton, Miss E M Widdowson, D SC, Dr D A K Black, and Dr W F Young Further particulars may be had from the hon programmes secretary of the society, Dr R J L Allen, c/o Beecham Foods Ltd, Brentford, Middlesex

Scottish Group—This group is holding a symposium in Aberdeen on Saturday, April 20, on clean food Further particulars may be had from Dr J Davidson, Rowett Research Institute, Bucksburn, Aberdeenshire

Revised Fees for Dentists

Changes in the fees payable to dentists for treatment under the National Health Service will come into force on April 1 The revised scale, which has been drawn up in consultation with the British Dental Association, is not designed to give an increase in the total remuneration of dentists but rather to achieve a better balance

More money is being devoted to the treatment of children's teeth, and in place of the present flat fee applying to any conservative treatment to a deciduous tooth varying amounts will be payable for different kinds of fillings, for vital pulpotomy, and for conservation by other means The removal of calculus, the removal of stain and polishing of the teeth also attract separate fees These changes will it is hoped offer further encouragement to the treatment of young people

Crash Helmets

On and after April 1 it will be an offence to sell, or offer for sale, a protective helmet for motor cyclists unless it is of a type authorised by Ministry of Transport regulations

Lipids and the Problem of Atherosclerosis

Prof R A Morton, F R S, will give an address on this subject to the Oils and Fats Group of the Society of Chemical Industry on Wednesday, March 13, at 7 P M, at the department of organic chemistry of the University of Liverpool

The Child and his Home

The British Social Biology Council is holding a summer school on this theme, for teachers, social workers, health visitors, and others, at Aix en Provence from Aug 24 to Sept 8 Further information can be had from the council, Tavistock House South, Tavistock Square, London, W C 1

Glasgow's Tuberculosis Campaign

To mark the opening of this campaign, Sir Geoffrey Todd is to give a lecture at the Institution of Engineers and Ship Builders, 39, Elmbank Crescent, Glasgow, C 2 on Wednesday, March 13, at 4 P M He is to speak on the prognosis of pulmonary tuberculosis in the light of modern treatment, with special reference to Midhurst Sanatorium

Ocular Manifestations in Clinical Neurology

Mr Joseph Minton will give six lecture demonstrations on this subject at the West End Hospital for Neurology and Neurosurgery, 91, Dean Street, London, W 1, on Tuesdays at 4 P M, beginning on April 9 Further particulars may be had from the secretary of the postgraduate medical school of the hospital

Dr Frank Falkner has been awarded a scholarship in medicine of the John and Mary Markle Foundation

The Tanner prize of the Royal Institute of Public Health and Hygiene for 1956 has been awarded to Dr Sheila Robinson

Diary of the Week

MARCH 3 TO 9

Sunday, 3rd

University College Hospital Medical School University Street, W C 1
10 15 A M Dr G I M Swyer Use of Hormones in General Practice (Clinical demonstration for general practitioners)

Monday, 4th

University College London, Gower Street, W C 1
5 P M Dr George Popjak Biochemistry of Fatty Acids and Cholesterol (First of three lectures)

Marlborough Day Hospital 38 Marlborough Place N W 8
8 15 P M Mr M M Simmons Dr D Russell Davis The Intelligent Offender—His Treatment in an Approved School

Tuesday, 5th

Royal College of Surgeons of England Lincoln's Inn Fields W C 2
3 45 P M Dr A J M Reese Atheroma (Erasmus Wilson demonstration)

St Mary's Hospital Medical School, Paddington W 2
5 P M Mr R M Feroze Dysfunctional Uterine Hæmorrhage

Institute of Dermatology Lisle Street W C 2
5 30 P M Mr B F D Cooke Disorder of Buccal Mucosa

West End Hospital for Neurology and Neurosurgery 91 Dean Street W 1
5 30 P M Mr G C Knight Diagnosis of Cerebral Tumours

Manchester Medical Society
4 30 P M (Medical School University of Manchester) *History of Medicine* Dr Peter Bishop *Life and Work of Thomas Addison*

Wednesday, 6th

Royal Society of Medicine 1 Wimpole Street, W 1
5 15 P M *History of Medicine* Prof F G Young F R S Glycogen 1857–1957 Dr Gordon Mestler Old Japanese Medicine
8 P M *Surgery* Mr Hedley Atkins Mr Murray Falconer Prof C F W Illingworth Mr F J Radley Smith, Mr W P Greening Hypophysectomy for Cancer

Postgraduate Medical School of London Ducane Road W 12
2 P M Dr Reginald Hudson The Heart Septa

Institute of Dermatology
5 30 P M Dr R W Riddell Problems of Therapy in Fungus Diseases

Institute of Diseases of the Chest Brompton London S W 3
5 P M Dr B G B Lucas Man and His Ventilation

Royal Institute of Public Health and Hygiene 28 Portland Place, W 1
3 30 P M Dr B C G Ackner Emotional Aspects of Bodily Complaints

University of Oxford
5 P M (Radcliffe Infirmary) Dr Paul Wood Pulmonary Hypertension

Midland Medical Society
8 15 P M (Birmingham Medical Institute 154 Great Charles Street, Birmingham 3) Dr C G Parsons *The General Practitioner and the Chesty Child*

Manchester Medical Society
4 30 P M (Medical School University of Manchester) Joint meeting with the *Liverpool Medical Institution* Dr R R Hughes Changes in E E G Produced by Biochemical and Endocrine Abnormalities Dr J D Hay Mr F R Edwards *Diagnosis and Surgical Treatment of Pulmonary Stenosis*

Nottingham Medico Chirurgical Society, 64 St James's Street
8 30 P M Dr D I McCallum Eyelid Œdema in Dermatology Dr J M Macfie Examination of the Hands Mr H H Renyard The Umbilicus

Royal Faculty of Physicians and Surgeons of Glasgow 242 St Vincent Street, Glasgow C 2
5 P M Mr D W Currie Results of Twenty one Years of Surgical Treatment of Cancer of the Cervix (Finlayson lecture)

Thursday, 7th

Royal Society of Medicine
5 P M *United Services* Surgeon Commander J M Cliff Dr N M Lloyd Rusby Spontaneous Pneumothorax

St John's Hospital Dermatological Society Lisle Street London W C 2
5 P M Dr G B Mitchell Heggs Dr A Whitlock Dr Desmond O Neill Psychiatry as an Aid to Dermatology

Midland Thoracic Society
7 30 P M (Queen Elizabeth Hospital Edgbaston Birmingham 15) Dr W W Jones Pneumoconiosis

Liverpool Medical Institution
5 15 P M (Medical School University of Liverpool) *History of Medicine* Mr J B Oldham Two Centuries Ago

University of St Andrews Queen's College Small's Wynd Dundee
5 P M Dr J McG Rogan Coalminers Pneumoconiosis

Friday, 8th

Postgraduate Medical School of London
10 A M Mr S H Wass Surgery in the Treatment of Ulcerative Colitis
4 P M Dr Denis Williams Focal Fits

Institute of Laryngology and Otology 330 Gray's Inn Road W C 1
3 30 P M Mr Anthony Radcliffe Nasal Catarrh

Institute of Diseases of the Chest
5 P M Air Commodore C A Rumball Cardio respiratory Assessment

THE NATURAL HISTORY OF ULCERATIVE COLITIS *

E R Cullinan
M.D Lond, F R C P
PHYSICIAN TO ST BARTHOLOMEW'S AND WESTMINSTER (GORDON) HOSPITALS

I P MacDougall
M.D Lond, M.R C P
CONSULTANT PHYSICIAN TO THE HERTFORD GROUP OF HOSPITALS, MEDICAL CHIEF ASSISTANT, THE GORDON HOSPITAL

Knowledge of the natural history of ulcerative colitis is necessary in assessing prognosis It is also important in deciding whether the treatment of a particular patient should be medical or surgical The majority of patients suffering from ulcerative colitis run an unpredictable course, and in these the decision whether to advise removal of the colon is often very difficult It was thought that some help might be gained by reviewing very briefly our personal experience of a large number of patients in one hospital

The natural history of the following series of patients illustrates the difficulty of forecasting the outcome, in most patients, from the previous course of the disease It also shows that those with a poor outcome did have certain common features which may assist in achieving earlier an accurate prognosis in future patients

The prevalence of ulcerative colitis in the population is difficult to estimate In 1946 one of us (E R C) admitted to hospital every patient who came complaining of chronic diarrhœa Of 99 consecutive cases, 41 were found to be of ulcerative colitis (Cullinan 1949)

Material

The material consists of 346 patients about whom we have up-to date information who first attended the Gordon Hospital, London, between July 1, 1947, and June 30, 1955—i e, exactly eight years. The series includes both "medical" and "surgical" cases 170 of the patients were under the personal care of one of us (E R C), the remainder were under the care of our surgical colleagues, and the majority were seen by one or both of us The figures are derived from a continuous follow-up which is being carried out by one of us (I P M.)

The few cases of regional and segmental colitis and those whose diagnosis was in doubt have been deliberately omitted The cases have been divided into three arbitrary groups according to the extent of colon involved

Group A (diffuse)—Those with evidence of involvement of the entire colon

Group B (distal)—Those with evidence of involvement of part of the colon continuous distally to the rectum

Group C—Those with sigmoidoscopic evidence of ulcerative colitis but negative X-ray findings

The division was made because, as will be shown, the severity and gravity of the disease differs markedly in the three groups Our justification for regarding these three groups as different degrees of the same disease process is that the sigmoidoscopic appearances were the same in all and the histological findings in rectal biopsies were identical (Lumb and Protheroe 1955) For example, in group C the 68 patients all underwent sigmoidoscopy 26 were selected at random for biopsy and 21 of these had histological findings indistinguishable from those of the patients in the other groups This does not prove the point, but the argument is reinforced by a further fact Besides the 68 patients who were "X-ray negative" at the last examination, 20 who were in this category when first seen later became "X-ray positive," 11 finally having the entire colon affected

We have seen 12 patients first recognised as being in group B (with the so-called "distal" colitis) later develop "diffuse" colitis (group A) It should be remarked that these changes were independent of the duration of the disease

TABLE I—DISTRIBUTION ACCORDING TO SEX AND EXTENT OF DISEASED COLON AT THE LAST EXAMINATION

—	Group		
	A	B	C
Male	53	57	24
Female	80	88	44
Total	133 (*38*%)	145 (*42*%)	68 (*20*%)

Table I shows the number of patients in each group at the time of the last examination

Table II shows the age at onset of symptoms, which ranged from 4 to 90 The great majority began between the ages of 20 and 50 In all groups women preponderate over men in the ratio of 60 40 There was no significant difference in the age at onset in the three groups

History

Previous History

The former health of the patients had been good There was no previous history of colonic disorders such as the syndrome of "irritable colon" Only 3 patients had a family history of the disease

TABLE II—AGE AT ONSET OF SYMPTOMS

Age		0–9	10–19	20–29	30–39	40–49	50–59	60–69	70–79	80–89	90	Total
No in all three groups	Male	2	12	33	30	36	12	4	4	0	1	134(*39*%)
	Female	3	21	63	54	34	18	16	2	1	0	212(*61*%)
	Total	5	33	96	84	70	30	20	6	1	1	346

Onset

The onset of symptoms was more often abrupt than gradual In each group the initial degree of illness was seldom severe, although early deterioration in some of the patients was rapid

Cause of the onset—We do not intend to discuss ætiological factors in ulcerative colitis, but must mention two We were again impressed by the importance of psychogenic factors in the ætiology, though their mechanism remains obscure Their recognition, although not calling for specialised psychotherapy, is most important for successful treatment

Another factor which demands explanation is the effect of pregnancy One of us (I P M) found that of the 100 women in this series who had been pregnant, a quarter ascribed the onset of the disease to pregnancy or the puerperium (MacDougall 1956)

Subsequent Course of the Disease

Those patients whose course was predictable from the onset were few Only 2 ran so violently acute and fulminant a course (with profuse and severe diarrhœa and the passage of blood, pus, and mucus, accompanied by grave constitutional illness starting within a few hours or days of the onset) that they would almost certainly die within days or weeks (usually of general peritonitis following perforation) Only 27 had unremitting severe symptoms, and only 11 were predictable in the sense

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* Read at the International Congress of Gastroenterology (5th meeting of l'Association des Societes Europeennes et Mediterraneennes de Gastroenterologie) held in London, July, 1956

TABLE III—DURATION OF SYMPTOMS TO DATE, TO OPERATION, OR TO DEATH (ALL 3 GROUPS)

Duration (yr)	<1	1–5	6–10	11–15	16–20	21–25	26–30	31–35	36–40	>40
No of patients	18	99	120	62	34	15	9	2	3	2

that they had annual or biannual relapses with persistent regularity The remaining 306 cases ran an unpredictable chronic course, often lasting for many years, marked by remission and relapse

Table III shows the duration of the disease to date, to operation, or to death It will be seen that about 70% of the cases have already lasted for over five years and that some have lasted for over thirty years

The mode and severity of the onset bore little relation to the subsequent behaviour of the illness and the most banal beginnings sometimes had very serious later developments In most cases the lengths of remissions and the severity of relapses were unpredictable We have carefully compared the course of the disease before the patient first attended for treatment with its subsequent behaviour and have found so little correlation that this is seldom of value

Mortality

The gravity of the attack and of the relapses, however, is very *different in the three groups* The *greatest* danger to life and the greatest severity of symptoms is, as would be expected, in group A where the entire colon is affected The danger to life in the three groups is shown in table IV

TABLE IV—MORTALITY (INCLUDING PATIENTS OPERATED ON) RELATED TO EXTENT OF COLON INVOLVED

—	Group			All groups
	A	B	C	
No of patients	133	145	68	346
No dead	20	8	0	28
Percentage dead	15	5 5	0	8

The disease in groups A and B was roughly comparable in duration, but it will be seen that there were three times more deaths in group A than in group B In group C the illness is non fatal 31 patients in group A showed involvement of the terminal ileum The mortality was the same in these as in the remainder of the group

Severity

The severity of symptoms of the initial attack and of relapses is directly related to the extent of colon involved

In group A (the diffuse type) the patient may gradually or suddenly become extremely ill There may be high fever, profound exhaustion, dehydration, toxicity, and extreme emaciation Severe diarrhœa is the rule

In group B (the distal type) the initial active phase and the relapses are usually associated with far less general upset and are characterised more by bleeding and anæmia There may be either diarrhœa or constipation

In group C, bleeding is usually the only symptom Occasionally there is a *little mild fever* The patients are often constipated, though sometimes the stools are loose

These differences of severity are illustrated in table V, which shows the course of the disease after the attack which first brought the patient to the Gordon Hospital

It will be seen that over half the patients in group A suffered severe or very severe symptoms, that over half in group B were in virtually normal health, and that in group C there were no severe symptoms at all

Other Criteria

The *extent of colonic involvement* is a useful guide to the probable outcome, but the intensity, severity, and duration of the attacks is almost as important as the extent of bowel involved Toxæmia, malnutrition dehydration, leucocytosis, anæmia, and certain systemic complications are indications of severe and potentially lethal disease

"Systemic complications" included malnutrition, hypoproteinæmia, oral ulceration, glossitis and cheilosis, erythema nodosum and pyoderma, polyarthritis, thrombophlebitis, iridocyclitis threatening blindness, and peripheral neuritis

An analysis of the whole group, after excluding the 68 cases in group C, in which there have been no deaths, revealed that the majority of the severely ill and fatal cases showed two or more of the following three features leucocytosis of 10,000 or more cells per c mm , (2) hæmoglobin below 70% , and (3) one or more "systemic complications"

This "toxic triad," as one of us (I P M) has named it, is far less commonly seen in group B than in group A, 28% of patients in group A had 2 of the features and only 4% in group B *But it is interesting to observe, in* retrospect, the striking difference in mortality between patients with none or one and patients with *two* of the three elements of this triad, the latter being nearly nine times the former (table VI) This cannot, of course, be used as a rule of thumb, but it does show that signs of severe toxicity are of equal importance whether part or all the colon is diseased

Local Complications -

Many of the patients had local complications in the bowel but these were not connected with fatality to the same degree as the systemic complications They included severe hæmorrhage, perirectal and pericolic lesions, strictures, and pseudopolyposis, and often required operative treatment In parenthesis, it is interesting that in two patients who had developed recto vaginal fistulæ, the fistulæ healed spontaneously without operation 6 patients in the series developed malignant degeneration They were all patients in group A who had had the disease for a long time—2 for eight years and the others for thirteen, nineteen, twenty five, and twenty-six years The patient who had had symptoms for thirteen years was interesting the carcinoma developed in a functionless colon, an ileostomy having been done three years before

Treatment

Influence of Medical Treatment

We shall not discuss the treatment of ulcerative colitis but wish to make three comments

TABLE V—SYMPTOMS AFTER TREATMENT

Symptoms *	Patients with symptoms (% of group)		
	Group		
	A	B	C
None	11	20	41
Trivial	8	31	45
Moderate	11	17	13
Severe	22	9	0
Very severe	35	0	0
Insufficient information	11	11	1

* Explanation of severity of symptoms

None No symptoms since recovery from attack which brought patient to Gordon Hospital

Trivial Occasional loose stools or rectal bleeding, with long remissions Work and recreation not interfered with

Moderate Diarrhœa in attacks (bowel actions 3–5 times daily often with blood) Hospital admission sometimes required Disease is a handicap interfering with but not usually preventing work or recreation. Often long remissions

Severe Continuous diarrhœa (bowels opened 3–8 times daily often with blood) or attacks of greater severity but with periods of remission Many of these patients have been operated on

Very severe Fulminating or relentless disease, usually fatal if operation withheld

TABLE VI—MORTALITY-RATE RELATED TO THE "TOXIC TRIAD" (ANÆMIA, LEUCOCYTOSIS, SYSTEMIC COMPLICATIONS)

—	Group A	Group B	Total
Patients with two features	36%	33%	35%
Patients with one feature or none	7%	3 6%	4 2%

The first is that four cardinal needs are vital to success in the general medical treatment of ulcerative colitis and may be summarised as follows meticulous and patient nursing, unremitting care in alleviating symptoms as they arise, detailed *attention* to nutrition, fluid and electrolyte balance, and the like and courage, patience, encouragement, and quiet confidence and faith of physician and nurse which transmit themselves to the sufferer It is difficult to overemphasise these needs Lack of attention, and gloom and despair, can kill

We have had little success with chemotherapeutic and antibiotic agents We have found neomycin useful in sterilising the stool as a preoperative precaution, for helping an open lesion in the rectum or anus to heal, and in the violently acute fulminating cases where perforation threatens Otherwise we have found them of little or no value in treatment

Only certain patients responded satisfactorily to corticotrophin (A C T H) or cortisone—usually those who were having a severe acute attack, particularly in the earlier stages of the disease When they were effective, the results were striking, and sometimes led to a complete remission These effects were of great value as a prelude to surgical operation in critically ill patients

Surgical Treatment

Sometimes the decision to advise operation is easy Certain complications threatening early death or grave disability are clear indications for surgery Again, when the course of the disease is severe and predictable, as in the acute fulminating type, or when there are long-continued, unremitting, severe symptoms with relentless deterioration of the patient, in spite of efficient medical treatment, it would be folly to withhold colectomy

The majority of cases of ulcerative colitis, however, pursue an irregular and largely unpredictable course, and it is important to decide which of these patients should be advised to have surgical treatment There is little doubt that some patients die for want of a timely operation, but the opposite extreme of removing the colon in every case would be an absurd policy The decision as to which cases should be selected for surgery grows in importance as the operation for removal of the diseased colon becomes safer, but it is still not to be undertaken lightly However lyrical one becomes, there is nothing poetic about an ileostomy The development of operations to restore the continuity of the bowel after resection of the colon, though very encouraging, is still in its early days Each individual case has to be judged on its own merits, but the paragraphs which follow crystallise our present general view, supported, we think, by the figures we have shown

The clinical course in X-ray negative cases (group C) is mild so long as there is no proximal spread

The outlook in the majority of cases of the *distal type* of X ray positive cases (group B) is usually relatively benign, and such patients are not likely to require surgery except for the relief of certain local complications We are satisfied that most of these patients have *less disability* than they would after surgery This enables one to plan for the majority a conservative course *and to* give a reassuring prognosis We have *already shown* that half of them are, for all practical purposes, in normal health

If the whole colon is affected (group A) the disease commonly causes death or *invalidism*, and *operation* is much more likely to be needed, although a [illegible] number of such patients do well with medical management

It is our opinion that all patients with evidence of severe toxicity, as previously defined, have a potentially lethal disease and should have their colons removed Furthermore, if the long-term effects of operations to restore continuity of the bowel after resection of the colon prove satisfactory, we think we should probably advise all patients who have the diffuse type of ulcerative colitis (group A), and do not quickly improve with *medical* management, *to* have a colectomy, and this would be our advice until the day when this strange disorder can be cured by medical means alone

One of us (I P M) receives a grant from the Gordon Hospital (Westminster Hospital's teaching group) Research Fund We are grateful to our surgical colleagues at the Gordon Hospital for allowing us unrestricted access to their patients, and to Miss H M Davies, the research secretary, for her help

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ADRENALECTOMY AND HYPOPHYSECTOMY FOR ADVANCED CANCER OF THE BREAST

A COMPARATIVE STUDY

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The treatment of *advanced mammary cancer* by modifying the endocrine *environment* may be said to have started in 1896, when *Beatson removed the ovaries* of two patients *with widespread metastases* and produced remissions *Lett reported a further series at a* meeting of the Royal *Medical* and Chirurgical Society in 1905, *and for many years subsequently oophorectomy* was *practised sporadically, resulting* in temporary improvement *in about a third of the patients*

Evidence that ovarian hormones are concerned in the *production of carcinoma* of the breast has since been *provided* by experiments on animals, notably those *of Lacassagne (1932), who* induced malignant changes in the *breasts* of male mice by injecting large amounts of *œstrone benzoate* Furthermore in recent years [illegible] instances have been recorded of carcinoma of the [illegible] developing in male patients who had received [illegible] of œstrogens for prostatic carcinoma (Graves and [illegible] *1952*)

While oophorectomy represented an [illegible] treatment of widespread breast cancer [illegible] obtained posed new problems, because [illegible] patients responded and even in the [illegible] benefit was temporary An explanation [illegible] in the secretion of œstrogens by [illegible]

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would be unaffected by the removal of the ovaries In 1945 Huggins performed adrenalectomy on patients with advanced disease, but they all afterwards died of adrenal failure, and the results were not reported until later (Huggins and Dao 1953)

Independently in this country, the first adrenalectomy for breast cancer was performed in November, 1947, by one of us (H J B A) at Guy's Hospital The object was to remove as much as possible of œstrogen secreting tissue, but, as cortisone was not available at that time, it was not possible to perform total adrenalectomy Both ovaries and about three-quarters of the left adrenal gland were removed at the first stage, and the whole right adrenal gland at the second stage Seven such cases of advanced breast cancer were operated on in this way, 'Eschatin,' 'Eucortone,' and deoxycortone acetate being used as supportive therapy for about 5 days after the second operation until the surviving fragment of the left adrenal resumed its function There was one postoperative death, and two cases showed slight remission These cases, also, were not reported, because it was thought that, if enough adrenal tissue were removed to affect the cancer significantly, the hazard to life would be too great, and the method was allowed to lapse

With the advent of cortisone, however, total adrenalectomy became a practical proposition, and, following the lead of Huggins, a fresh start was made at Guy's Hospital By November, 1953, when hypophysectomy was introduced as an alternative method of treatment, eighteen cases of advanced breast cancer had been subjected to oophorectomy and total adrenalectomy in two stages, and this had become a standard procedure for patients with inoperable growths who were unsuitable for radiotherapy and had not responded to hormones

Although total adrenalectomy with oophorectomy proved more effective than oophorectomy alone, there was the same inconsistency in the results On the assumption that the failures and relapses might be due either to aberrant adrenal tissue, which could be controlled by removal of the pituitary gland, or possibly to a carcinotrophic substance secreted by the pituitary itself, hypophysectomy became the next logical step Encouraging results were reported by Luft and Olivecrona (1953), and the first hypophysectomy for breast cancer was done at Guy's Hospital in November, 1953, by one of us (M A F)

From the first reports it was obvious that hypophysectomy was not going to provide the final answer to metastasising carcinoma of the breast Many patients still did not respond, and others relapsed after initial improvement The question whether hypophysectomy offered any clear advantage over total adrenalectomy with oophorectomy was obviously therefore of great importance, and it is with this question that the present investigation was concerned

Selection of Cases

During the past 3 years adrenalectomy or hypophysectomy has been considered for all patients with advanced cancer of the breast for whom the possibilities of direct surgery irradiation, and hormone therapy have been exhausted Cases in this category were to be discarded only if they were regarded as quite unsuitable for any operation, the patients being moribund Only one case has, in the event, been discarded on such grounds—because of multiple secondary deposits in both lungs and extreme dyspnœa at rest In another case, which was selected for hypophysectomy, the patient died of the disease before the operation could be undertaken

A few patients have been left out of the series because they or their doctors specified which of the two operations should be performed In the remainder, comprising the sixty here reviewed, the type of operation was decided by a method of random selection which is accepted as precluding bias towards one operation or the other (Atkins 1956)

Technique of Adrenalectomy

Preoperative

The patient is admitted to hospital 3 days before operation, so that a final check can be made on the stage which the disease has reached Visible or palpable lumps are again measured, and fresh X-ray photographs are taken of bone or chest lesions Hæmoglobin is estimated and samples of urine are taken for analysis of the 17 keto steroids (see accompanying paper Allen et al (1957))

Cortisone is given in preparation for the first stage, because, if one adrenal has been destroyed by growth, removal of the other will deprive the patient of all her adrenal tissue

Since preoperative preparation with cortisone has been used, the support of the blood pressure both during and after operation has presented few problems In the early cases an intravenous drip of $\frac{N}{5}$ saline solution and 4% dextrose was maintained at both stages of the operation and during the immediate postoperative periods in case supporting fluid should be needed urgently, but in the later cases a drip has been set up only for the second stage Blood has been given when there was an associated anæmia Any fall in blood pressure during operation has been readily combated by a head down tilt, or very occasionally by intravenous methyl amphetamine ('Methedrine') A noradrenaline drip has never been required

As control of the blood pressure has been so successful, anæsthesia has presented few problems unless there was some associated disease A non explosive anæsthetic must be used in view of the need for diathermy and the proximity of the pleura *Because of the position required for operation,* controlled respiration has been found necessary both to provide a quiet operation field and to combat the reduction in tidal excursion The standard thiopentone induction, followed by endotracheal nitrous oxide and oxygen and supported by intravenous tubocurarine and pethidine has proved ideal for this purpose In positioning the patient, great care has to be taken to avoid pathological fracture of the ribs or vertebræ

Operative

The original two stage procedure through the flank has been persisted with because we decided not to modify our procedure while it was under investigation But it also has certain inherent advantages It is, on the whole, safer than the method of removing both adrenal glands at the same sitting, and it has the advantage, over the abdominal approach that enlargement of the liver by secondaries does not gravely impede the operation on the right side, and a good exposure is always possible, enabling accessory adrenal tissue in the vicinity to be found and removed

At the first stage the abdomen is explored and oöphorectomy performed This is done whether or not the ovaries have been allegedly destroyed by X rays or by previous surgery The patient is then turned on to the left side and, after removal of the twelfth or the eleventh rib, whichever is the more prominent, the right adrenal is removed through the flank 10 days later the left adrenal is removed by the corresponding route

Postoperative Management

For all practical purposes the postoperative regime after the first adrenalectomy is the same as after the second There is always the possibility that, at the first operation, the only functional adrenal gland has been removed, and therefore full cortisone cover may have to be provided. Table I gives the basic plan of administering cortisone, deoxycortone salt, and antibiotics throughout both operations Although the plan has been adhered to in most cases, it is only a general guide

We provide penicillin and streptomycin cover during both operations *This is necessary for three reasons* (1) owing to a low blood pressure the patient may have to be kept flat in bed for longer than usual thereby increasing the likelihood of chest infection, (2) many patients have chest secondaries and therefore have little respiratory reserve if they contract a slight infection, and (3) cortisone favours the development of infection in the chest or the wound

Morphine is not given as a postoperative analgesic, because the presence of secondaries in the liver would delay its breakdown Pethidine 50–100 mg is used instead

Except in the immediate postoperative period the nursing care is the same as that after any major operation Owing to

TABLE I—ADRENALECTOMY PREOPERATIVE AND POSTOPERATIVE RÉGIMES

Day	Cortisone	Deoxycortone acetate	Sodium chloride	Antibiotics
Preoperative 1, 2	50 mg, I.M. b.d.			B.d.
1st stage (op. 2 P.M.)	100 mg I.M. 6 A.M., and on return from theatre			,,
Postoperative 1, 2	50 mg I.M. 6-hrly			,,
,, 3, 4	50 mg orally b.d.			,,
,, 5, 6, 7	,, ,,			—
,, 8				B.d.
,, 9 (preop. 1)	50 mg I.M. 12 A.M., 6 P.M., and 12 P.M.			,,
2nd stage (op. 2 P.M.)	100 mg I.M. 6 A.M. and on return from theatre	5 mg I.M. 6 A.M.	5 g orally 6 A.M.	,,
Postoperative 1, 2	50 mg I.M. 6-hrly	5 mg I.M.	Saline solution I.V.	B.d. for 4 days
,, 3, 4, 5	50 mg orally b.d.	,,	5 g orally decreasing by 1 g a day	
,, 6, 7	25 mg orally t.d.s.	,,		
,, 8, 9	25 mg orally b.d.		In food	
,, 10	,, ,, ,,	300 mg implant and 5 mg I.M.	,,	
,, 11–14	,, ,, ,,	Decrease I.M. dosage by 1 mg daily	,,	
,, 15 onwards	,,		,,	

the poor general condition of many of these patients wounds tend to heal slowly. Accordingly, stitches are left in longer than usual, especially the continuous skin suture in the loin incision at the first stage. (This is left in during the second operation because of the risk of the wound's breaking down while the patient is being turned on the table.)

Postoperative Complications

The abdominal incision broke down in one case, on the 8th postoperative day. The first stage loin incision also broke down in a further case, on the 1st day after the second stage. Both healed well on further suture. There was one case of wound infection, which cleared under antibiotic therapy, and there were three cases of urinary infection. Two of these responded quickly to treatment, but in the third the infection persisted until the patient died, when it was found at necropsy to be due to growth in the bladder wall. There was one severe postoperative chest complication—a massive collapse of the left lung which precipitated the patient's death. Apart from this there were several minor chest complications, but these resolved quickly under treatment. There have been no cases of deep vein thrombosis and no pulmonary emboli.

Technique of Hypophysectomy

Preoperative

Patients are usually admitted to hospital 7–10 days before the operation. The first 2–4 days are occupied in assessing the stage of the disease and in obtaining such data as the urinary excretion of 17 ketosteroids and the uptake of radioactive iodine by the thyroid gland, as a base line for subsequent determination of residual pituitary function. For 6 days before the operation cortisone is given: at first the dosage is 50 mg daily by mouth, but during the last 2 or 3 days it is increased, reaching 400 mg (in divided doses) on the day of operation, half by mouth and half intramuscularly. During this long period of preoperative preparation the opportunity is also taken to aspirate massive pleural effusions or ascites so as to lessen dyspnœa and facilitate anæsthesia.

Operative

The operations are done under intratracheal anæsthesia (nitrous oxide, oxygen, and ether, or intravenous pethidine). A small right frontal craniotomy is performed with the patient in a slight reversed Trendelenburg position. This differs only in details from that described by Olivecrona (Luft and Olivecrona 1953) and by Bronson Ray (Pearson et al. 1956). The anterior limb of the bone flap is cut obliquely above the frontal air sinus so that its outer angle lies immediately above the external angular process of the frontal bone and so level with the floor of the anterior cranial fossa. From this direction (which makes an angle of 20–30° with the sagittal plane) the right frontal lobe is lifted off the anterior cranial fossa, and the chiasmal region is approached. Ready access to this region is always obtained by sucking cerebrospinal fluid (C.S.F.) from the cisterna chiasmaticus, and in no instance has preliminary drainage of C.S.F. either by the lumbar or the ventricular route, proved necessary. The two optic nerves and the chiasma are then uncovered by incising the arachnoidal wall of the cisterna chiasmaticus. Finally any remaining arachnoidal tissue in the concavity of the chiasma is divided, revealing the infundibulum (pituitary stalk) and the diaphragma sellæ.

The pituitary stalk is then clipped low down with a silver clip and divided below this, flush with the diaphragma. Next, the diaphragma is incised in a Y-shaped or X-shaped manner up to the line of the circular sinus, revealing the yellow pituitary gland. The gland itself is teased out of its fossa with a small dissector, sometimes in one piece but usually in fragments. Slight to moderate venous bleeding from the walls of the pituitary fossa often takes place during this stage but usually ceases after the bulk of the gland has been removed. The removal of the gland is completed by scraping the walls of its fossa with curettes and by inserting appropriately angled suction tubes. The most elusive portion of the gland is that tucked beneath the right optic nerve.

The pituitary fossa then appears as a small cavity lined by smooth red fibrous tissue. A pledget of cotton wool steeped in Zenker's fluid has been inserted into the fossa of all but 7 of the 30 patients for 2 or 3 minutes to necrose any tiny fragments of pituitary tissue which might have escaped removal. Precautions are taken during this manœuvre to prevent spilling of the fixative outside the pituitary fossa, and at its completion the walls of the fossa always appear grey. Finally, in all but two cases, before the craniotomy is closed, a plug of "cold curing" acrylic paste was placed in the pituitary fossa and allowed to set into a hard plate to prevent any possible regeneration of the pituitary stalk into the pituitary fossa.

Usually the operation progresses readily step by step, but in a few cases certain difficulties are encountered. In seven cases the chiasma was prefixed—i.e., less than 5 mm from the tuberculum sellæ—leaving little room for inserting the instruments. This difficulty, however, was overcome, as a rule, by chiselling away the hinder 3–4 mm of the tuberculum. In no case did section of the chiasma or of one optic nerve prove necessary for the exposure. In one case of prefixed chiasma however, the diaphragma sellæ was evidently tilted downwards and backwards away from the line of vision, the operation consequently was abandoned, and the case counted as a failure for hypophysectomy. In most cases a pint of blood was transfused during the operation, and in no case were hypotensive arterial techniques or hypothermia employed.

Postoperative

In general, the postoperative management causes no more concern than that after an operation for pituitary tumour. Recovery of consciousness is prompt, and the patient is usually drinking and eating again within a few hours.

Cortisone to a total of 350 mg is usually given on the day following operation, partly by mouth and partly intramuscularly; this is decreased in stages to an oral dose of 25 mg twice daily by the 8th day, at which level it is subsequently maintained. The scalp stitches are usually all removed by the 4th day, and, if the carcinomatous condition allows, the patient got out of bed between the 5th and 8th postoperative days.

Long-term Treatment

Patients who have been subjected to adrenalectomy or hypophysectomy are exposed to certain hazards for the rest of their lives. If these dangers are to be minimised, it is essential that maintenance therapy should be most carefully supervised, and that the closest coöperation should exist between the hospital and the general practitioner. It is our practice to see each patient as an outpatient at 4-week intervals, and doctors are asked to communicate with the hospital immediately if any untoward symptoms develop in any of these cases between visits.

At each attendance at hospital, the condition of any neoplastic lesion is assessed and the patient's weight and blood-pressure are recorded. Special inquiry is made about lassitude, anorexia, nausea, vomiting, or anything that might suggest infection.

In hypophysectomy cases the serum cholesterol level is estimated from time to time to assess thyroid function. Electrolyte studies have been carried out in all patients in whom there was reason to suspect incipient adrenal deficiency clinically. The importance of rising serum potassium and blood urea levels has been emphasised in this connection.

Though hypophysectomised patients require certain additional therapeutic measures (see below), the maintenance treatment of all the patients was made as similar as possible.

Cortisone

The standard dosage is 25 mg. twice daily by mouth. This probably represents an increase of about 50% above the glucocorticoid production of a normal person, but it provides an added safeguard against minor stress and infections; and, although a few patients developed some rounding of the face on this dosage, no serious side effects have been observed. Occasionally patients who are going downhill have been temporarily improved subjectively by raising the dosage of cortisone to 75 mg. or 100 mg. daily, but the necessity for such an increase has always been an ominous prognostic sign signifying that the carcinoma was progressing rapidly.

The importance of a very substantial increase in cortisone dosage at the time of an acute infection or accident is discussed below.

Deoxycortone Acetate

Though cortisone 50 mg. daily provides adequate replacement therapy for the adrenal glucocorticoids, its effect on the metabolism of salt and water is by no means always so satisfactory, with the result that, unless additional therapy is given, arterial hypotension, excessive depletion of sodium with hyperkalæmia, and a rise in the blood-urea level may occasionally develop. While this complication can usually be avoided by giving large quantities of sodium chloride, the administration of a mineralocorticoid seems to be a wise procedure, and all our patients received an implant of deoxycortone acetate 300 mg. before discharge from hospital. Thirteen patients (nine adrenalectomies, four hypophysectomies) were slightly hypertensive in the ensuing months on this routine, but the blood-pressure of most of these had been slightly raised before operation, and in only one case were any symptoms reported which could in any way be attributed to hypertension. Three patients (two adrenalectomies, one hypophysectomy) required reimplantation at 9, 9, and 16 months because their blood-pressure was tending to fall to hypotensive levels.

Sodium Chloride

Sodium chloride in the form of capsules is not given routinely to our patients save in the immediate period following adrenalectomy. We do, however, use it as a "fine adjustment" to keep the blood-pressure in the normotensive range. It is given as salt capsules in doses of up to 4 g. daily. Patients who tend to have a raised blood-pressure are forbidden table salt. Additional sodium chloride was very rarely required in the hypophysectomy cases.

Special Maintenance Therapy after Hypophysectomy

Phenobarbitone.—To minimise the possibility of epileptic fits all the patients received phenobarbitone 30 mg. twice daily for a year after hypophysectomy. After discharge from hospital no fits occurred except in one patient who was known to have cerebral metastases.

Control of diabetes insipidus.—Thirst and polyuria, often severe, usually developed within a week of hypophysectomy, but occasionally the onset was delayed a month or more. They were temporary and cleared spontaneously between the 4th and 11th months in all the survivors. In many patients sleep was seriously disturbed. Satisfactory control was usually obtained by the insufflation of posterior pituitary snuff 40 mg. from once to three times daily. One patient could tolerate only half this dose. In the early postoperative period injections of vasopressin tannate 5 mg. in oil were occasionally required each 2nd or 3rd day.

Thyroid.—Most patients showed a substantial gain in weight after hypophysectomy. Though this was partly due to an increase in appetite and general well-being, there can be no doubt that incipient thyroid deficiency often contributed to it. Some patients became frankly myxœdematous. These changes were not usually obvious until after the passage of several months, but in three cases they developed within a few weeks. In view of any possible effect it might exert on the carcinoma, it had been decided not to administer thyroid extract routinely; but in nine patients the onset of definite myxœdema made it essential. It was given by mouth in the dosage of 30 mg. twice daily, starting 2–18 months after the operation. The serum-cholesterol level, which in one case rose to 502 mg. per 100 ml., provided a simple satisfactory test for measuring the deficiency of thyroid during surveillance. The administration of thyroid did not appear to affect the neoplasm in any way, though the number of patients observed is too small for any statistical conclusions to be drawn. In fact, we feel that we were rather too hesitant in giving thyroid and consider that it should probably be administered to the majority of these patients after hypophysectomy.

Testosterone.—In view of the possible effect on the carcinoma, no patients in this series received testosterone at any time after these operations.

Management of Infections and Accidents

Although hypophysectomised or adrenalectomised patients can remain in good health on the maintenance therapy outlined above, the onset of an acute infection or the stress of an accident or an operation calls for a substantial increase in the adrenal steroids. As these patients cannot provide this from their own sources, fatal collapse may follow unless the cortisone dosage is increased. During any pyrexial illness, therefore, the daily amount of cortisone should be increased to about 150 mg.; and this must be combined with large doses of antibiotics. Vomiting is a danger sign of incipient adrenal collapse; but it is sometimes absent, and the blood-pressure may remain within normal limits until a few hours before death.

The dictum that, because it depresses the natural response to infection cortisone should be withheld at these times cannot be too strongly condemned. It is equally important to combat the stress of an operation or an accident by a similar increase in dosage, and any adverse effect upon tissue healing is unimportant.

Three of our patients died after fracture of the femur.

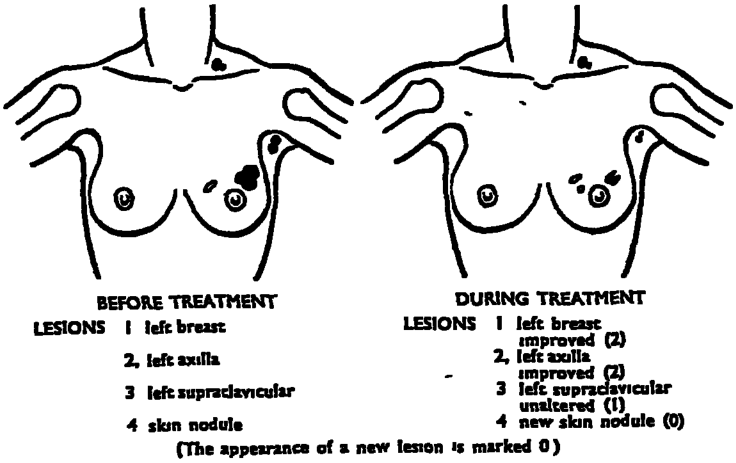
In two cases, both adrenalectomies, the fracture was pathological and a Thomas splint was applied. Unfortunately they were admitted as emergencies, and the cortisone was continued at the maintenance dose of 50 mg. daily. Both patients died within 3 days.

The third case, a hypophysectomy, was particularly tragic because the patient was doing extremely well and the fracture was in a healthy femur. She was admitted to a hospital where she was not known and remained well for 4 days on her maintenance dosage of cortisone. On the 4th day the femur was exposed and pinned under general anæsthesia, and she collapsed with arterial hypotension and died within 12 hours.

If such tragedies are to be avoided, it seems sensible to give all these patients a letter or card stating the necessity for increasing the dosage of cortisone at times of stress, so that they can hand it to any doctor who may be called to attend them if they are taken ill or injured away from the care of their own practitioners, and we intend to introduce this procedure.

Method of Assessment of Results

To assess the value of any treatment applied to cases of advanced cancer at the breast clinic, and particularly in comparing one method of treatment with another, it has been necessary to use the "mean clinical value" (M.C.V.) system introduced by Walpole and Paterson (1949) whereby a number between 0 and 12 is assigned to the patient at each 4-weekly visit according to her response to treatment.


BEFORE TREATMENT
LESIONS 1 left breast
2, left axilla
3 left supraclavicular
4 skin nodule
DURING TREATMENT
LESIONS 1 left breast improved (2)
2, left axilla improved (2)
3 left supraclavicular unaltered (1)
4 new skin nodule (0)
(The appearance of a new lesion is marked 0)

$$\text{M C V} = \frac{\text{Total marks}}{\text{No of lesions}} = \text{Average mark} \times 6 \text{ to produce a suitable number}$$

Maximum = 12
No effect = 6
Minimum = 0

$$\text{In present case M C V} = \frac{2+2+1+0}{4} \times 6 = 7.5$$

Fig 1—Assessment of mean clinical value

The system is applied by establishing a base-line for each demonstrable lesion when the patient is first seen and before treatment is begun Lumps are carefully measured, skin lesions photographed, radiographs of chest and skeletal lesions taken, and abnormalities measured and recorded With the exception of pain, subjective symptoms have not been used as factors in determining response The treatment is then applied and the patient seen again in 4 weeks' time Each lesion is again assessed. If the lesion has improved it is given 2 marks, if stationary, 1 mark, and if worse, 0 The marks are then added, and the total is divided by the number of lesions, giving an average mark for the whole disease Such a figure would be awkward to handle, so the result is multiplied by 6

In this way, if all the lesions are responding, the average mark is 2 and the M C V 12, if all the lesions are stationary, the average mark is 1 and the M C V 6, and, if all are deteriorating, the M C V is 0 When, as not infrequently happens, some lesions are responding and others are failing to respond or are deteriorating, any value intermediate between 0 and 12 may be obtained The working of the scheme is illustrated by a hypothetical case in fig 1

Each 4 weeks the patient is reassessed and a fresh M C V allotted, in this way a chart of the patient's progress can be made, and a typical chart following, for instance, œstrogen therapy is shown in fig 2 If one of the factors used in computing the M C V is radiological, a new radiograph is not taken every 4 weeks but at every third visit—i e, after 12 weeks have elapsed—and the previous value of the radiological factor is used to compute the M C V. in the two intervening assessments

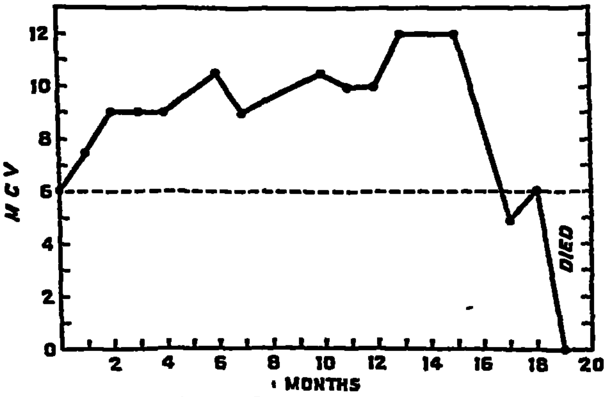


Fig 2—Typical chart of progress after œstrogen therapy

It must be understood that the state of any lesion is always compared with the *original* state of that lesion and not with its state at the previous visit Thus a patient who has been responding to treatment may cease to respond and begin to deteriorate, but the deterioration is not reflected in the M C V chart, because the lesions are still better than they were before treatment began This is a weakness of the method which cannot be avoided and it accounts for the somewhat precipitate drop in the chart shortly before death The workers at the breast clinic have, however, had many years' experience of this system and are convinced that it gives an accurate numerical assessment of the patient's response to treatment, particularly when comparative figures are required

In comparing the results of a series of patients treated by one method with a series treated by another it is possible to construct two charts One chart represents the average M C V of all the patients after 1 month, 2 months, 3 months, and so on, treated by one of the two methods The other does the same thing for the second method of treatment In this way the general effect of the two methods of treatment can be compared at a glance (fig 3) In constructing this chart, and to obtain the average in the later months, patients who have died maintain their representation on the chart with a mark of 0 Thus, when all the patients have died, both graphs reach zero

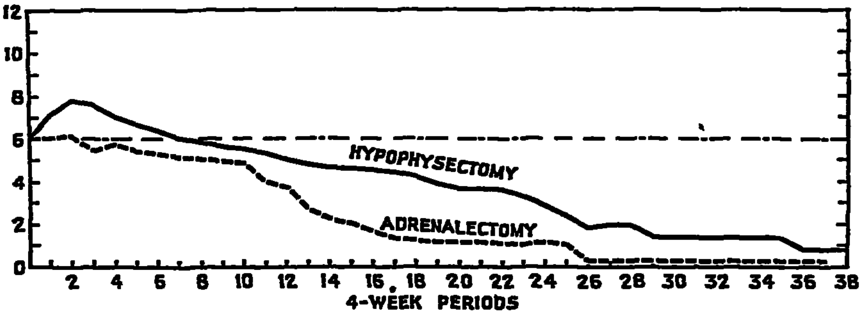


Fig 3—Average M C V (4-weekly records) of all adrenalectomy and hypophysectomy cases.

Results

Comparison of Groups

Although the thirty cases in each group were selected by random sampling, it was possible that, by chance, one group might have had a predominance of a particular type of case Tables II–V have therefore been compiled to compare the more important preoperative features of the cases falling into the two groups It can be seen that the incidence of these features in the two groups is about the same, indicating that they are comparable

The diagnosis was confirmed histologically in twenty-six of the thirty patients in each group In the eight cases not so confirmed the manifestations were so gross and characteristic that the diagnosis was not considered to be in any doubt

Mortality and Morbidity

Adrenalectomy—Of the thirty patients submitted to this operation twenty have now died One of these deaths, from massive pulmonary collapse 24 hours after

TABLE II—AGE IN YEARS

Operation	Youngest	Oldest	Average
Adrenalectomy	39	69	53
Hypophysectomy	36	73	54

the first stage adrenalectomy and oophorectomy, is held to be due to the operation If this case is included, four patients died within 1 month and nine within 3 months of operation In one case, where the ovaries could not be removed because of massive pelvic secondaries, the operation was technically impossible

There were few serious sequelæ as a direct result of the operation Two patients had addisonian crises some months after operation, but both responded well to treatment Two had depressive states during the first 2 months, one of these responded well to electroconvulsive therapy, but the other died from the carcinoma before psychiatry could be applied Two patients died after pathological fracture of the femur, these have already been mentioned and were deteriorating rapidly at the time of their accidents One patient developed an incisional hernia through the scar in one loin, but this was symptomless and needed no treatment

Hypophysectomy —Of the thirty patients submitted to this operation seventeen have now died No death was due to the operation Three patients died within 1 month and five within 3 months of operation, in none of these cases was death accelerated by surgery Two of the seventeen deaths were due to causes other than carcinoma of the breast one patient, aged 73, died of heart-failure 4 months after operation, and the other of arterial hypotension following open reduction of a fractured femur 6 months after operation, both were otherwise doing well One patient had a depressive state which recovered without treatment

TABLE III—MENSTRUAL HISTORY

Operation	Premenopausal	Menopausal	Postmenopausal	Unknown (hysterectomy)
Adrenalectomy	5	1	23	1
Hypophysectomy	3	3	21	3

The operation was technically impossible in one case owing to the abnormal configuration of the pituitary fossa This patient subsequently underwent adrenalectomy and is therefore included in both groups, the M C V for hypophysectomy being recorded as 0

Some degree of diabetes insipidus developed in all cases usually in the 1st week, but this complication was occasionally delayed until the 3rd week, and vasopressin, either as an injection of the tannate in oil in the acute stages or as snuff, was sometimes necessary The symptoms progressively declined and were usually insignificant by the 6th month

A bitemporal field defect was observed in six cases, but in only one did it cause trouble Most of the patients had unilateral anosmia, a few had bilateral anosmia, and none complained of it

Conclusions

The object of this investigation was to determine which operation (adrenalectomy or hypophysectomy) conferred greater benefit in cases of advanced cancer of the breast —without regard to the type of cancer or the patient's age We wanted a statistically valid answer rather than a *clinical impression*

Table VI shows that, of the patients who have already died, those who underwent hypophysectomy have survived on an average 2 months longer than those who underwent adrenalectomy If all the cases are included the patients who underwent hypophysectomy survived on an average 4 months longer than those who underwent adrenalectomy The longest survival after hypophysectomy was a year longer than the longest survival after adrenalectomy

TABLE IV—RESPONSE TO HORMONES

Operation	Poor	Fair	Good
Adrenalectomy	19	9	2
Hypophysectomy	22	6	2

The progressive mortality of the two groups is given in fig 4, which shows that during the period of follow up the mortality-rate after adrenalectomy climbed more steeply than that after hypophysectomy

By calculating the M C V we have compared the degree of benefit conferred When all the M C V in both groups are recorded on the same chart, the picture is too confusing for immediate analysis It may be simplified by taking an average of the M C V at each 4 weeks of all the patients treated by one method and constructing a single-line graph exemplifying an average response for that method A similar single line is constructed for the other method (fig 3) In this way the relative effects of the two methods can be readily appreciated

These findings (table VII) suggest that, in the circumstances of the investigation, if the ablation of endocrine tissue is indicated in a case of advanced cancer of the breast, hypophysectomy is to be preferred to adrenalectomy with oophorectomy We have been advised, however, by Dr P Armitage, who, with the kind cooperation of Prof A Bradford Hill, analysed our results, that this difference is not statistically significant in the conventionally accepted sense The degree of significance is indicated in table VIII

TABLE V—MANIFESTATIONS

Operation	Primary growth not removed	Secondaries in						
		Breast	Skin	Glands	Liver	Chest	Bone	[illegible]
Adrenalectomy	8	11	16	18	6	8	18	3
Hypophysectomy	6	5	14	14	5	11	16	3

TABLE VI—SURVIVAL AFTER OPERATION

	Survival (expressed as the number of four week periods survived) for each individual case																				Average length of survival (weeks)	
																					All patients	Dead patients
Adrenalectomy																						
Alive	21	21	18	12	12	10	10	9	7	3											32	21
Dead	17	16	16	15	13	12	8	6	4	4	3	2	2	2	2	1	0	0	0	0		
Hypophysectomy																						
Alive	38	37	28	21	24	23	18	13	13	9	7	6	2								48	32
Dead	29	22	19	14	12	7	6	5	4	3	3	3	2	1	0	0	0					

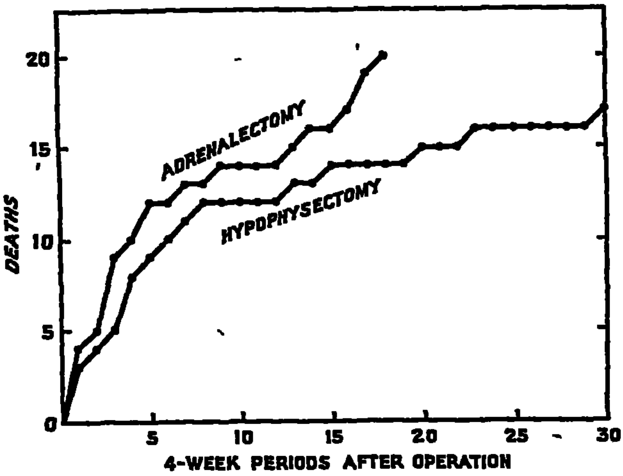


Fig 4—Mortality of two groups at 4-week periods after operation

Review of Reasons for Success or Failure

The fact that some cases respond while others do not may often depend on the nature of the growth—i e , whether or not it is what Huggins has termed "hormone-dependent" On the other hand, certain other factors may be important In the case of adrenalectomy, for instance, there may be accessory adrenal tissue which is at some distance from the operation site and is not removed at the operation, or other organs may take over the elaboration of œstrogen when the ovaries and adrenal glands have been removed Furthermore, after this operation the growth-promoting hormone of the pituitary gland is unaffected, and this hormone may be of importance in maintaining the cancer

TABLE VII—AVERAGE M C V

M C V	Hypophysectomy	Adrenalectomy
At 3 months	7 90	5 70
At 6 months	6 49	5 54
Last record	4 70	3 11
Average during survival	7 35	6 03

Likewise in the case of hypophysectomy the operation may not be complete Other workers have assessed the completeness of the operation on the basis of certain tests of pituitary function, but in our experience these tests are inconclusive Thus Luft and Olivecrona (1953, 1955) utilised the fall in the blood eosinophils with intramuscular injection of adrenaline, and the fall in the daily urinary excretion of 17-ketosteroids, as indicating how far pituitary function was destroyed We, however, found that, in our patients, the blood-eosinophil levels were constantly so low (less than 100 cells per c mm) that the response to adrenaline was valueless Again, probably because we gave rather larger doses of cortisone for maintenance therapy, the urinary excretion of 17-ketosteroids seldom decreased but stayed at 7–8 mg per day Ray and his collaborators (Pearson et al 1956) relied on tests of thyroid function they estimated the uptake of radioactive iodine and the amount of protein-bound iodine in the serum We also used these tests, in nineteen of our patients, and likewise found that the levels fell to low or very low values, indicating much diminution of thyroid function However, we were disappointed to find that this did not prove that the whole of the pituitary gland had been removed

TABLE VIII—STATISTICAL EVALUATION OF RESULTS

M C.V	Difference between means ± standard error
At 3 months	2 20 ±1 2 (t=1 73 , P=0 09)
At 6 months	0 95 ±1 44(t=0 66 P=0 51)
Last record	1 60 ±1 34(t=1 19 , P=0 24)
Average during survival	1 32 ±0 97(t=1 35 P=0 18)

Thus, in fatal cases which came to necropsy the pathologists usually reported that, to the naked eye, the pituitary fossa appeared empty However, on careful histological examination, Prof C W Harris and Dr J V Cavanagh have found microscopic fragments of glandular tissue in all six cases so far examined, and provisional estimates place the amount of residual glandular tissue as 1–10% of the anterior lobe In five of the cases so examined the patient had not responded to operation, but the sixth patient had benefited considerably and died after an operation for traumatic fracture of the femur 6 months after hypophysectomy while the carcinomatous lesions were still regressing Thus an absolutely complete hypophysectomy is not essential for producing regression

We must face the fact that, in some of our surviving patients, the hypophysectomy, although extensive, may still have been incomplete, and therefore we must consider other explanations of the benefit Several workers have shown that, in laboratory animals, if the pituitary stalk is cut through and an obturator is inserted to prevent reunion of the stalk with the gland, the gonadal, adrenal, and thyroid functions will be depressed in much the same way as after complete hypophysectomy (Harris 1955) In such circumstances the anterior lobe of the pituitary gland often shows histologically only slight necrosis The essential factor appears to be the interruption of the portal venous circulation of the pituitary gland , for if the stalk is allowed to reunite with the gland, the portal circulation regenerates and the animal regains its normal endocrine functions How far these experimental observations can be applied to man is not yet known

Dorothy Russell (1956) has reported that, in two patients operated on for craniopharyngioma, extensive necrosis of the pituitary gland followed section of its stalk without insertion of an obturator Neurosurgeons who have divided the pituitary stalk for breast carcinoma have subsequently found only a small proportion of the anterior lobe atrophic (Connolly 1956, Le Beau 1956)

A controlled trial of surgical hypophysectomy versus section of the pituitary stalk (with precautions to prevent its regeneration) therefore seems necessary to elucidate the rationale of our operation , for not only did we divide the pituitary stalk and attempt to remove the gland but also we inserted an acrylic plate to prevent regeneration of the portal circulation to any fragments which might remain

Comment

In this clinical experiment the differences between the results of hypophysectomy and those of adrenalectomy in the treatment of advanced carcinoma of the breast are not statistically significant Nevertheless there is a definite trend in favour of hypophysectomy , and it may well be that, with larger numbers of patients, significant differences will appear It must be realised, however that these results depend on a first class neurosurgical service, and today facilities are not yet available for all patients to be submitted to hypophysectomy

For this reason we are interested in alternative methods of destroying the pituitary gland, such as those practised in this country by Forrest and Peebles Brown (1955) We hope that, with the cooperation of the authorities of Liverpool University, it will be possible to utilise the techniques described above to compare the clinical course of a series of cases treated by surgical hypophysectomy with that of a series in which the hypophysis has been destroyed by proton bombardment with the synchrocyclotron

Further investigation into the relative merits of hypophysectomy and pituitary-stalk section is also planned

Summary

A controlled series of patients with advanced cancer of the breast were operated on—half by adrenalectomy with oophorectomy, and half by hypophysectomy

The type of operation was decided by random selection

The results of these operations were compared by the method of "mean clinical value" and by the survival-rate

In the circumstances of the investigation the overall results of hypophysectomy seem to be superior to those of adrenalectomy with oophorectomy, but the results are not statistically significant

Neither operation appears to hold out prospects of permanent cure Possible reasons for this are discussed

Our thanks are due to Dr P Armitage, of the department of medical statistics at the London School of Hygiene and Tropical Medicine, for analysing our results statistically, to the Editor of the *Leeds Medical Journal* for permission to reproduce figs 1 and 2, and to Miss J Thorne for her accurate and painstaking work in keeping the M C V records We thank Miss Sylvia Treadgold for her help in producing the diagrams We are also indebted to Prof G W Harris for his advice, to Dr J G Gibson and Dr J H Ray for the radio active iodine studies, to Dr R C Willcox for determining the protein bound iodine, and to Dr P J Helliwell for a note on the anæsthesia

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THE EXCRETION OF 17-KETOSTEROIDS IN THE URINE OF PATIENTS WITH GENERALISED CARCINOMATOSIS SECONDARY TO CARCINOMA OF THE BREAST

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In an accompanying paper Atkins et al (1957) have compared the results of adrenalectomy with those of hypophysectomy in the treatment of 60 cases of mammary carcinomatosis *From the outset of their investigation* it was clear that a preoperative criterion was needed to distinguish which patients were likely to benefit from either procedure The importance of having such a criterion is emphasised by their observations that only half of the cases showed any improvement from either operation

It seemed possible that the solution of this problem might be found in differences in the preoperative excretion of hormones by such patients For this reason it would be useful to have a complete picture of the urinary excretion of pituitary sex, and adrenocortical hormones When our work started, however, the methods available for estimating pituitary hormones and œstrogens were in various ways open to criticism and were not easily applied as a routine in the laboratory We therefore decided to study the excretion of the 17 ketosteroids, because these reflect to some extent the hormonal activity of the adrenal cortex and can easily be estimated

It soon became obvious that there was no significant difference in the preoperative excretion of total neutral 17-ketosteroids between patients who benefited from operation and those who did not We therefore turned our attention to the study of the 17-ketosteroid fractions obtained by chromatography of the total neutral fraction on alumina columns This paper gives a preliminary report on our findings

Patients Studied

The 60 cases described by Atkins et al have been the subject of our investigation, but, because of the time taken to complete each estimation, only 15 of them have so far been completely studied Of these 15, 7 underwent adrenalectomy and 8 hypophysectomy (table I) The youngest was aged 40, the oldest was 59, and all were postmenopausal except for 2 who were at the menopause and 1 who had had a previous hysterectomy All had had male hormones preoperatively, except 1 who had had stilbœstrol only, 4 had taken both male and female hormones The table shows the specific hormone taken immediately preoperatively and the interval between the last dose and the first collection of urine It also shows the sites of the secondaries and whether the primary growth was removed or not The longest surviving patient has been followed up for twenty-four months and the shortest surviving for seven months, 7 deaths are indicated by asterisks

Methods

On admission to the ward urine was collected for seventy-two hours from each patient Further seventy two hour collections were obtained after operation at intervals of a fortnight, a month, three months, and six months These collections were preserved with crystalline thymol and salicylic acid (Bisset et al 1948) We deal here only with the preoperative collections

Extracts from the seventy-two hour collections of urine were prepared according to the technique of Dingemanse et al (1952) Their method was then modified as follows

Aliquots of each extract containing 8–12 mg of total neutral 17 ketosteroids, dissolved in 10 ml of benzene, were adsorbed on columns containing 30 g of alumina equilibrated over 19 7–21 0 N sulphuric acid The chromatograms were developed with benzene, benzene *plus 0 1% ethyl alcohol*, benzene plus 0 5% ethyl alcohol, and benzene plus 2 0% ethyl alcohol The total *Zimmermann* reacting substances (Zimmermann 1935) in each fraction were then estimated by the method of Holtorff and Koch (1940)

This method permits the separation of 11 deoxy 17 ketosteroids from those with a carbonyl or hydroxyl function at the eleventh carbon atom The 11 deoxy 17 ketosteroids consist primarily of etiocholanolone, dehydro epiandrosterone, androsterone, and their derivatives These compounds are the metabolites of testosterone, Δ 4 androstene-3 17 dione and dehydroepiandrosterone, to a lesser extent they reflect the metabolism of certain of the adrenocortical C^{21} steroids having a hydroxyl group at the seventeenth carbon atom but lacking a carbonyl or hydroxyl function at the eleventh carbon atom They are eluted from the column in fractions 20–60 In fractions 65–85 are eluted 17 ketosteroids having a hydroxyl or carbonyl group at the eleventh carbon atom This group includes 11 hydroxyetiocholanolone, 11 hydroxyandrosterone, 11 ketoandrosterone, and 11 ketoetiocholanolone They are present in the urine as the metabolic end products of the metabolism of cortisone, hydrocortisone, and adrenosterone

TABLE I—CLINICAL DETAILS OF 15 PATIENTS WITH MAMMARY CARCINOMATOSIS

Case no	Age (yr)	Menopause	Preoperative treatment with hormones	Hormone taken before first collection of urine	Interval between last dose and first collection of urine	Primary growth removed	Secondaries in						
							Breast	Skin	Gland	Liver	Chest	Bone	C N S
1*	50	At	Male	Testosterone propionate	4 days	+			+	+		+	
2*	59	Post	Male	Testosterone propionate	3 mos	+	+	+				+	
3*	47	Post	Male	Testosterone propionate	2 mos	+			+			+	
4*	55	Post	Female	Stilbœstrol	5 mos	+	+	+	+				+
5*	55	At	Male	Testosterone propionate	7 weeks	+		+	+			+	
6	56	Post	Female and male	Testosterone propionate	8 mos			+	+				
7	54	Post	Male	Testosterone propionate	5 days	+						+	
8	55	Post	Female and male	Methyl testosterone	3 days	+			+		+	+	
9	52	Post	Male	Testosterone propionate	2 days	+						+	
10*	53	Post	Male	Testosterone propionate	33 days	+	+	+	+				−
11	40	Hysterectomy	Male	Testosterone propionate	10 days				+			+	
12*	52	Post	Male	Testosterone propionate	12 days	+	+	+	+			+	
13	53	Post	Female and male	Methyl androstenediol	30 days		+	+	+				
14	56	Post	Male and female	Stilbœstrol	During collection	−			−	+			
15	48	Post	Male	Testosterone propionate	7 weeks	+			+		+	−	

* Died

The method has certain well-known limitations

(1) We did not use any preliminary separation into ketonic and non ketonic fractions with Girard's reagent T This has the effect of introducing an error into the colorimetric computation of our results owing to the presence of non ketonic chromogens in some fractions

(2) Peaks which are represented on the charts do not contain one steroid alone but probably contain one which is there in predominant quantity and, possibly, several others which may be eluted with the main one in very much smaller quantities—i e , the method, as we used it, does not permit the resolution of very closely related substances For these reasons we do not attach much quantitative significance to the concentration of steroid found in each individual peak

(3) The acid hydrolysis of steroid conjugates in urine, which is used in this method, dehydrates trace amounts of 11-hydroxylated-17 ketosteroids to their Δ 9 derivatives which are eluted in group I

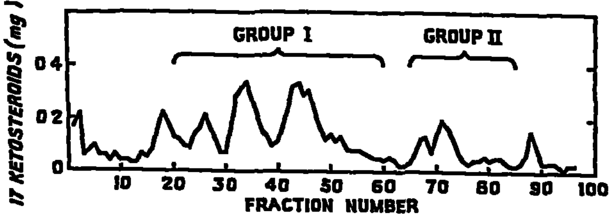

Fig 1—Excretion of 17-ketosteroid fractions in pooled urine from 20 healthy people

(4) In our hands the method has proved extremely time-consuming, and we do not consider it suitable in its present form for routine use

However, in view of the results we have obtained we consider it reasonable to compare the amount of steroids present in the first group (fractions 20–60) with the total amount of steroid material in the second group (fractions 65–85) Thus we have expressed as a ratio of the total amount of substances reacting with Zimmermann's reagent in group I to the total amount of substances giving the same reaction in group II

Results

The results can be shown graphically by plotting the quantity in each fraction against the fraction number When these plots are joined by a continuous line, it can be readily seen, by the peaks produced, in which fractions the 17-ketosteroids appear in greatest amounts

Fig 1 is the graph obtained for the 17 ketosteroids of pooled normal urines Breakdown of individual normal urines has shown that this is a representative picture If the total ketosteroids are worked out for the two groups in this figure, it is found that group I derivatives exceed group II in relative quantity by about 4 1 (4 1) This ratio naturally varies from one normal to another, but, if the quantity in group I is divided by that in group II, the result is usually about 3 or 4 and always more than 1

Fig 2 shows the graph obtained from the urine of a patient about to undergo hypophysectomy, and it can be seen that it is essentially normal in this respect The ratio of group I to group II is 3 7

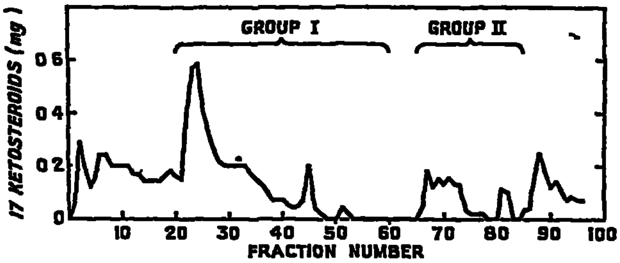

Fig 2—Preoperative excretion of 17 ketosteroid fractions in a patient who benefited from operation (case 7)

We have now investigated the preoperative urines of 15 patients and have calculated the ratio of group I group II in each case The result is shown in table II, together with the total 17-ketosteroids of these patients It can be seen that, although there is some variation from the normal, in 11 of the 15 cases the ratio is more than 1

In view of the 4 discrepant cases we tried to correlate the ratios of group I group II with clinical response to operation To do this we have used the " mean clinical value " (M C V) method of assessment (Walpole and Paterson 1949 , see also Atkins et al 1957)

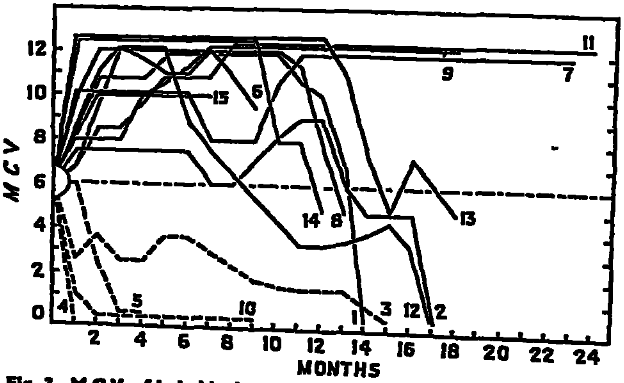

Fig 3—M C V of individual cases plotted on a single chart *continuous lines*, cases with ratio group I group II greater than 1 *interrupted lines*, cases with ratio less than 1

Fig 3 shows the result obtained when the M C V records for these 15 patients are plotted on a single chart It can be seen that, of these 15, 11 gave a fair to good response to either adrenalectomy or hypophysectomy, and that 4 showed no response at all and went straight downhill The graphs in fig 3 have been numbered to correspond with the case numbers in table II Comparison reveals that the 4 patients who did badly are those in whom the ratio was less than 1—i e , in these 4 patients the normal ratio of group-I group II 17-ketosteroids was reversed If all the M C V records of those patients with ratios greater than 1 are resolved to a single line, and the same done with those with ratios less than 1, the difference is more striking (fig 4) The charts of the fractional 17-ketosteroid excretion for these 4 patients are shown in detail in figs 5–8 It is, of course, impossible to say whether they had an excess of corticoid products in group II or less than normal androgenic products in group I

TABLE II—RATIO GROUP I TO GROUP II, AND TOTAL NEUTRAL 17-KETOSTEROIDS EXCRETED IN 72 HOURS

Case no	Ratio	Total 17 ketosteroids (mg per 72 hr)
1	1 2	6 2
2	1 4	24 0
3	0 9	12 3
4	0 9	9 2
5	0 9	22 0
6	1 6	13 2
7	3 0	10 6
8	2 6	14 0
9	1 7	31 0
10	0 4	46 0
11	3 7	10 2
12	3 4	28 0
13	1 9	12 0
14	1 2	10 9
15	3 0	23 7

Kellie (1955) found that, in a certain proportion of patients with neoplastic disease, there was a relative decrease in the excretion of 11-deoxy-17-ketosteroids and therefore a higher proportion of 17-ketosteroids with a carbonyl or hydroxyl group at C 11 Pincus et al (1955) found this to be a normal feature of ageing in healthy people The ages of the present 4 patients who showed a reversion of their excretion ratio of group-I (11-deoxy-17 ketosteroids) to group II (11 oxy 17-ketosteroids) were 47, 55, 55, and 53, hence it seems unlikely that ageing could have explained the finding We have no data on the ratio of group I group II in healthy women of these ages, but Pincus et al (1955) found that, even in women aged 70–79, the sum of the quantities of androsterone and etiocholanolone excreted in the urine exceeded that of the 11 oxygenated and 11 hydroxylated derivatives of these substances

Segaloff et al (1951) found that patients with mammary carcinomatosis who did not respond to treatment with testosterone propionate had an increased urinary excretion of glycogenic corticoids during treatment, whereas the patients who benefited from treatment had a decreased excretion of glycogenic corticoids They regarded this finding as of doubtful significance

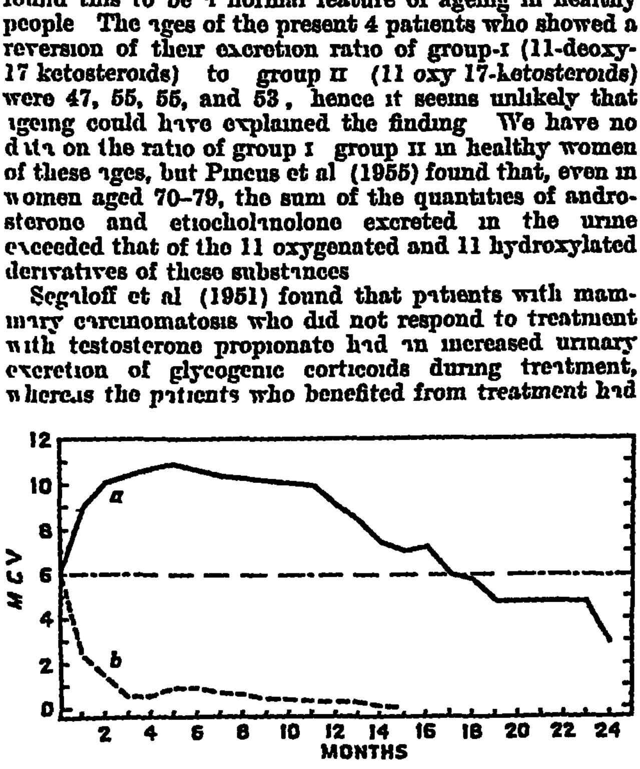

Fig 4—Resolution of M C.V into two lines a, ratio group I group II greater than I , b ratio less than I

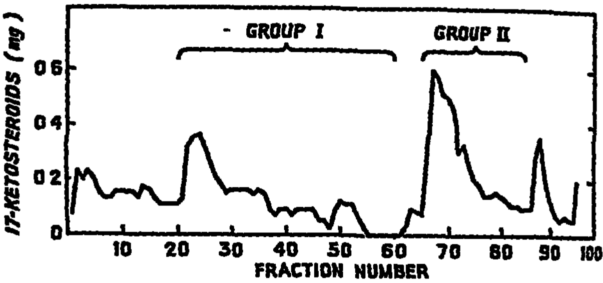

Fig 5—Case 3 preoperative excretion of 17 ketosteroid fractions (patient did not benefit from operation)

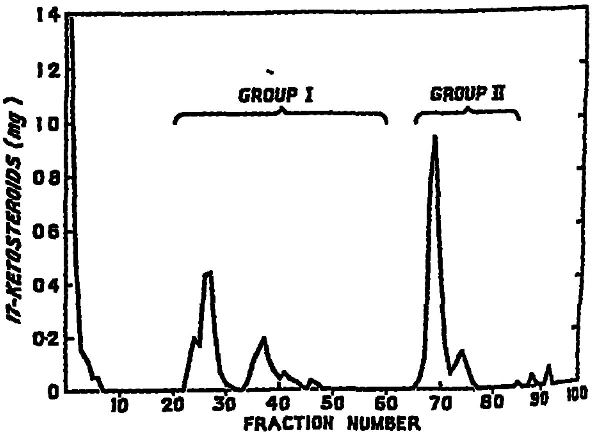

Fig 6—Case 4 : preoperative excretion of 17 ketosteroid fractions (patient did not benefit from operation)

Discussion

Treatment of advanced mammary carcinoma by altering the endocrine balance by various means is not new (Beatson 1896, De Courmelles 1922, Farrow and Woodard 1942, Haddow et al 1944) It was in 1941 that Huggins and Hodges described as "hormone dependent" those tumours of the prostate which responded to this type of treatment So long as treatment was by administration of sex hormones, the diagnosis of hormone dependency was a therapeutic one, but with the advent of major surgery (Huggins and Bergenstal 1952, Perrault 1952) it became desirable to foretell before operation which patients were likely to benefit Since then many attempts have been made to assess hormone dependency by various methods Emerson and Jessiman (1956) treated patients having bony metastases with provocative doses of stilbœstrol and measured the urinary calcium while the patients were on a constant dietary intake of calcium A rise in the urinary excretion of calcium indicated that the tumours were hormone dependent These workers further tested their patients by administering cortisone , and, if the urinary calcium fell and subjective symptomatic improvement occurred, they concluded again that the tumours were hormone dependent It seems to us that this method has the following disadvantages (1) it is only applicable to patients with bony metastases , and (2) the provocative doses of stilbœstrol may initiate a sudden deterioration in the patient's general condition which calls for immediate operation

We would like to have estimated the mammotrophic potency of our patients' urine (Hadfield 1956), but with the facilities at our disposal this was not possible

Huggins and Dao (1952) thought that the histological characteristics of the tumour might indicate the suscepti bility to endocrine treatment in certain cases, but this has not been the experience of one of us (J L H) in the present series Furthermore Wolff (1957) has failed to correlate preoperative mitotic cell counts with response to treatment

We do not suggest that our findings necessarily indicate hormone dependency in the tumours of the patients investigated, nor at this stage are we prepared to make any deductions from them about the relative proportions of the various adrenocortical steroids secreted (Dorfman 1954)

Not unexpectedly, in our studies of postoperative excretion of 17-ketosteroids, we found that in every case there was a complete reversal of excretion pattern compared with the normal steroids of group I were almost completely absent, whereas those of group II were much increased This presumably reflects the metabolism of the cortisone on which these patients were maintained a similar suggestion has been advanced by Strong et al (1956) An example is given in fig 9

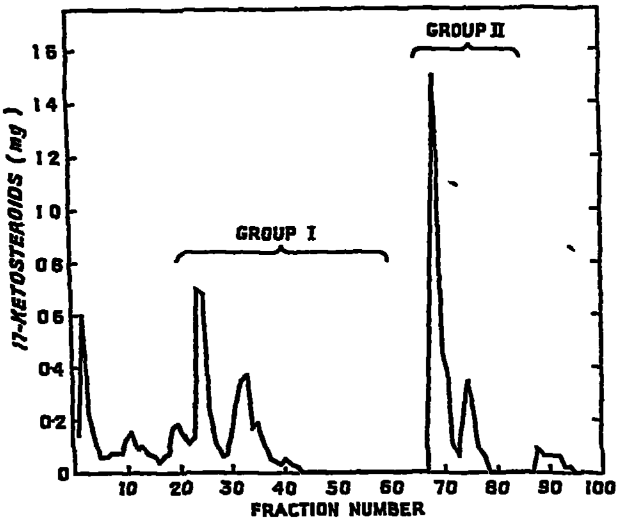

Fig 7—Case 5 preoperative excretion of 17-ketosteroid fractions (patient did not benefit from operation)

The similarity between this excretion pattern and that obtained preoperatively in the 4 patients in this series who did not respond to operation is striking From this it seems possible that the operation failed in these 4 cases because it did not alter decisively the internal hormonal environment, at least in as much as this is reflected in the results of fractional determination of 17-ketosteroids

The success or failure of an operation therefore may depend on its ability to produce a sudden change, with all its cellular metabolic consequences, in the hormonal environment of the tumour It is, however, common experience that operation merely defers the progress of the disease, and sooner or later all patients relapse It is therefore not impossible, in view of the similarity of the preoperative excretion of these 4 patients to that obtained after operation, that they had previously undergone a change in hormonal environment, from which they may or may not have benefited, and were at the time of coming to operation in the terminal stages of their disease.

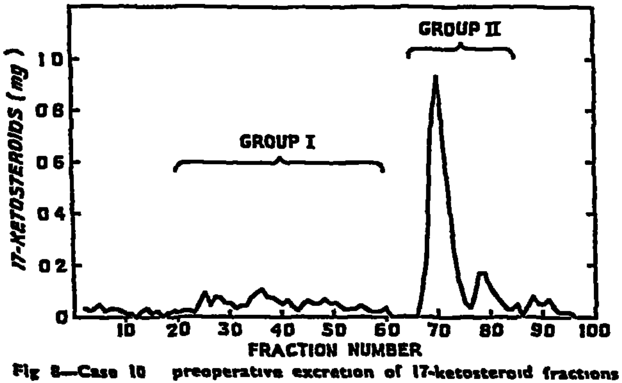

Fig 8—Case 10 preoperative excretion of 17-ketosteroid fractions (patient did not benefit from operation)

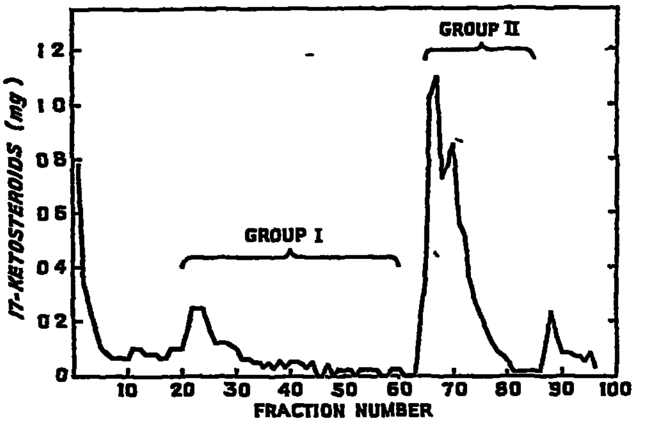

Fig 9—Excretion of 17 ketosteroid fractions a month after operation (patient maintained on cortisone 50 mg daily)

Summary

The excretion of the fractions of total neutral 17-ketosteroids in the urines of 15 patients with mammary carcinomatosis has been studied 11 patients benefited from either adrenalectomy or hypophysectomy, and 4 did not

The ratio of 11-deoxy-17-ketosteroids to 11-oxygenated or -hydroxylated-17-ketosteroids has been estimated in these patients

In those patients who benefited from operation the ratio was greater than 1 and the excretion pattern approximated to that found in healthy subjects In those who did not benefit the ratio was less than 1 and the excretion pattern closely resembled that found after operation

These results are discussed

We are grateful to Mr H J B Atkins, of the department of surgery, Guy's Hospital, Mr Murray Falconer, of the Guy's-Maudsley Neurosurgical Unit, and Dr K S MacLean, of the department of medicine, Guy's Hospital, for permission to study their patients, and Miss A M Norton for help with the technical work.

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ISOLATION OF VIRUSES RELATED TO ECHO VIRUS TYPE 9 FROM OUTBREAKS OF ASEPTIC MENINGITIS

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From the Virus Reference Laboratory, Colindale, London

BETWEEN September and December, 1955, material from patients in an outbreak of aseptic meningitis in East Suffolk (Garnett et al 1957) was received at the Virus Reference Laboratory, from Dr P H Martin of the Public Health Laboratory, Ipswich The material consisted of throat-washings, cerebrospinal fluid (C S F), fæces, and paired samples of serum

Virus Investigations

The C S F s, throat-washings (after centrifugation at low speed to remove gross debris), and bacteria free fæcal suspensions were inoculated into tissue culture tubes of HeLa cells and of monkey-kidney first-passage cells Three tubes of each cell type were used per specimen The inoculum consisted of 0 5 ml per tube of C S F , throat-washing, or 10% fæcal suspension, but in some instances 0 1 ml of a fivefold ultracentrifuge concentrate of fæcal suspension was used After preliminary incubation for one hour at 37°C the fluids were removed and replaced with fresh medium Cytopathogenic agents were readily isolated in monkey kidney but not in HeLa cells Details of the isolations are given in the accompanying table The newly isolated strains of virus were not neutralised by antiserum against the three types of poliomyelitis virus or against the Coxsackie viruses group A type 9 or group B types 1–5 inclusive

ISOLATIONS FROM EAST SUFFOLK MATERIAL

—	No	Last day post-onset, of a positive specimen	Virus isolated	No virus isolated
Patients	11		7	4
Fæces	11	10th	6	5
Gargles	10	3rd	4	6
C S F s	9	4th	5	4

Intraperitoneal inoculation into mice less than 24 hours old with first or second passage tissue culture-fluid suspensions of these strains resulted in varying degrees of paralysis amongst each litter, a proportion of the inoculated mice dying while others remained apparently unaffected Signs of infection in the mice were usually present four to five days after inoculation Histological examination of affected mice showed a generalised necrosis of varying severity in the skeletal muscles, the central nervous system and the visceral organs were unaffected The lesions suggested an infection by the Coxsackie A group of viruses

Serological Investigations

A number of sera showed in both neutralisation and complement fixation tests that there was no evidence of recent infection by the poliomyelitis viruses Tests by Dr P S Gardner for evidence of infection with the influenza A, B, and C viruses, the adenovirus group, mumps, psittacosis group viruses, lymphocytic chorio meningitis virus and *Rickettsia burneti* were negative, as were tests for leptospiral infection

All convalescent sera tested showed high neutralising antibody titres against one of the newly isolated strains of virus, and two patients had a greater than fourfold rise in neutralising antibody against their own strain of virus during the course of illness An antiserum prepared in a rhesus monkey against one of the strains of virus neutralised the homologous virus and also all the other strains isolated This antiserum subsequently has been found to neutralise virus strains isolated during 1956 from outbreaks of aseptic meningitis in Nottingham, Leicester, Sheffield, including the Haynes strain (Tyrrell and Snell 1956), Coventry, Hereford, South Middlesex, West Germany, and a strain obtained from Dr Rhodes, Hospital for Sick Children, Toronto, where it had been isolated from a child in the course of an outbreak of aseptic meningitis similar to that reported by Garnett et al (1957)

This antiserum also neutralised two strains of virus isolated at the Virus Reference Laboratory from the Bourn outbreak of aseptic meningitis (McLean and Melnick 1957), the prototype Hill strain of Echo virus type 9 received from Dr A B Sabin, and strains of virus isolated from babies during an outbreak of mild meningitis in East London in 1954 (Crawford et al 1956)

There have been two features of interest in the 1956 outbreaks from which these serologically related viruses were recovered (1) the presence of a rash noted in only a *proportion* of the patients who excreted virus; and (2) the effect of these viruses on newborn mice Even after one or two passages in tissue culture a number of strains failed to affect such mice, although others, including strains from the same outbreak, readily induced paralysis Further investigation of this phenomenon is in progress

Summary

Strains of virus, related to Echo virus type 9, have been recovered from cerebrospinal fluids, throat washings, and fæces of patients in a number of outbreaks of aseptic meningitis A proportion of these strains have been found to cause lesions of a Coxsackie group A character in newborn mice Rising or high titres of neutralising antibody against these viruses have been observed in the serum of patients, and tests with other possible ætiological agents have been negative

Acknowledgment is made to Dr J L Hamilton Paterson for histological reports, Dr A B Sabin and Dr D A J Tyrrell for strains of virus, Dr P H Martin and all those who submitted material for investigation, and Dr P S Gardner for the results of serological tests

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AN OUTBREAK OF
ASEPTIC MENINGITIS OF VIRUS ORIGIN
IN EAST SUFFOLK

D G GARNETT
M B Camb

A BURLINGHAM
M R C S

GENERAL PRACTITIONERS, LEISTON, SUFFOLK

D VAN ZWANENBERG
B M Oxfd, D P H, D C H

ASSISTANT PHYSICIAN, ST HELEN'S HOSPITAL IPSWICH

The Leiston Outbreak

A SYNDROME suggestive of meningeal irritation was first observed by one of us (D G. G) in two adjacent villages a mile to the south of Leiston, at the beginning of September, 1955 These early cases occurred among young adults, predominantly male, and were the most severe of the outbreak They presented three essential symptoms (1) very intense and intractable headache,

(2) equally intractable vomiting, and (3) fever The illness was marked by short duration and an early return to work Soon cases began to appear among children and became more varied in symptomatology and duration, and, generally speaking, milder The disease, which was unlike any in our experience, appeared to be neither poliomyelitis nor cerebrospinal fever, although in some ways resembling both

New cases appeared every other day, and after a fortnight the infection spread into Leiston, mainly on a new housing-estate, so that by the end of the month we had seen 80 cases In October further cases appeared in various parts of the town, and there was a small spread to a village 3 miles to the north Dr P M Acheson, of Aldeburgh (4 miles to the south), informed us that he had experienced at the time, or shortly before, cases similar in type, while Dr A L Forster, of Yoxford (6 miles north of Leiston), had 1 severe case which was found to be a definite contact of one of our early cases, and which he had admitted to hospital Information was also received that an outbreak comparable in character had occurred in Lowestoft (25 miles to the north) in August (Hughes 1955, Eastwood 1956)

Finally, the local infection died out at the beginning of November, by which time we had seen upwards of 130 cases from 90 houses (2 or more cases in 25 houses) from a population of 5500 The cases involved all ages up to 50, with 40% appearing in the primary school age (5–11)

Symptoms were of varying intensity, and after an incubation period of two to four days consisted of any or all of

(1) Fever lasting up to four days, usually 100–101°, sometimes 103°, and in one patient 105°F (a boy of 6)

(2) Frontal headache, always described as across the forehead or behind the eyes

(3) Nausea and vomiting, frequent at the onset and incessant for two or three days in severe cases

(4) Pain of the neck and shoulders in more than half the patients, demonstrated by inability to flex the head to the knees This ceased when patients became afebrile

(5) Flushed face, suffused eyes, and photophobia

(6) Oral fœtor and a white tongue

(7) Rash in over 25% of cases (all except 3 in children) This usually appeared on the third day and consisted of blotchy reddish purple or pink macules on the face with or without a mixed rubelliform eruption on the neck, trunk, and extremities, which faded without staining in two or three days Numerous petechiæ on the trunk were present in 1 case

(8) Relapse occurred in 7 cases (3 of which were in children), up to six days after the onset, and was often worse than the initial attack

Recovery was complete in every instance, usually in two to five days, without paralysis, lymphadenopathy, or other residual effect

On the advice and with the cooperation of Dr P H Martin, of the Ipswich Public Health Laboratory, serum, garglings, and fæces were sent to the Virus Reference Laboratory, Colindale, in the following two cases

A girl of 15 was the 2nd case in a family of 11 In this family 7 children were involved over a period of nine days She had a flushed face with fever, vomiting, and backache, and recovered in four days The specimens were taken on the second day and blood was also taken after ten days and three months

A woman of 24 had fever (101°F) and frontal headache for two days and on the third day felt better and went out shopping The following day her son, aged 6 years, was feverish with headache and backache That evening she had a return of headache and fever which was worse the next day when the specimens were taken Blood was also taken after ten days and three months

AGE-DISTRIBUTION OF CASES

Age group (yr)	0–4	5–11	12–18	19–29	30–39	40–49	51	Total
Male	10	30	12	8	9	4		73
Female	13	23	5	11	4	2	1	59

Cases Admitted to Hospital

Some of the most severe cases of this illness in the region were admitted to hospital in Ipswich At first these came from the Leiston area As the epidemic spread there were further cases from the areas between Leiston and Ipswich, and finally a small series of cases came from Bramford to the north-west of Ipswich

Of the 15 hospital cases 14 were admitted because of signs of meningeal irritation, the other patient developed a pneumonia following a particularly severe bout of vomiting

While the patients were in hospital the distinction from non-paralytic poliomyelitis and other virus meningitis was not always clear In comparison with equivalent cases of poliomyelitis, these patients complained of more severe headache, and considerably more vomiting, and they all had a characteristic white furred tongue Only 3 patients developed rashes while in hospital The rash appeared on the face and upper trunk, rather bluish red with ill-defined margins, macular, but in irregular "blotchy" patterns The rash lasted one or two days

A lumbar puncture was performed on 11 of the patients The abnormalities in the cerebrospinal fluid (C S F) varied slightly, depending on the day of illness The C S F s obtained early in the illness showed high cell-counts of the order of 200–1000 cells per c mm with polymorphs predominating, but fluids collected later in the illness, as in other types of virus meningitis, showed a considerable predominance of lymphocytes On the whole, cell counts were higher than one would expect to find in cases of non paralytic poliomyelitis of similar severity The total protein in the 11 cases was never found to exceed 60 mg per 100 ml, and in 6 out of the 11 it did not exceed 30 mg per 100 ml Headache and vomiting were considerably relieved by lumbar puncture All patients made a complete recovery without any specific treatment White cell counts were within normal limits and Paul-Bunnell tests were negative Specimens of fæces from 9, gargle from 8, C S F from 9, and sera only from 7 were sent to the Virus Reference Laboratory from 15 of these cases, and from a similar case that was admitted to the local general hospital

Strains of virus were isolated from the girl of 15 described above and from 7 of the hospital patients and, as described by Boissard et al (1957), they were all immunologically similar and were related to the Echo-9 type of enteric virus (Committee on Echo Viruses 1955)

Summary

An illness occurred in Suffolk in September, 1955, which we had not seen before The predominant signs and symptoms were fever, headache, nausea and vomiting, pain in neck and shoulders, flushed face, photophobia, and, in about 25% of the cases (mostly children), a macular rash, often rubelliform in type Recovery was usually rapid and always complete, without paralysis or other residual effects

A large number of cells were present in the spinal fluid of the patients admitted to hospital, these were predominantly polymorphonuclear leucocytes in the early stage, and lymphocytes later

Strains of virus immunologically related to the Echo-9 type of enteric virus were isolated from the cerebrospinal fluid of 5 patients, from the stools of 6, and from throat washings of 4

Dr. Robert Fells Library
S. M. S. Medical College

We wish to thank Dr J W Paulley for permission to include details of the case admitted under his care, Dr R Wilton and Dr I Staddon who sent some of these cases into hospital for investigation and subsequently collected further specimens for investigation, and Dr P H Martin, Public Health Laboratory, Ipswich, for laboratory examination of the cerebrospinal fluids

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MENINGITIS OF VIRUS ORIGIN

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IN July, 1956, the first examples of what appeared to be a new type of aseptic meningitis were admitted to the Leicester Isolation Hospital and Chest Unit This disease, apparently widespread all over England, was most prevalent in the Midlands Descriptions of a similar illness appeared under such titles as Trent valley fever, Nottingham meningitis (*Lancet* 1956), lymphocytic meningo encephalitis (Lyle 1956a), and seasonal aseptic meningitis (Karzon et al 1956) This paper gives a brief description of findings in the first 100 cases admitted to the Leicester Isolation Hospital between July 4 and Nov 23, 1956

Incidence

It is impossible to assess the number of cases in the population at large, because the disease is not notifiable and many cases were not admitted to hospital Of the 100 patients admitted to hospital, 58 were male and 42 female The age distribution is shown in table I, and the way in which the cases were divided between city and county, month by month, is set out in table II 4 cases involving hospital staff are included in the survey It will be noted that at the beginning of the epidemic there were more admissions from Leicester city than from the county

There was striking familial aggregation, as illustrated in table III

Usually, 1 or 2 members only of any one household were sent to hospital by the general practitioner, who, upon confirmation of the diagnosis, treated other members at home Some contacts had a mild illness only

Clinical Features

Dates of onset ran continuously, suggesting dissemination by contact rather than a common source Cases in any one household occurred at intervals of six to ten days

The onset was acute in 90 cases, and the hour of onset could often be obtained—e g, two lorry drivers were taken ill at the wheel, a policeman fainted on the beat and some school-children were taken ill in class 10 patients, however, gave a one to two weeks' history of insidious onset

TABLE I—AGE DISTRIBUTION

Age (years)					
1–5	6–10	11–20	21–30	31–40	41–55
13	31	14	23	14	5

TABLE II—MONTHLY DISTRIBUTION BETWEEN CITY AND COUNTY

—	July	August	Sept	Oct	Nov
City	14	18	8	10	3
County	7	3	9	23	5
Total	21	21	17	33	8

TABLE III—NUMBER OF CASES IN FAMILY

Number of cases per family	Number of families
1	71
2*	13
3*	8
4*	2
5*	1
Total	95

* Including some unconfirmed cases

Clinically the disease resembled the major illness of poliomyelitis without paralysis The presenting symptom was usually severe headache, as I had occasion to experience In children this was often preceded by vomiting Table IV gives further details There were no hallucinations, disorientation, unconsciousness, or abnormal neurological signs in any of the patients Pyrexia varied between 99°F and 105°F (average 102°F), lasting three to five days and subsiding by lysis in 90 cases

Illustrative Cases

(1) A man of 41 Admitted to hospital on Oct 11 On waking up on Oct 10 had rigors, frontal headache, which became worse, and frequent vomiting When neck rigidity developed he was transferred to hospital On Oct 10 his younger daughter had similar symptoms, was treated as flu, and improved after four days On admission 102·5°F pulse 84, respiration 26, alert and cooperative, no abnormality on physical examination except some neck rigidity Lumbar puncture 190 cells per c mm (78% lymphocytes), protein 60, chlorides 620, sugar 68 mg per 100 ml Blood Hb 96%, white cells 5300 per c mm (polymorphs 76%, lymphocytes 20%, monocytes 4%) Urine normal Afebrile after five days When seen on Nov 29 he was well, no further headaches and back to work for three weeks

TABLE IV—SYMPTOMS AND SIGNS

Symptom	No of cases
Pyrexia	100
Headache	100
Frontal and retro orbital	46
Others	54
Neck rigidity	96
Back stiffness	83
Vomiting	88
Maculopapular rash	16
Rigors	19
Photophobia	15
Drowsiness	8
Abdominal pains	8
Sore throat	4
Enlarged lymph glands	3
Constipation	Common

(2) A girl of 12 another daughter of previous patient Admitted on Oct 19 with twenty-four hours' history of headache, pyrexia, and vomiting Headache was bitemporal On admission 101°F, pulse 112 No abnormality on physical examination, except some neck rigidity Lumbar puncture 48 cells per c mm (85% lymphocytes), biochemistry normal Blood Hb 82%, white cells 6000 per c mm (polymorphs 73%, lymphocytes 27%) Urine normal Symptom free and afebrile from the sixth day onwards When seen on Dec 6 perfectly well

On Oct 25 her mother felt vaguely ill and sick and had a headache All this subsided after 2 days

In this family of 4 people, 2 had the typical condition and 2 must be assumed to have had a mild form only The intervals of onset were five days, eight days, and seven days respectively

Laboratory Findings

Routine diagnostic procedure in all cases included one or more lumbar punctures, full blood-count and film, and examination of urine Throat swabs were taken for culture, and specimens of cerebrospinal fluid (C S F)

TABLE V—HÆMATOLOGICAL FINDINGS

—	Findings	No of cases
Hb	Normal	100
White cells	Normal to slightly raised	77
	2900–4500	31
	10 000–13,000*	2
Average white count	5500	100
Neutrophils	70 % or more	100

* Superinfection with streptococci present if these 2 cases are excluded the average white count is 5380

fæces, blood, and throat washings were taken for complete virological studies

The blood findings are summarised in table V No toxic changes and no abnormal cells were seen in blood films

A Paul-Bunnell test in a number of cases was negative Throat swabs did not yield pathogenic organisms on culture, except for β hæmolytic streptococci (2), *Staphylococcus aureus* (1), *Streptococcus pneumoniæ* (1), and *Hæmophilus influenzæ* (1) Urine was normal in all cases

C S F pressure was often slightly raised and lumbar puncture sometimes improved headache No readings were taken from children The findings are given in tables VI and VII 3 patients with an initial C S F cell count exceeding 1000 per c mm showed a marked reduction in cell count three to four days later and in 3 others the initially only slightly raised count trebled C S F chlorides and sugar were within normal limits in all cases Bacteriological cultures of C S F were sterile

TABLE VI—ABNORMAL CEREBROSPINAL FLUIDS

—	No of cases	
Abnormal on admission	73	
Normal on admission	27	
Changes three to four days after admission		6
No change at second lumbar puncture		6
No second lumbar puncture performed		15
Total	100	27

Virological Studies

Throat washings, C.S.F., and fæces from all patients were cultured for virus Blood was taken in the acute and in the convalescent phase for serological tests Unfortunately, a second specimen of blood was not obtained from all patients

Virological studies on the first 30 cases were done at the Virus Reference Laboratory, Colindale, London From 22 of these cases a cytopathogenic agent was isolated in 19 cases from fæces, in 15 cases from C S F, and in 16 instances also from throat washings Furthermore in 1 case adenovirus (A P C group) was isolated, and in 1 case polio virus type I

A positive neutralisation test was obtained with the sera of 22 patients, using the virus isolated from one of them These viruses are similar to but not identical with Echo-9 virus (Boissard et al 1957) This virus belongs to a group recently isolated from the human intestinal tract during aseptic meningitis It has been proved distinct from poliomyelitis and Coxsackie virus (University of Buffalo 1956)

TABLE VII—CHANGES IN CEREBROSPINAL FLUID

—	No of cases	
Normal cell count	21	
Raised cell count	79	
5–100 cells per c mm		33
101–500		35
501–1000		6
1001–2593		5
		79
Lymphocytes below 35 %		3
Lymphocytes 50–100 %		76
		79
Proteins normal	59	
Raised proteins (all cases associated with pleocytosis)	41	
36–50 mg per 100 ml		20
51–100 mg		13*
101–150 mg		8
Average 66 3 mg (normal 10–35)		41

* In 1 patient proteins rose to 200 mg per 100 ml five days after admission

Complement fixation tests were negative for influenza A and B, psittacosis, lymphogranuloma venereum, Q fever, atypical pneumoniæ, lymphocytic choriomeningitis, and mumps, and positive in 1 case with normal C S F for adenovirus (A P C group)

Differential Diagnosis and Treatment

Differential diagnosis from non-paralytic poliomyelitis was difficult at the onset of the epidemic The virus meningitis is the less severe illness, with nuchal and spinal muscle spasm of shorter duration and more rapid recovery Familial aggregation is frequent, as opposed to its rarity in poliomyelitis Several cases sent to hospital as non-paralytic poliomyelitis were found to be meningitis of virus origin Some cases sent to hospital as virus meningitis proved to have a different condition—tonsillitis with meningism (5), meningococcal meningitis (1), cerebral abscess (1), neurosyphilis (2), tuberculous meningitis (2), paralytic poliomyelitis (3), cerebral thrombosis (1), and subarachnoid hæmorrhage (2) These points emphasise the importance of establishing the diagnosis by lumbar puncture in all cases presenting as meningitis

Apart from 2 patients initially suspected of having meningococcal meningitis who had a short course of penicillin, no specific treatment was given The common analgesics proved ineffective and had to be supplemented by pethidine Patients were kept in bed for seven to ten days and were advised upon discharge to rest for a further week

There was no mortality 89 patients were well when seen as outpatients six weeks after discharge, but most of them admitted to intermittent headache (especially after exertion) Recovery was slow and tiredness and mild depression were common There was no residual paresis, ataxia, or headache in children 10 patients complained spontaneously of frequent headache, and 1 patient had to be readmitted to hospital eight weeks after discharge for lumbar puncture, which proved normal

Discussion

The disease described here, which we call meningitis of virus origin (M V O), presents some distinctive clinical and pathological findings acute onset, pyrexia, and headache in all cases, signs of meningeal irritation and vomiting in most cases, rubelliform rash over face and upper extremities, sparing the trunk, and photophobia in some cases Incidence was highest in children and young adults On clinical evidence the present series appears homogenous, in spite of variations in C S F findings, in view of the incomplete virological studies, however, there is as yet no certainty of a common ætiological factor From 22 cases a virus akin to Echo virus type 9 was isolated, and from 1 case polio virus type I, but from 1 patient with normal C S F, adenovirus (A P C group) was isolated We do not know whether the normal C S F in this case was coincidental

The first isolated instances of an aseptic meningitis similar to the one described here were noted in 1955, and recently accounts appeared under various names in Britain and America The cases described in this paper differ from those described earlier—e g, in Nottingham meningitis (*Lancet* 1956), vertigo, and nystagmus were reported to be frequent and vomiting rare There were no rash and no prostration, and the maximum C S F cell count was 20 lymphocytes per c mm Dodd's (1956) clinical and laboratory findings, however, vary from ours in detail only Hesling (1956), on the other hand, reported severe lymphocytic leucocytosis, and an erythemato papular rash, mainly over trunk and face, in his 2 cases

The 125 cases of lymphocytic meningo encephalitis reported by Lyle (1956b) were similar to our cases, in particular in C S F findings 48 of his patients, however, had acute and severe myalagia, and though only 24 had much neck stiffness, 68 had neurological abnormalities not encountered in our series Some of Lyle's cases also had hepatitis or abnormal liver function tests The disease as seen by us did *not* usually conform to McAlpine's (1947) criteria of encephalitis (nystagmus, photophobia, and neck stiffness after fever and headache), as did the cases described by Lyle

Our series bears most resemblance to 24 cases described by Karzon et al (1956) in the U S A, which was called "seasonal aseptic meningitis" The causal agent isolated from Karzon's patients was Echo virus strain 6 Onset in July, household aggregation, and age incidence were all similar to those observed here The preponderance of males and the short duration of the epidemic described by Karzon might be accounted for by the localised outbreak in a closed community

There is little similarity between the condition described here and the outbreak at the Royal Free Hospital in 1955

Summary and Conclusions

100 patients suffering from an aseptic meningitis were admitted to the Leicester Isolation Hospital between July 4 and Nov 23, 1956 The main clinical features of the disease were acute onset, headache, pyrexia, vomiting, neck and back rigidity, and occasionally a rubelliform rash and photophobia A predominantly lymphocytic pleocytosis was found in the C S F of most patients Adenopathy was not a feature of the disease All patients recovered without specific treatment, and with no serious sequelæ A cytopathogenic virus related to Echo virus type 9 was isolated from fæces, C S F, and throat swabs in several cases It is concluded that this essentially benign disease is probably not identical with Lyle's lymphocytic meningo-encephalitis, but shows clinical similarity with cases described by Karzon and by Dodd

ADDENDUM

Since the present survey was concluded, more cases of N V O, some of increased severity, have been admitted to this hospital Monthly incidence is on the decline

I wish to thank Dr J C H Mackenzie, consultant and physician superintendent, for permission to publish this paper and for his helpful criticism, Dr N S Mair and Dr H J Mair for help and advice on virology and Dr J P Anderson and Dr J R Barton for the use of some of their case notes

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"Would any one of us, taken with a grievous illness far from home, care to be nursed by a keen diagnostician, an amateur microscopist or an earnest student of pathology? What we want is a nurse who loves nursing, and the sicker we are the more we long for someone who can combine wife, sister and mother rather than an efficient technician, however well intentioned Knowledge of sick people is gained by being with sick people and though this knowledge once acquired can be greatly enhanced by book learning, that learning itself can not be a substitute for the bedside experience The fine arts of nursing are only unimposing to those who have never themselves been gravely ill"—Dr JOHN [illegible] and Dr HUMPHRY OSMOND, *Canad med Ass J* 1956 752, 75

METABOLIC EFFECTS OF CARBUTAMIDE IN SELECTED DIABETICS

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THE mechanism whereby certain sulphonamides exert a hypoglycæmic and (in certain diabetics) an anti diabetic effect remains a matter of debate

The following explanations have been suggested inhibition *or destruction of glucagon secreting α cells* (Franke and Fuchs 1955, Mellinghoff 1955, Von Holt et al 1955, Ferner and Runge 1956), insulin sparing action (Kinsell *et al* 1956, Mohnicke 1956), inhibition of insulinase (Mirsky 1956, Mirsky et al 1956), increased production of insulin (Gepts et al 1955, 1956, Loubatières 1955, Ashworth and Haist 1956), *depression of gluconeogenesis by a direct effect on the* pituitary gland and the adrenal cortex, and increased permeability of the cells to glucose, possibly due to release of an inhibitor of hexokinase (Best 1956)

Although none of these hypotheses has been proved, in-vitro experiments have shown that hypoglycæmic drugs reduce the activity of certain enzyme systems in the liver (Clarke et al 1956, Hawkins et al 1956, Mohnicke and Knitsch 1956)

Many diabetics have already been treated with oral sulphonamide, but the results show that sulphonamide is no substitute for insulin and is only effective in "those subjects who possess a source of appreciable amounts of endogenous insulin" (*Wrenshall and Best 1956*)

Only a few clinical studies concerned with metabolic investigations have been published We report here *such studies made on diabetics treated with carbutamide* ('B Z 55')

Material

18 patients were kept in hospital for a few weeks on a 1500-calorie diet (carbohydrates 180 g, fats 50 g, and proteins 60 g) Afterwards they were under ambulatory control with a slightly more liberal diet Gross over weight was reduced before the start of treatment During the treatment the patients maintained their weight After 1–3 months' treatment the patients were readmitted for control metabolic studies

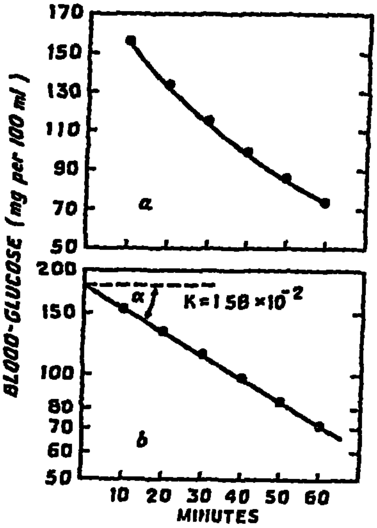

Fig 1—Intravenous glucose-tolerance curve in healthy people *a*, mean of observed values *b*, semilogarithmic line derived from *a*

16 of these patients, aged 42–82 had diabetes of the middle age onset type, they had or

had had some obesity but never acidosis, and their diabetes never needed much insulin treatment

Of the other 2 patients case 16 had had diabetes for twenty years, and occasionally ketosis had needed high-dosage insulin therapy, and case 18, aged 26, had mild recently discovered diabetes together with signs of adrenocortical hyperactivity (hirsuties, decreased menstruation, and increased urinary excretion of 17-ketosteroids)

Treatment

After an initial period of observation uniform treatment was given with carbutamide 4 g on the first day, 2 g on the second, and 1 g daily thereafter Occasionally, during protracted treatment, the dosage was reduced to 0·5 g daily

Methods

Glycosuria and glycæmia were frequently tested for by the Somogyi/Schaffer-Hartmann technique

Before any treatment, between the 6th and the 10th days of treatment and after 1, 2, or 3 months the following studies were made

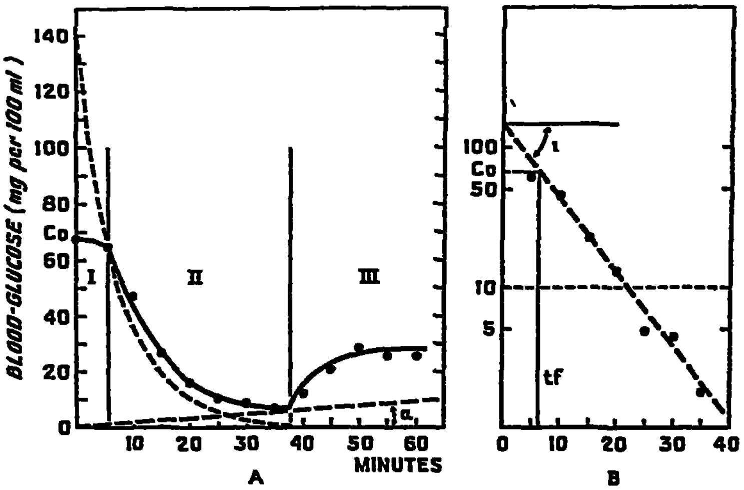

Fig 3—A, hypoglycæmic curve in healthy person after intravenous injection of insulin 0·1 u per kg of body-weight, I, first period, probably corresponding to fixation of insulin in tissues (tf), II, second period, corresponding to progressive lowering of blood-glucose level (Co) (exponential curve), III, third period, characterised by secondary rebound II corresponds either to exponential formula without residue or (as here) to exponential formula, with residue (a) Mathematical analysis yields this factor a corresponding to persisting output of glucose by liver (Franckson 1957)

B, after deduction of a logarithmic values of hypoglycæmic curve fall on straight line whose slope is indicated by t

(1) *Intravenous-glucose-tolerance Test*—It has been shown in this laboratory that, 10–60 minutes after a rapid intravenous infusion of glucose 0·33 g per kg of body-weight in a 50% solution, the rate of clearance of glucose from the blood is related to its uptake by the tissues Mathematical analysis of the blood glucose curve yields a glucose assimilation coefficient (Conard et al. 1953) (fig 1) In healthy people this factor is related to age and nutrition but is constant for any given person Its value ranges from 1·1 to 2·8, the mean figure calculated in 73 people being 1·8 ± 0·3 In diabetes it lies between 0·1 and 0·9 mean value 0·5 ± 0·2 (Conard 1955) (fig 2)

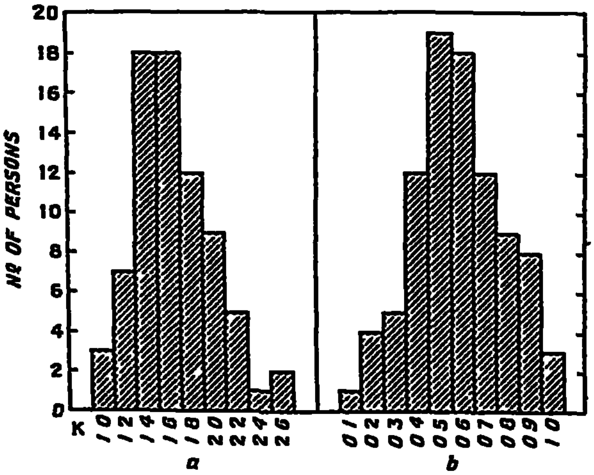

Fig 2—Distribution curve of glucose-assimilation coefficient (K) a, in 75 healthy people b, in 92 diabetics (Conard 1955)

(2) *Combined Intravenous Glucose and Insulin Test*—In this test, the same procedure is used with crystalline insulin 0·1 u per kg of body-weight added to the intravenous glucose The increase in the glucose assimilation coefficient is directly related to the activity of the injected insulin (Conard 1955)

(3) *Intravenous Insulin Test*—The intravenous injection of crystalline insulin 0·1 u per kg of body-weight induces a hypoglycæmic curve which, between the 5th and the 30th minutes after the injection, follows an exponential law From these curves Franckson (1957) calculated two factors one (i) corresponds to the actual hypoglycæmic effect of the hormone, the other (a) expresses the output of glucose by the liver (fig 3) In healthy people factor a is very small (0·0–0·5), indicating that, during insulin induced hypoglycæmia, the liver's output of sugar is very small

(4) *Blood-cholesterol and Total Lipids*—These were estimated in some of the patients—by the method of Schoenheimer and Sperry for cholesterol and Bloor's method for the total amount of fat in the blood

(5) *Plasma proteins* were estimated by Van Slyke's method and separated by electrophoresis on Whatman paper no 1.

Results

In all the cases the diabetic condition definitely improved, judged by the decrease of glycosuria, the fasting blood-sugar level, and the maintenance of body-weight For 18 cases the mean fasting blood-glucose level was 178 mg per 100 ml before treatment and

TABLE I—EFFECT OF CARBUTAMIDE ON FASTING BLOOD-GLUCOSE LEVEL, MEAN VALUES OF GLUCOSE ASSIMILATION COEFFICIENT, AND INSULIN ACTIVITY

Case no	Mean fasting blood-glucose levels (mg per 100 ml)		Glucose assimilation coefficient					
			Intravenous glucose test			Combined intravenous glucose and insulin test		
	Before therapy	During therapy	Before therapy	After treatment		Before therapy	After treatment	
				6–8 days	1–3 mos		6–8 days	1–3 mos
1	150	80	0·8	1·9	0·6	3·4	3·4	3·7
2	225	125	0·6	0·9	0·7	1·0	2·2	2·3
3	215	160	0·4	1·0		0·6	1·6	
4	130	120	1·2	0·3	1·0	2·4	0·9	1·9
5	150	80	0·4	0·5	0·5	2·1	3·2	2·1
6	115	75	0·6	0·6	0·7	1·5	1·3	
7	180	100	0·2	0·4	0·4	1·6		
8	200	90	0·7	0·9	0·7			
9	130	90	0·6		0·7	2·5		
10	170	90	0·4	0·2	0·4			
11	230	150	0·6	0·4	0·6	2·0	2·0	
12	180	150	0·5	0·5				
13	122	83	0·5	0·7		1·8	4·3	
14	228	138	0·5	0·5		3·0	1·4	
15	125	60	0·9	1·9				
16	275	125	1·3	1·5		2·1		
17	170	70	0·4	0·6		2·5		
18	150	75	0·8	0·8	0·8	3·5	3·1	3·5
Mean value	175	103	0·6	0·8	0·7	2·1	2·4	2·7
Standard deviation	(46)	(31)	(0·3)	(0·5)	(0·2)	(0·5)	(1·1)	(0·8)

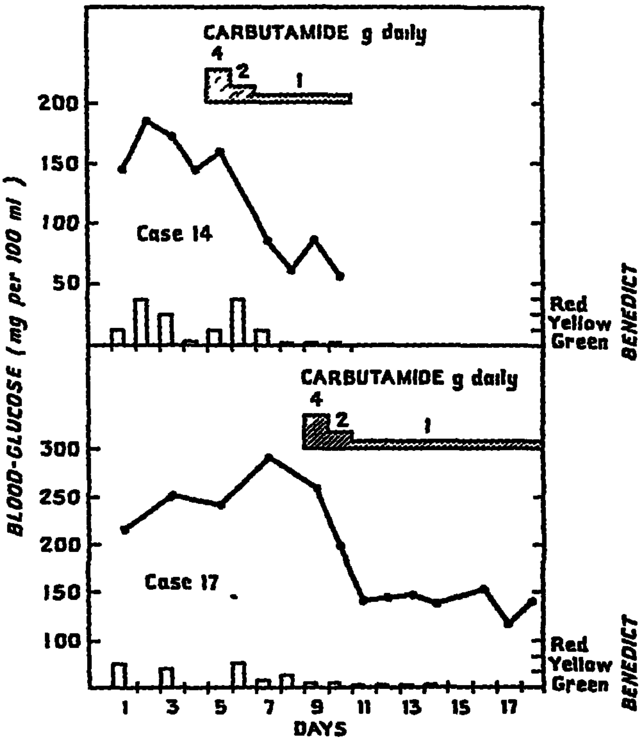

Fig 4—Effects of sulphonamide therapy on glycæmia and glycosuria.

103 mg per 100 ml during treatment (table I) In case 16 the treatment was discontinued and insulin had to be given because of a surgical operation Fig 4 illustrates data from cases 14 and 17

There was no change in the glucose-assimilation coefficient (table I) except a transient improvement during initial treatment in cases 1, 3, and 15 The mean values before treatment, after the first week of treatment, and after prolonged therapy were respectively 0 6, 0 8, and 0 7

The result of the combined intravenous glucose-insulin test was not altered 2 1 before treatment, 2 4 after initial treatment, and 2 7 after protracted treatment

The insulin tolerance tests showed important changes during treatment the hypoglycæmic curves were definitely lower than before sulphonamide treatment Fig 5 shows the mean curves before and after initial treatment

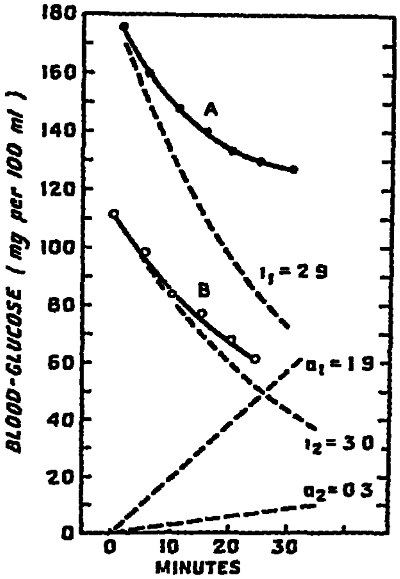

Fig 5—Mean blood-sugar levels A before treatment, B after a week's treatment. Analysis of curves shows factor i unchanged High value of factor a before treatment was much lower after treatment.

Analysis of the individual curves (table II) indicated that, during pretreatment observation, the insulin activity (i = 3 3) was hampered by a large output of glucose by the liver (a = 0 8–3 5, mean 1 5) During treatment the hypoglycæmic insulin effect remained unchanged (3 4 after initial treatment, and 3 5 after prolonged treatment) On the other hand, the output of glucose by the liver decreased considerably (a = 0 after 1 week, and 0 02 after 1–3 months' therapy) Th decrease was constant in all the cases studied In cas 6 and 10 arrest of treatment was followed by a return of factor *a* to its initial value

Discussion

In sulphonamide treated diabetics several workers have not found any sign of improved utilisation of glucose, either by studying postprandial blood glucose levels (Wolff et al 1956), tolerance of oral glucose (Duncan et al 1956), or differences in blood glucose levels between arterial and venous blood (Hunt et al 1956, McKenzie et al 1956)

One of the fundamental characteristics of the diabetic *state is the inability of the tissues to remove blood* glucose at a normal rate (Bastenie 1956) This abnormality is shown by a decrease of the glucose assimilation coefficient The hypoglycæmic sulphonamides do not correct this Duncan (1956) and Duncan et al (1956), using a similar technique, obtained similar results Therefore it can be concluded that, in diabetics, hypoglycæmic sulphonamides do not act by increasing the *output of insulin or by either sparing or boosting* the activity of pre-existent insulin Only in 3 cases was such an effect detectable during initial treatment The transient improvement in the uptake of glucose is probably explained by a stimulation of the β cells, such as has been observed in acute experimental studies by *Loubatieres (1955) and Gepts et al (1956)*

TABLE II—EFFECT OF TREATMENT ON INSULIN SENSITIVITY IN 17 DIABETICS

Case no	Factor i (hypoglycæmic effect)			Factor a (hepatic glucose output)		
	A	B	C	A	B	C
1	4 5	3 8	2 1	1 5	0	0 2
2	3 2	2 3	4 5	2 0	0 7	0
3	2 0	2 2		1 5	0	
4	1 9	3 4	2 3	1 0	0	0
5	4 3	4 7	3 5	1 2	0	0
6	3 3	3 9	1 2*	1 0	0	0 4*
7	2 4	4 0	1 8	2 2	0	0
8	2 6	2 4		1 5	0 5	
9	4 9	4 6	3 2	0 8	0 7	0
10	2 8	3 3	3 9*	1 2	0	1 0*
11	1 0	2 0	4 3	1 0	0	0
12	2 4	2 6		1 5	0	
13	7 5	4 6		1 6	0	
14	2 6	3 3		3 5	0 9	
16	3 4	3 0		3 0	1 5	
17	3 5	7 2		0 4	0	
18	4 2	10 0	6 3	0 4	0	0
Mean value Standard deviation	3 3 (1 5)	3 4 (2 1)	3 5 (1 6)	1 5 (0 8)	0 25 (0 4)	0 0* (0 0)

A before treatment
B after initial treatment (5–8 days)
C after protracted treatment (1–3 mos)
*Treatment stopped before test values discarded from statistical analysis

The hypoglycæmic effect of insulin (judged by the combined glucose-insulin test or by the value of factor i calculated from the intravenous insulin test curves) also remained unchanged These observations again seem to rule out a true insulin sparing effect of the sulphonamide

The most interesting observation concerns the considerable constant progressive decrease in the value of factor *a*

According to Soskin and Levine (1946) a very important characteristic of the diabetic state is the absence of the normal control of gluconeogenesis in the liver As is shown in the present investigation and confirmed in more extensive studies by Franckson (1957), during insulin induced hypoglycæmia diabetics do not usually show the depression of the hepatic glucose output observed in healthy people The correction of the

TABLE III—TOTAL NEUTRAL FATS AND CHOLESTEROL IN SERUM OF 7 DIABETICS TREATED WITH CARBUTAMIDE

Case no	Neutral fats (mg per 100 ml)		Total cholesterol (mg per 100 ml)	
	A	B	A	B
2	1150	1025	374	245
3	980	850	317	231
5		1020	267	300
6	1024	760	196	213
7	1050	950	254	280
11			323	222
18		1150	242	236

A before therapy B, after therapy

abnormality by the hypoglycæmic sulphonamide may be responsible for the lowering of the fasting blood-glucose level This effect is best explained by the finding that hypoglycæmic sulphonamides inhibit the action of glucose 6-phosphatase (Hawkins et al 1956) If this explanation be the true one, it means that sulphonamide treatment corrects only the end-stage of the diabetic process (i e, the abnormal output of glucose by the liver) and not the diabetes

In the absence of increased production or activity of insulin the gain in weight observed in sulphonamide-treated diabetics on a free diet cannot be explained by increased lipogenesis from enhanced assimilation of glucose Decrease of glycosuria can only partly explain this gain in weight Increase in the amount of pyruvic acid in the blood (Steigerwald et al 1956) may point to re-utilisation in the liver of the newly formed and unexcreted glucose More observations are needed before we can conclude, from the return of the raised blood-cholesterol level to normal (Bohle et al. 1956), that the mobilisation of lipids from the liver is decreased by sulphonamide treatment

The blood-protein pattern, studied before treatment in 8 cases, showed, compared to the values observed in healthy people, a decrease in the percentage of albumin and a slight increase in β and γ globulins Prolonged treatment did not much change the abnormalities, but the possibility exists that, in 3 cases, a low value of the percentage of the albumin fraction was partly corrected by the therapy If this observation is substantiated by further studies, it points to reduced breakdown of protein and resynthesis of albumin in the liver from unexcreted glucose

Summary

18 diabetics (all except 2 being of the obese-aged type) were given carbutamide therapy partly under well-controlled conditions Intravenous glucose-tolerance tests, intravenous insulin tests, and combined intravenous glucose and insulin tests were made before treatment, after initial treatment, and after protracted treatment, and the levels of total lipids, cholesterol, and proteins in the serum were studied

The results show that sulphonamide treatment induces no increased uptake of glucose by the tissues Therefore the improvement of the diabetes cannot be ascribed to an increase of either secretion or activity of insulin

The activity of exogenous insulin remains unchanged Hence it may be concluded that no insulin sparing action is demonstrable

During insulin-induced hypoglycæmia the maintenance of a large output of glucose by the liver is characteristic of diabetes This abnormality is corrected by sulphonamide treatment

The action of carbutamide in diabetes is probably best explained by the discovery of Hawkins et al (1956) that sulphonamides inhibit hepatic glucose 6-phosphatase

Studies on the levels of cholesterol and proteins in the serum are too limited to permit conclusions However, some observations seem to be in keeping with the idea that the unexcreted glucose may be re-utilised in the liver for the synthesis of albumin, and that less protein and less fat are katabolised

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ACUTE SPONTANEOUS MEDIASTINAL EMPHYSEMA

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THE term "acute spontaneous mediastinal emphysema" was first used by Hamman (1937), but Laennec (1827) described it under the name of "interlobular emphysema" Thanks largely to the experimental work of the Macklins (1944) its ætiology is now better understood The condition, however, remains uncommon and is still imperfectly described in many textbooks

Ætiology

PORTALS OF ENTRY OF AIR

There are five possible portals of entry of air into the mediastinum

(I) *Through Ruptured Marginal Alveoli*—The Macklins (1944) have shown both experimentally and by clinical correlation that, if a pressure gradient exists between the alveoli whose bases rest against bronchi, bronchioles, blood-vessels, connective tissue septa, and pleura (the so called "marginal" alveoli) and the structures against which they lie, rupture may take place, letting air into the underlying connective tissue, creating pulmonary interstitial emphysema If the escape of air is considerable it will dissect the tissues along the pulmonary blood vessels to the mediastinum If this process continues air accumulates in the mediastinum under ever increasing tension, interferes with the circulation by compression of the great vessels, and embarrasses the heart This tension is relieved by the escape of air into the neck, axilla retroperitoneal tissues, or one or both pleural cavities The conditions which predispose to pulmonary interstitial air were classified by the Macklins (1944) into three groups (*a*) those in which there is first an atelectasis of some part of the lung, followed by overinflation in adjoining regions in the same lung or the opposite lung, (*b*) those in which there is a decreased blood supply to the pulmonary vessels with lowered vascular pressure, often associated with increased intra alveolar pressure or overinflation, and (c) those in which there is a general overinflation of alveoli with or without increased intra-alveolar pressure

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(2) *Through Mucosa of Upper Respiratory Tract*.—The mucosa may be injured as a complication of endotracheal anæsthesia (Barrett and Thomas 1944, Jones 1945), trauma, or tracheostomy (Champneys 1884)

(3) *Through apical pleura* as a result of surgery or of accidental trauma (Bowden and Schweizer 1950)

(4) *Along the carotid sheath or the fascial planes of neck* as a complication of block dissection of the neck (Aiken and Smith 1953) or other neck surgery (Bowden and Schweizer 1950)

(5) *From pneumothorax*, which may be spontaneous, traumatic, or artificial (Macklin and Macklin 1944, Davidson 1951)

CLINICAL CAUSES

The following list includes all the conditions (traumatic and non-traumatic) in which mediastinal emphysema has been found or the known predisposing factors may be present (Macklin and Macklin 1944, Aisner and Franco 1949) infectious diseases (infections of upper respiratory tract, measles, tuberculosis, pertussis, pneumonia, influenza, diphtheria, smallpox, &c), space occupying lesions of the lungs or the mediastinum, inhaled foreign bodies, atelectasis in the newborn (due to prematurity or following the inhalation of meconium, mucous secretions, &c , before or after birth), bronchiectasis, bronchial asthma, chronic bronchitis and emphysema, parturition, violent coughing, violent exercise, acts of straining, acute obstructive laryngitis (diphtheria, streptococcal infection) playing of wind instruments, glass-blowing, &c , endotracheal anæsthesia, resuscitation by intratracheal insufflation or with a respirator, positive-pressure inhalation therapy, silicosis, pneumothorax, tracheotomy, cervical surgery, pulmonary infarction, lung blast, caisson disease, hiccup, and trauma to neck or chest

Clinical Features

SYMPTOMS

The severity and nature of the symptoms depends on the degree of distension of the tissues and on the location and accessibility of the escape channels In severe cases the lung, as a consequence of interstitial emphysema, may become extremely voluminous and rigid, causing orthopnœa and dyspnœa

The commonest and most important presenting symptom is pain in the chest (Scott 1937, Miller 1945, Fagin and Schwab 1946, McCabe 1947), which is often mistaken for angina pectoris or for myocardial infarction The onset is usually but not always sudden It is not usually related to respiration but may be worsened by coughing Its location is variable, the commonest sites being precordial or substernal, but it may be felt almost anywhere in the chest It may radiate to neck, shoulders, arms and back The intensity varies from very mild discomfort to severe agonising pain, which may be transient or last several days and usually disappears gradually

Other symptoms include palpitation, sweating, dysphagia, a feeling of fullness in the neck, anxiety, and crackling in the tissues If the air has passed retroperitoneally, there may be pain in the back, if it has passed into the abdomen, there may be abdominal pain

SIGNS

There may be very few physical signs in a mild case, and it seems likely that for this reason, many cases of this type are not diagnosed However, the combination of mediastinal crepitation, decrease or obliteration of cardiac dullness, subcutaneous emphysema, and pneumothorax is pathognomonic

Air in the mediastinum produces sounds that have been described in many different ways (Fagin and Schwab 1946, Aisner and Franco 1949), the commonest terms being "crackling," "clicking" "bubbling," and "crunching" The sounds are usually most easily detected with the patient in the left lateral recumbent position and during the expiratory phase of respiration They can be so faint as to be mistaken for a pericardial friction rub and have been shown to be related to the cardiac cycle (Hoffman et al 1943, Fagin and Schwab 1946) The crunching sound synchronous with systole was originally described by Hamman (1937), is usually known as Hamman's sign, and is regarded as pathognomonic of air round the pericardial sac

Pneumothorax with mediastinal emphysema is nearly always left sided No adequate explanation has ever been offered for this It is present in about 60% of cases

The subcutaneous emphysema is usually in the neck, the supraclavicular and infraclavicular fossæ, and the axillæ Occasionally it may be found elsewhere (Adcock 1943)—in the back, the abdomen, and even the extremities—but this is rare

The temperature and blood-pressure are usually unaffected, unless a cardiac tamponade effect occurs as a result of mediastinal obstruction, in which case the blood-pressure falls considerably This is a sign of grave prognostic significance and indicates that steps should be taken to relieve mediastinal tension

The respirations may be increased, particularly in the presence of pneumothorax, but the tachypnœa is usually mild

The X-ray appearances are typical of those of air in the tissues Air-streaks along fascial planes and pockets of air in the subcutaneous tissues are usually readily detected It is most important to have lateral radiographs of the chest because small pockets of air either behind or in front of the heart may be otherwise missed

There are usually no gross electrocardiographic changes It is said that 25% of cases show positive findings (Aisner and Franco 1949), but no characteristic pattern is present The usual abnormalities that have been described are changes in the T waves, deviation of the ST segments from the iso-electric line, and reduced voltage (Hamman 1939, Miller 1945, Fagin and Schwab 1946, Littman 1946), but pneumothorax per se may produce similar changes (Master et al 1937, Bourne 1940)

Different Diagnosis

All other causes of either acute or subacute pain in the chest have to be excluded angina pectoris, pericarditis, myocardial infarction, pulmonary embolism mediastinitis, dissecting aneurysm of the aorta, pleurisy, intercostal myalgia, &c

The chief difficulties are that the pain is very similar to that of primary cardiac disease, dyspnœa, cyanosis, and distension of the neck veins may be present, and the electrocardiographic changes may simulate an infarct (Hamman 1934, Scott 1937, Miller 1945, McCabe 1947)

However, the diagnosis is usually simplified by the following facts

(1) Mediastinal emphysema commonly occurs in a younger age group

(2) There is no severe shock, fever, tachycardia, hypertension, leucocytosis, or raised erythrocyte sedimentation rate

(3) In most cases some or all of the typical signs of mediastinal emphysema already described are present

Treatment

This is usually only symptomatic, the air being quickly absorbed from the tissues However, in those cases in which increased mediastinal pressure is causing extreme respiratory or cardiac embarrassment the following methods have been suggested

Waring (1944) advised the use of a high pressure chamber to reduce the volume of air in the mediastinum

Cliff (1955) suggested multiple incisions into tissues

When a pneumothorax is present needle aspiration of the thorax has been advised by Gumbiner and Cutler (1941) and Heald and Wilder (1949)

When a tension pneumothorax is present, thoracotomy with continuous underwater drain may prove life saving (Aisner and Franco 1949, Borne et al 1955)

If incision into the tissues is contemplated, the suprasternal notch is the site of choice (Gaudrault and Chalmers 1941, Aisner and Franco 1949) Karns and Daue (1948) recommend mediastinotomy in severe cases Needle aspiration of subcutaneous emphysema has also produced symptomatic relief

Chemotherapy is recommended in all cases, to prevent or treat respiratory infections (Schwartz et al. 1946)

Course and Complications

Mediastinal emphysema is usually benign but may become malignant under the following conditions

(1) When local compression of the blood vessels or of the heart interferes with the circulation

(2) When massed air-bubbles in the pulmonic interstitial tissues splint the lungs in inspiration, making further respiration progressively difficult or impossible

(3) When the pressure in the mediastinum rises too high owing either to blocking of the usual escape routes into the neck and retroperitoneum or to a massive escape of air into the mediastinum

(4) When air escaping into both pleural cavities causes bilateral pneumothorax

(5) When there is serious inflammation in the lungs

(6) When cough or other factors create a tension pneumothorax

(7) When the condition is a sequel to atelectasis of the newborn

Case-reports

Case 1—A boy, aged 4 years, started measles four days before admission For the first two days after the appearance of the rash he was not in any way distressed Then cough with increasing breathlessness developed, the dyspnœa becoming much more acute on the day of admission There was no history of previous illness and no complaint of chest pain.

On examination he was breathless, ill, and slightly cyanosed, with temperature 100 8°F, respirations 60 a minute, and gross surgical emphysema all over his chest and extending into both sides of his neck and face Moist râles were heard on both sides of his chest No clinical evidence of pneumothorax Radiography of his chest showed gross surgical emphysema of his chest wall, mediastinum, and both axillæ (fig 1), consolidation in middle zone of left lung, no pneumothorax Hb 77%

Treatment and Progress—Nursed in an oxygen tent and treated with sedation and full doses of tetracycline the boy steadily improved over the next week, the surgical emphysema becoming absorbed in four days, and subsequent recovery being uneventful

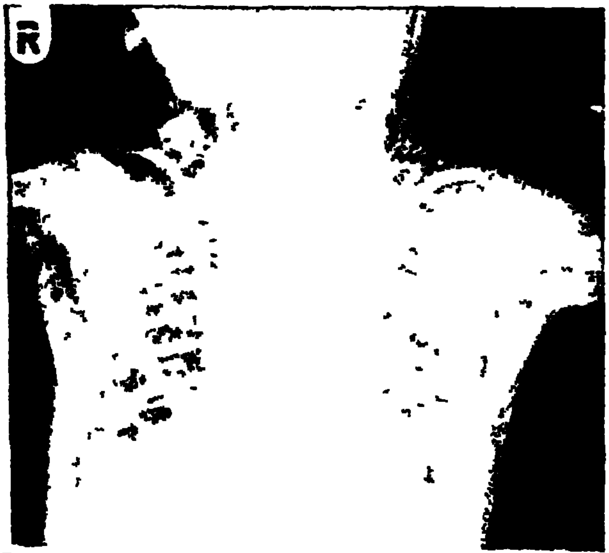

Fig 1—Case 1 gross emphysema of superior mediastinum neck and both axillæ

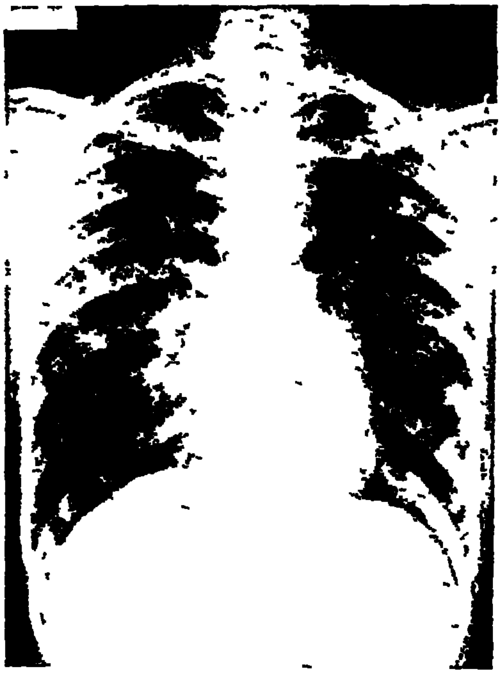

Fig 2—Case 2 air in fascial planes of neck, mediastinum, and axillæ Note characteristic air-streaks in superior mediastinum

Comment—This case would fit well into the Macklins' (1944) group *a* atelectasis due to bronchopneumonia and overinflation due to coughing causing mediastinal emphysema The child was severely ill on admission, his dyspnœa being due partly to bronchopneumonia and partly to interference with respiration by the mediastinal emphysema Nevertheless the condition cleared up rapidly without specific treatment to relieve the emphysema

Case 2—A male bank-clerk, aged 17, had been quite well until just before admission He swallowed a glass of fizzy lemonade and five minutes later suddenly felt a severe constricting pain in his throat, front of chest, epigastrium, and left side

On examination he was pale and anxious but not dyspnœic, with surgical emphysema of his neck and left chest wall a to and fro "pericardial rub," and no evidence of pneumothorax Radiography of his chest showed emphysema of his neck, left axilla, and mediastinum (fig 2), no abnormality of lung fields, no pneumothorax After a barium swallow no abnormality was seen Blood examination showed Hb 97%, white cells 10,000 per c.mm (polymorphs 76%, eosinophils 6%, lymphocytes 17%, monocytes 1%)

Treatment and Progress—A Ryle's tube was passed and left in situ for thirty six hours On rest in bed and penicillin therapy the boy made an uneventful recovery, the surgical emphysema resolving in ten days

Comment—The cause of this mediastinal emphysema is unknown The drinking of fizzy lemonade five minutes before the onset cannot be dismissed The patient was not ill at any time, and there was no need to consider any further treatment than that given The friction noise heard over the precordium was recognised to be due to emphysema around the heart (Hamman's sign) but initially sounded remarkably like a pericardial friction rub

Case 3—A man, aged 35, had six years history of nausea and epigastric pain A barium meal had shown a large active ulcer on the lesser curve of his stomach and persistent deformity of the duodenal cap The patient had not responded to medical treatment and partial gastrectomy was advised

Operation proceeded normally, a Polya-Hofmeister retrocolic gastrectomy being done During the operation the emergency oxygen was accidentally turned on for about one to two minutes with the expiratory valve of the anæsthetic mask which there is a general overinflation of alveoli with or without increased intra alveolar pressure

(2) *Through Mucosa of Upper Respiratory Tract*—The mucosa may be injured as a complication of endotracheal anæsthesia (Barrett and Thomas 1944, Jones 1945), trauma, or tracheostomy (Champneys 1884)

(3) *Through apical pleura* as a result of surgery or of accidental trauma (Bowden and Schweizer 1950)

(4) *Along the carotid sheath or the fascial planes of neck* as a complication of block dissection of the neck (Aiken and Smith 1953) or other neck surgery (Bowden and Schweizer 1950)

(5) *From pneumothorax*, which may be spontaneous, traumatic, or artificial (Macklin and Macklin 1944, Davidson 1951)

CLINICAL CAUSES

The following list includes all the conditions (traumatic and non-traumatic) in which mediastinal emphysema has been found or the known predisposing factors may be present (Macklin and Macklin 1944, Aisner and Franco 1949) infectious diseases (infections of upper respiratory tract, measles, tuberculosis, pertussis, pneumonia, influenza, diphtheria, smallpox, &c), space occupying lesions of the lungs or the mediastinum, inhaled foreign bodies, atelectasis in the newborn (due to prematurity or following the inhalation of meconium, mucous secretions, &c , before or after birth), bronchiectasis, bronchial asthma, chronic bronchitis and emphysema, parturition, violent coughing, violent exercise, acts of straining, acute obstructive laryngitis (diphtheria, streptococcal infection), playing of wind instruments, glass blowing, &c , endotracheal anæsthesia, resuscitation by intratracheal insufflation or with a respirator, positive-pressure inhalation therapy, silicosis, pneumothorax, tracheotomy, cervical surgery, pulmonary infarction, lung blast, caisson disease, hiccup, and trauma to neck or chest

Clinical Features

SYMPTOMS

The severity and nature of the symptoms depends on the degree of distension of the tissues and on the location and accessibility of the escape channels In severe cases the lung, as a consequence of interstitial emphysema, may become extremely voluminous and rigid, causing orthopnœa and dyspnœa

The commonest and most important presenting symptom is pain in the chest (Scott 1937, Miller 1945, Fagin and Schwab 1946, McCabe 1947), which is often mistaken for angina pectoris or for myocardial infarction The onset is usually but not always sudden It is not usually related to respiration but may be worsened by coughing Its location is variable, the commonest sites being precordial or substernal, but it may be felt almost anywhere in the chest It may radiate to neck, shoulders, arms, and back The intensity varies from very mild discomfort to severe agonising pain, which may be transient or last several days and usually disappears gradually

Other symptoms include palpitation, sweating, dysphagia, a feeling of fullness in the neck, anxiety, and crackling in the tissues If the air has passed retroperitoneally there may be pain in the back, if it has passed into the abdomen, there may be abdominal pain

SIGNS

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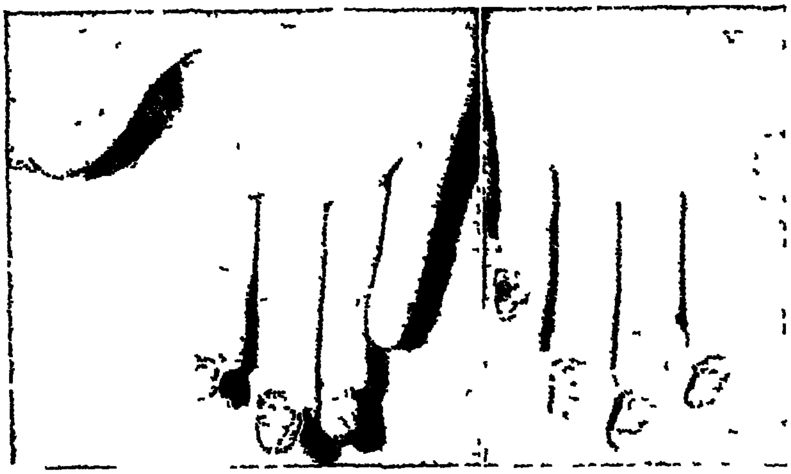

Sloughing gangrenous tips of fingers

and Kahn reactions were negative The Donath-Landsteiner reaction was negative The serum electrolyte levels were within normal limits The urine was loaded with red cells and contained granular casts and albumin Cold agglutination tests on the blood were within normal limits

Treatment and Progress —Tolazoline hydrochloride was given intravenously and later intramuscularly without effect Cortisone acetate was also used without producing any improvement The child's general condition remained good He had no pain in his fingers His renal condition slowly improved blood, albumin, and casts disappeared from his urine, and the blood-urea level returned to normal Radiography of his chest showed nothing unusual His toes, the lobes of his ears, and the tip of his nose became normal in the second week His left thumb also resolved completely, but the ends of his other digits became gangrenous and sloughed (see figure) Renal-function tests were normal before discharge, after eleven weeks in hospital

Follow up —When seen ten months after his initial admission the boy was back at school, and had remarkably little disability He had lost the tips of all his digits except the left thumb, but the stumps had healed well, and he could use them normally. The fact that the left thumb was spared considerably lessened the resulting disability

This case is regarded as one of arterial damage due to sensitivity to sulphadimidine Schmid (1953) described a case in an adult with peripheral symmetrical gangrene of this type but rather more severe, which he attributed to sensitivity to a sulphonamide and penicillin In the present case the boy did not have penicillin until after hæmaturia was observed, and the peripheral gangrene followed in four days Hence it seems likely that the damage was done before penicillin was given

My thanks are due to Mr J MacGouran, M S.R , for the photographs

REFERENCE

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Medical Societies

ROYAL SOCIETY OF MEDICINE

Effects of Smoking

THE section of medicine met on Feb 26, with Dr G E BEAUMONT, the president, in the chair, to discuss the physiological and medical effects of smoking

Prof J H BURN, F R S (Oxford), described experiments (many of them carried out in his laboratory) on the cardiovascular effects of nicotine He first referred to the statements made about the amount of nicotine yielded by cigarettes, and said that Ling and Wynn Parry had found that the smoke entering the mouth from one cigarette contained not more than 1 0 mg , while the amount absorbed when inhaling was about 0 3 mg

Smoking, by sympathetic stimulation through the stellate ganglion and the production of adrenaline, increased the heart rate and raised the blood-pressure by about 10–20 mm Hg (more in hypertensive patients) It caused vasoconstriction in the skin, shown by a diminution of blood flow in the warm hand on plethysmography That this action was peripheral, and not entirely ganglionic, had been shown by perfusing the denervated ear of a rabbit through a cannula in the artery and measuring the *venous outflow* Even in the absence of ganglia, the vasoconstrictor effect was blocked by hexamethonium and reversed by tolazoline The effect might be due to release of adrenaline or noradrenaline from local chromaffin tissue, which would account for the ill effects of smoking in thrombo angiitis even after sympathectomy

The direct effect of nicotine on the coronary arteries was to dilate them, but the constriction caused by vasopressin (through nicotine's stimulation of the supraoptic nucleus) might outweigh this effect Vasopressin had been recovered from the urine after cigarette smoking Nicotine might directly affect the myocardium, which contained noradrenaline and possibly chromaffin tissue After smoking the T wave of the electrocardiogram was flattened , there were changes in the ballistocardiogram only in patients with coronary artery disease Ectopic rhythms were sometimes caused Filter-tips did not abolish these effects Some tolerance to the antidiuretic effect of nicotine might be seen in smokers, but as we grew older we might lose our power to metabolise nicotine Nicotine stimulated peristalsis , the mechanism was not clear

Dr RICHARD DOLL said that 20 retrospective studies had shown a significant association between smoking cigarettes and lung cancer The association held only for oat cell, squamous cell, and undifferentiated carcinomas, and not for adenocarcinomas Two prospective studies were now in progress Among British doctors questioned in 1951 as to their smoking habits, early results had shown sharp differences in the death-rate from lung cancer , the incidence was low in non-smokers but increased as the number of cigarettes smoked increased The association with pipe smoking was less striking Similar trends, though much less marked, were seen in the death-rates from coronary thrombosis, and from other respiratory diseases, where the trend was chiefly due to an association with bronchitis Other types of cancer and other diseases showed no trend in either direction Smokers who had given up smoking had a lower mortality from lung cancer than those who had not A similar study was being made in the United States by Hammond and Horn on 200,000 men The results so far reported indicated that the death rate from lung cancer was ten times as great in cigarette smokers as in non smokers

Dr Doll discussed and dismissed possible causes of bias It had been suggested that the diagnosis of lung cancer was made more often in smokers , but if only histologically proven cases were accepted, the association with smoking was even greater than in the whole series An effect due to selection of an unrepresentative sample of men, because of a tendency of non smokers to reply more readily than heavy smokers to questions about smoking habits, would be expected to apply to all diseases, and the effect would wear off in time, whereas the trend had been about the same in each year of the British investigation and was becoming greater in the almost closed, thus giving full pressure of oxygen in the lungs The surgeon then found much surgical emphysema in the mesentery of the transverse colon Most of the mesentery was emphysematous, but during the operation, which continued to proceed normally, could be felt to be rapidly resolving The patient was taken back to the ward and made an excellent recovery Slight surgical emphysema of the neck was detected, but this quickly resolved in one to two days There were no signs in the chest and no evidence of pneumothorax

Comment —The cause of the emphysema in this case could well be the overinflation of the alveoli with increased intra alveolar pressure—the Macklins' (1944) group c— due to the high oxygen pressure in the lungs during anæsthesia The rapidity of resolution of the surgical emphysema could be due to the speed in which oxygen is normally absorbed by the tissues (considerably quicker than the nitrogen in normal air) The patient had no symptoms from his emphysema and at no time was made ill by it The mediastinal emphysema here escaped mainly into the retroperitoneal tissues and only slightly into the neck This case is of interest because of the unusual way in which the mediastinal emphysema arose and the unusual escape route for the air

Discussion

Although mediastinal emphysema is a well recognised complication of trauma to neck and chest and of neck surgery, its spontaneous or non-traumatic origin is not so widely realised It is quite possible, in view of the multiplicity of predisposing factors and the common occurrence of some of them, that minimal examples of this condition may not be always diagnosed, and in this connection it is emphasised that a postero anterior radiograph of the chest may not show air in front or behind the heart and great vessels Only a lateral view can virtually exclude mediastinal emphysema, and such a view should always be taken when a patient has an unexplained chest pain

An interesting point in the present cases is the absence of pneumothorax Of 50 published cases (Hamman 1934, 1937, 1939 McGuire and Bean 1939, Kirshner 1939, Morey and Sosman 1939, Wolff 1940, Matthews 1941, Pinkney 1941, Styron 1941, Caldwell 1941, Miller 1941, Murphy and Zeis 1942, Griffin 1942, Meek 1942, Kellogg 1942, Dassen and Fongi 1942, Adcock 1943, Greene 1943, Lintz 1943, Munroe and Webb 1943, Hoffman et al 1943 Israel 1943, Miller 1944, Fagin and Schwab 1946, Schwartz et al 1946, Cliff 1955) 30 had a left sided pneumothorax The coexistence of a pneumothorax seems to make the prognosis worse, although in most of the published cases the pneumothorax was small

The term "spontaneous" was originally used because no cause was known Nowadays, however, a predisposing cause can be found in most cases, but occasionally (as in case 2) there is no obvious cause The term "spontaneous," however, should be retained to denote that the condition is not due to trauma

Summary

Three cases of non traumatic mediastinal emphysema are reported because of their relatively mild nature, minimal physical signs (in two cases), ætiology, and rapid recovery

Two of the cases could be assigned to known causes, but the cause of the third is unknown

I wish to thank Dr F S W Brimblecombe and Dr C J Fuller for advice and encouragement Dr A J Daly, Mr K P S Caldwell and Dr W J Walter for permission to publish case reports Mr R Dyson for photographs and the librarian of the B M A library for help with the literature

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References continued at foot of next column

SYMMETRICAL PERIPHERAL GANGRENE AS A TOXIC REACTION TO SULPHAMEZATHINE AND PENICILLIN

J M BARBER
M D Belf, M R C P E
CONSULTING PHYSICIAN, NORTH DOWN HOSPITALS

Y A MACILWAINE
M D Belf
PATHOLOGIST, ARDS HOSPITAL, NEWTOWNARDS, CO DOWN

VERY many toxic reactions to sulphonamides and to penicillin have been described, but symmetrical gangrene appears to be extremely rare

A boy, aged 12 years, was admitted on Feb 20, 1956 There was nothing significant in the family history, in particular no history of allergy He had had measles, mumps, and chickenpox Two weeks before admission he developed otitis media This was treated with sulphadimidine 2 g initially followed by 1 g four hourly for seven days His ear responded satisfactorily, but at the end of the week he had painless hæmaturia Penicillin was substituted for the sulphadimidine Four days later the tips of the boy's ears, the end of his nose, and the tips of all his fingers and toes were cyanosed and became gradually worse Penicillin was withheld, and he was admitted to hospital

On admission he was not distressed His temperature was 99 4°F He had incipient gangrene of the tips of all his fingers and, to a much less degree, his toes The digits, the lobes of his ears, and the extreme tip of his nose were blue and cold He had gross hæmaturia There were no abnormal physical signs in heart, lungs, abdomen, and central nervous system

Investigations —Hb 9 2 g per 100 ml , red cells 3,300,000 per c mm , packed cell volume 31%, mean corpuscular volume 95 c μ, mean corpuscular Hb concentration 31%, white cells 15,600 per c mm (neutrophils 79%, eosinophils 3%, monocytes 2%, lymphocytes 16%) There was nothing abnormal in the blood films The serum bilirubin was normal The blood urea was 60 mg per 100 ml The Wassermann

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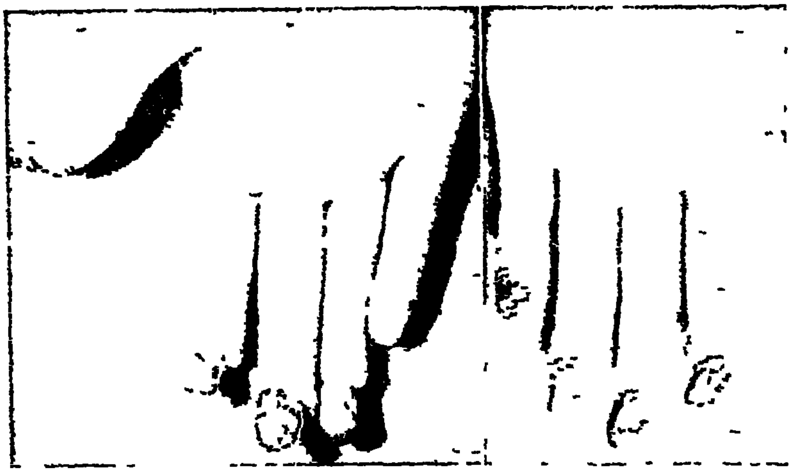

Sloughing gangrenous tips of fingers

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THE section of medicine met on Feb. 26, with Dr G. E. BEAUMONT, the president, in the chair, to discuss the physiological and medical effects of smoking.

Prof. J. H. BURN, F.R.S. (Oxford), described experiments (many of them carried out in his laboratory) on the cardiovascular effects of nicotine. He first referred to the statements made about the amount of nicotine yielded by cigarettes, and said that Ling and Wynn Parry had found that the smoke entering the mouth from one cigarette contained not more than 1.0 mg., while the amount absorbed when inhaling was about 0.3 mg.

Smoking, by sympathetic stimulation through the stellate ganglion and the production of adrenaline, increased the heart rate and raised the blood-pressure by about 10–20 mm. Hg (more in hypertensive patients). It caused vasoconstriction in the skin, shown by a diminution of blood flow in the warm hand on plethysmography. That this action was peripheral, and not entirely ganglionic, had been shown by perfusing the denervated ear of a rabbit through a cannula in the artery and measuring the venous outflow. Even in the absence of ganglia, the vasoconstrictor effect was blocked by hexamethonium and reversed by tolazoline. The effect might be due to release of adrenaline or noradrenaline from local chromaffin tissue, which would account for the ill effects of smoking in thrombo-angiitis even after sympathectomy.

The direct effect of nicotine on the coronary arteries was to dilate them, but the constriction caused by vasopressin (through nicotine's stimulation of the supraoptic nucleus) might outweigh this effect. Vasopressin had been recovered from the urine after cigarette smoking. Nicotine might directly affect the myocardium, which contained noradrenaline and possibly chromaffin tissue. After smoking the T wave of the electrocardiogram was flattened; there were changes in the ballistocardiogram only in patients with coronary-artery disease. Ectopic rhythms were sometimes caused. Filter-tips did not abolish these effects. Some tolerance to the antidiuretic effect of nicotine might be seen in smokers, but as we grew older we might lose our power to metabolise nicotine. Nicotine stimulated peristalsis; the mechanism was not clear.

Dr RICHARD DOLL said that 20 retrospective studies had shown a significant association between smoking cigarettes and lung cancer. The association held only for oat-cell, squamous cell, and undifferentiated carcinomas, and not for adenocarcinomas. Two prospective studies were now in progress. Among British doctors questioned in 1951 as to their smoking habits, early results had shown sharp differences in the death-rate from lung cancer; the incidence was low in non-smokers but increased as the number of cigarettes smoked increased. The association with pipe smoking was less striking. Similar trends, though much less marked, were seen in the death rates from coronary thrombosis, and from other respiratory diseases, where the trend was chiefly due to an association with bronchitis. Other types of cancer and other diseases showed no trend in either direction. Smokers who had given up smoking had a lower mortality from lung cancer than those who had not. A similar study was being made in the United States by Hammond and Horn on 200,000 men. The results so far reported indicated that the death-rate from lung cancer was ten times as great in cigarette smokers as in non-smokers.

Dr Doll discussed and dismissed possible causes of bias. It had been suggested that the diagnosis of lung cancer was made more often in smokers; but if only histologically proven cases were accepted, the association with smoking was even greater than in the whole series. An effect due to selection of an unrepresentative sample of men, because of a tendency of non-smokers to reply more readily than heavy smokers to questions about smoking habits, would be expected to apply to all diseases and the effect would wear off in time, whereas the trend had been about the same in each year of the British investigation and was becoming greater in the

American investigation It was unlikely that smoking merely determined the site of a cancer which would have developed elsewhere if the patient had not smoked, because there was no reduction in the incidence of cancer at other sites in heavy smokers

Another suggestion was that the results arose because heavy smoking was commoner in cities—i e, among those more exposed to atmospheric pollution But the figures showed that, so far as British doctors were concerned, heavy smoking was in fact as common in the country as in the city, and non smoking as uncommon, thus atmospheric pollution was not the factor Another suggested factor was alcohol, since heavy drinkers were often heavy smokers, but it had been shown that there was no significant difference in the prevalence of lung cancer between drinkers and abstainers if smoking habits were kept constant

The mortality-rate from lung cancer had risen with the consumption of cigarettes, but about twenty years later Cigarette consumption in this country had been relatively constant since 1946, and the annual increase in the number of deaths from lung cancer might be expected to cease *in the course of the next one or two decades* There was in general a good correlation between the death-rate from lung cancer and the cigarette consumption in different countries, though the death rate was higher in Britain and lower in the United States than would be expected from comparison with other countries

Hyperplasia and metaplasia of the bronchial epithelium had been shown to be commoner in smokers than in non-smokers, and 3 4 benzpyrene (which has been found in tobacco tar) had produced similar changes in human foetal lung in tissue culture

Dr **Neville Oswald** looked at the question from a clinician's point of view He said that smoking often made angina worse and always made thrombo angiitis worse Swallowing excessive tracheal secretion might explain the adverse effect of smoking on peptic ulcer He wondered whether there was a threshold beyond which smoking caused lung cancer A study of Civil Servants had shown only a slight trend towards a higher incidence of mild respiratory symptoms or bronchitis in smokers than in non smokers Many patients seen at the Brompton Hospital on account of bronchitis had given up smoking and felt better for it

In the discussion, Dr W C **Boake** (Melbourne) reported an investigation of a group of 118 ordinary adults in Cleveland, Ohio, for whom careful records of common acute respiratory illnesses had been kept for up to six years There was no correlation between smoking and the incidence or severity of these illnesses Of the symptoms, he confirmed the common impression that smokers coughed more, though they had no more sputum They had fewer sore throats—perhaps because they had one all the time and did not notice them Mr F A **Williamson Noble** said that the carbon monoxide produced by smoking appreciably increased the oxygen need of aviators Dr **Horace Joules** pointed out that effective legislation about chimney sweep's cancer did not come till a hundred years after the discovery of its cause, and predicted a million deaths from lung cancer in this century in England and Wales unless people stopped smoking

The **President** observed that 15 of the audience had been smoking at the start of the discussion, but only 1 at the end

Ætiology of Pre-eclampsia

A meeting of the section of obstetrics and gynæcology on Feb 22, with the president, Mr **Alan Brews**, in the chair, discussed the causes of pre-eclampsia

Prof J C **McClure Browne** said there were as many theories on this subject as there were obstetricians Eight or nine years ago the work of Baker [1] and Bastiaanse and Mastboom [2] had revived interest in the placenta as the supposed starting point of the chain of events which culminated in eclampsia If placental ischæmia could indeed cause a rise in systemic blood-pressure, it was logical to suppose that pre eclamptic toxæmia would develop when the pregnant uterus was overdistended, as in hydramnios and twins, and sometimes in the primigravida Professor Franklin and Mr Sophian had shown that distension of the pregnant rabbit uterus would cause a renal cortical ischæmia, which could be held to account for the albuminuria and so on But McGaughey and his colleagues [3] had lately failed to demonstrate a specific uterorenal reflex in the dog

Up till 1948, no-one had shown that placental ischæmia existed in pre eclampsia, and Professor Browne described experiments which he and his colleagues performed to decide this point When the placenta was situated anteriorly it was possible to inject a tracer dose of ^{24}Na into the choriodecidual space and to record the time taken for it to be cleared by the maternal placental circulation In a normal woman between 38 and 40 weeks the mean half-period for clearance was 21 seconds, in pre eclampsia it was 65 seconds In essential hypertension, however, where the hypertension has antedated the pregnancy the same degree of ischæmia was found It was concluded, therefore, that the placental ischæmia was the result and not the cause of the hypertension of pre eclamptic toxæmia We were astounded, Professor Browne declared, at the big reduction in maternal placental blood-flow when hypertension was present, but careful rescrutiny of the methods and results had confirmed the findings

The clear evidence that hypertension causes placental ischæmia, and not the other way round, suggested that the uterine-tension theory of pre eclampsia was wrong The exponents of this theory held that the tension of the primigravid uterus, or the presence of twins or hydramnios, produced placental ischæmia and if the intra uterine tension was reduced (e g, by rupturing the membranes), *then the ischæmia was diminished* and the toxæmia immediately improved But this was certainly not Professor Browne's experience in clinical obstetrics there were many instances of serious deterioration after surgical induction in pre eclamptic toxæmia

Dr **Norman Morris** said that Professor Browne's pioneer work had stimulated Dr Payling Wright and himself [4] to investigate the clearance rate of ^{24}Na from the myometrium 0 3–0 4 ml of ^{24}Na Cl, with an activity of between 5 and 10 microcuries, was injected into the myometrium A Geiger counter was then arranged over the site of injection and the rate of clearance of the ^{24}Na was recorded Normotensive women gave an average time to half value of 4 1 min In mild pre eclampsia (diastolic pressure 85–95 mm Hg) the average was 7 7 min, and in severe pre-eclampsia (diastolic over 95) it was 15 3 min These figures strongly suggested that pre eclampsia was associated with a significant reduction in myometrial blood-flow and that this was probably the main cause of the reduced placental blood flow observed by Professor Browne Further observations showed how the clearance-rate seemed to be progressively reduced as the blood-pressure rose Lowering the blood pressure with protoveratrine improved the clearance rate Experiments were then designed to determine the effect of exercise upon the clearance rate of ^{24}Na both from the myometrium and from the anterior belly of the quadriceps The results suggested that during exercise blood-flow to the uterus was reduced but quickly returned to normal when the exercise stopped This reduction in uterine flow was probably the result of a generalised splanchnic vasoconstriction, since, in the non-pregnant, exercise also reduced the renal blood-flow

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[1] Baker J C *J Obstet Gynæc, Brit Emp* 1948, 55 756

[2] Bastiaanse M A van B Mastboom J L *Ned Tijdschr Geneesk* 1949 93 2609

[3] McGaughey H S Weller H Anslow W P *Amer J Obstet Gynec* 1956 72 549

[4] Morris N et al *Lancet*, 1955 i, 323, *Ibid*, 1956, ii, 481

Turning to the clinical significance of these findings, Dr Morris pointed out that in pre eclampsia it was well established that rest usually prevented deterioration while physical activity caused exacerbation Reduction of salt intake was also beneficial, though the reasons for this were not clear The precise origin of the pressor mechanism was also unknown Mr Sophian thought it originated largely from the kidney, others thought it came from the placenta, still others believed that it might arise in the adrenal or pituitary The harmful effect of exercise strongly suggested that the increased splanchnic vasoconstriction that resulted in some way also further stimulated and perpetuated the production or activity of the pressor factor, thus establishing a vicious cycle Many women progressed to moderate or even severe pre eclampsia before they were seen Dr Morris wondered what would happen if all primigravidæ over 30 weeks were treated as though they already had mild pre eclampsia might not then the pattern of severity of pre eclampsia be much changed ?

Dr Morris found it hard to accept that pre eclampsia was primarily due to myometrial resistance to stretch or to a uterorenal reflex Pre eclampsia was certainly *not* associated with a consistently increased intra uterine pressure If the stretch theory was right, why was it that twins, acute hydramnios, and pregnancy in a rudimentary horn did not always give rise to pre eclampsia ? Furthermore why could pre eclampsia occur in association with an extra-uterine pregnancy ?

Mr JOHN SOPHIAN's theme was cortical renal ischæmia and the stimulus that provoked it—the uterorenal reflex initiated by stretching of the resisting uterine muscle Discussing renal hæmodynamics, he said that it had hitherto been held that there was a uniform single circulation in the kidney and that the regulation of glomerular filtration depended on the ratio of afferent to efferent arteriolar resistance But Pappenheimer had lately emphasised the fact that, since the afferent arteriole was shorter and at least 50% wider than the efferent, its effective resistance must be small compared with the efferent resistance Pappenheimer had also disproved the explanation of extraction-ratio values put forward by the Homer Smith school, and his observations provided a new and accurate yardstick for determining hitherto occult changes in renal circulation —changes responsible for the ischæmia which, in Mr Sophian's view, underlay the pre eclamptic process To explain renal hæmodynamics, two intrarenal circulatory processes must be envisaged one offered a greater resistance to blood flow than the other, and it was not very efficient in extracting circulating substances and consequently had a smaller oxygen need Pappenheimer's two circulations were in parallel, whereas the Trueta dual circulation was in series, but there were many points of similarity between the two This idea of a dual intrarenal circulation immediately shed new light on pre eclampsia according to this thesis, ischæmic and anoxic changes were occurring occultly in the kidney —changes that explained the œdema, albuminuria, and hypertension of pre eclampsia

Turning to the part played by the uterus in initiating the renal changes, Mr Sophian said he had no doubt that myometrial resistance to stretch explained the events Dysmenorrhœa, uterine inertia, and pre eclampsia seemed to arise preponderantly in women whose cervix has not been stretched by a full time fœtus—suggesting that an intact cervical innervation had a share in their production This innervation might be responsible for keeping up isometric tension in first pregnancies and thereby adding to the resistance to stretch Proof of this increased tension was partly derived from biochemical studies and partly from tocometric tracings Moreover, Reynolds had pointed out that whereas the multiparous uterus tended to become globular after mid-pregnancy, the primigravid organ became elongated, connoting a rise of tension He had also shown the existence of such heightened tension in toxæmia Increase in circulating adenosine in toxæmia was shown to indicate both uterine muscle ischæmia and an increased isometric tension of the muscle

In addition to the histological proof of the uterorenal reflex, biochemical evidence had lately been provided by McGaughey et al ,[3] who had shown that a mean reduction of 23% in the urinary clearance of *p*-aminohippuric acid followed acute distension of the uterus in dogs—a clear indication of reduced renal plasma flow induced by the reflex

The reduced circulation observed in the uterus of pre eclampsia was due in the first place to the resisting tension in its walls and later (and additionally) to the constriction of its vessels provoked by the pressor substances from the ischæmic kidney, which also responded similarly to exercise, as Dr Morris had indicated As for the effects of treatment, release of liquor relieved uterine tension, the uterorenal reflex subsided, and the toxæmia abated Similarly, the death of the fœtus relieved the toxæmia because the resulting flaccidity of the fœtus and the reduction in the turgescence of the myometrial circulation lessened both stretch influences and uterine tone, and thus improved the mother's condition

Mr Sophian discounted the rôle of the placenta because (*a*) toxæmia could recur during labour, days after its quiescence on the death of the fœtus, and (*b*) hormones were not of primary ætiological significance [5] These facts disproved toxin production and abnormal hormonal action by the placenta There was further proof of this although the interstitial-fluid space was 40% larger in the toxæmic than in the healthily pregnant woman, this space in the fœtuses of both toxæmic and normal mothers showed no expansion Yet there was evidence, in the mastitis of the newborn males, that maternal œstrogen passed the placental barrier

Reviews of Books

Experimental Design and its Statistical Basis

D J FINNEY, M A, SC D, F R S, reader in statistics in the University of Aberdeen London Cambridge University Press 1955 Pp 169 30*s*

ALTHOUGH his early experience in the development of experimental design lay in the field of agriculture, Dr Finney has written an excellent introduction to the tactics of experimentation for scientists in general which should be valuable to medical research-workers in particular

The mathematical background is minimal, but the rationale of the science of experimental design in the Fisherian tradition is clearly set out The compact style requires close attention, but the reader will be rewarded by a clear understanding of the notions underlying such experimental designs as randomised blocks and Latin squares The relevance of these simpler designs to medicine is made obvious by some well chosen examples of clinical trials and tests of experimental or observer variation Experimentation in genetics and the more complex designs involving confounding are briefly covered A chapter on sequential experiments, including an outline of " staircase methods " in bio assay, should stimulate pharmacologists to reconsider their plans for laboratory assessments of therapeutic agents

This text can be confidently chosen by the medical scientist as a primer in the experimental method

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[5] Sophian, J *Amer J Obstet Gynec* 1956 72, 693

Marshall's Physiology of Reproduction

3rd ed Vol 1 part 1 Edited by A S PARKES, D SC, SC D, F R S National Institute for Medical Research, London London Longmans, Green 1956 Pp 688 150s

THE second volume of the new edition of this enormous and useful book has already appeared The first volume has itself undergone fission

Part 1 contains, in addition to Marshall's own original first chapter, chapters on the morphology and anatomy, reproductive cycle, œstrous cycle, ovarian changes, and changes in the non-pregnant female adnexa, throughout the vertebrates The matter is presented phylogenetically in each chapter, and there is little overlapping between the morphological and physiological accounts The material reviewed is drawn mainly from publications before 1948 The time lag is unfortunate, but not excessive in view of the size of the task and the fact that all the contributors are active in research A 4th edition is already in preparation

The "perennial controversy" about the neogenesis of ova in adult mammals, which has been conducted for so long between Dr Parkes on the one hand and Sir Solly Zuckerman, his leading contributor, on the other, is nicely but rather briefly reviewed by Dr F W R Brambell in the chapter on ovarian changes

The merits of this book as a source for all biological workers are already recognised, and in the new edition they are if anything increased Human reproduction is treated in its strictly comparative context, but the book ought to be consulted regularly by any medical worker who attempts to supplement his understanding of human physiology by experiments on animals Perhaps the chief merit of such extended reviews is that they hammer home the diversity of animal physiology and the dangers and profits of analogy—both are important in medicine, if we remember the long period of obstruction in endocrinology which resulted from the confusion between œstrous and menstrual cycles, and which Marshall himself did much to end The corresponding defect of large reviews is that they tend to perpetuate error by diverting inquirers from the original papers, but the choice of contributors to this book and the excellent bibliographies reduce this risk Even at the cost of further increase in size and price, a growing need becomes evident for the inclusion of a parallel treatment of reproductive behaviour The new volume is expensive but indispensable to those who deal with its subject-matter

Chirurgie orthopédique des paralysies

R MERLE D'AUBIGNÉ, professeur de clinique chirurgicale orthopédique et réparatrice à la Faculte de Médecine de Paris, J BÉNASSY and J O RAMADIER, chirurgien assistants des Hôpitaux de Paris Paris Masson 1956 Pp 430 4200 fr

THIS is the first volume of the *Collection de Chirurgie Orthopedique* planned by that good friend of this country, Prof Merle d'Aubigne, and if the standard of this book can be maintained the subsequent fourteen volumes can be sure of a warm welcome The book is directed towards the young surgeon who wants to know not just what could be done but rather what should be done for any particular condition It is essentially concerned with treatment, each chapter dealing with the mechanical and dynamic aspect of its subject All standard procedures are fairly assessed Poliomyelitic paralyses are not included as they are to be the subject of a separate volume This well-balanced book will prove most useful to the surgeon confronted with these often difficult exercises in surgical judgment

Lectures in Immunochemistry

MICHAEL HEIDELBERGER, PH D, emeritus professor of immunochemistry College of Physicians and Surgeons, Columbia University, New York New York Academic Press London Academic Books 1956 Pp 150 32s

THIS is a collection of lectures delivered during the past ten years in Tokyo, Paris, Marburg, and New Brunswick

The topics range from general aspects of immunity to quantitative analytical methods of serology The lectures are reproduced as they were delivered, and they have not been edited to weld them into a coordinated whole Characteristically Heidelberger remarks "this small volume is an indolent man's response to the urging of his friends that he write a book" *All serious students of immunity will welcome* these discussions of subjects with which the author has been familiar so long Heidelberger's interest in immunology began with coöperation with O T Avery in studying the specific polysaccharides of pneumococci, extended to the development of quantitative analytical methods in serology, and included searching studies of complement, whose functions in immunity reactions are still something of a mystery

Neoplasms of the Domesticated Mammals

E COTCHIN, M R C V S, department of pathology, Royal Veterinary College, London Review series no 4 of the Commonwealth Bureau of Animal Health, Farnham Royal, Bucks 1956 Pp 100 20s

VETERINARY surgeons have not, in the past, been greatly interested in pathology Recently, however, a new enthusiasm for this subject has arisen in teaching schools

The purpose of this book is threefold to interest veterinary surgeons and pathologists in the subject, *to encourage the* study of material which, as Prof R A Willis pointed out in 1948, is largely wasted, and to provide a background of knowledge (including references to published work) about tumours in animals for the use of experimentalists, who often have to decide whether a certain neoplasm has been induced by the treatment employed

The scope of the book is limited to tumours in the horse, ox, sheep, pig, dog, and cat A series of 930 spontaneous tumours in rabbits, guineapigs, rats, and mice has recently been reviewed by C Tamaschke (*Strahlentherapie*, 1955, 96, 150) Each of the 1000 works listed in the bibliography has been seen by the author, who adopts a reasonably critical attitude to incomplete or misleading descriptions—which must have been very difficult in a field where "Many of the papers consulted were of a rather anecdotal nature"

The nomenclature, based on that proposed by R A Willis (*Pathology of Tumours* London, 1948) *for human tumours* is simple and comprehensive The tumours of each system are considered in paragraphs relating to the various species one by one This method tends rather to break the sequence of the text but is useful for reference to the facts about a particular species The bibliography is good, and there is an index

This book will be a valued addition to pathological reference libraries, and it will be hailed with gratitude by all experimentalists whose field in any way touches neoplastic diseases

Classics in Arterial Hypertension

ARTHUR RUSKIN, M D, F A C P, associate professor of internal medicine, University of Texas Medical Branch consultant to the U S Public Health Service Hospital Galveston, Texas Springfield, Ill Charles C Thomas Oxford Blackwell Scientific Publications 1956 Pp 358 72s

THIS compilation will be of great interest to all physicians with a scholarly interest in the unsolved problems of hypertension in our ageing population

Workers quoted range from Stephen Hales to Harry Goldblatt, and include 19th century British contributions by Bright, Johnson, Gull, Sutton, Gowers Albutt, and Mahomed Writings of Korotkoff Riva Rocci Tigerstedt, and many others are included While many will welcome the opportunity to read the *ipsissima verba* (*even in translation*), some may be surprised at the lack of balance between the selections and the omissions Mahomed's paper on scarlatinal nephritis written at the age of 25, is given at length, while his later and more interesting paper dealing with essential hypertension is left out Volhard and Fahr get short mention but are not quoted Potain's work on hypertension is sketched but the extract from his paper on gallop rhythm admittedly of great excellence, is rather outside the main theme

Dr Ruskin has produced an appetiser We hope that he or a colleague will later provide a greater variety of morsels

THE LANCET

LONDON SATURDAY, MARCH 9, 1957

Hypophysectomy for Cancer

HYPOPHYSECTOMY was first described for breast cancer in 1952–53,[1,2] not long after HUGGINS and BERGENSTAL[3] had established total adrenalectomy as a practical procedure in 1951 Adequate data are now beginning to accumulate so that the relative value of the two operations can be assessed Hypophysectomy has several theoretical advantages over adrenalectomy By removing the gonadotrophic and adrenocorticotrophic stimuli, it might be expected to eliminate œstrogens from the body more completely than is possible by combined oophorectomy and adrenalectomy Œstrogens and pregnanediol have been found in the urine even after oophorectomy and adrenalectomy,[4,5] which suggests that accessory adrenal or other œstrogen-secreting tissue may be left behind, and accessory adrenal tissue has in fact been demonstrated in the region of the cœliac artery[6] and in the broad ligament[7] On the other hand, STRONG et al[5] did not detect any increase in the output of œstrogens and pregnanediol in patients who had undergone oophorectomy and adrenalectomy and were then given an intravenous infusion of corticotrophin Actually, even hypophysectomy does not necessarily eliminate œstrogens from the urine[4], but the elimination of prolactin may be of equal importance[8,9], and the elimination of growth hormone might be a further advantage of hypophysectomy for breast cancer Growth hormone is known to increase the incidence of certain tumours in rats, whereas hypophysectomy reduces it[10,11] This influence of growth hormone has been observed in a patient with breast cancer who was in a state of remission after bilateral oöphorectomy and adrenalectomy, followed by hypophysectomy injections of growth hormone for 18 days led to a steady increase in urinary calcium and phosphate excretion, in the same ratio as that of calcium to phosphate in bone, suggesting that the growth hormone had induced bone destruction by stimulating the growth of bone metastases[12–14] Another reason for the trial of hypophysectomy in the treatment of malignant disease is that only 13 instances have been reported of cancer in association with panhypopituitarism, and in none of these did the growth arise in the breast or ovary[15] The only theoretical objection to hypophysectomy is that cancer of the female breast and genital tract occurs more often in hypothyroidism than in hyperthyroidism and that after partial thyroidectomy a greater proportion of women between the ages of 40 and 60 have breast or genital cancer than in the average population of the same age[16] Likewise, in laboratory animals, thyroid deficiency sometimes permits a more florid growth of the breast[17]

Benefit from hypophysectomy has so far been largely confined to patients with carcinoma of the breast Most of the reports have come from LUFT and OLIVECRONA and their colleagues in Stockholm[18] and from PEARSON and RAY and their associates at the Sloan-Kettering Institute, New York[12–14] A preliminary report from the Royal Free Hospital, London, has lately appeared[19] and this week we publish details about what is probably the largest series from this country, studied by Mr ATKINS and his colleagues at Guy's Hospital LUFT et al[18] noted objective remissions after hypophysectomy in 22 (54%) out of 41 patients with breast cancer in whom accurate assessment was feasible (that is to say, shrinkage of visible, palpable, or radiological metastases, or increased bone density without progression of the old metastases or appearance of new ones), some of the remaining patients had only temporary symptomatic improvement A similar remission-rate (56%) was achieved in other reported cases, compared with 45% after total adrenalectomy and oophorectomy The duration of remission in LUFT et al 's patients had so far averaged 17 months (only 1 out of 14 was still in remission after 2 years), compared with an average of 9 months after adrenalectomy and oophorectomy They do not, however, feel justified as yet in regarding this difference as conclusive PEARSON et al[13] recorded subjective remissions after hypophysectomy in 21 (51%) out of 41 cases, and the average remission to date was 6 5 months KENNEDY[20] claims objective remissions in 18 (64%) out of 28 patients lasting an average of 7 6 months, with regression of the primary growth, recalcification of the osteolytic lesions, shrinkage of the lymph-nodes and pulmonary and hepatic metastases, and disappearance of skin nodules The Guy's team are the first to compare the results of hypophysectomy and adrenalectomy within their own experience Their findings suggest that the over-

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[1] Perrault M. *Bull Soc méd Hôp Paris*, 1952 68 209

[2] Luft, R Olivecrona H *J Neurosurg* 1953 10, 301 see leading article, *Lancet* 1956, i 676

[3] Huggins C, Bergenstal D M *J Amer med Ass* 1951, 147 101

[4] Bulbrook R D, Greenwood F C 53rd annual report of the Imperial Cancer Research Fund London 1956 p 13

[5] Strong J A Brown, J B Bruce J Douglas M., Klopper, A I Loraine, J A *Lancet* 1956 ii 955

[6] Graham L S *Cancer* 1953, 6, 149

[7] Falls J L *Ibid*, 1955, 8 143

[8] Lyons W R, Johnson R E, Cole R D, Li C H Hypophyseal Growth Hormone, Nature and Actions New York, 1955, p 461

[9] Nelson W O Ciba Foundation Colloquia on Endocrinology London 1952 vol 4 p 402

[10] Moon H D Simpson M E, Li C H Evans H M. *Cancer Res* 1950 10 297 304 549, *Ibid*, 1950, 11, 535, *Science*, 1952 116 331

[11] Koneff A A Moon H D Simpson M E, Li, C H Evans H M. *Cancer Res* 1951 11 113

[12] Pearson O H *Advanc intern Med* 1956, 8, 215

[13] Pearson, O H Ray, B S, Harrold C C, West C D, Li M C, Maclean, J P, Lipsett M B *J Amer med Ass* 1956, 161, 17

[14] Lipsett M B, Pearson, O H *Med Clin N Amer* May, 1956, p 773

[15] Archer, B H *N Y St J Med* 1953, 53 328

[16] Loeser A A *Brit med J* 1954, ii, 1380

[17] Trentin J J Hurst, V, Turner, C W *Proc Soc exp Biol*, *N Y* 1948, 67, 461

[18] Luft R Olivecrona H, Ikkos, D, Nilsson L B, Ljunggren H *Amer J Med* 1956 21, 728

[19] Baron, D N *J clin Path* 1956, 9, 358

[20] Kennedy, B J *Amer J Med* 1956, 21, 721

all results of hypophysectomy are superior to those of adrenalectomy, and their patients survived on the average 4 months longer after hypophysectomy than after adrenalectomy, but they emphasise that the differences were not statistically significant. Objective remissions have also followed hypophysectomy in 3 cases of carcinoma of the male breast.[13 18] The results of hypophysectomy in carcinoma of the prostate have been less promising, as have those of adrenalectomy, though temporary objective remissions have been achieved in a few patients in whom endocrine therapy had been ineffective or in whom the condition had relapsed after such treatment.[12 13 18] The operation has been of no benefit in malignant melanoma,[12 13 18 21] hypernephroma,[3] chorioncarcinoma,[12 13 18] seminoma,[22] adrenocortical carcinoma with Cushing's syndrome,[23] carcinoma of the thyroid,[12] and reticulum-cell sarcoma.[12]

There is still no satisfactory means of predicting which patients with breast cancer will respond to adrenalectomy or to hypophysectomy. The histological characters of the tumour are of no help, and there is no correlation between counts of mitotic cells and the response to treatment.[24] There is also no difference between responsive and unresponsive cases in the urinary output of œstrogens and gonadotrophins.[5] Now, however, Dr MERIVALE and his colleagues, on p. 496, report that the ratio of 11-deoxy-17-ketosteroids to 11-oxygenated or 11-hydroxylated 17-ketosteroids was greater than one in the 11 patients who benefited from adrenalectomy or hypophysectomy and less than one in the 4 patients who did not respond (in these 4 cases the pattern of preoperative excretion resembled the postoperative pattern). Estimation of mammatrophin likewise promises to be of value in assessing the hormone-dependence of breast cancer. This substance, which is probably prolactin, is present in the urine of all normal pre-menopausal women during the second half of the menstrual cycle, and in some 38% of normal post-menopausal women. This figure accords with the proportion of human breast cancers which are hormone-dependent—that is, approximately 30%. From a limited series of observations, it seems that a high output of mammatrophin is usually associated with a significant regression of the growth after hypophysectomy, and conversely.[25–27] Studies of the calcium balance may also help when there are osteolytic metastases: the urinary calcium excretion in such cases falls after oophorectomy and rises with the administration of œstrogens,[28 29] and it has been suggested that a rise in urinary calcium excretion in response to a provocative dose of œstrogen, or a fall in excretion induced by cortisone, may indicate that the tumour is hormone dependent and therefore likely to respond to adrenalectomy.[29] LUFT et al.[18] suggest tentatively that in post-menopausal women the chances of benefit from hypophysectomy become progressively less after the menopause and that women over 60 are unlikely to respond; their results also suggest that the response was less satisfactory when the growth had been present for a long time and when there were extensive metastases in the liver and brain. KENNEDY[23] states that the pre-menopausal patient with advanced cancer of the breast who responds to therapeutic castration will probably respond to subsequent hypophysectomy, and that post-menopausal women who respond to œstrogens or androgens will probably also improve after hypophysectomy. And further remissions may result from hypophysectomy in patients who have already undergone oophorectomy and adrenalectomy. PEARSON et al.[12 13] believe that a favourable response to oophorectomy or androgen therapy means that the patient is likely to respond to hypophysectomy, but failure to improve on androgens or œstrogens does not preclude a subsequent response to hypophysectomy.

Some of the disappointments in the early days of hypophysectomy were undoubtedly due to the incomplete removal of the anterior lobe. Better results have been obtained since ZENKER's solution was applied to the sella to necrose remnants of pituitary tissue.[12 18] (RUSSELL's findings[30] indicate that division of the pituitary stalk is followed by selective necrosis of the anterior pituitary and almost total loss of pituitary secretion; but the promise of this simpler procedure does not seem to have been fulfilled.) The development of signs of hypopituitarism serves as a guide to the completeness of hypophysectomy.[14] If the gland has been completely removed, adrenal insufficiency appears within 2 to 3 days if no cortisone is given. The usual replacement therapy is 200–300 mg. cortisone daily, starting on the day before operation, and decreasing gradually after operation to 50 mg. daily by the end of the first week.[13 18] The Guy's team use larger doses (up to 400 mg. daily) for several days before operation, and they implant 300 mg. of deoxycortone acetate after operation. Occasional patients need no maintenance therapy, even though subsequent necropsy has shown that all anterior pituitary tissue was removed. After hypophysectomy the urinary 17-ketosteroid output falls to 0·5–2 mg. per 24 hours, the growth of axillary and pubic hair is retarded, and menstruation ceases; vaginal smears become post-menopausal in character after 1 week and completely atrophic after 2 to 4 weeks. Gonadotrophins usually disappear from the urine after 2 to 3 weeks but occasionally not for 2 to 3 months; but there are no definite menopausal symptoms. Hypothyroidism invariably develops, and the serum level of protein-bound-iodine usually begins to drop after a week and may fall to zero. A prompt fall is good evidence that the hypophysectomy has been complete. The ^{131}I uptake of the thyroid gland may fall equally promptly, but it often stays at about 10% of normal for some months and the thyroid gland may remain palpable for several months. The serum cholesterol level rises slowly by an average of 60 mg. per 100 ml. Clinical myxœdema does not usually appear until 1 to 2 months have elapsed and sometimes not for 4 to 6 months. 60–180 mg. of dried thyroid daily is needed to maintain a euthyroid state. A mild and variable degree of diabetes insipidus develops in

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[21] Shimkin, M. B., Boldrey, E. B., Kelly, K. H., Bierman, H. R., Ortega, P., Naffziger, H. C. J. clin. Endocrin. 1952, 12, 439.

[22] Gilbert-Dreyfus, Pertuiset, B., Savoie, J. C., Sebaoun, J. Ann. Endocr. Paris, 1954, 15, 351.

[23] Knowlton, A. I., Pool, J. L., Jailer, J. W. J. clin. Endocrin. 1954, 14, 20[illegible]

[24] Wolff, B. Guy's Hosp. Rep. 1957, 106, 53.

[25] Scowen, E. F., Hadfield, G. Cancer, 19[illegible], 8, 890.

[26] Hadfield, G., Young, J. S. Brit. J. Cancer, 1956, 10, 4[illegible]

[27] Hadfield, G. Brit. med. J. 1956, i, 91, 1307.

[28] Pearson, O. H., West, C. D., Hollander, V. P., Escher, G. C. J. clin. Endocrin. 1952, 12, 925.

[29] Emerson, K., Jessiman, A. G. New Engl. J. Med. 1956, 254, 252.

[30] Russell, D. S. Lancet, 1956, i, 46[illegible]

50–60% of patients[19 20] The polyuria can often be controlled by posterior-pituitary snuff (40 mg one to three times daily), sometimes pitressin tannate in oil (5 mg) is needed intramuscularly every second or third day[12 13 20] Other sequelæ of the operation include defects in the visual fields, anosmia, and occasional transient hemiplegia or oculomotor palsy[13 14] The operative mortality is said to be no higher than that of adrenalectomy (PEARSON[12] puts it at not more than 10%), and those who respond well may be able to return to a normal life

Ileitis, Ileostomy, and Cortisone

IT has been suggested that ulcerative colitis is the non-specific outcome of antecedent trauma from a variety of causes[1]—a hypothesis peculiarly difficult to establish, though a statistical approach based on reliable case-histories might prove profitable Meanwhile, the fringes of the central problem of what causes ulcerative colitis are being lightened in several ways, and ileitis provides an example Ten years ago it was common to hear about the dangers of retrograde ileitis following ileostomy The condition had a high mortality, and it was thought that ileitis secondary to the colonic disease spread rapidly up the small intestine after the interference of an ileostomy McCREADY et al[2] held that ileostomy was contraindicated in such circumstances, and, in order to avoid fistula and ileostomy diarrhœa, DENNIS[3] took the precaution of examining the ileum histologically at the site of section and, if he discovered evidence of ileitis, chose a higher level with normal ileum for the ileostomy COUNSELL[4] studied 18 cases of colo-ileitis from a series of 107 treated by primary colectomy or ileostomy and subsequent colectomy, he found that ileitis healed after either ileostomy or primary colectomy, whether the site of the stoma was involved or not BROOKE's results[5] were substantially the same in a late follow-up of 126 patients, excluding a patient with colo-ileitis who died from obstruction, ileitis did not recur in 14, half of whom had been followed for over three years

Why is there this discrepancy between the views of McCREADY et al and DENNIS and the evidence of COUNSELL and BROOKE? COUNSELL's explanation that a confusion had arisen between two conditions is probably correct WARREN and McKITTRICK[6] drew attention to the condition of ileostomy dysfunction, a complication arising soon after operation and made manifest by colic and much loss of fluid from the stoma This condition can arise without previous ileitis, and it is ascribed by some to partial obstruction at the stoma, by others to serositis at and proximal to the ileostomy Here is ileitis secondary to ileostomy, but differing histologically from ileitis secondary to ulcerative colitis Moreover, it can be responsible for perforation, which does not occur in the ileum affected by colo-ileitis, and it may lead to serious trouble and even death from electrolyte depletion It seems reasonable to suppose, therefore, that the ascending ileitis feared by McCREADY et al was due, not to pre-existing ileitis, but to an inefficient stoma, and COUNSELL has observed the condition following colectomy for familial polyposis Certainly "ascending ileitis" is rarely if ever seen today after an ileostomy, and this change coincides with a big fall in the incidence of ileostomy dysfunction—a fall brought about by the simple technique of mucosal eversion, which reduces stomal obstruction[5] and which is also thought by some[7] to eliminate serositis Other things have doubtless contributed to this improvement for example, catheters are no longer left indwelling at the ileostomy after operation, as was the custom ten years ago, and electrolyte imbalance, involving sodium and potassium in such a way as to render small-bowel propulsion less effective, is now better understood In centres where ileostomy is undertaken by experienced surgeons, an undiagnosed Crohn's lesion or enterocolitis, as described by COOKE and BROOKE,[8] is as likely to be the cause of post-ileostomy ileitis as is ileostomy dysfunction though COUNSELL's study of 200 cases at St Mark's Hospital shows that there is still doubt about the existence as a separate entity of the condition which COOKE and BROOKE described

Ileostomy dysfunction caused trouble in 130 of WARREN and McKITTRICK's 210 ileostomy patients, and it was responsible for the death of 7, its elimination is therefore a considerable achievement But no sooner is one bugbear overcome by surgery than another arises That cortisone can induce and prolong remissions in ulcerative colitis has been clearly proved by the Medical Research Council trial[9], but there are some patients who fail to respond and seem to be worse than before COOPER et al[10] noted that preoperative steroid therapy can make the colon friable at operation, and BROOKE[11] has drawn further attention to this hazard Dilatation of the colon, usually in its transverse part, was observed in the pre-cortisone era, and was a sign of impending perforation The same condition seems to develop with greater rapidity and malignancy under the influence of cortisone, and the bowel wall disintegrates to such an extent that it becomes replaced by whatever lies adjacent to it, usually the parietes or small bowel thus raising new and unusual difficulties for the surgeon trying to remove the colon The atony accompanying the dilatation can sometimes be so gross and extensive that colic results from the attempts of the small gut to propel its contents vis-a-tergo through the amotile reaches in front of it This colic and the gross abdominal distension have sometimes induced a mistaken diagnosis of mechanical obstruction by a stricture (in fact, stricture in ulcerative colitis rarely causes obstruction, probably because the fæces are so fluid) Ulcerative colitis is primarily a disease of the mucosa, though often the submucosa is affected as well, but when the colon is dilated, ulceration may be seen histologically to have attacked the muscle coat causing degeneration and destruction of muscle fibres over a wide area Dilatation and disintegration of the colon in cortisone-treated patients is probably due simply to the mechanical effect of a

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1 Brooke, B N Lancet 1953 i 1220 Lumb G Protheroe, R H B Ibid 1955 ii 1208
2 McCready R J Bargen A Dockerty, M B Waugh J M New Engl J Med 1949 240 119
3 Dennis C Surgery 1945 18 435
4 Counsell B Brit J Surg 1956 44, 276
5 Brooke B N Lancet 1956 ii 532
6 Warren R, McKittrick L S Surg Gynec Obstet 1951 93, 555
7 Hill L D Stone C S Pearson C C Arch Surg Chicago, 1956 72 968
8 Cooke W T Brooke B N Quart J Med 1955 24 1
9 Truelove S C Witts L J Brit med J 1954 ii, 375 Ibid, 1955 ii, 1041
10 Cooper D R Stahlgren, L H Ferguson L K Ann Surg 1956 144 19
11 Brooke B N Lancet, 1956 ii 1175

bowel wall of rotten fabric giving way under the load of its contents, and not to a state of inertia due to potassium loss. Indeed, serum-potassium levels are not consistently low in such patients, and serum values below 3·0 m eq. per litre have been recorded without dilatation. Besides, potassium depletion as seen in steatorrhœa or Crohn's disease causes a small-bowel atony leaving the colon relatively less disturbed, whereas the colonic distension of ulcerative colitis is seldom associated with similar small bowel changes. The fabric seems to rot as ulceration advances unchecked into the muscle, perhaps because cortisone hampers an adequate inflammatory response in this layer. There is substance, therefore, in the suggestion[11] that the degree or depth of damage to the bowel wall should be assessed radiologically before corticoids are given. If pockets are seen outside the bowel lumen or if what has been called "pseudohaustration" is apparent, these should be taken as danger signals, since ulceration has then certainly reached the submissive muscle layer.

Annotations

POLIOMYELITIS VACCINE

IT is almost two years since poliomyelitis vaccine was licensed for manufacture in the United States, and since then manufacturers, doctors, and the public have had their share of anxiety. But there is little cause for alarm in last week's news that distribution of the latest batch of the British vaccine must be delayed until a colour change in certain vials of vaccine, in store since mid-November, has been investigated. As things have turned out, it would of course have been better to defer the announcement from the Ministry of Health about the distribution of the vaccine until it had passed its final scrutiny.

The vaccine contains a colour indicator of pH which is a useful guide to the metabolic state of the tissue culture during growth of the virus. A change in pH during storage (indicated by the vaccine changing from pink to yellow) might be due to bacterial contamination which had escaped detection earlier in the manufacturing process. This has not apparently been a serious complication in the past. The cause of the pH change is now being investigated. The delay thus involved, disappointing though it is, illustrates the enormous care that is being taken to make the vaccine as safe and effective as possible.

There are clearly many difficulties still to be overcome in producing poliomyelitis vaccine, and at a recent meeting of the New York Academy of Sciences Dr. J. E. Smadel reported that, even after two doses of present-day commercial vaccine, antibodies sometimes failed to appear in children with no pre-existing antibodies to any of the three poliomyelitis viruses. Smadel thought that this might be due to the current practice of ensuring safety by repeated filtration, and consequent loss of antigenicity. From the start, the fundamental trouble with formalinised poliomyelitis vaccine has been the narrow margin between a vaccine which has not been sufficiently inactivated and contains live virus and a vaccine which has been over-formalinised and is not a sufficiently potent antigen. The result has been that different batches of vaccine supposedly made by the same methods, have varied greatly in their behaviour. It may have been unwise to invest so much in formalinised vaccine, and the possibilities of inactivating the virus in other ways should still be investigated.

DOCTORS AND UNEMPLOYMENT BENEFIT

A FEW years ago it would have been unthinkable that doctors should draw unemployment benefit, but some of them are doing so today. Most of these unemployed doctors are no more than temporarily out of work, and they are usually young men who have had difficulty in getting a house job, though there are rare instances where a hard-pressed registrar has asked for help. As we have earlier observed,[1] circumstances can arise whereby weeks and even months may be lost by a newly qualified man between his first and second preregistration jobs; and no longer can this period be filled profitably by a locum tenancy in general practice. During one appointment of six months few housemen can save much against a rainy day and some of them naturally turn to the State for support during the temporary lean period. Indeed, they have already contributed money as an insurance against this very predicament.

Another influence, perhaps more forceful than the preregistration year, is the climate of the times. As taxation eats into personal income and contributions to National Insurance make further inroads, it seems hard to reproach professional men for claiming their due from the State when they are in difficulties. On the other hand, it was no doubt the prevalence of the "claim-what-you-can" attitude, rather than real hardship, which led a newly registered doctor, who had a month to wait before his next appointment, to claim unemployment benefit for that period, with allowances for his two children, though his wife, also a doctor, would be continuing to earn. He even wondered whether he might successfully apply for National Assistance because the mortgage rates on his house were high. He had no doubts about getting unemployment benefit *for the* whole period, since it seemed unlikely that the labour exchange would be able to find him a job in his "trade" which he would in any case have to refuse because of the job to which he had already been appointed.

Such a story may shock doctors of an older generation; nevertheless, we hope they will not support the action of the dean of one medical school who (we understand) refuses testimonials to any man who has drawn unemployment benefit. Doctors have all the rights of other citizens, including the right to behave how they wish in such matters; and there are undoubtedly instances of genuine need.

FRACTURE OF THE ODONTOID PROCESS

CONSIDERABLE violence is usually necessary to fracture the odontoid process of the axis, and the injury is now most commonly seen after road accidents. The mechanism of the fracture has aroused much interest. Undoubtedly the sudden movement of the head upon the upper cervical spine imposes an immense strain upon the odontoid, which is probably damaged by a combination of traction and leverage through the alar ligaments. Wusthoff[2] has emphasised the importance of the transverse ligament in the production of *odontoid fractures*, but in certain lesions the anterior arch of the atlas must be of equal importance. Patients with this injury usually have severe pain, often radiating to the occipital region. The head is sometimes rotated, making X-ray examination difficult, and the patient may support it with his hands. Paraplegia is present from the start in about 10% of the patients who survive the immediate injury; but the proportion may really be *much* higher, since severe cord damage at this level is always fatal.

Up to the age of 6 years the primary centre of ossification of the odontoid is separated from the centre for the body of the bone by a cartilage plate. Blockey and Purser[3] have shown that in the young child the injury is similar to an epiphyseal separation, and is normally followed by firm bony union In the adult, however, bony union is uncommon and occasionally a late paraplegia follows Although this complication usually appears within the first year after injury, it has been reported as long as 28 years later If the paraplegia is due to instability, then early spinal fusion might be expected to lessen its incidence

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[1] *Lancet*, 1955, i, 240.
[2] Wusthoff *Arch f. Chir* 1923, 183, 73.
[3] Blockey, N. J., Purser, D. W. *J. Bone Jt Surg* 1956, 38B [illegible]

The early treatment of the fracture demands traction, and the skull calliper is undoubtedly the best method Careful positioning may assist reduction if the fragment is displaced, and by flexing or extending the head accurate alignment of the fragments is possible Even for the undisplaced fracture, light traction affords a convenient method of immobilisation If the fracture can be maintained in a good position for 3 months it may well unite, although even then fibrous union is not uncommon Such a result is compatible with good function and freedom from pain, but nervous complications may ensue

DEODORANTS AND THE SKIN

DEODORANTS are amongst the most commonly used cosmetic preparations, and they are marketed in the form of liquids, creams, pastes, powders, or sticks They are of two types substances which destroy or obscure the odour and those which, being astringents, diminish the flow of perspiration Most preparations contain a proportion of each type The first group includes such substances as sodium perborate, zinc peroxide, hexamethylenetetramine, chloramine-T, chlorothymol, oxyquinoline sulphate, perfumes, and essential oils Among the astringents, which act by precipitating skin proteins, thus blocking the ostia of the sweat-ducts, are formaldehyde, aluminium chloride, sulphate, and phenolsulphonate, zinc salicylate and phenolsulphate, tannic acid, and the tannates Formaldehyde is now rarely used, since, in an effective strength, it is a primary irritant The very efficient aluminium salts are often used in liquid preparations, they are also primary irritants and sensitisers, but their irritant effect can be eliminated by buffering the solution with urea

Dermatitis caused by deodorants is usually confined to the axillæ, where it takes the form either of a sharply limited erythematous vesicular eruption or a folliculitis Patch testing will confirm the cause of the eruption and distinguish it from dress shield dermatitis Rubin et al [1] have lately described a new type of local skin reaction in the axilla after the use of certain deodorants They record 4 cases in detail and they mention that they have already seen 11 other similarly affected patients Of the first 4 patients, 3 had used stick deodorants and 1 a liquid preparation After periods varying from two days to a month, irritation and an eruption suddenly appeared in the axillæ The rash consisted of dusky reddish-brown discrete papules 1–4 mm in diameter They were closely set in the domes of the axillæ and more sparsely placed at the periphery The lesions looked semitranslucent but no fluid could be extracted by puncture An "apple jelly" appearance was produced by diascopy Treatment with superficial X rays and topical hydrocortisone had little effect except for a slight yellowing in colour and moderate scaling

Histological sections from a biopsy specimen of an axillary papule from each patient showed a tuberculoid granuloma situated in the corium It consisted of epithelioid cells and Langhans giant cells surrounded by lymphocytes in typical tuberculoid pattern Necrosis was absent The sharp delineation of tubercles as seen in sarcoidosis was lacking The infiltrate lay along the course of the blood vessels Foreign bodies could not be detected by polaroscopic examination The stick deodorant used by 3 patients contained apart from the commonly used ingredients, sodium zirconium lactate, but this substance could not be demonstrated spectrographically in the biopsy specimen from 1 patient The lotion used by the 4th patient contained chlorhydroxyaluminium sulphate but no zirconium

Rubin et al say they cannot be certain of the cause of this granulomatous eruption They mention a linear distribution of lesions and they are now investigating the possible rôle of razor abrasions They do not say whether any or all of their patients wore dress shields and if so whether sensitivity to them had been excluded In any case, this type of granulomatous reaction is unusual and further observation is needed

OPEN HEALING OF TUBERCULOUS CAVITIES

EVEN after long periods of chemotherapy for chronic pulmonary tuberculosis, tubercle bacilli can often be cultured from the walls of cavities in resected specimens by simple [1] or elaborate [2] methods, and we have referred [3] to some of the changes in the lesions after chemotherapy Perhaps the most important, and certainly one of the most interesting, aspects of chronic tuberculosis is open cavity healing in the lungs—a type of healing recognised as very rare before the days of chemotherapy [4] Auerbach [5] pointed out that open cavity healing was commoner after chemotherapy (his examples referred to treatment with streptomycin plus *p*-aminosalicylic acid), that the cavity walls were thinner the sooner treatment was begun, and that the draining bronchus was re epithelialised Thomson [6] showed that the incidence of open cavity healing had risen remarkably with the introduction of isoniazid, and that two-thirds of such cavities became completely healed, though areas of minute ulceration were still present in the other third No tubercle bacilli could be seen in sections of the walls In resected lesions including more than cavities, Allen [7] found that over 10% were positive on culture and 10% on smear In 10% of Allen's patients the disease became active again after chemotherapy, even after conversion (by a combination of all three drugs) of gastric washings and sputum, and Allen recommends surgery after three or four months' chemotherapy, especially for thick-walled cavities, caseous masses over 2 cm in diameter, and bronchial stenosis or bronchiectasis

A careful clinical, pathological, and bacteriological study of persistent thin-walled cavities has lately been reported by Keers et al [8] From the first 10 out of 14 patients who had such cavities and whose sputum had been converted by a few months' chemotherapy of various combinations, the lesions were resected after a further four months' or more chemotherapy The walls of the cavities were sometimes uniformly smooth and sometimes trabeculated, and others showed large or small granular areas with or without caseous material or thin pus Histologically, the picture was just as variable, and there was evidence of activity even in cavities which looked smooth and shiny None of the cavities showed complete epithelialisation, though in several of them epithelium had grown from the junction between cavity and bronchus for 2 or 3 cm along the cavity wall Elsewhere a smooth fibrous wall sometimes seemed to have a surface layer of flattened fibroblasts Tubercle bacilli were identified (4 times by culture and 4 times by smear) in 5 out of 9 cavities from 8 patients Altogether 11 positive cultures were obtained from 3 patients (4 cavities) and of these, three strains from 1 patient were found to be resistant (two completely to P A S and partially to streptomycin, one partially to streptomycin), but all were sensitive to isoniazid and all were sensitive to a combination of the three drugs These results suggest that the common finding in America [9] of organisms sensitive to isoniazid after treatment with streptomycin and isoniazid is due not so much to the antagonism to streptomycin of the desoxyribonucleic acid in the cavity contents as to the low dose of streptomycin (1 g every third day), which means that the streptomycin and isoniazid cannot exert their mutual protection Keers and his colleagues combine their observations to show that only one of the cavities in their series could be described as "healed" and even then there was active tuberculosis elsewhere in the lungs They have 4 other cases with similar lesions under chemotherapy, and they point out that, while resection gives valuable information, more conclusive evidence can come only from long clinical follow up of such patients treated by chemotherapy alone

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[1] Rubin I Shapiro A H Weber L F Neuhauser I J Amer med Ass 1956 162 953

[1] See *Poumon* 1954 10 465 and the next 7 articles
[2] Hobby G L Auerbach O Lenert T F Small, M J , Comer, J V *Amer Rev Tuberc* 1954 70 191
[3] See leading article *Lancet* 1955 i 599
[4] Auerbach O *Transactions of the 12th* Conference on Chemotherapy of Tuberculosis U S Veterans Administration 1953 p 224 Medlar E M *Amer Rev Tuberc* 1955, 71 part ii 92
[5] Auerbach O *Amer Rev Tuberc* 1955 71 165
[6] Thomson J R *B.J* 1955 72 158 601
[7] Allen A P *Arch intern Med* 1956 98, 463
[8] Keers R Y Riddell P W Reid L *Tubercle Lond* 1956 37 401

Stewart et al [10] investigated bacteriologically and histologically 71 resected specimens of lung tissue, including 50 pulmonary cavities 11 were described as having smooth shiny walls, and no tubercle bacilli were cultured from 9 of them The 2 patients from whom bacilli were recovered had had less than twelve months' effective chemotherapy before operation The most important conclusion of this detailed investigation was that drug resistance and the duration of effective chemotherapy were the main factors affecting healing Viable bacilli were obtained from 96% of caseous foci and 95% of cavities in these patients in whom drug-resistant bacilli had been demonstrated in the sputum at any time, but the corresponding figures for the drug-sensitive group were 9% and 17% Only 2% of the lesions from patients who had had twelve to eighteen months' treatment were positive Stewart et al claim that chemotherapy can sterilise tuberculous lesions and that open healing of cavities can be achieved provided that only those combinations of drugs known to prevent the emergence of resistant bacilli are used and that treatment is continued for at least twelve months Even longer treatment may give greater chances of healing, and two years would not now be considered out of the ordinary Stewart et al suggest that a long period of chemotherapy may often prove a satisfactory alternative to surgical treatment This possibility is attractive, but some may feel that the evidence does not yet justify looking at ring shadows in the radiograph with anything but disfavour

The introduction of isoniazid is one of the reasons why it has been possible to collect so large a series of persistent thin walled cavities as Keers et al [8] have done The fact that isoniazid was part of the treatment of 11 of their 14 patients and in 12 of them radio opaque material entered 13 cavities, supports Thomson's finding that open healing of cavities is commonest after isoniazid Further support for this view comes from a study of urinary tuberculosis with cystitis, Borthwick [11] showed that the three combinations of streptomycin, isoniazid, and P A S all gave good results, but streptomycin plus P A S was more likely to lead to severe bladder contracture, isoniazid plus P A S was followed by practically no bladder contracture, and streptomycin plus isoniazid came in between the two in this respect Thus, if the aim is to produce fibrosis in any tuberculous lesion, streptomycin especially with P A S may be the best treatment (though the evidence that streptomycin promotes fibrosis is by no means complete) and to avoid fibrosis and promote as much resolution as possible, isoniazid plus P A S may be the choice And it may turn out that the same principle applies to lung cavities according to the density of their walls and the possibilities of drainage for thick-walled cavities which would never resolve but could be sealed off, streptomycin plus P A S may be best, for thin-walled cavities, to get as much drainage and then resolution as possible, a combination including isoniazid may be most effective At present however the choice of drugs cannot be based on these possibilities for one thing, they are little more than speculation and for another, different types of lesion are often found in the same patient

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[9] Russell W F jun Dressler S H Middlebrook G Denst J *Amer Rev Tuberc* 19[illegible] 71 441

[10] Stewart M Turnbull F W A MacGregor R *Tubercle Lond* 1956 37 3[illegible]

[11] Borthwick W M *Ibid* p 120

OFFICIAL OR PROPRIETARY?

FEW people have welcomed the Government's action in multiplying the prescription charges [1] A less unpopular line of attack on the National Health Service drug bill has been the effort to dissuade doctors from prescribing proprietary drugs, which are often (though not always [2]) more expensive than similar drugs supplied under the official title Many doctors agree in principle, but feel that certain proprietary preparations have an advantage in practice over the corresponding official preparations even though their content is apparently identical This view is supported by the findings of Bagnall and Stock,[3] who subjected 343 samples of barbiturate tablets to tests specified in the *British Pharmacopœia* The two most important of these are the disintegration test, which measures the capacity of the tablet to break up in the stomach, and the uniformity test, which measures the weight of the drug in the tablet [4] Thus the uniformity test determines whether the patient is receiving the intended dose, and the disintegration test is a guide to whether or not the drug will be absorbed Of the 343 samples, which included drugs marketed under both official and proprietary titles, 79 failed to conform to pharmacopœial standards, most failures were in the disintegration test 11 of the samples were proprietary mixtures which need not have complied with the *B.P.* requirements, but in fact all did so

Bagnall and Stock point to the startling difference in quality between the tablets of different manufacturers No fault was found in the 83 samples which represented four firms, but of the 67 samples representing two other firms no fewer than 42 were below standard The age of a tablet influences its disintegration, but 5 year old tablets from some firms behaved better than 5 week-old tablets made by others, and even 18 year old tablets made by one firm still fulfilled the *B P* requirement There were some surprising variations in the dose of active material among tablets of a given batch (up to 25%), and $^1/_2$ grain tablets were found in a tin labelled $1^1/_2$ grains.

Some drug manufacturers, on both sides of the Atlantic, spend a lot of money on research which is important even indispensable Other firms with lower standards make no such contribution, and they can thus undersell their competitors, but their products may be inferior Though a higher price does not guarantee a better product, a lower price often means a poorer one, even though both preparations carry the same pharmacopœial name If a doctor's experience has convinced him that certain proprietary medicines are better than those which may be supplied as official equivalents it is clearly his duty to reject what he considers an inferior substitute Until stricter control has ensured that the *B.P.* standards are maintained and that preparations which do not satisfy them are rarely if ever supplied, the Government cannot assure prescribers that official preparations are invariably as effective as the corresponding proprietaries

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[1] See *Lancet* 1956 ii, 929

[2] *Ibid* 1951 ii 815

[3] Bagnall H H Stock F G *Pharm J* 1956 177 441

[4] British Pharmacopœia London 1953 p [illegible]

Special Articles

PAPWORTH'S RESULTS

Rehabilitation of the Tuberculous under the Ministry of Labour Training Scheme 1948-55

OWEN CLARKE
M.D Camb, M R C P
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MEDICAL DIRECTOR, PAPWORTH AND ENHAM-ALAMEIN VILLAGE CENTRES

THE main effort made by the community on behalf of the disabled worker and his family takes the form of financial grants The idea of Papworth, first propounded by Varrier-Jones forty years ago, has been different—namely, to provide the tuberculous with work and wages under sheltered conditions

Up to the outbreak of the late war the hospital and industries at Papworth developed steadily, and they were able to play a part in the industrial war effort But, when more and more Servicemen required rehabilitation, there was obviously need for schemes of training that could be started early in treatment, while the men were still receiving their Service pay, and which should be directed to fitting them for normal civilian employment as soon as they were restored to health

The introduction of the National Health Act of 1948 opened the way for Papworth to extend this side of its work, and a coördinated scheme was started with the Ministry of Labour, who recognised Papworth and Enham-Alamein as training centres

The Scheme

Under this scheme patients can come to Papworth or Enham-Alamein as soon as they are fit for three hours work daily, and increase gradually to six hours daily No hard and fast rules are made about the length of residence, each patient is considered on his needs and training may last as long as three years The object is to place him in self-supporting work as soon as possible, though the aim must always be to see him trained sufficiently to command trade-union membership

A positive sputum is no bar to admission indeed it is one of the best reasons for admission because chemotherapy can be safely continued during training Papworth, because it is also a sanatorium, can offer earlier training than other centres which accept also men with other forms of disability

Selection

After perusal of radiographs and reports, patients (both men and women) are accepted on the assurance that the local chest physician thinks them fit to start three hours' work daily at once A few are interviewed first, but most of them arrive virtually unchecked and with little idea of their future programme

Some of our trainees were "old lags" whom chest physicians hoped to get rid of, some had been promised a house at once, some were youngsters whose careers had not yet started and who were eager to train, but most were ordinary folk whose lives had been upset by tuberculosis and who hoped for a fresh start in life

The first three months is regarded as a probationary period during which the trainee, the chief medical officer, and the industrial manager can assess the future The patient may not, in fact, be fit enough to start work, he may be uncooperative or unsuitable for training, or he may not like what he finds and may prefer to go home In view of our method of acceptance this trial period is a valuable safeguard

Seven Years' Results

From 1948 to 1955 926 men and women were accepted for training at our two centres, Papworth and Enham-Alamein Of these, 63 (7%) did not complete the probationary period Of the remaining 863, 211 were still in training at the time of the review Of the 652 who had terminated training 162 (19%) had been "colonised"—i e, they had reached a standard of industrial proficiency acceptable to the appropriate trade union and had been offered work at Papworth A further 60 trainees had completed training to the satisfaction of the authorities, but had decided not to remain at Papworth Many had been offered employment nearer their homes

Reasons for Leaving Prematurely

409 (47%) ended their training prematurely for the following reasons

To take other work	120
To a different training course	23
Marriage	15
Other domestic troubles	61
Unsettled (own request)	66
Discharged (unsuitable)	47
Unfit (requiring treatment)	70
Died	7

It will be seen that a third of this group left either to take other work or to change on to a different training scheme Obviously it is not possible to provide more than a few trades at one centre, and transfers to other centres were arranged by the authorities if the man seemed a responsible person, medically fit, and likely to continue training These figures show that 365 (56%) of those who left the scheme had either completed training (34%) or found work elsewhere, they form the obvious successes

Those who left to take other work usually had found more suitable or more congenial employment nearer home Many of them had come to Papworth because they could not get such work, and their departure was a satisfactory sign of increasing skill and increased confidence in themselves

The "domestic" reasons for leaving cover the sad difficulties which accompany long separation it is wisest to recognise the inevitable, and if the man returns home the disruption of a family may often be avoided One effort at rehabilitation is of small significance in a man's life, compared to the permanent tragedy of a broken marriage In considering requests for early discharges and extra leave the training centre must always be prepared to compromise

The 66 who left of their own accord because they were 'unsettled," and the 47 who were discharged as unsuitable together make 13% of the entry This percentage is comparable to the self discharge rate of many sanatoria Most of them had not been on the training scheme for six months and were still only doing three hours work daily It may be that an adequate explanation of their progress had not been given to them, or that they were temperamentally unsuited to a long apprenticeship Whatever the cause, in this group the training was unsatisfactory, though they were assessed as suitable during their probation

Length of Training

Of the 402 who left, 278 had been training for more than six months, and 265 were working five hours or more a day The following figures show the time spent at each grade of training by those who completed the training (A) and those who did not (B)

	(A)	(B)
3 hours' work daily	25 weeks	23 weeks
5 hours' work daily	31 weeks	23 weeks
6 hours' work daily	41 weeks	11 weeks

The real difficulty thus lay in the long period on six hours daily which was needed to reach an adequate industrial standard Obviously training cannot be really intensive until the man is working almost a full day Those who liked the work stayed the full time those who were impatient, or needed better money left as soon as they felt confident of their *medical* stability, or sought a livelihood elsewhere regardless of the risk to their health

When considering the length of the training it must be remembered that most of the trainees were starting industrial work at a time when they would otherwise be doing grade work in a sanatorium The first six months, therefore, is one of careful medical control The training is recognised by the trade unions as apprenticeship in a trade the usual apprenticeship in ordinary industry is three, five, or more years, and a shorter period is accepted for medical trainees only because they are older men and can progress to responsibility more quickly

On the average, trainees spent six months on three hours work only, to allow adequate rest during the afternoons This is essentially a period of medical rehabilitation The period on five and six hours' work is industrial training Usually the trainees are ready for colonisation during the second year, but 68 severely disabled patients took over twenty-four months

Absenteeism

We have defined absenteeism as any absence from work of less than four consecutive weeks, whatever the cause Longer periods of absence are considered as relapse This criterion is stricter than that used by the Ministry of Labour for fit people in normal industry, and yet, as the following figures show, our results are as good

Daily work span	Absenteeism during training	
	Subsequently colonised	Left before colonising
	(total 162) (%)	(total 469) (%)
3 hours	4 5	6 8
5 hours	5 2	6 7
6 hours	4 5	6 7

In both groups the absentee rate is remarkably constant, but it is lower among those who later colonised The records of 50 settlers who have worked in the colony for upwards of thirty years showed the same absentee-rate of 4 5% The rate throughout industry for 1953 was 4 2% Judged by these figures, the worker who has had tuberculosis is reliable and industrious, and does not have an unduly high absentee-rate There is so much at stake, and his chances of employment are relatively so much less, that this is to be expected

Relapse

Any absence from work for more than four consecutive weeks was counted as a relapse This obviously includes many cases in which the illness was unrelated to tuberculosis—e g, one fractured femur due to a motor accident

Of the 631 trainees 149 had a " relapse " during training, but 86 were able to resume training after treatment, and 24 of these did in fact later colonise These figures were for 1948–55, and it is uncertain what effect long term chemotherapy will have on relapse rates

The fact that so many of those who relapsed were able to go on with their training shows the value of a training centre where patients can if need arises be admitted into hospital, and after treatment resume training without losing the benefit of their previous experience Only under such conditions can training be started early in a disease whose prognosis is so fickle This arrangement gives the maximum of security and opportunity to the marginal cases in which the patient would otherwise have no hope of regaining his economic independence within a reasonable time No private employer could be expected to carry such a risk no standard scheme of training for a fixed period on a full day's work could accept these patients in the early stages without excessive risk

Sputum-positive Patients

Village settlements have been criticised for abandoning their original principles in order to achieve economic success Most of the patients admitted nowadays, it is said, are so fit that rehabilitation is unnecessary There are two replies to this assertion

Firstly, most of the trainees have come to Papworth because they were unable to find employment near home This may have been due to their medical condition or to natural reluctance and anxiety about resuming work after a long period of treatment in which the need for rest was so constantly emphasised In either case training for a trade was valuable because it produced a feeling of confidence and ability as well as giving the man a skill with which to earn his living

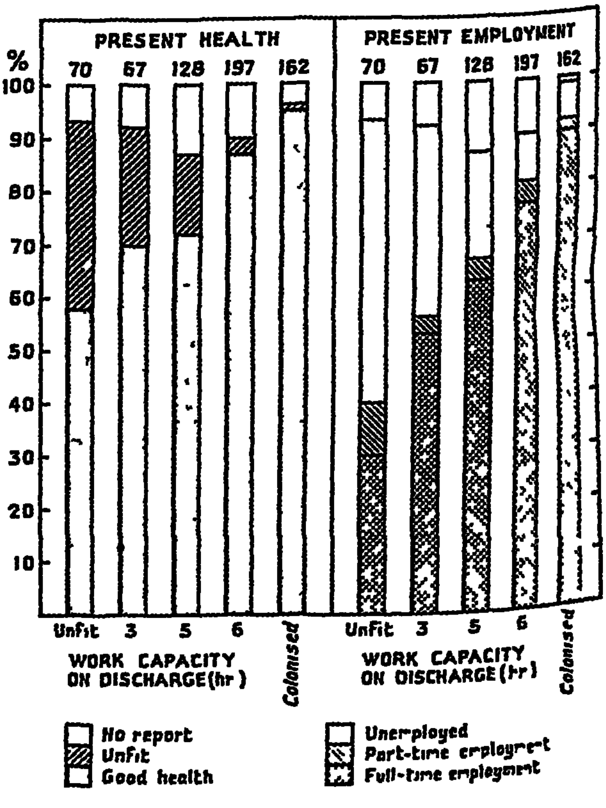
Secondly, 214 (25%) of those accepted for training had a positive sputum on admission, and they have been included in all the results discussed During their training chemotherapy and/or collapse therapy was started in an attempt to convert the sputum One of the earliest trials of ambulant chemotherapy reported in this country was done on these trainee patients

In 137 patients the sputum was converted during training, and has remained negative during the follow up period 77 patients remained sputum-positive throughout, but 15 of these were not considered suitable for any treatment

Follow-up

Of the trainees who left the scheme either by colonisation or to return home 91% have been traced and have provided information of their present status, health, and employment (see chart) 88% remain under regular medical supervision

The term " good health " implies that the man feels well, is living a reasonably normal active life, and has



been told by his doctor that he is fit for work Those who persisted with their training show a better health record and a better employment state

Of those who left while only doing three hours' work, 76% are now considered fit, but only 51% are in full-time work. Of those who remained to a six-hour grade 87% are reported fit and 77% are fully employed Of the colonists 90% are in full work at union rates of pay

Only 5% have managed to find part-time jobs To advise a patient to take light unskilled part-time well-paid work is as unrealistic today, even in a period of full employment, as it was at the birth of Papworth

Discussion

The nature of tuberculosis and the rôle of the settlements has changed since they were founded Today treatment can aim at recovery and subsequent employment For many patients their old job is open others have no job or an unsatisfactory one A long illness offers them opportunity to train for a better job

Rehabilitation in tuberculosis should start at the time of admission to hospital and should continue until the man is satisfactorily placed in employment It should be more than a diversion or occupational therapy · it should be practical training in a chosen trade The trainee deserves the same individual attention as a patient his rehabilitation must be planned in the same way as his treatment As early as possible he should start a few hours' work in a factory, again doing a normal man's job and producing sensible saleable articles

Time must not be wasted with purposeless grade work and futile occupation to pass the time Time is precious to a young man, and doctors must not regard as trivial the valuable months of other people's lives Rising morale due to clinical recovery must be harnessed as the driving force of full and final economic recovery

If this is true in tuberculosis it is also true of many other diseases which leave a disability and prevent return to previous employment In many of them treatment and training could proceed together, and the time could be used to good purpose instead of being a burden on the mind Often the period of illness can be used to train a man for a job within his future capacity and ensure his continued economic independence

Papworth has changed its routine to keep abreast of requirements the Ministry of Labour scheme is built on that experience and its results are good

MEDICAL INSURANCE AGENCY

THE Medical Insurance Agency, which this month reaches the half-century mark, was puny in its earliest years and none too robust in those that followed, but now, in full maturity, it is massive and sound, vindicating the judgment of the two men who had the idea of bringing it into being These two were Dawson Williams, editor of the *British Medical Journal,* and Squire Sprigge, editor of *The Lancet* The story goes that, meeting for luncheon, they fell to talking of the large commission which an agent had received for a life assurance policy taken out by a doctor, and this led them to agree that an organisation should be set up to secure the best possible terms for each doctor, paying rebates to the insured persons and turning over the surplus to medical charities

The first meeting of the Agency (known until 1913 as the Medical Insurance Committee) was held on March 7, 1907, under the chairmanship of Radcliffe Crocker, treasurer of the British Medical Association (Throughout its fifty years the Agency has been powerfully supported by the association, but has always operated independently) In 1909, on Crocker's death, G E Haslip took over the chairmanship, approaching his task with lively vigour In its first years the Agency had been concerned chiefly with insurance against risks under the Workmen's Compensation Act of 1906, but in 1909 motor-car business was undertaken and proved immediately successful, and in the next few years life assurance increased apace After Haslip died in 1924, Sir Humphry Rolleston was appointed chairman, holding office until he resigned in 1942, when he was succeeded by Sir Robert Hutchison When he, in turn, resigned in 1947, Dr James Fenton was elected, and he continues in office

In the early years after the late war, the Agency arranged many loans for the purchase of practices When the National Health Service Act came into force in 1948, these purchases stopped, but the gap was largely filled by loans for housing Since the end of the war the business transacted by the Agency has grown impressively Whereas in 1946 premiums collected amounted to £450,000, in 1956 they totalled over £2 million, and whereas in 1946 £5000 was distributed to medical charities, by 1954 the figure had increased to £24,500 Much of this success can be ascribed to two men—Dr Henry Robinson, the hon secretary since 1938, and Mr A N Dixon, the general manager After his appointment, Dr Robinson took a leading part in a thorough overhaul of the Agency's affairs, and it was decided to secure a trained insurance expert as manager Mr Dixon's appointment (he was one of 550 candidates) resulted

The Agency's reputation stands deservedly high In seeking insurance through it a doctor serves well not only himself and his own family but others less fortunately placed It is not often that two such diverse purposes can be so surely achieved by a single step

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Medicine and the Law

Subject to Correction

A COLLIERY worker, whose right eye had been injured in an accident at work in 1936, suffered a further injury at work, this time to his left eye, in March, 1955, as a result of which he was rendered almost totally blind He claimed disablement benefit under the National Insurance (Industrial Injuries) Act, 1946, which requires, where a worker has suffered injury to a " paired organ," that the medical board must assess the extent of disablement in accordance with regulation 2(5) of the National Insurance (Industrial Injuries) (Benefit) Regulations, 1948 Two medical boards made provisional awards assessing the extent of the disablement at 100%, but a third board, in March, 1955, made no award The worker thereupon appealed to the Medical Appeal Tribunal at Newcastle-upon-Tyne, which, on June 13, 1956, made an award assessing the disablement at 20% That award showed clearly that the tribunal had overlooked the requirements of regulation 2(5)

The worker applied *ex parte* to the Divisional Court of the Queen's Bench Division, asking *inter alia* for an order of *certiorari* to quash the tribunal's decision on the ground that there was a manifest error of law on the face of that decision The Divisional Court dismissed the application, but the Court of Appeal gave leave to appeal When the appeal came on for hearing, counsel for the Ministry of Pensions and National Insurance and for the tribunal conceded that there was such an error and did not oppose the application for *certiorari*, he also stated that the tribunal would redetermine the claim and make a new assessment, but the Court took time to consider whether it had jurisdiction to make the order asked for, in view of the fact that section 36(3) of the Act of 1946 provides that " any decision of a claim or question . shall be final "

Lord Justice DENNING, reading his reserved judgment, said that it was clear that the tribunal had gone wrong in law, and its error appeared on the face of the record The point then arose as to the effect of section 36(3) of the Act of 1946, which said that "any decision of a claim or question shall be final" Did those words preclude the Court of Queen's Bench from issuing an order of *certiorari* to bring up and quash the decision? On looking again into the old books his Lordship found it very well settled that the remedy by *certiorari* was never to be taken away by any statute except by clear and explicit words The word "final" was not enough, it meant only "without appeal" It made the decision final on the facts but not on the law

The value of this ancient writ was well shown by the present case, for it was only by reason of it that a workman blinded at work had obtained the industrial-insurance benefit to which he was by law entitled, as now acknowledged on all hands The order must issue to quash the tribunal's decision The tribunal would consider the claim afresh and no doubt come to a right decision on it

Lord Justice ROMER, concurring, said that it would have been deplorable if the Court had been constrained to hold that the decision of a medical appeal tribunal, however obviously wrong in law, was immune from review by Her Majesty's Courts The tribunals did their work conscientiously and efficiently, but in the nature of things they were bound to go wrong from time to time in matters of law Their members consisted in the main of people who had devoted their lives to activities far removed from the study and practice of the law and neither by *training nor experience could they be expected to have* that knowledge of the principles of construction which was so necessary for the proper understanding and application of the statutes and regulations which often came before them

Lord Justice PARKER delivered a concurring judgment The appeal was allowed

Regina *v* Medical Appeal Tribunal *Ex Parte* Gilmore *Court of Appeal* (Denning Romer and Parker *L JJ*) Feb 24 1957 David Turner Samuels (Gaster & Turner for I E Geffen, Durham) Rodger Winn (solicitors Ministry of Pensions and National Insurance)

M M HILL
Barrister at-Law

Difference in Technique not Negligence

On Aug 19 and 23, 1954, the plaintiff, then aged 54, a voluntary patient in a mental hospital suffering from an anxiety state was given electro convulsive therapy (E C T) During the course of the treatment on Aug 23, he sustained bilateral "stove in" fractures of the acetabula In accordance with his normal practice the doctor treating the plaintiff had given the E C T "unmodified"—i e, without using relaxant drugs and without applying any form of restraint other than to support the plaintiff's chin and to hold his shoulders The treatment was given while the plaintiff was lying on a couch and the precautions taken were the use of a gag and the presence of nurses on each side of the couch in case he fell off The plaintiff sued the hospital management committee for damages for his injuries, his case was, in effect, that they were negligent (1) in failing to warn him of the risks involved so that he had had no chance of deciding whether or not to take those risks, (2) in failing to use any relaxant and/or anesthetic drug, and (3) since they had not used any relaxant drug, in failing to provide at least some form of control beyond that which was given The defendants denied negligence

The doctor who had been in charge of the plaintiff gave evidence to the effect that he was normally opposed to the use of relaxant drugs as he considered that there was, with their use a risk of mortality while he considered the risk of fracture with unmodified E C T to be minimal, he said that he only gave relaxants in selected cases where the risk of unmodified E C T would be greater than usual, and that there was no special reason why the plaintiff should have been given a relaxant drug Witnesses called by either side gave evidence as to the different techniques which they adopted in giving E C T some used restraining sheets, some relaxant drugs, some manual restraint, but all agreed that there was a firm body of opinion which was opposed to the use of relaxant drugs as a matter of routine although one witness, called by the plaintiff, preferred to accept the risk of relaxant and eliminate the risk of fracture The witness called for the plaintiff considered that, if a relaxant drug were not given, it would be unwise to give E C T without some form of manual restraint, the defendants' evidence was that they used to provide manual control but had not done so since 1951, that it was their view that the less restraint there was, the less the risk of fracture, and that that view was borne out by their experience Two of the witnesses treated their patients in an ordinary hospital bed covered by the bedclothes, and one of those agreed that the mattress and bedclothes to a certain extent absorbed and restrained the convulsive movements of the patient As to warning patients of the risk, it appeared that it was the practice of defendants' doctor to say little about the treatment and to wait for the patients to ask questions, he did not think it desirable to say anything about risks unless asked, if asked, he said that there was a very slight risk The plaintiff's witness thought that it was not right not to warn a patient of the risk of fracture It also appeared from the evidence that the nature of the plaintiff's injury was exceptional

Mr Justice MCNAIR, summing up to the jury, said that they must bear in mind the enormous benefits which E C T conferred upon patients suffering from certain forms of mental illness The use of E C T was progressive and they might well think that even today there was no standard settled technique with which all competent doctors would agree on all points Where there was a difference of opinion among medical men, a doctor was not negligent if he acted in accordance with a practice accepted by a competent body of medical men skilled in that particular art In other words a doctor who acted in accordance with a particular practice was not negligent merely because there was a body of opinion which took a different view, but at the same time that did not mean that a doctor could obstinately and pig headedly carry on with some old technique if it was proved contrary to substantially the whole body of medical opinion It was not for the jury to decide which of two practices was the better

The allegation that the failure to warn was negligent raised two questions First, did good medical practice require that a warning should be given to a patient before receiving E C T? The jury might well think that a doctor, dealing with a mentally sick man and having a strong belief that his patient s only hope was E C T should not be criticised if he did not stress the dangers which he believed to be minimal If they thought that a warning should have been given, then the second question was what difference would it have made? The plaintiff, the only person who could have answered had not been asked that question, and unless they were satisfied that he would not have taken the treatment if he had been warned they might well think that there was nothing in that point As to the other allegations of negligence it was for the jury to decide on the evidence whether or not the defendants, in failing to take the action which the plaintiff alleged should have been taken had fallen below the standard of practice recognised by a reasonably competent body of medical opinion The evidence as to the use of restraints showed that there were different ways of carrying out the treatment but it was not right to take that as condemning the practice adopted by the defendants

The jury found for the defendants, and his Lordship entered judgment for the defendants, with costs

Bolam v Friern Hospital Management Committee Queen's Bench Division (McNair J, and a jury) Feb 26, 1957 N R Fox Andrews, Q C, and Roger Ormrod (Pennington & Son), James Stirling Q C and E Sutcliffe (J Tickle & Co)

J F LAMB
Barrister at Law

Public Health

A TUBERCULIN SURVEY OF 1285 ADULTS WITH SPECIAL REFERENCE TO THE ELDERLY

D GIANNINI
L R C P E
REGISTRAR

R S SLOAN
M B Glasg, D P H
LATE JUNIOR HOSPITAL MEDICAL OFFICER

RUCHILL HOSPITAL, GLASGOW

TUBERCULIN testing in the course of routine clinical work at this hospital has disclosed a surprisingly high number of non-reactors among older people For this reason a systematic survey of adults was made

Material

Tuberculin tests were made on persons aged more than 15 It was impossible to survey the general population, but it was thought that a survey of patients admitted to hospitals serving the northern area of Glasgow would be sufficiently representative Certain patients were excluded

(1) Those with, or suspected of having, tuberculosis

(2) Those with conditions which affect tuberculin sensitivity—e.g, acute illnesses, illnesses producing grave debility, collagen diseases, and reticuloses

(3) Those receiving treatment which might affect tuberculin sensitivity—e g, cortisone and corticotrophin

Methods

Tuberculin sensitivity was tested for by the injection of Old Tuberculin (Evans) into the skin of the volar aspect of the forearm The initial dose was 10 T U (0 1 ml of 1/1000 dilution O T) Care was taken to exclude technical errors—e g, from a leaking syringe—but, to make doubly sure, a second test, using the same dilution of Old Tuberculin, was made if the result of the first was negative If this second test was negative, a third test, using 100 T U (0 1 ml of 1/100 dilution O T) was made

The results were read at seventy-two hours If the greatest diameter of the area of induration was 6 mm or more, the test was regarded as positive

To ensure uniformity, both of us were present when the tests were made and the results read

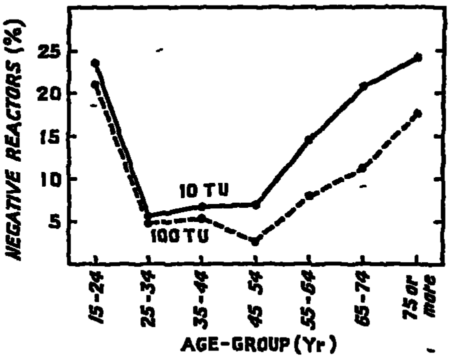

Fig 1—Negative tuberculin reactors in 1285 patients (695 male and 590 female)

Results

1285 patients (695 males and 590 females) were tested

Table I shows the distribution of negative reactors to tuberculin in successive age groups It will be seen that almost 25% were negative to 10 T U (1/1000 O T) in the age-group 15–24 In the next three age-groups the proportion of negative reactors was very much smaller, but, from the age group 55–64 onwards, the proportion increased, until in the age-group 75 or more it was similar to that in the age-group 15–24 The trend for non-reactors to 100 T U (1/100 O T) was similar Fig 1 shows this distribution graphically

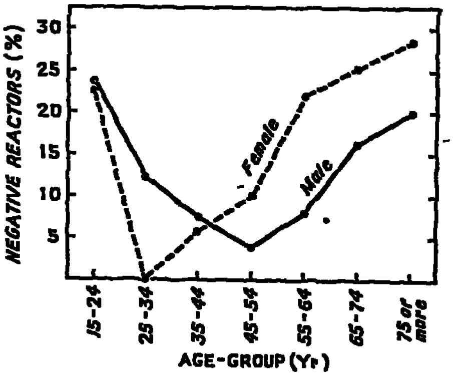

Fig 2—Negative tuberculin reactors to 10 T U according to sex in 1285 patients

Table II presents the distribution of negative reactors to tuberculin in successive age-groups for males and females separately In males there was a gradual decrease in the percentage of non reactors both to 10 T U and 100 T U from the age group 15–24 to the age group 45–54, whereas in successive age-groups over the age of 55 there was a corresponding gradual increase The proportion of female non-reactors to 10 T U decreased very

TABLE I—AGE-DISTRIBUTION OF NEGATIVE TUBERCULIN REACTORS AMONG 1285 ADULTS

Age group (yr)	15–24	25–34	35–44	45–54	55–64	65–74	75 or more
No of persons	124	105	157	228	242	230	199
Negative to 10 T U 1/1000	29 (*23 4%*)	6 (*5 7%*)	10 (*6 4%*)	15 (*6 6%*)	34 (*14 1%*)	47 (*20 4%*)	47 (*23 6%*)
Negative to 100 T U 1/100	26 (*20 9%*)	5 (*4 8%*)	8 (*5 1%*)	5 (*2 2%*)	18 (*7 4%*)	25 (*10 9%*)	34 (*17 1%*)

TABLE II—NEGATIVE TUBERCULIN REACTORS, MALE AND FEMALE, IN SUCCESSIVE AGE-GROUPS

Age group (yr)	15–24	25–34	35–44	45–54	55–64	65–74	75 or more
Males (695)							
No of persons	71	50	81	126	138	118	111
Negative to 10 T U 1/1000	17 (*23 9%*)	6 (*12%*)	6 (*7 4%*)	5 (*3 9%*)	11 (*7 9%*)	19 (*16 1%*)	22 (*19 8%*)
Negative to 100 T U 1/100	17 (*23 9%*)	5 (*10%*)	4 (*4 9%*)	1 (*0 8%*)	6 (*4 4%*)	7 (*5 9%*)	14 (*12 6%*)
Females (590)							
No of persons	53	55	76	102	104	112	88
Negative to 10 T U 1/1000	12 (*22 6%*)	0	4 (*5 3%*)	10 (*9 8%*)	23 (*22 1%*)	28 (*25%*)	25 (*28 4%*)
Negative to 100 T U 1/100	9 (*17%*)	0	4 (*5 3%*)	4 (*3 9%*)	12 (*11 5%*)	18 (*16 1%*)	20 (*22 7%*)

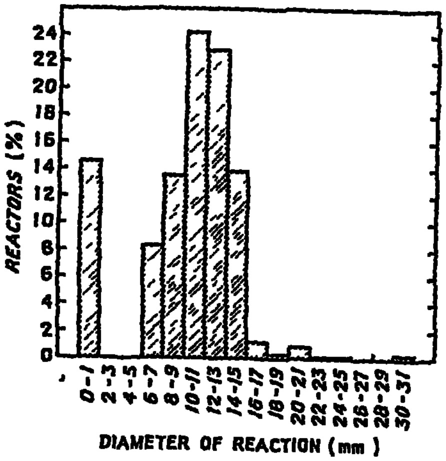

Fig 3—Reactions to 10 T U by size in 1285 patients

sharply from 22 6% in the age-group 15–24 to nil in the age-group 25–34 and increased again sharply from the age group 35–44 onwards The trend for female non-reactors to 100 T U was similar It is seen too that the proportion of non-reactors was larger among females than among males after the age of 45 Fig 2 shows graphically the distribution of non-reactors to 10 T U (1/1000 O T) in males and females

Fig 3 shows the distribution of reactions to 10 T U (1/1000 O T) by size in 1285 patients Fig 4 shows similarly the distribution of reactions to 100 T U (1/100 O T) by size in 188 patients who were negative to two 10 T U (1/1000 O T) tests Experience has shown that, in recording the size of reactions, there is a bias in favour of approximating to even numbers (Meyer 1951), in figs 3 and 4 reactions are therefore recorded as 0 and 1 mm , 2 and 3 mm , 4 and 5 mm , &c It is seen that, with both dilutions of O T , positive and negative reactions are clearly separated

Fig 5 is designed to show the influence of sex and age on the size of positive reactions For each age group the average size of reaction is shown in males and females It is seen that the average size of positive reactions in males was greatest in the age group 25–34 and progressively diminished in succeeding age groups In females the average size of reaction was greatest in the age group 15–24 and decreased progressively in succeeding age groups until it reached its lowest limit in the age group 55–64 It increased somewhat in the age group 65–74 and again in those aged 75 or more Although the average size of reaction was smaller in the older age groups than in the younger age groups, the difference was only 2 mm Histograms of the size of reactions were made for each age group of the sexes separately These displayed a well-marked mode around 9–13 mm for both sexes and for all age groups up to the age of 54 The succeeding decade showed a more even spread over 6–15 mm , and thereafter there was no constant picture

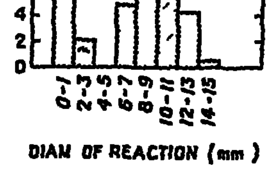

Fig 4—Reactions to 100 T U by size in 188 patients

Discussion

If the adult hospital population surveyed is representative of the population at large, it seems that, after the age of 55, the proportion of negative reactors increases with age Few published reports of tuberculin surveys include all age groups, but the results of Furcolow et al (1948) Meyer (1951), and Bellomo (1952) are similar to our own It is true that Bellomo states that the younger the individual the less likely is he to be a reactor to tuberculin, but Bellomo's figures show an increase in the proportion of negative reactors in people aged more than 60 Amazon (1943) and Coury and Marland (1948) found in old people an increase in the proportion of negative reactors in successive age groups, but that found by Coury and Marland was not striking

The comparatively high proportion of negative reactors in the older age groups in the present investigation can scarcely be explained on the basis that these people have never been infected with tuberculosis, for there is no evidence to suggest that during their earlier years they were less exposed to infection than were later generations, indeed the reverse is the case

Moreover Amazon (1943) and Groth Petersen and Wilbek (1955) found radiological evidence of previous tuberculosis in many elderly persons in whom tuberculin tests were negative Indeed Groth-Petersen and Wilbek concluded that, although a negative 10 T U test in persons aged less than 50 probably indicated absence of previous infection with tuberculosis, this interpretation could not be made in the case of persons aged more than 50 The fact that the investigations of Groth Petersen and Wilbek showed negative reactions in persons with evidence of previous tuberculosis in chest films tends to dispose of the improbable proposition that a high percentage were never infected at all

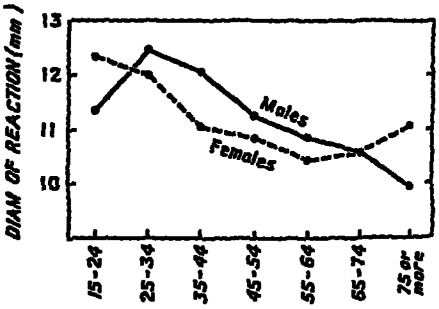

Fig 5—Average size of positive reactions to 10 T U by size and sex in 1285 patients

The increasing proportion of negative reactors in the older age groups could be explained by a waning of skin sensitivity to tuberculin with the passage of time Eventual complete loss of skin sensitivity might indicate that the tubercle bacilli in the body had died or, if still living, they had ceased to provide a sufficient stimulus On the other hand, it might simply be that, with age, the skin loses its power to react to various stimuli including tuberculin

The assumption that the reaction to the tuberculin test tails off gradually with age until it disappears is not supported by the results of this investigation It seemed that an all or none law operated In all cases in which a negative reaction was recorded to 10 T U (1/1000 O T) there was no induration at all , and in the negative reactors to 100 T U (1/100 O T) there were only four reactions with any induration, and these measured 2–3 mm , well below the 6 mm measurement required for a positive result

The significance of a positive reaction to the tuberculin test in relation to the quantity of antigen injected has been studied by Bates et al (1951) and Palmer (1953) who concluded that most reactions elicited by a small dose intradermal test (5 T U) indicated infection with tubercle bacilli, but that a positive reaction only to a large dose test, such as 100 T U or 250 T U , might be non specific They suggested that, in certain geographical areas, this large dose reaction might indicate infection by an organism antigenically related to the tubercle bacillus but non pathogenic for human beings

Palmer (1953) also found a wide scatter in the sizes of reaction to large doses of tuberculin (250 T U), making the separation of positives from negatives arbitrary In the present series there was a clear cut separation of positive and negative reactors to 100 T U (fig 4)

The morbidity and mortality from pulmonary tuberculosis in older men are comparatively large, and acute forms of tuberculosis are not uncommon in the older age-groups (Rich and McCordock 1929, Spain 1947, Ball et al. 1951, Lees and Munro 1954, Allan et al 1956) There may be some connection between loss of skin sensitivity to tuberculin and susceptibility to tuberculosis, but, as the proportion of non-reactors among elderly women is even greater than among elderly men, and the morbidity and mortality among elderly women are much less than among elderly men, it seems that other and more important factors operate

Summary

A tuberculin survey of hospital patients aged 15 or more was made, 1285 patients (695 males and 590 females) being tested

Patients with diseases or receiving treatment likely to affect tuberculin sensitivity were excluded

An initial injection of 10 T U was given followed by a further injection of 10 T U if the result of the first test was negative If this second test was negative, a third test, using 100 T U, was made

After the age of 34 in women and 54 in men the proportion of negative tuberculin reactors increased in successive age-groups

We are grateful to Dr A W Lees and Dr G W Allan for their help and encouragement, the clinicians of the Western District Hospital, Stobhill Hospital, and Ruchill Hospital for their coöperation in this investigation, and the Board of Management for Glasgow Northern Hospitals for assistance

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Infectious Diseases in England and Wales

Disease	Week ended February			
	2	9	16	23*
Diphtheria	5	9	2	2
Dysentery	1097	1290	1274	1296
Encephalitis				
Infective	2	5	6	1
Post infectious	2	3	2	2
Food poisoning	181	165	187	139
Measles excluding rubella	13 049	16 752	19,710	21 317
Meningococcal infection	32	28	30	26
Ophthalmia neonatorum	21	20	21	27
Paratyphoid fever	10	3	6	8
Pneumonia primary or influenzal	661	720	676	625
Poliomyelitis				
Paralytic	28	21	31	30
Non paralytic	9	13	6	9
Puerperal pyrexia	234	232	270	237
Scarlet fever	865	869	831	890
Smallpox				
Tuberculosis				
Respiratory	631	666	643	672
Meninges and C N S	9	5	7	6
Other	78	70	74	80
Typhoid fever	3	6	1	1
Whooping-cough	3302	3148	3163	3190

* Not including late returns

In England Now

A Running Commentary by Peripatetic Correspondents

The view has lately been expressed that the sculpture on the proposed Government building in Marylebone should not consist entirely of mongoloid women in an advanced state of elephantiasis Why ever not? It seems a magnificent Trans-Ural gesture for reorientation of the foreign-policy facies which we present to the wider world The œdema of our dependent parts at least is realistic The fragments of our civilisation may one day be dug out of the rubble of our self-immolation to stand alongside the masterpieces of the fifth century B C in some global museum

How instructive it will be to bequeath a record of our pathology The accessory auricles and polymastia of Roman statuary will be eclipsed by the twilight genius of the Atomic Age I wonder if the new-world research-workers will divine that we carved hydrocephalic and anencephalic busts for Burlington House long before our genes mutated in the First Ionisation Period Perhaps they will feel pity for the exfoliative dermatitis of bronze portraiture, admire the acromegaly of our business tycoons, envy the androgen activity of our virile torsos Will we have time to immortalise our ladies swinging back to Titian, or shall we just scratch their vital statistics on the foundation stones of deep shelters? But some of our artistic efforts seem likely to puzzle comparative anatomists Learned arguments will flow whether our central abdominal and thoracic foramina were congenital or acquired. Our known heroic habits of pneumonectomy and splenectomy will possibly support the latter view, although experimental work will be most frustrating to reproduce our collateral circulation and famous spinal rigidity It may be left to some philosopher to guess that the vacant space is where our psyche used to perch

There is really a lot to be said for the artist capturing the impression of movement in our medical life before it gets any more fossilised of its own accord I am all for writing and carving on the walls of public buildings And if we are to combine reorientation with tradition, why not adorn the Inland Revenue with a stony statue, many-armed and palms outstretched, the spirit of our times embodied with a risus sardonicus, tongue-tied in tetanic spasm?

* * *

"Hullo," I said, "it's old Halifax! What are you doing here?"

"Just browsing"

We had been students in the same year He was a practitioner in the next town, and we met by chance from time to time—on this occasion in a second-hand bookshop We always discussed the same subject

"I heard from Herman Jones the other day," said Halifax putting down the book he had been holding "He's an orthopod now, you know"

"He would be," I remarked "I ran into Little Billie at a conference recently Do you know what he's doing? He's a general, if you please!"

'No! I see that Slinky Syme has achieved his ambition of becoming a gynæcologist in Poshmouth, of course"

"Every man to his choice Do you remember Chambers, that studious fellow? I'm surprised to see that he's a school medical officer"

"Yes I'd have thought he'd be a professor of something As for dear old Runty, who never graced any of the lectures with his attendance, he's a research wallah at some place outside London"

'Well, well! We seem either to have run absolutely true to type or to have become complete paradoxes By the way, Halifax, what about yourself? Did you not want to be a plastic surgeon, if I remember rightly?"

'Maybe I did, but it didn't work out that way What about you? You were always keen to be a doctor on one of the Hebrides, weren't you?"

"Yes, I was"

The conversation lapsed "What's your book?" I half-expected it to be *The Story of Surgery* or something like that He handed it to me without speaking *An Introduction to Economics* I read "That," said Halifax, "seems to put it in a nutshell"

* * *

Many drivers must have experienced fog vertigo while motoring Giddiness arises while the car is in motion and also on getting out of the car immediately after it has stopped In both you have an illusion of horizontal displacement in the long axis of the car While driving it leads to a false idea of speed and even of the direction of movement of the car On stepping out of the stationary car there is vertigo for a second or so in the opposite direction from the car's motion It is something like the vertical vertigo I get in a totally enclosed lift and seems to be due to the absence of adequate fixation for the eyes For instance, I find it does not occur if I can fixate on the rear lights of a car ahead or on street lights

The absence of adequate stimuli for fixation and the capacity of the brain to organise visual stimuli leads to visual illusions of almost hallucinatory quality when fog is dense but unevenly so I remember being terrified one night to see a line of tanks advancing across my path out of a dense fog on one side They disappeared as the car drew nearer and their illusory nature was confirmed No doubt fatigue also plays a part in this phenomenon, because it can occur at night without fog

It is difficult to avoid these illusions A windscreen placed far from the driver makes things worse because the eye focuses on spots and reflections of the car interior rather than the dim contours further away This can hardly be altered without rebuilding the car Simpler solutions are to keep the windscreen spotlessly clean, to shade panel lights, and even to paint the facia and controls matt black as some experienced rally-drivers do in order to prevent reflections in the screen I am told the effect is restful and has a strong functional appeal, but so far my wife has prevented me from attempting it No doubt summer will be here again before I can convince her that it is worth trying

* * *

It was the first Saturday in March, the day that summer came to London just nine months late At 5 P M I was about three-quarters through a long clinic which had already lasted three hours A patient came in, "Lovely weather you are having," he said "And so are you," I replied, making what I thought was an apt rejoinder 'But I have had to work in it," he retorted

* * *

Our sanatorium is on the moors, a couple of miles from the nearest little town, and we have a bus to transport the staff There is a proper bus-stop in the main street where the passengers get on and off The bus is irreverently known to the townsfolk as the Tubercular Circular

* * *

St Cynthia's Hospital, Delphi —Applications are invited for the post of SENIOR REGISTRAR for general medical duties, *including the care of patients The appointment will be made* for a probationary period of 1 year, after which the successful candidate will have charge of beds and consultant status will follow on the retirement of the present senior physician in 3 years There will be no opportunities for teaching or unoriginal research

Applicants should have engaged in active medical practice for more than 8 years, of which at least 6 years should have been spent outside a teaching hospital The post demands sound clinical judgment, high competence, wide experience, and familiarity *with modern medical thought, and possession* of the M R C P is a disadvantage Canvassing and the submission of references and testimonials will disqualify, and applicants are expected to furnish proof of their abilities There will be no formal interview but it is incumbent on candidates to call upon each member of the selection committee composed entirely of the senior medical staff of the hospital Arrangements may be made through the hospital secretary to ensure that the interviews are completed in the same day Where it is intended that published work should be taken into consideration, one reprint of each article should be submitted in advance, and such work will be judged on its merit

Applications (one copy) should reach the Medical Director by 17th March, 1997

Letters to the Editor

X RAYS AND LEUKÆMIA

SIR,—In our preliminary communication [1] we reported the existence of an association between diagnostic irradiation during pregnancy and later development of leukæmia or cancer in the child Dr Reid (Feb 23) has revived the suggestion that this association might depend simply on a coincidence between two otherwise unrelated facts (*a*) that primiparæ are more likely than multiparæ to be referred for radiography, and (*b*) that first-born infants may be more liable than others to develop malignant disease during childhood Our records confirm the truth of both (*a*) and (*b*), hence Dr Reid's explanation has a certain prima facie plausibility However, as previously reported,[2] a higher incidence of antenatal irradiation is still found among our cases when comparison is restricted to controls of corresponding parity The case/control contrast is in fact just as great after standardisation for parity (and for the proportion of twin births) as when this factor is ignored The risk associated with primogeniture and the risk associated with antenatal irradiation are therefore two quite distinct entities

Dr Reid is justified in stressing that, on the evidence of our figures, over 90% of the cases of malignant disease in children under 10 years of age (which are in any case rare) must be due to causes other than diagnostic irradiation It follows that the risk *to* life associated with irradiation in utero must be *small*, nevertheless our report has a practical implication if the risk of *not* performing an antenatal X-ray examination is also small

Two other reasons for exercising greater caution in this matter than Dr Reid yet feels to be necessary should also be mentioned In the first place there is the small but inescapable genetic damage to be considered According to Osborn's estimate [3] just over a quarter of the genetically significant radiation resulting from diagnostic radiology is received by children before they are born Secondly, *it is not safe to assume that* the cases of leukæmia and cancer which occur within the first decade of life represent the whole "first generation" cost of exposing fœtuses to X rays The data on leukæmia following the atomic explosions in Japan do not give "any clear indication that the incidence has yet begun to diminish by the end of the ninth year" [4] In seventeen confirmed cases of malignant disease following irradiation for thymic enlargement the *average* interval between treatment and onset was nine years [5] Our own data also suggests that the *relative* risk of death from malignant disease for children who are irradiated in utero is as high as ever after eight or nine years even *though the absolute* risk has diminished by these ages

ALICE STEWART
J W WEBB
B D GILES
D HEWITT

Department of Social Medicine
University of Oxford

COST OF HOME CARE FOR THE ELDERLY

SIR,—I read with interest your note on this subject (Feb 23, p 435) Nearly two years ago the borough treasurer of Reading and I compared the cost to both national and local public funds of maintaining an elderly person in a new bungalow with that of maintaining him in purpose built part III accommodation We postulated two visits per week from a district nurse and a varying number of hours per week from a home help *It became* apparent that in such a situation it was cheaper to main tain an elderly person in the part-III accommodation once he required more than fourteen hours' domestic help per week.

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[1] *Lancet* 1956 ii 447
[2] *Ibid* p 573
[3] Osborn S B *In Hazards to Man of Nuclear and Allied Radiation* H M Stationery Office 1956, p 117
[4] *Ibid* p 86
[5] Simpson C L et al *Radiology* 1955 64 840

I endorse the hope of the governors of the National Corporation for Old People that further attempts will be made to compare the cost of institutional and domiciliary care of the elderly This subject grows in importance as more and more old people require help from central or local public funds. There are cogent reasons why the elderly should not be admitted into institutional accommodation, whether hospital or part III, but I wonder whether some people are not assuming too readily that it is cheaper to maintain them outside such accommodation Unfortunately the issue is often clouded by the distinction between local and central government services.

Medical Officer of Health's Department
Reading
E HUGHES

BRONCHIAL CARCINOMA

SIR,—It was with interest that we read Mr Vernon Thompson's letter (Feb 23) giving figures to show the time taken to refer cases of bronchial carcinoma to a thoracic surgical unit As physicians who specialise in diseases of the chest we were surprised at the delay which arose at the chest clinic This has, therefore, led us to analyse our cases seen at the chest clinic at this hospital during the past three years They total 75 and can be divided into three groups

The first is made up of 38 cases where at the first clinical examination bronchial carcinoma was diagnosed but which were judged to be inoperable because of metastases outside the chest or because of poor general condition with, for example, chronic bronchitis and emphysema. Most of these cases were discussed with, and many investigated by, our thoracic surgical colleague The diagnosis was confirmed in as many cases as possible by bronchoscopy, or gland biopsy, or sputum examination, so that we could speak with certainty to the relatives and plan appropriate treatment with the family doctor

The second group is made up of 28 cases in which when they were first seen, or shortly afterwards, "probable carcinoma which might be operable" was diagnosed clinically and the patients were immediately referred to a thoracic surgical unit for further investigation and treatment In this group the surgeon found 15 to be inoperable at bronchoscopy or thoracotomy, resection was possible in the remaining 13

There is a third group of 9 cases in which the diagnosis was delayed because the development of the carcinoma was masked by various other conditions

It can be seen from the accompanying table that of 75 cases 59 were diagnosed immediately and a further 7 within six weeks. In 9 cases the diagnosis was delayed The average time taken for the 28 cases in which the patients were admitted for operative assessment was three weeks, of which investigation at the chest clinic accounted for three days

ANALYSIS OF CASES OF BRONCHIAL CARCINOMA AT A CHEST CLINIC

—	Delay in diagnosis (weeks)								
	0	1	2	3	4	5	6	>6	Totals
Inoperable on clinical examination	35			1	1	1			38
Inoperable on bronchoscopy or thoracotomy	14						1		15
Resections	10	1	2						13
Delayed diagnosis								9	9
Totals	59	1	2	1	1	1	1	9	75

The third or late-diagnosis group included 3 patients with known tuberculosis in which the average time for diagnosis was three months A further man was under observation for eleven months on account of a small lesion considered to be tuberculous This cavitated and tubercle bacilli were reported in his sputum Since the cavity became appreciably larger despite three months chemotherapy lobectomy was done and a cavitating carcinoma found. A case with bronchitis was observed with a slowly increasing area of infiltration This was thought to be tuberculous, but after seven months a bronchoscopy showed a squamous-cell carcinoma Operative treatment was precluded because of bronchitis, but the patient responded well to radiotherapy It took us nine months to diagnose carcinoma which occurred in a woman who was under treatment by us for acute systemic lupus erythematosus, with pulmonary manifestations (in the press) One case presented as an empyema at the site of a known bronchiectatic lobe, and an underlying carcinoma was not recognised for nine weeks In an elderly bronchitic man collapse of a lobe developed after he had been under observation for five months, carcinoma was diagnosed clinically, but his general condition did not allow further investigation In a further, uncomplicated, case diagnosis was delayed for six months, during which time he was seen by locums

Mr Thompson, in order to avoid delay, advocates an X-ray service so that general practitioners can refer cases directly to a thoracic surgical unit In the majority of our last group it is unlikely that this would have happened on the appearances of the initial radiograph

The adequate recognition of carcinoma of the lung is only a part of the adequate management of chest diseases in general This can be carried out at chest clinics only if they are staffed by well-trained people and have efficient radiological and laboratory facilities

There was little or no delay in the diagnosis of most of our cases, yet the number helped by surgery was small This is because the disease has an insidious onset, tends to occur in elderly patients who are commonly disabled by chronic bronchitis, and is often well advanced by the time the patient attends the chest clinic

The success of surgery depends mostly on the histological character of the tumour Many patients with slowly growing tumours, such as squamous-cell carcinoma, do well with surgery despite long histories

Ashford Hospital
Ashford Middlesex.
P E BALDRY
B GOLBERG

SIR,—Mr Thompson analysed 135 cases of lung cancer operated on at the London Hospital in 1954 and found an average delay of 6 4 months between first symptom and attendance at the department of thoracic surgery He blames chest physicians for much of the delay in diagnosis Apparently all cases came to him through a chest clinic and not one direct from a general practitioner or general physician This is unusual and does not obtain in our area In previously published larger series, a similar delay before operation has been reported. Most of these reports relate to the days before the development of the modern chest clinic, and thus the delay referred to by Mr Thompson is shared with other physicians radiologists, and general practitioners

The prognosis of cancer of the lung paradoxically appears to improve with the delay before operation, and thus careful assessment before surgery and exclusion of other disease is reasonable In the Midlands, the commonest cause of hæmoptysis is chronic bronchitis It would be impracticable for a thoracic surgeon to see all cases with this or other symptoms of chest disease which so frequently occur in middle aged or elderly men

With the concurrence of thoracic surgeons in this area, some chest physicians bronchoscope possible cases of cancer of the lung within ten days of first consultation Before this cytological examination of the sputum will have been made Consultative sessions between thoracic surgeon and chest physician are regularly held in a chest clinic or thoracic surgical unit, and the patients are operated upon as soon as there is a vacant surgical bed—the total delay is usually rather less than two months

We suggest that facilities for expert cytological examination of the sputum should be extended Bronchoscopic examination by either physician or surgeon should be commonplace and widely available Radiography of the chest is more important than auditory examination, and we entirely agree that radiographic facilities for general practitioners should be provided At that stage, it should not be necessary for cases to be filtered through either a physician or a surgeon

Worcester E N MOYES
Warwick P G ARBLASTER

SIR,—Mr Thompson has rightly castigated the chest physicians for delay in sending patients with bronchial carcinoma to the thoracic surgeon This indictment must apply not only to the chest physician but also to the bulk of the medical profession

A normal chest X-ray by no means excludes the presence of bronchial carcinoma, but it is perhaps asking too much either of the radiologist or the general practitioner to discriminate between those patients who should be referred to the thoracic surgeon and those who may safely be discharged from surveillance

At this clinic it is our normal practice, whether or not the chest X-ray is normal, to investigate in the following manner all patients with hæmoptysis of unknown cause and all patients aged 30 or more who have recently had a localised pulmonary lesion noted on clinical or radiological examination (1) immediate bronchoscopy and if necessary bronchography, (2) for six months, monthly clinical and radiological review, (3) for three years, clinical and radiological review at three-monthly intervals We would stress that these investigations are essential even in the presence of a normal chest X-ray Only if patients are investigated in this way can we hope to diagnose the early bronchial carcinoma

Baguley Hospital, Manchester P F JONES
T M WILSON

SIR,—Attacks on colleagues such as that made by Mr Thompson are fortunately rare However, it is pleasing to find that some thoracic surgeons realise that an operable case of bronchial carcinoma is urgently in need of treatment Delays in admission to a thoracic surgical unit of upwards of four weeks are common, and we wonder what would happen to the waiting list if only cases with a doubtful chest radiograph were admitted direct to such units The main factor in the early diagnosis of bronchial carcinoma is always to keep such a diagnosis in mind Symptoms commonly precede radiological changes, and the institution of further investigations should not be delayed because radiological examination is negative

Edgware General Hospital Middlesex R GRENVILLE-MATHERS
H J TRENCHARD

SIR,—Mr Thompson seems to take an unduly pessimistic view of the work done in the chest clinics in this country

There must be many chest physicians who, like myself, were trained by him and who are capable not only of diagnosing bronchial carcinoma on clinical and radiological findings, but of proving the diagnosis by bronchoscopy should it be necessary to do so In spite of this the sad fact remains that of 16 cases of proved bronchial carcinoma picked up during the first few months of our general practitioner referral miniature radiograph service, none has proved operable The average delay between miniature radiograph and bronchoscopy has been about three weeks Is it possible that the publicity campaign in the press is having the opposite of the desired effect ?

I have gained the impression that patients who really fear that they have a carcinoma of bronchus are afraid to go to their doctors to have the diagnosis proved and that in many cases the delay is in the period before reaching the general practitioner

Croydon Chest Clinic D PARADISI

THE DISINTEGRATIVE ACTION OF THE NERVOUS SYSTEM

SIR,—It has long astonished me to hear it repeatedly stated that modern medicine is "integrative" and "holistic" and that the tendency is for it to become more so, when in fact, exactly the opposite is the case Medical science in the twentieth century is essentially analytical and disintegrative as progressive specialisation clearly indicates, nor is this to be deprecated, for it is in this very power to isolate and deal with the multiplicity of factors affecting a person's well being that the power of medicine lies

The emergence of psychological medicine as an effective force, whatever its philosophical implication is just another specialty, in practice, another "system" the disorders of which have to be correlated with the rest

This extraordinary confounding of opposites is, surely, an expression of our revulsion against 19th century materialism and its consequent tendency to degrade human values Holistic and similar integrative philosophical systems serve to reassert in our minds the unique intrinsic value of each individual, and hence determine our attitude towards our patients, and our profession But this, Sir, is Faith Science is a different matter

London, S W 11 J F ROBINSON

UNMARRIED PARENTHOOD

SIR,—It is hardly proper for someone from "a moral agency dabbling with sex" to intervene when one doctor accuses another of unphysiological thinking every profession has its courtesies I may, however, perhaps ask Dr Tuthill (Feb 23) what he means by morality, Does he assume that "what is moral" means simply "what most people do" ? If there were a tendency for more and more swindlers to come before the courts would that fact make swindling more "moral" than before ? If more and more patients die of cancer of the lung, are we to revise our standards of health, and regard that cancer as a normal condition of civilised man ?

This pathetic appeal to "changing circumstances and increasing knowledge" as a means of slipping off our obligations is surely discredited by now This Council is so concerned with accurate knowledge that our workers were able to supply some of the statistics from which this discussion arose but the statistical method is not the whole of philosophy There has to be a dogma at the heart of morality—a belief by which peoples or nations determine to live, first because they believe it to be true, secondly because they see that it makes sense of the knowledge they have The dogma at the heart of Christian sex morality is that coitus is a sacramental act for the expression and enrichment of a partnership to which a man and a woman have committed themselves irrevocably in love, and for the procreation of children within that partnership, and there alone

This dogma does justice to the wholeness of human nature we do not regard our bodies as cleverly contrived toys, to be played about with for the sake of thrills, we do not limit our concept of sex to genital activity, nor have we only negative counsel for lovers who have to wait for their marriage Our dogma, which carries of course, its own discipline within it, meets the facts of human nature and of human and social need, and its confirmation is amply demonstrated in the history of civilisations as well as in the consulting rooms of responsible psychiatrists The facts which appear to have alarmed your correspondents so immoderately are because our dogma is ignored they afford no ground for argument that it should be revised

Without this dogma, in fact, sex becomes like an organ enlarged, a faculty uncoordinated with the rest of personality; men and women are tantalised, then cheated of that which they most hope for, children suffer the injustice of being born unwanted or without a natural home, women are exploited—in the long run, the woman pays most in societies which loosen sexual morality, and society itself drifts into those very barbaric and subhuman notions which seem to underlie Dr Tuthill's letter—that sex is but an appetite analogous to that behind eating and drinking, that the "tragedy" of the unmarried mother is not "very serious" while the adoption societies cannot meet the demand for all the babies which she can produce (an interesting variant, by the way from the attitude of your other correspondents for whom the illegitimate child appeared to be the *only* tragedy in premarital intercourse)!

A healthy society is not ashamed to affirm the basic principles by which it lives. What we want, do, and are depends on what we believe

Church of England Moral Welfare Council
Church House Dean's Yard
London, S W 1

ENA M STEEL
General Secretary

PEDICULOSIS CAPITIS

SIR,—As one who looked after the fate of a large part of Dublin's louse population in dermatological practice during six years, I was interested in the findings of Dr Nelson and Mr Cromie (Feb 23) in regard to the superiority of 'Esoderm' over other remedies for pediculosis capitis As they note, by far the most important aspect of this condition is the frequency of reinfestation Of my last 500 hospital cases, 20% suffered from pediculosis capitis (apart from any other skin disease) and of these about a third (7%) had become reinfested

The head louse is common among poor families in Dublin and, as a great many of them cannot afford shampoos, a cleansing agent such as esoderm would be extremely useful But the problem is obviously one to be dealt with principally by improving living conditions, and by education in hygiene, and will not be solved by insecticides The idea, therefore, that the nursing staff of the school and public-health services should be one is excellent

I may add that it is well recognised that, in young patients from the poor areas of Dublin, dandruff is nearly always mechanised.

London W 1   **BETHEL SOLOMONS**

TOWARDS PREVENTING SUICIDE

SIR,—I was most interested in the letters published in your columns relating to the detection and prevention of would-be suicides

It has long been a theory of mine that many suicides could be prevented by the creation of a society on similar lines to Alcoholics Anonymous

That is to say, a permanent service would have to be established which would be prepared to accept calls from any person who was desperate and seeking help In many cases suicide would be prevented if the would-be suicide could find a sympathetic listener and counsellor who would listen to all his troubles and give him assistance and encouragement Once it became generally known that such advice and help were forthcoming and would be suicides were urged to get in touch with the society and to suspend any drastic action at least until a member of the society should have time to call on them within the next 24 hours I believe the psychological effect—even if only a natural curiosity to know how the counsellor would react to the problem—would cause them to hesitate Of course it would be essential that such a service should be a night and day service with an easy telephone number to memorise and voluntary helpers in all the larger towns Such helpers should not belong to medical or religious bodies, nor should they be trained social workers or psychiatrists but simply men and women who have themselves known troubles and overcome them and who have both experience and understanding Preferably, of course, the root cause of the trouble should be ascertained before sending the counsellor (in such general terms as ill health, money matters, business, love affair) so that a person could be chosen to help who had overcome a similar problem in the past

Could not such a scheme be started under the auspices of some interested organisation?

Paris.   **A WATNEY**

OLD PEOPLE IN HOSPITAL

SIR,—I am sure everyone will agree with Dr Trevor Howell's remark last week that there is frequently a social problem behind the admission of elderly patients to hospital Solving this problem is usually difficult, but not impossible a proportion, however, remain insoluble, at least to me It is these patients, or rather ex-patients, who constitute the more or less permanent residents to whom Dr Rang refers (Feb 23)

Of the 32 beds available (only 26 were filled at the time of Dr Rang's experiment) over 20 are filled with elderly persons suffering from a profound disability which does not, however, require skilled nursing care They have no relatives, or none willing or able to take care of them, while the local authority either considers their disability too severe for admission to a welfare home or pleads lack of accommodation Failing a more generous interpretation of the meaning of Section 21 of the National Assistance Act that "it shall be the duty of every local authority . to provide accommodation for persons who by reason of age, infirmity or any other circumstances are in need of care and attention which is not otherwise available to them" or the provision of more such accommodation by the local authority, it is difficult to see how this anomaly can ever be remedied

London, S W 1   **AMULREE**

POLYNEURITIS AS A CAUSE OF "AMYOTONIA CONGENITA"

SIR,—Dr Chambers and Dr MacDermot have rendered a signal service in delineating (Feb 23) the diagnostic features of infantile polyneuritis Less praiseworthy, in my opinion, is their choice of heading They clearly regard amyotonia congenita as a miscellaneous group of conditions, having in common only their occurrence in infancy or early childhood and the generalised hypotonia exhibited by those affected This is a distortion of Oppenheim's original concept and obscures the very real advance which his contribution provided

This consisted in drawing attention to a condition of generalised muscular hypotonia in infants, dating from birth and showing a tendency to gradual improvement Oppenheim believed it was a disease-entity and due to delayed development of the muscles including their innervation. He anticipated therefore, that the muscles would appear normal on orthodox histological examination. Much of the confusion over the nature of this condition is the result of other conditions, now better defined and more easily recognised, having been incorrectly diagnosed as amyotonia congenita I am particularly referring to cases of Werdnig-Hoffmann disease, of congenital or intra uterine onset being mistakenly diagnosed as amyotonia congenita If there do, in fact, exist *formes frustes* of Werdnig-Hoffmann disease, as suggested by Arthuis,[1] muscle biopsy may be required to make the correct diagnosis In infantile polyneuritis, as Chambers and MacDermot so usefully point out, an elevated protein content in the cerebrospinal fluid may be sufficient to make the diagnosis clear

It is quite possible that Oppenheim himself wrongly diagnosed as amyotonia congenita infants with one of these other conditions. No one is infallible Nevertheless, the fact remains that there is a small group of infants who show all the clinical features of amyotonia congenita, as described by Oppenheim,[2] including congenital onset and tendency to improvement, and also yield muscle biopsies entirely free from abnormality of the muscle fibres (6 cases recently reported by Walton[3] under the heading of benign congenital hypotonia) and with completely normal intramuscular nerve endings[4] or at the most an appearance of immaturity[5]

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[1] Arthuis M L'amyotrophie spinale *infantile* de Werdnig Hoffmann, Paris 1954

[2] Oppenheim H *Mschr Psychiat Neurol* 1900, 8, 232

These cases may in time be shown to have more than one ætiology, but as long as there remain obscure cases of congenital hypotonia with normal muscle histology and favourable outcome, the application of the term *amyotonia congenita* is still appropriate To give new names to these cases (e g, essential and primary hypotonia of young infants,[6] delays in the appearance of tone,[4] benign congenital hypotonia[3]) is not to throw new light on their essential nature, but merely gives the uninitiated reader the impression that new diseases have been described

I would therefore submit that a more suitable title for this otherwise excellent paper would have been "infantile polyneuritis simulating amyotonia congenita"

Midland Centre for Neurosurgery
Smethwick
A L WOOLF

PROTECTION OF TESTES IN DIAGNOSTIC RADIOLOGY

SIR,—In an annotation last week you refer to the need to reduce the radiation dose administered by diagnostic methods without diminishing their efficiency

Most diagnostic X-ray departments do not seem to take any special precautions to protect the testes from irradiation when films are taken of the pelvis or neighbouring organs Though the genetic risk from such exposure is small,[7] it could be diminished greatly by shielding the testes as a routine This should not present undue technical difficulty, it seems unreasonable to wait for evidence to show just how much genetic damage can be done by low-dose irradiation of human testes

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ANDREW HERXHEIMER

RHEUMATOID ARTHRITIS WITH CHRONIC LEG ULCERATION

SIR,—I fear that Dr Allison and Dr Ray Bottley (Feb 9) have drawn quite unjustifiable conclusions from their failure to heal chronic leg ulcers in rheumatoid patients In the past three years I have seen four cases similar to those cited by them The record of the fourth patient, at present under treatment is as follows

A housewife, then aged 30, began to have rheumatoid arthritis in 1920 After seven years' anti-rheumatoid treatment an ulcer appeared on her right leg This did not heal until fifteen years later—and then only when she had been in bed after the removal of a stone from her right kidney Her rheumatoid arthritis steadily increased in severity, and in 1948 she was further crippled by an ulcer on the left leg (the right meanwhile remaining completely healed) In the past eight years she has had no less than four unsuccessful skin grafts, interspersed with numerous long periods of bed rest in hospital Eventually the ulcer encroached on two-thirds of the circumference of the leg above the ankle, at this stage amputation was advised—and refused

When she came under my care, twenty weeks ago, her ulcer measured 270 sq cm in area (18 × 15 cm) She was (and still is) very severely deformed by rheumatoid arthritis, with virtually no free ankle movement She had reached the stage of walking almost on hands and feet, using the backs of her proximal phalanges as forepaws This was so obviously a chronic ulcer resulting from venous stasis consequent on loss of lower-limb muscular activity, that a confident prognosis could be given immediately and she was ordered to bed—despite her protests that this had been tried many times before (as with the Middlesex cases) After two weeks of this regime the ulcer measured 180 sq cm, after six weeks 100 sq cm, after twelve weeks 21 sq cm, after sixteen weeks 10 sq cm At present it is 4 sq cm in area and I expect it to be soundly healed in six weeks

Why should this be so when previous bed rest had proved so unsuccessful? The answer is quite simple—it was not bed rest in the hospital sense of the term

When a patient is put to bed, as treatment for an ulcerated leg, everyone imagines that the aim is to rest the leg—hence the term "bed rest" This is a complete misconception, for this mode of therapy should involve an *active* process—namely, promoting venous return and thus abolishing the interstitial tissue œdema which is preventing healing A patient who is allowed to wander in and out of bed from time to time is not doing this A patient sitting up in bed, even if she never gets out of it, is doing her ulcer about as much good as by standing in a queue The only way to promote venous return in bed is to have the patient lying flat (one pillow for the head) and the foot of the bed raised at least 9 inches, for it is only then that the heart level is below that of the leg, the peripheral veins cease to be distended, and the venous pressure becomes consistently negative

I suggest that the diagnosis of lupus erythematosus cannot yet be sustained in the cases described by Dr Allison and Dr Bottley

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STANLEY RIVLIN

ANTI-HISTAMINE DRUGS IN CHOLERA

SIR,—In 1952 I described the prevention and cure of uræmia in cholera, by means of intravenous administration of vitamin C and intramuscular injection of an anti-histamine drug in the kidney region.[1]

In the epidemic of 1954 three anti-histamine drugs were administered separately without vitamin C (Previously vitamin C alone had failed to start urination in 30% of uræmic cases[1])

The anti-histamine drugs tested were (1) mepyramine maleate ('Anthisan'), 2 ml of 2·5% solution, (2) chlorpromazine hydrochloride ('Largactil'), 12·5 mg in 6 cases and 6 mg in 5 cases, and (3) promethazine hydrochloride ('Phenergan'), 2 ml of 2·5% solution 55 culture-positive cases of cholera with established uræmia were studied

Mepyramine failed to start urination in 3 of 11 cases (27%), chlorpromazine failed in 2 of 11 cases (18%), promethazine failed in 1 of 17 cases (6%) In 16 control group cases there was no urination in 4 (25%)

Thus the group treated with mepyramine (given alone) fared no better than the controls Chlorpromazine possibly gave slightly better results, but it was found to have a special drawback in cholera, causing a dangerous depression of blood-pressure By contrast promethazine seemed to be of definite help, and its administration led to no untoward reactions

We made extensive trials of combined treatment with vitamin C and promethazine in the severe cholera epidemics of 1955 and 1956

In all cases where urination did not occur within two hours after infusion of saline solution, promethazine was given intramuscularly in the kidney region Patients who did not urinate within the following eight hours were given vitamin C 500 mg intravenously In a few cases administration of both the anti-histamine drug and the vitamin C had to be repeated every twelve hours

Since 1954, as was then anticipated, there has not been a single uræmic death in my ward In 1955 and 1956 cases of cholera treated here numbered 1610 and 1175, and the corresponding mortality rates were 7% and 4·7% This is in sharp contrast to the figures for Calcutta as a whole (elsewhere in the city treatment is by saline infusions only), the figures for 1955 and 1956 being 32% and 36·5%[2]

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[3] Walton J N Lancet 1956 i 1023

[4] Woolf A L Proc R Soc Med (in the press)

[5] Coërs C Pelc S Acta neurol belg 1954 54 166

[6] Sobel J Med J Rec 1926 124 [illegible]

[7] The Hazards to Man of Nuclear and Allied Radiation H M Stationery Office 1956 paras [illegible] 260 appendix K table 2

[1] Chatterjee H N Lancet 1952 ii 90

[2] Chatterjee H N Proceedings of Indian Science Congress 43rd Session Agra Calcutta 1956 part 3 p [illegible]

I should like again to emphasise that the acute renal changes in cholera are non-inflammatory and non proliferative[3] These changes, which are temporary and completely reversible,[3] are quite unlike those found in other forms of acute and subacute nephritis

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HEMENDRA NATH CHATTERJEE

DISCREPANCIES IN THE ERYTHROCYTE-SEDIMENTATION TEST

SIR,—The explanation quoted by Dr Groen (Feb 23) is not applicable to the discrepancies in the E S R test we described (Feb 2) This is made clear in the last two paragraphs under the subheading " Results " We have now seen discrepancies (arithmetical difference between duplicates) in citrated blood of 40 mm, 26 mm, and 18 mm, in addition to less serious ones

We regret that we did not refer to the valuable paper by Strom[4] Our article, however, was primarily concerned with the frequency and possible clinical significance of the discrepancies in rheumatic fever

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W D ALEXANDER
M M ANDREWS

EFFECT OF UNABSORBED RADIOGRAPHIC CONTRAST MEDIA ON THE CENTRAL NERVOUS SYSTEM

SIR,—Mr F L Davies[5] has detailed the adverse effects of unabsorbed contrast media in the subarachnoid space He emphasises the desirability of removing as much of the oil as possible after myelography or during operation

He is particularly concerned with " diminishing the chances of the substance entering the cranial cavity " Since this is most likely to occur after cervical myelography, I wish to draw attention to the technique of this examination I have described,[6] which prevents the flow of oil through the foramen magnum, no matter how extreme the degree of Trendelenburg position employed The principle consists in the maintenance of hyperextension at the atlanto occipital joint throughout the examination

Department of Radiology,
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F DALITH

MUNCHAUSEN'S SYNDROME

SIR,—The following case of this condition may be recognised by some of your readers

A red haired cook or post office worker, aged 44, appears in the casualty department with a history of increasing headaches, vomiting, drowsiness, and rapidly deteriorating vision The optic discs show changes that, to the uninitiated, appear sometimes to be those of optic atrophy, and at others those of bilateral papillœdema, the visual fields are grossly constricted She is very obese and states that she has been gaining weight rapidly, and she is usually somewhat reluctant to come into hospital

X rays of the skull show two round burr holes in the anterior frontal region the history she gives to account for these is that she had an accident some years ago and " a clot of blood " was removed from the brain She also has a much-scarred abdomen with a discharging sinus, alleged to be due to an old tuberculous peritonitis

When surgical measures to relieve the increased intracranial pressure are suggested, she discharges herself from hospital, but discharge can be achieved more rapidly by confronting her with her previous admissions to hospital I have seen her twice at this hospital, and also twice at Mile End Hospital, and a casualty officer there recognised her as having attended his old hospital, Charing Cross She has also been in Hillingdon Hospital The frontal burr holes for prefrontal leucotomy were I believe made at a hospital near London Obesity is an occasional complication of this operation, as well as an occupational hazard of cooks The fundal changes are those of opaque nerve fibres which almost surround the disc on both sides and make the patient instantly recognisable

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K W G HEATHFIELD

DRINKING SEA-WATER

SIR,—Three men were rescued a short time ago after drifting for six days on a raft in the Mediterranean They are reported to have followed the " Bombard system " and drunk measured amounts of sea-water, as they had no fresh water[1] Their story has naturally received considerable publicity, and the inference is usually drawn that they survived because they drank sea-water I believe they were lucky to survive in spite of it, and, in view of the importance of this question to future castaways, I should like to present the results of some calculations I have made

From the point of view of a castaway the important question is whether drinking sea water increases or decreases the time he can survive without fresh water A direct experimental answer to this obviously cannot be obtained for man, all one can do is to attempt to calculate from experimental data how nearly a lethal point has been approached (A study of mortality in lifeboats after sinkings during the late war[2,3] does, however, provide a very convincing "natural experiment ")

Suppose first that the men had not drunk sea water In a climate such as that over the Mediterranean, which is a favourable one for survival as it is neither cold enough to cause death from cold nor hot enough to cause sweating, an inactive man without food or water loses about 1 3 litres of body water a day[4] This comes to 7 8 litres in six days, or 11% of an average body-weight This loss might incapacitate a man, but it is well inside lethal limits Adolph and his associates[5] considered a loss equal to 20% of the body's weight, incurred rapidly in the desert, likely to cause death, more severe dehydration can probably be tolerated if the loss takes place slowly So far as death from dehydration is concerned, it appears that if the men had not drunk sea water they should have been able to survive for about twice the time they actually were adrift Further calculation based on the excretion of electrolytes by fasting and dehydrated men[6] shows that in six days the osmolar concentration of their body fluids would have risen by 10%

The castaways are stated to have drunk 3 tablespoonfuls of sea water every two hours from 6 A M till 8 P M, which amounts to 12 fluid ounces a day The salinity of the Mediterranean is 3 7–3 8%,[7] and so in six days they would have taken in 2 litres of water and 2600 milliosmols of electrolytes, predominantly sodium chloride If this had been retained in the body, the overall water balance would have been improved by 2 litres but the osmolar concentration of the fluids of the body would have risen to 28% above normal. Furthermore, sodium is largely confined to the extracellular space, and this would be expanded, at the expense of cell-water, which would be depleted by a third of its volume The available experimental data[6,8,9] suggest that, after the first day of drinking sea-water, increasing amounts of the ingested salt are excreted, at the cost of body water Calculation based on the salt excretion and urine volumes found experimentally suggests that at the end of six days the concentration of the men's body fluids would have been 24% above normal Their overall water balance would be about the same as if they had not drunk sea water, but their cells would have lost proportionately twice as much water as their extracellular fluids Death can probably be caused by severe hypertonicity alone, or by severe loss of cell water, or by a combination of lesser degrees of both changes[10–12] The *combination calculated is probably not far short of a lethal level*, and it is certainly worse than if the sea water had not been drunk Furthermore, the rate at which water was being lost in the urine would be increasing, and at any later time even the overall balance of water would be worse than if sea water had not been drunk

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[3] Chatterjee H N *Trans R Soc trop Med Hyg*, 1941, 34, 333
[4] Strom J *Acta med scand* 1938 96 365
[5] Davies F L *Lancet* 1956 ii, 747
[6] Dalith F *Radiol clin* 1956 25 212

[1] *Times* Feb 5 1957
[2] McCance R A Crosfill J W L, Ungley, C C, Widdowson E M *Spec Rep Ser med Res Coun, Lond* 1956 no 291
[3] *Lancet* 1956 ii 879
[4] Hervey, G R McCance, R A *Proc nutr Soc* 1954 13, 41
[5] Adolph, E F et al Physiology of Man in the Desert New York 1947
[6] Hervey, G R, McCance, R A *Proc roy Soc B*, 1952 139, 527
[7] Harvey H W Recent Advances in the Chemistry and Biology of Sea Water Cambridge, 1945
[8] Ladell W S S *Lancet* 1943, ii 441
[9] Whillans M G, Smith, G F M *Canad J Res (E)*, 1948, 26 250

Theory thus suggests that, although survival for six days is not incompatible with the amount of sea water these men drank, it is unlikely that they could have survived for much more than a day or so longer, as compared with the several days possible if they had not drunk sea water Even if drinking sea-water does lead to increased well being in the early stages, all the evidence is that its late effects are disastrous Castaways *cannot know the duration of the "experiment"* in advance, and they should on no account drink sea water

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G R HERVEY

NEONATAL COLD INJURY

SIR —Dr J W Farquhar mentions (Feb 16) some grave dangers of warming by short wave diathermy If he wants to warm cold babies, internal warming by the Khalil/Mac Keith intragastric balloon[13–15] is safe and simple The logic of the method is supported by the work of Andjus,[16] Parkes,[17] and others

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PAUL E POLANI

GOVERNMENT AND PROFESSION

SIR,—Your excellent editorial last week suffers from two main defects One is a defect of memory on previous occasions the threat of mass withdrawal has been effective and has not harmed the profession, so the argument that it is an alien procedure falls to the ground The other is that the idea you put forward in its place—of individual resignation—is perfect, except for the fact that terms of service and remuneration are negotiated centrally, and not individually, and that individual resignations are therefore of no value

What is more serious is the way in which you attempt to rally the "fainthearts" and give them justification *for not following their colleagues*

I know *The Lancet* tries to be objective and fair Unfortunately the profession faces a situation where "reason" is not likely to be triumphant It is the most serious situation the profession has ever had to face Literally it is that we must stand absolutely united and meet force with force or perish It grieves me that the editor of a responsible medical journal should not realise what the issues are

Two (or is it three ?) wars ago I sat in the fastness of G H Q in an administrative post I set myself two maxims *(a)* my colleague—who is also a doctor—at the scene of operations knows the right answer and it is my duty to help him to get what he needs, *(b)* the Government is always wrong Those same maxims hold true today

London W C 1

J L McCALLUM

SIR,—Your leading article last week suggests that, rather than a complete withdrawal from the National Health Service, only those general practitioners who are dissatisfied with their lot should resign

From the press and other reports, it would seem that the majority of doctors are dissatisfied with the present scale of remuneration, but, come what may, they have guaranteed that their patients will not suffer as a result of whatever action they may take

The public has now become used to a service from which it can obtain free medical attention and advice and drugs at a nominal cost A return to private practice on the part of their doctor would merely send them along to a neighbouring practitioner remaining in the service

This is especially true in the poorer urban areas—in which many dissatisfied doctors practise—where the patients might find it difficult to find the money for consultations and visits and impossible to pay for the new and expensive drugs which have been produced since July 5, 1948

The matter is an economic one, it is political only in that our pay comes from Treasury sources Should present conditions continue, the standard of medical practice can only deteriorate

Liverpool

MERVYN GOODWIN

"DOCTOR"

SIR,—There are good reasons for patients using the title of doctor when describing physicians and surgeons who may not hold a university doctorate degree, and at the present time it is well to remember them Past generations of general practitioners, as well as our surviving elders, have been the only freely accessible men with a higher education and integrity Because of this, patients brought problems, *demanding time* sometimes expense, and always wisdom, that were far removed from medicine or surgery They were, and sometimes are still, too uncomfortable in the company of the priest, too frightened of the police, and too timid to consult their headmasters Politicians might be hard to trust, the lawyers they could not afford Their doctors were on their side, and patients found that doctors would care for them and their problems without thought for themselves

I believe this to be true especially in this country, and perhaps it is a pity that in this country the qualifying degree is not a doctorate in medicine It might remind us of our heritage and assure patients who might be disturbed in changing times

We need to be reminded that our profession is concerned with an ideal rather than materialistic way of life It is a service However excellent our auxiliary help, we must preserve our right to attend confinements of our patients, to vaccinate and inoculate those whose parents wish us to do it, and to attend old people and report our own cases to geriatric centres So to those who say that family doctors will not provide for geriatric clinics, clinics for school children, and infant and maternity patients unless they are paid extra for doing so, we must reply that all these are being done now without this extra payment

Does the public connect with the title of doctor a code of ethics and a sense of service beyond which might be considered reasonable by a physician and surgeon ? This is important, because to disillusion the public in this would bring discredit, It behoves the public and each of us to have the faith that doctors have the highest standard of service and code of behaviour To lose this and receive badly needed financial assistance will be no victory Doctors do not strike

London E 17

JAMES H S MORGAN

FRACTURES OF FEMUR DURING E C T

MR H D W POWELL (Salford Royal Hospital, Salford 3), writes

I am interested in the orthopædic problems of simultaneous bilateral fractures of the femoral neck sustained during convulsive therapy I should be grateful if anyone who knows of such cases would kindly let me have details of them

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[10] Elkinton J R, Taffel M *J clin Invest* 1942 21 787
[11] Winkler A W, Elkinton J R, Hopper J jun, Hoff H E *Ibid* 1944 23 103
[12] Elkinton J R, Winkler A W *War Med* 1944 6 241
[13] Khalil H H, Mac Keith R C *Brit med J* 1954 ii 734
[14] Khalil H H *Proc R Soc Med* 1957 50 786
[15] Khalil H H *Lancet* Jan 26 1957 p 185
[16] Andjus R Cited by Billingham R E *Penguin New Biology* 1955 18 73
[17] Parkes A S See Billingham R E *Loc cit*

Parliament

Royal Commission on Remuneration

On Feb 28 the Prime Minister announced that this commission would have the following terms of reference

To consider (*a*) How the levels of professional remuneration from all sources now received by doctors and dentists taking any part in the National Health Service compare with the remuneration received by members of other professions, by other members of the medical and dental professions, and by people engaged in connected occupations ,

(*b*) What, in the light of the foregoing, should be the proper current levels of remuneration of such doctors and dentists by the National Health Service ,

(*c*) Whether, and if so what, arrangements should be made to keep that remuneration under review , and to make recommendations

He could not fix a date by which the commission must report but he would certainly urge the chairman to proceed without delay

Mr John Rankin Is the Prime Minister aware that a B M A spokesman quoted in the press said that his reference to an interim adjustment is extremely obscure, and that it might mean any of a number of things, some of which would be entirely unacceptable ? Will the right hon Gentleman not make his attitude on the interim adjustment clear beyond a peradventure, or does he wish to give the tough boys in the B M A the ammunition necessary to destroy the Health Service ? The Prime Minister The sentence which I put into that letter means exactly what it says, and I do not wish to make any interpretation of it this afternoon At the same time, we are always in touch with the leading members of the profession, and either my right hon Friend or I will be very willing to make any further explanation at an appropriate moment

Mr Frank Beswick Is the Prime Minister aware that if, as the result of any uncertainty as to the meaning of the phrase "interim adjustment," any damage is done to the Health Service the people of this country will not forgive him ? Can he say why he cannot make it quite clear, both to allay apprehension on the part of doctors and also in fairness to those who may be invited to serve on this commission, that the commission is not now intended, as was originally the case, simply to dodge the issue, and does not preclude any interim negotiations upon salary-scales ? The Prime Minister The hon Member is very fond of making statements for which he has very little ground He prefers to rely rather upon innuendo than fact The commission was never intended for the purpose of dodging this issue Members on both sides of the House know the very difficult circumstances that surround some of these problems I am convinced that the commission will be able to act rapidly and effectively, and I am very hopeful that we shall reach a good point of view between all concerned in this matter

Dr Edith Summerskill Will not the Prime Minister say whether the terms of reference which he has mentioned will enable the commission to take into account the conversations conducted at the inception of the service between the Government and the doctors ? Further, will he again consider interpreting this phrase, because the attitude of the profession during the next few months may be guided by what he says now ? The Prime Minister On the first point raised by the right hon Lady I have not the record of these conversations with me at the moment Therefore, if she pressed me upon the matter, I should have to ask for notice I think it would be a matter for the commission itself to decide With regard to the right hon Lady's second point, I should prefer to leave the matter as it is at the moment I feel quite certain that we shall be able to make good progress in this affair

Mr Marcus Lipton asked the Prime Minister what communications he had received from medical organisations since his announcement of a Royal Commission on doctors' pay The Prime Minister replied I have received a letter from the Negotiating Committee of the medical profession, which has been published together with a copy of my reply Mr Lipton Is the Prime Minister aware that if he has another look at his reply he will see that the English is bad and the meaning obscure ? Will he say why he is so curiously unwilling to say whether this proposed interim adjustment may also apply to general practitioners ? The Prime Minister I am sorry about the English I am always ready to take advice from a very expert source I think the best thing I can do is to try to get the commission started, and I hope, with great confidence, that we shall be able to clear up the other issues as we go along

Mr E G Fletcher . Will not the Prime Minister agree that, whatever may be the case for a Royal Commission to examine the overall question of doctors' pay, there is a strong case for some immediate interim adjustment of doctors' remuneration, and will he acknowledge that and remove all the misunderstanding by making his position clear ? The Prime Minister Yes, Sir For that reason, I made reference to it in my letter

Mr Arthur Blenkinsop Will not the Prime Minister agree that, as he has made this specific reference in his letter to the British Medical Association, it is highly desirable that he should clarify it so that further dispute may be avoided ? The Prime Minister No, Sir I think that all this will move along satisfactorily The first thing to do is to get the commission appointed, which I am very hopeful will be quite soon What I have said in answer to supplementary questions has made it quite clear that my right hon Friend or I are very ready to take up these further questions with the Negotiating Committee

Mr G S Lindgren In view of the Prime Minister s intervention in this industrial dispute, will he also recommend to industry generally that it should give an interim award on outstanding pay-claims ?

Lung Cancer and Smoking

Speaking on the *motion for the adjournment* on March 1, Mr Marcus Lipton said that there was now statistically an incontrovertible association between cigarette smoking and lung cancer and asked the Government what they were doing to let the people know about this disturbing fact He realised that in raising this matter he was confronted with formidable difficulties £880 million a year was spent on tobacco Out of every £1 spent in the shops, 2*s* 6*d* was spent on tobacco and each adult incurred an average expenditure of 9*s* 4*d* a week Four million places were licensed for its sale, and the yield from duty produced £668 million in the last financial year, a record figure

Mr Lipton went on to recapitulate Ministerial pronouncements on the subject from Feb 12, 1954—"I accept the Committee's view that the statistical evidence points to smoking as a factor in lung cancer"—to the latest of Feb 25, 1957—"I propose to ensure that the public are kept informed of all relevant information as and when it becomes available" So far the Minister of Health had refused to accept the advice of his Standing Advisory Medical Committee that effective steps should be taken to make the facts known to the public and to counteract propaganda in favour of smoking Mr Lipton thought that it would be a grave dereliction of responsibility on the part of the Minister and the present Government if they deliberately continued to blind themselves to the seriousness of the situation and refused to take further action immediately He asked the Government not to shelter behind a stale and outworn formula but to do the job for which the Ministry of Health was appointed and paid—to protect and improve the health of the people

Mr Richard Fort, a lay member of the Medical Research Council, suggested that Mr Lipton had seemed more concerned with scoring cheap points off the tobacco companies and the Government than with considering one of the more complicated medical problems of our time He had failed to emphasise that the kind of work needed to find out the reasons for the statistical facts was very complicated and difficult scientific work Three points on which much more work was needed were (1) statistical analysis , (2) the effect on animals of the products from burning tobacco , and (3) the complex problems connected with smoking, air-pollution, chronic bronchitis, and lung cancer

Mr J K Vaughan-Morgan, parliamentary secretary to the Ministry of Health, said that the Government had *not hesitated to announce to the public any discovery* as and when it became available But though we must give full publicity to the knowledge which was *available,* we must not indulge in any form of sensationalism Carefully controlled inquiries had shown statistically that smokers had a significantly higher mortality-rate from lung cancer than have non-smokers The figure increased in direct proportion to the amount smoked, until among life-long heavy smokers, who may be defined as those smoking about 25 cigarettes a day, it appeared that about one in ten can be expected to die of lung cancer before the age of 75 Among heavy and continuous smokers of cigarettes—that is, those smoking substantially more than 25 a day—the death-rate from lung cancer was about *forty* times that among non-smokers The rates among pipe-smokers for the same amount of tobacco smoked were less than among cigarette-smokers Those who had given up smoking had significantly lower rates than those who had continued to smoke

There were many ways of interpreting the statistical evidence and it was difficult to reduce the evidence to average figures, but without doubt these findings constituted prima-facie statistical evidence that smoking carried a risk of lung cancer in human beings But we must view this mortality-rate and these risks with a due sense of proportion Of *a total of 518,000 deaths* in England and Wales in 1955, 17,000 were due to lung cancer out of a total of 91,000 for all *forms of cancer* That 17,000 compared with 28,000 *for* bronchitis and 70,000 for coronary disease and angina, apart from other forms of heart-disease Lung cancer was not our only problem, nor must it be our only preoccupation, nor should we give it any more priority than the figures justify *Nevertheless, it was undoubtedly the case that* the lung cancer figures continued to show a steady *increase, which had varied from 5 7 to 8 2%* per annum over the past five years

The Medical Research Council was engaged in research on the *relationship* between smoking and *lung* cancer, the long-term aim being to identify those constituents of tobacco smoke which might be active in producing cancer There had recently been built a laboratory at Exeter *for fundamental* work on the chemical analysis of *tobacco,* which was *the first fruits of the grant of a* quarter of a million *pounds* from the *tobacco* companies of this country Research was also going on in hospitals and universities all over the country

The Medical Research Council was currently reviewing the existing evidence, and its considered views should be available before long The Government would *give* those views their full and urgent consideration and he reiterated the pledge that the public *would be informed of all* the evidence *as* it becomes available *A pamphlet,* lately issued by the Ministry of Education, gave considered and helpful advice on the subject It was the firm intention of the Government to reveal the truth as it came to light, but we must avoid *any* unnecessary *sensationalism on this very difficult subject*

During much of the debate about half a dozen members were present

Paying for an Ambulance

On March 1 Sir FRANK MARKHAM moved the second reading of the National Health Service (Amendment) Bill, a measure which is more circumscribed than its title suggests The Bill gives effect to a recommendation of the Guillebaud Committee by permitting local authorities *to provide ambulances on a repayment* basis for purposes outside the National Health Service Act The purposes which the Guillebaud Committee had chiefly in mind were large public gatherings, such as race meetings or football matches The promoters are willing to pay the *local authorities for providing* an ambulance service, but at present the local authorities are not able to provide it Sir Frank gave an assurance that it was not the intention that this Bill should be the thin end of the wedge for making other payments for ambulance services *necessary* Mr VAUGHAN-MORGAN speaking for the Government at the end of the debate reiterated this assurance The measure, *he added* would permit the local authorities to provide a stand by service, at present strictly speaking, they could provide an ambulance only *after the event* He thought that the proposal might *also* be useful to some industrial undertakings, such as the National Coal Board, who had by law *to* provide an ambulance service for their employe-

The Bill was read a second time

QUESTION TIME

Remuneration of Junior Hospital Staff

Mr A BLENKINSOP asked the Minister of Health whether he would reopen negotiations with the medical profession for an interim settlement of their claim, pending the full review to *be undertaken by a Royal Commission* —Mr DENNIS VOSPER *replied* I am glad to be able to say that the Government are prepared immediately to recommend the management side of the appropriate Whitley Council to offer to negotiate an interim increase in the remuneration of hospital medical and dental staff up to and including the grade of senior registrar

Mr BLENKINSOP Does not the Minister recognise that his answer is merely a stonewalling answer ? When will he give us some information with regard to the interim negotiations in respect of general practitioners ?—Mr VOSPER It is not quite a stonewalling answer, because it relates to the Government's decision to offer to negotiate immediately for junior hospital doctors On that question I am still awaiting a reply from the Negotiating Committee

Cost of Prescriptions

Mr BLENKINSOP asked the Minister the average cost per prescription under the National Health Service for the month *of December, 1956,* and how this compares with the average cost in December, 1955 —Mr VOSPER *replied Approximately 5s 6½d,* which is about 11*d* more than in December, 1955

Mr BLENKINSOP Does the Minister realise that there has been a serious further increase in the cost per prescription since the new charges were imposed ? *Does not that show the very grave danger of the advice to doctors to prescribe larger* quantities per prescription ?—Mr VOSPER A great part of this increase occurred before the new prescription charge was introduced and it was also due in part to the increased chemists' remuneration and the release of new drugs, such as cortisone Only in part was it due to the new prescription charge As far as that is concerned, I should like to see the results for February and March before coming to a definite conclusion

Mental Patients

Dr A D D BROUGHTON asked the Minister of Pensions and National Insurance the number of patients in mental hospitals in England and Wales who, by reason of having been given a prison sentence before being certified as of unsound *mind, are not eligible for National Insurance* benefit —Mr J A BOYD CARPENTER There are about 200 mental patients who were certified while undergoing a prison sentence which has not yet expired I have no figures for the number detained under section 7 of the Criminal Lunatics Act, 1884 Under *decisions of the National Insurance commissioner* persons in both these categories are at present disqualified from receipt *of National Insurance benefits* Dr BROUGHTON Does not the Minister agree that these unfortunate people are harshly treated in respect of National Insurance benefits ? Is he *aware that if mental disorder had been recognised* and these people *certified before* court proceedings, they would not *suffer* the penalty of losing their National Insurance benefit including even the taking away of tobacco tokens from old age pensioners ? Will he be good enough to look into the matter *and consider the possibility of amending the* law ?—Mr BOYD CARPENTER I am not without sympathy for the hon Member's point of view, which I believe is shared by a number of people who have studied the subject I must, however await the Royal Commission's report which may affect the underlying *law,* but *I have in* mind, *when that report* is received, to refer this matter to my National Insurance advisory committee

Mr L D L DU CANN asked the Chancellor of the Exchequer why retirement pensioner patients in mental hospitals who would otherwise be entitled to tobacco tokens are deprived of them —Mr ENOCH POWELL replied Retirement pensioners are by statute entitled to tobacco tokens only if they receive their pension by means of weekly orders Their entitlement ceases if their order books are withdrawn, as happens when *the hospital concerned draws the pensions in bulk*

Anthrax Committee of Inquiry

Mr IAIN MACLEOD Minister of Labour, has announced the *appointment of a committee to consider*

the existing legal provisions concerning the importation of goods infected or likely to be infected with anthrax and the [illegible] to be taken in connection with such imported goods for the protection of the health of persons

The last full scale inquiry into the question of precautions against anthrax was made forty years ago

Blind Workers

The annual maximum grant to local authorities towards the cost of the provision of employment facilities for approved blind workers will be increased from £100 to £150 per worker from April 1 in view of the increase in costs

Research in Delinquency and Recidivism

A total of £10,934 has been paid by the Home Office, under section 77 of the Criminal Justice Act 1948, to assist research on the causes of delinquency and the treatment of offenders, and a further £1000 is awaiting payment In addition £2488 has been spent by the Social Survey as an allied service on behalf of the Home Office for research on these subjects

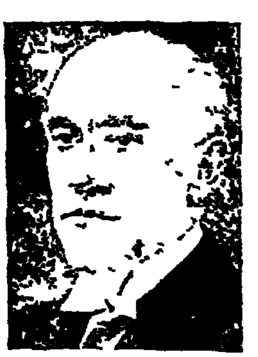
Obituary

HUGH STANNUS STANNUS

C B E , M D Ph D Lond , F R C P , D T M & H

By the death of Hugh Stannus on Feb 27 tropical medicine has lost one of its oldest advocates, who was in many ways a pioneer

He was born in 1877, the only son of Prof Hugh Hutton Stannus, F R I B A Educated privately, he studied medicine at St Thomas's Hospital where he qualified in 1901 After holding house-appointments there he was appointed resident surgeon to the Hertford British Hospital in Paris There he learned to speak fluent idiomatic French and attended the clinics of Poirier and Babinski



In 1905 he was appointed medical officer to the King's African Rifles in British Central Africa and later was posted to Nyasaland as medical officer with headquarters in Zomba He found himself much at home in primitive Africa with avenues of inquiry and research enticing him on every hand, and in the years before the outbreak of the first world war he made an intense study of anthropology and ethnology on the many interesting and primitive tribes of Nyasaland His chief work was a monograph on the Wa-Yao people, which was well illustrated He also published papers on pellagra, trypanosomiasis, blackwater fever, and piroplasmosis Indeed the seeds of all his later work on the nutritional and venereal diseases were sown during his early tropical service He was one of the first if not the first, to draw attention to pellagra in Central Africa, as he saw it in Zomba prison in 1910 He pointed out the symmetry of the rash and disposed of the maize theory" of its causation In 1911 he took his M D and was awarded the university gold medal

From 1914 to 1918 he served as principal medical officer of the Nyasa-Rhodesian Forces fighting von Lettow in Tanganyika On his return to England after the war he was offered the post of director of medical services of the newly constituted Tanganyika Territory but his health had been undermined and he was advised to refuse it He therefore determined to make a fresh start in England and after a year s postgraduate study he settled in consultant practice in London He became physician to the French Hospital in Soho, where he remained till he retired in 1943 He was also associated with the old Hospital for Tropical Diseases at Endsleigh Gardens, and he was medical adviser to the Board of Inland Revenue and the High Commissioner for Rhodesia, and consultant to the Ministry of Pensions and Somerset House He was a sectional editor of the *Tropical Diseases Bulletin* He was elected F R C P in 1931

In 1937 Stannus became interested in lymphogranuloma inguinale He was the first to describe a case of this infection acquired in England and his most important book, *A Sixth Venereal Disease*, was published at this time In 1937 he returned to the age-old question of the relationship of yaws to syphilis During the late war he was consultant to the Ministry of Health on diseases of malnutrition and with Prof V Sydenstricker and Dr R Brunel Hawes started the rapid nutritional surveys He also became interested in the ocular manifestations of ariboflavinosis which he summarised in his Lumleian lectures to the Royal College of Physicians in 1944 In 1942 he propounded a new theory on the ætiology of tropical sprue.

He was a chevalier of the Legion of Honour and of the Ordre de la Santé Publique , he held the Médaille de la Reconnaissance Française In 1948 he was awarded the Treacher Collins prize and last year he was appointed C B E He had also been a master of the Founders' Guild of London, and his interest in the history of the guild and of London perhaps led him to take up genealogy as a hobby R B H relates how

to this he brought a passion for accuracy He would not accept any statement on family tradition however plausible when tracing a family unless he found documentary evidence confirming it This led him on to searching hundreds of wills in Somerset House and ancient birth registers in many towns and villages as well as writing to and travelling to meet anyone who might give him any clue in his search. In one instance he suspected a man whose parentage was in doubt to be a natural son of George IV He got into correspondence with a descendant in America who possessed a portrait of this man and obtained a photograph of this picture Armed with this he searched until he obtained an engraving of George IV at the same age and in a similar posture to compare them. His genealogies must be remarkable not only for their accuracy but even more so because they included notes of events in the lives of those he recorded He took great pleasure in the discussion of fresh ideas and puzzling cases, and his death will be a real loss to his many friends who delighted in his conversation

P M -B writes

Stannus was well liked and especially respected by the younger members of the profession for his ever helpful attitude. His was a distinctive personality, with rather a hesitant speech adorned with little mannerisms He would roll his eyes upwards, on being addressed, as if in alarm, break out into a smile, with a chuckle and ending in a kind of sigh He was slightly built with a forward stoop, and a peculiar swinging gait He always looked half famished, but he was tough indeed, because he survived many years of ill health In habit of mind he was critical , he could be argumentative and never took facts for granted

G P writes

Hugh Stannus's scholarly distinctions carried his reputation beyond these islands but of this quiet humble man more could be written Those nearest to his professional life on the staffs of his hospitals and those who served under, and with, him on committees will never forget his charm and gentleness in his dealings alike with patients and colleagues and how, diffident as he always was in the defence of his own interests, in support of a colleague on a cause which he felt to be just he would, in a flash, become a raging lion

In his younger days he was athletic and I well remember him, not so many years ago, swimming vigorously up and down the baths on a Saturday morning The last decade of his life was crippled by rheumatism, but this in no way diminished his cheerfulness and youthful enthusiasm Although a consulting physician in a circumscribed field, his interest in progress in all branches of medicine and surgery was intense, and he enriched any discussion in which he took an always humble part

JAMES BEAVER MENNELL

M.A , M D Camb

Dr J B Mennell consulting physician in physical medicine to St Thomas's Hospital London, who died at his home at Liss, Hampshire on March 2, at the age of 77, pioneered the use of physical methods for reablement after fractures and other injuries

From St Paul's School he went to Pembroke College Cambridge, and thence to St Thomas's Hospital, from which he qualified in 1908 For the next twenty-seven years he worked without interruption at St Thomas's His earliest appointments there included those of casualty assistant and house-surgeon, and even by then he had recognised the serious gap in the treatment of injuries after the initial phase P B writes

To summarise Dr Mennell's professional activities by saying that his life was devoted to massage, manipulations, and remedial exercises would be a gross inaccuracy and an injustice He was essentially a man of great clinical acumen who broke away from tradition, and with much courage and perseverance set out to apply physical methods to therapeutic ends His interest in the field which must ever commemorate his name began when he was still a student at St Thomas's Hospital, and observed that the after treatment of fractures was virtually non existent After qualification, his concern with after treatment of fractures and injuries in outpatients was rekindled, and very soon after he was appointed in the then "department of physical exercise" an unofficial clinic for fractures and trauma evolved under him

As a pupil of Lucas Championnière he employed initially the methods of his teacher, but he soon modified these and developed his many techniques aimed at early restoration of function Many of these, considered unorthodox at the time, have now become a matter of routine, and in this sense can Dr Mennell be looked upon as having laid the foundation of rehabilitation

J B, as he was affectionately called by his colleagues, was a dedicated man and never spared himself despite the indifferent health which forced him to retire from hospital work before his time in 1935

His writing his lecturing, and his starring in a film which he directed himself bear witness to his industry after retirement, and account for his deserved reputation as a teacher and a clinician, not only in this country and the Commonwealth but on the Continent and in America

Much of his energy was spent in the interest of physiotherapists, and the school of physiotherapy at St Thomas's Hospital owes much of its success to his encouragement and enthusiasm His continued and devoted concern with physiotherapy earned him the chairmanship of the council of the Chartered Society of Physiotherapy after retirement, while at St Thomas's Hospital his memory was kept alive in a bursary for teachers of physiotherapy, which bears his name At the time of his death, he was still president of the Old Physiotherapy Students' Association

Dr Mennell had served as president of the section of physical medicine of the Royal Society of Medicine, and as a member of the council of the British Association of Physical Medicine His books included *Physical Treatment by Movement, Manipulation, and Massage*, *Backache*, and *The Science and Art of Joint Manipulation*

He is survived by his widow and three sons

WILLIAM STOBIE

O B E, M A Oxfd, M D Edin, F R C P, J P

Dr William Stobie, for long consultant for tuberculosis to Oxford and to Oxfordshire and a past mayor of the city, died at his home at Cumnor on March 2 at the age of 70

He was born in Edinburgh and was educated there at George Watson's College and the university He graduated M B in 1908 and the following year he went to Oxford to become Osler's house-physician at the Radcliffe Infirmary Later he held other resident appointments under the late Dr A G Gibson and at the Eye Hospital His knowledge and interest in general medicine had thus been firmly established and discerningly stimulated before he began to specialise in diseases of the chest His work was given this direction by Osler's foundation of the Oxfordshire Association for the Prevention of Tuberculosis Stobie was chosen as its first medical officer, and to begin with he visited the outlying clinics by motor bicycle, and a colleague, recalling Stobie's still earlier experience as an assistant on horseback and push-bike, affirmed that "there is no doubt that he felt safer on these more primitive modes of progression than in his later motor-cars"

During the 1914–18 war Stobie did not lose touch with Oxford He served as medical officer with the Oxford and Bucks Light Infantry For his work he was twice mentioned in despatches and appointed O B E After his return to civilian life he took the M D in 1921, and five years later he was appointed physician to the Osler pavilion for diseases of the chest at the Radcliffe Infirmary In 1934 he became consultant in tuberculosis to the city and the county The same year he was elected F R C P and in 1938 the university conferred on him the degree of M A When the National Health Service was started in 1948 he became consultant in diseases of the chest to the United Oxford Hospitals and clinical lecturer in the university He retired from these posts in 1952

In the midst of these professional responsibilities Stobie did not neglect his responsibilities as a citizen In 1930 he had become an alderman and the following year he was elected mayor of the city In 1932 he became a justice of the peace, and in 1951 he was elected chairman of the Oxford bench

A colleague writes

Few men can have had more friends than William Stobie—friends to whom he gladly gave more than most of them were able to give him in return In thinking about his unusually full life, one is at first confused by the variety of his many-sided activities We remember him first and foremost as "a good doctor" who always put the patient first—a memorial that many of us would deem sufficient in itself His chief professional work lay in the treatment and prevention of tuberculosis, but he never lost his interest and enthusiasm in general medicine and in medicine related to ophthalmology But Stobie's boundless mental and physical energy led him into many other branches of service to his fellow men, both in war and peace We think of him as mayor of Oxford as refereeing rugby football matches, as chairman of the bench as a rose grower, as a formidable expert on committee procedure, and an outspoken critic, yet the kindliest and most hospitable of men We think of him as a small square man always friendly, with a tremendous laugh on the appropriate occasion, and always busily employed in doing something to help someone else We remember him with gratitude and affection

In 1914 Dr Stobie married Miss Irene Taylor of Shelsley Walsh, Worcestershire She survives him with their two sons and their daughter

HERBERT CALDER ELDER

M B Edin, M R C P E, D P H

Dr H C Elder, late chief tuberculosis officer of Edinburgh, died on Feb 23 at the age of 68 He was educated at Harris Academy, Dundee, and at the Universities of St Andrews and Edinburgh, graduating M B Edin in 1917 His appointment as house-physician to Sir Robert Philip at the Edinburgh Royal Infirmary was the origin of his life-long interest in and enthusiasm for tuberculosis A year after his appointment in 1919 as assistant tuberculosis officer to the corporation of Edinburgh, he was elected M R C P E He was promoted to the post of chief tuberculosis officer after nine years' service, and he held this appointment until he retired in 1953

At an early stage in his career he developed a special interest in the diagnostic procedures applicable to diseases of the chest, and he became one of the pioneers of bronchography in this country Recognition of his capabilities as a clinician, and of his extensive knowledge of tuberculosis, led to his appointment as lecturer in this subject to the school of medicine of the Royal Colleges of Edinburgh in 1930 He resigned from this post in 1939 at the outbreak of war

A colleague writes

Dr Elder's gifts of intense concentration and grasp of essential detail became evident in the skill with which he solved any pertinent problem and in his mastery of the wide variety of subjects in which he was interested He was an accomplished musician with a profound regard for the [illegible] He [illegible] a fluent French linguist and, in his youth, a crack golfer He tried to cloak a shy and retiring disposition with a brusqueness which was often misinterpreted But his patients, whose interests and welfare were always his concern, were usually quick to recognise that his strictness as a disciplinarian was equalled by his warm humanity and innate kindliness

Dr Elder leaves a widow

Notes and News

WOMEN CANDIDATES ONLY?

FOR some months doctors and patients in Edinburgh have been discussing whether a consultant vacancy in the Southern hospital group of the city should be restricted to women andidates The regional hospital board proposes to combine wo part time appointments—one previously held by a woman at the Bruntsfield and Elsie Inglis Hospitals, the other held by a man at the Deaconess and Longmore Hospitals—to form a new post of consultant to the whole hospital group The hospital management committee think that in open competition a woman candidate might not be appointed to this combined post, and they are disturbed because there would then be no woman medical specialist in the whole South-Eastern region, and because the change would break the tradition of the Bruntsfield and Elsie Inglis Hospitals, which have been staffed by women since their foundation over fifty years ago The Secretary of State for Scotland has also received protests from the Edinburgh local medical committee and executive council and the Medical Women's Federation, and a petition signed by 20,000 people He has announced, nevertheless, that he has decided not to interfere with the discretion of the regional hospital board He adds that the board "have emphasised to him that should a woman candidate prove herself worthy in open competition she would be appointed to the combined post with their fullest confidence"

THE DENTAL SCENE

THE annual clinical meeting of the Guy's Hospital Dental School was held last Saturday Besides the clinical cases there were numerous table demonstrations, which are always useful guides to new developments and methods in operative dental surgery—as well as serving to recall the various small, but often important points which tend to be forgotten in the press of routine dental practice The ordinary dental engine still appears to be the best instrument for cavity preparation, in spite of the rival claims of air propelled abrasive dust and ultrasonic drills The emphasis is now on high speed engines, with diamond or carbide burs, rotating at five or six times the speed formerly used, and Mr W A Vale showed what could be accomplished with such a machine in the rapid and painless preparation of cavities At the moment the limitations of this method are those imposed by the ability of the handpiece to stand continuous high-speed running

The dental students are now encouraged to do original work, and the results of several ingenious and promising lines of research were on view A problem that is still unsolved is whether the dentinal tubules contain nerve fibrils J W Fernhead,[1] of the London Hospital, claims to have demonstrated their presence, but Guy's remains sceptical and holds to the view that pain during cavity preparation is caused by changes in hydrostatic pressure transmitted through the tubules to the pulp Work is still in progress and perhaps by next year the answer will be known for certain

In a lecture which he called Rock Around the Gas Room, Dr W S McConnell contrasted—often with masterly understatement—the hospital gas room of today with that of twenty five years ago Despite the attractions of cyclopropane, nitrous oxide and oxygen remains the standard anæsthetic for all dental patients over 4 years of age, but adjuvants and premedication are used freely when there are any possibilities of anæsthetic difficulties Ethyl chloride, once given as a routine to children, is no longer used at all instead divinyl ether, by itself, is given to children under 4, and for induction to children up to 6 Discussing the numerous drugs from which the anæsthetist can now choose, Dr McConnell emphasised the value of intravenous pethidine for the apprehensive patient He also remarked that in the ordinarily recommended dosages the barbiturates, methylpentynol, chlorpromazine, and an inert substance had all proved equally effective—or ineffective—in reducing apprehension in the dental chair

A lecture by Prof M A Rushton was illustrated by radiographs and photographs of some of the more unusual dental cases referred to him during the year by dental practitioners Although some may regard oral pathology as one of the more esoteric branches of dental practice the size of his audience showed the great interest in this subject Afterwards he introduced a short teaching film on Biopsy Techniques made by Mr B E D Cooke—a valuable film not only for students but also for any dental surgeons who wish to ensure that their biopsy specimens will have the greatest value for the pathologist

HOME-MADE

A REVIEWER may occasionally allow himself the pleasure of commenting on the excellence of the production of a work, and it gives particular pleasure to commend that of Dr J Gibson's [1] pamphlet on St Lawrence's Hospital, Caterham, for it was set up and printed by the patients

The Caterham Metropolitan Asylum (as the hospital was originally called), and its twin hospital at Leavesden, opened in 1870 to "such harmless persons of the chronic or imbecile class as could lawfully be detained in a workhouse" The hospitals owe their existence to the Metropolitan Poor Act, which was so largely inspired by Florence Nightingale Under this act, the board of what was called ("with a reckless disregard of initials," says Dr Gibson in his pleasing account) the Metropolitan Asylum District decided to build the two hospitals to an identical design Many buildings have been added since, even in 1875 there was a swimming bath

Over 300 patients were admitted in the first year, and by 1877 the numbers had reached about 2000 In the early years most patients were psychotic, but now, of the total 2200, 2000 are mentally defective They include children over the age of 5 years, some of whom are admitted only for short periods during which their parents cannot look after them Most of the patients have severe degrees of deficiency, but useful occupation or instruction is found for many of them The illustrations include photographs of a modernised ward, a classroom, and the new printing shop (provided by the Nuffield Provincial Hospitals Trust) where the pamphlet was produced

HELP FOR DISABLED PEOPLE

A SERIES of articles has been appearing in the *Social Service Quarterly* in recent years on what is being done to help disabled people This series has proved very popular, and the first fifteen articles have now been published in book form [2]

As the late Dame Georgiana Buller pointed out in her introduction, there are few tasks—if indeed any—which call for complete physical integrity The remaining essays are concerned with what can be done to train and use the able remnant of the maimed person Some cover specific disabilities (such as deafness) or specific groups (such as school leavers), others discuss organisations at world and at county level There is much useful factual information, including an enlightening account of many ingenious but simple devices (such as a fixed nailbrush for the one handed man) which can make life at home or at work much easier

The picture this booklet presents of what can be done is as encouraging as it is stimulating To quote Dame Georgiana Buller again, "Pity is a cheap emotion and a negative one True sympathy—feeling with—demands the effort of comprehension and is productive of results"

University of Cambridge

On Feb 23 the degree of M B was conferred by proxy on R H Lavelle

Royal College of Surgeons of England

Mr A Lawrence Abel will deliver the Bradshaw lecture on Thursday, March 14, at 5 P M, at the college, Lincoln's Inn Fields, London, W C 2 He is to speak on diseases of the large intestine

Victor Horsley Lecture

Sir Geoffrey Jefferson, F R S, will deliver this lecture at the house of the British Medical Association, Tavistock Square, London, W C 1, on Friday, April 12, at 5 30 P M This is the centenary of Horsley's birth and Sir Geoffrey is to speak on his life and work

Society for Social Medicine

This new society will hold its first scientific meeting in Birmingham from Sept 24 to 26 The hon secretary is Dr Alice Stewart Department of Social Medicine, 8, Keble Road, Oxford

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[1] J Anat 1957 (in the press)

[1] Gibson J St Lawrence's Hospital Caterham Surrey 1870–1956 Printed at the hospital Pp 13

[2] The Welfare of the Disabled National Council of Social Service, 26, Bedford Square, London W C 1 Pp 101 5s

Chest Diseases and the Family Doctor

A weekend course on this subject for general practitioners is to be held at Norwich on April 13 and 14 Further particulars can be had from the Tuberculosis Educational Institute, Tavistock House North, London, W C 1

Blindness in Mental Deficiency

A meeting on this subject will be held at the Fountain Hospital, Tooting Grove, London S W 17, on Wednesday, March 13, at 5 30 P M The speakers will be Prof Arnold Sorsby, Dr L Crome, and Dr C E Williams

Humane Technique in the Laboratory

The Universities Federation for Animal Welfare is holding a symposium on this subject at Birkbeck College, Malet Street, London, W C 1, on Wednesday, May 8, at 9 45 A M, under the chairmanship of Prof P B Medawar, F R S

Institute of Diseases of the Chest, London

There will be a discussion for general practitioners at this institute (in the grounds of the Brompton Hospital, S W 3) on Tuesday, April 9, at 2 30 P M, on hay fever and asthma Further information may be had from the secretary of the institute

British Association of Physical Medicine

The annual meeting of this association will be held on April 5 and 6 at the Middlesex Hospital, London, W 1 The programme includes a discussion on poliomyelitis, when the opening speakers will be Dr R W Gilliatt, Mr D M Brooks, Dr B E W Mace, and Squadron Leader C B Wynn Parry Further particulars may be had from the association, 45, Lincoln's Inn Fields, W C 2

National Association for Mental Health

The subject of the annual conference of this association, which is to be held at Church House, Westminster, London, S W 1, on April 11 and 12, is to be The Maladjusted Child—the Underwood report and after The speakers will include Dr Kenneth Soddy, Dr John Bowlby, and Dr Mildred Creak Further particulars may be had from the association, 39, Queen Anne Street, W 1

Sixteen specialists from nine countries are visiting London hospitals to see demonstrations in anæsthesia They are taking part in a course arranged by the British Council and the Faculty of Anæsthetists of the Royal College of Surgeons of England

Diary of the Week

MARCH 10 TO 16

Monday, 11th

UNIVERSITY COLLEGE LONDON, Gower Street W C 1
5 P M Dr George Popjak Biochemistry of Fatty Acids and Cholesterol (Second of three lectures)
POSTGRADUATE MEDICAL SCHOOL OF LONDON, Ducane Road, W 12
1 P M Prof A C Frazer Steatorrhœa
INSTITUTE OF DERMATOLOGY, Lisle Street, W C 2
5 30 P M Dr R G Cochrane Leprosy

Tuesday, 12th

ROYAL COLLEGE OF PHYSICIANS OF LONDON Pall Mall East, S W 1
5 P M Prof J R Squire Functions of the Plasma Proteins (First of two Oliver Sharpey lectures)
ROYAL SOCIETY OF MEDICINE 1, Wimpole Street W 1
8 P M *Psychiatry* Prof Erwin Stengel Dr Hunter Gillies Diagnosis of Schizophrenia
ST MARY'S HOSPITAL MEDICAL SCHOOL Paddington, W 2
5 P M Prof Robert Cruickshank Use of Antibiotics
INSTITUTE OF DERMATOLOGY
5 30 P M Dr Cochrane Leprosy
WEST END HOSPITAL FOR NEUROLOGY AND NEUROSURGERY, 91 Dean Street W 1
5 30 P M Mr Joseph Minton Ocular Manifestations in Clinical Neurology (First of two lectures)
CHELSEA CLINICAL SOCIETY
8 30 P M (Rembrandt Hotel Thurloe Place S W 7) Colonel L Van Der Post Some Personal Experiences of Primitive Africa
MANCHESTER MEDICAL SOCIETY
8 P M (Clinical Sciences Building York Place Manchester 13) *Surgery* Mr A F Robinson Dr M P Cole Hormones and Adrenalectomy in Metastatic Breast Carcinoma, Dr Ralston Paterson Postoperative Radiotherapy in Breast Cancer

Wednesday, 13th

ROYAL SOCIETY OF MEDICINE
8 P M *Proctology* Mr P Warren History of Excision of the Rectum Mr I F Bonham Benign Stricture of the Colon Mr Harold Dodd Pelvic Abscess Mr A Lawrence Abel and Mr Gordon Ungley Hæmorrhoids or Piles (Colour film)
ST MARY'S HOSPITAL MEDICAL SCHOOL
12 NOON Dr C A H Watts Psychology and Psychia
Family Doctoring
POSTGRADUATE MEDICAL SCHOOL OF LONDON
2 P M Dr Henry Haber Cellular Nævi and Melanomata
INSTITUTE OF DERMATOLOGY
5 30 P M *Dr R W Riddell Histological Diagnosis of Fun-*
Infections
INSTITUTE OF DISEASES OF THE CHEST Brompton S W 3
5 P M Dr Paul Wood Aortic Stenosis
ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE 28 Portl
Place, W 1
3 30 P M Dr J S Anderson Infectious Diseases
UNIVERSITY OF OXFORD
5 P M (Radcliffe Infirmary) Prof Pierre Lacroix Experimental Study of Bone Grafting Operations
MANCHESTER MEDICAL SOCIETY
4 30 P M (Medical School, University of Manchester) Pathology Dr R F Jennison, Dr F A Langley Plasma
Pneumonia
ROYAL FACULTY OF PHYSICIANS AND SURGEONS OF GLASGOW 242, St Vincent Street Glasgow
5 P M Mr George Smith Cardiac Hypertrophy—an Experimental Study (Watson lecture)

Thursday, 14th

ROYAL COLLEGE OF PHYSICIANS OF LONDON
5 P M Professor Squire Functions of the Plasma Pro
(Second of two Oliver Sharpey lectures)
ROYAL COLLEGE OF SURGEONS OF ENGLAND Lincoln's Inn F
W C 2
5 P M Mr Lawrence Abel *Diseases of the Large Inte*
(Bradshaw lecture)
UNIVERSITY OF LONDON
5 30 P M (University College, Gower Street W C 1) Prof
A H Schultz D PHIL *Old and New Views Conce*
Man's Specialisations
ROYAL SOCIETY OF MEDICINE
5 P M *Ophthalmology* Prof Vladimir Cavka (Belgrade) Clin
and Experimental Study of Ophthalmo-neurological
Symptoms in Lesions of the Frontal Brain
INSTITUTE OF DERMATOLOGY
5 30 P M Dr G C Wells Use of Steroids in Dermatology
NUFFIELD ORTHOPÆDIC CENTRE
8 30 P M (Wingfield Morris Orthopædic Hospital Oxford)
Mr D Ll Griffiths Volkmann's Contracture—Second
Thoughts
LIVERPOOL MEDICAL INSTITUTION, 114, Mount Pleasant Liverpool 3
8 P M *Pathological Meeting* Dr J N Marshall Chalm
Thymectomy and Splenectomy in Pure Red Cell Anæ

Friday, 15th

ROYAL SOCIETY OF MEDICINE
5 P M *Epidemiology and Preventive Medicine* Dr W P D
Logan, Prof A C Stevenson, Dr W C Cockburn
Ascertainment of Disease
8 15 P M *Radiology* Prof Robert McWhirter Evaluation of
Treatment Policies in Malignant Disease (Presidential
address)
POSTGRADUATE MEDICAL SCHOOL OF LONDON
10 A M Sir Harry Platt, F R C S Causes and Prevention of
Deformity
4 P M Prof C H Stuart Harris Respiratory Virus Infecti
FACULTY OF RADIOLOGISTS
5 P M (Royal College of Surgeons) Dr Martin Bodian Neo-
plastic Diseases in Childhood
ROYAL MEDICO-CHIRURGICAL SOCIETY OF GLASGOW
8 30 P M (Royal Faculty of Physicians and Surgeons of Glasgow) Mr G E
Dr J F Crooks Cervical Spondylosis Mr G E
Schofield Post-gastrectomy Diarrhœa Dr C Dougla
Aftermath of Puerperal and Post-abortive Sep

Appointments

ANDERSON, G L, M B Durh school M O, co Durham
* BROOKES, V S, M B Birm, F R C S part-time consultant surgeon United Birmingham Hospitals at the Children's Hospital, Birmingham
JACKSON, T F M, L R C P I school M O, co Durham
JAMES, J A, M B Lond, F R C S part-time consultant orthopædic surgeon mid Worcestershire H M C
LLOYD ROBERTS, G C, M B Camb, F R C S part-time consultant in orthopædic surgery, St George's Hospital London
MORRISSEY, D M, M CH N U I, F R C S part-time [illegible] surgeon United Birmingham Hospitals and Dudley and Stourbridge H M C
STENHOUSE, R A, L M S S A, D I H M O H, Downham Market

Liverpool Regional Hospital Board

ANNIS, DAVID, CH M L'pool, F R C S assistant consultant general surgeon Clatterbridge General Hospital
LOTHIAN, K R, M B N Z, F R C S assistant consultant general surgeon, St Catherine's Hospital, Birkenhead
MURPHY, A I, CH M L'pool, F R C S assistant consultant general surgeon Birkenhead General and St Catherine's Hospitals
PARRY, F W, CH M L'pool, F R C S consultant general surgeon Bootle and Waterloo Hospitals

* Amended notice

Births, Marriages, and Deaths

DEATHS

HARRIS.—On Feb 23, at his home, Merrow Down, [illegible] Sussex, Charles Poulett Harris, M D, aged 8

THE PREVENTION OF TUBERCULOSIS*

W D W BROOKS
CBE, DM Oxfd, FRCP
PHYSICIAN TO ST MARY'S HOSPITAL AND TO BROMPTON HOSPITAL, LONDON

> "The preservation of health is, without doubt, of all blessings in this life the first and fundamental one"
>
> DESCARTES (1637)

IT is of paramount importance in Darwin's evolutionary theory that a species must adapt itself to its surroundings or perish, and this law is well illustrated by the relationships which may be established between a host and its parasites We know that when a parasitic micro-organism colonises a new host one of three things may happen There may be adaptation by both, producing a carrier-state, or adaptation may fail because, in one way or another, the host destroys the parasites, or, after a Pyrrhic victory represented by a fatal illness for the host, both he and his parasites die together Each of the last two possibilities represents a failure by the micro-organism to adapt itself to its environment, unless in either event the struggle is sufficiently protracted, and the circumstances propitious enough, to permit transference to another host before the micro-organism dies Since a majority of mankind is infected with tubercle bacilli, and since it would be vain, as yet, to hope to suppress all sources of tuberculous infection quickly, even in those parts of the world healthiest in this respect, the effective prevention of the disease in man must rest essentially upon a proper understanding of these principles Clearly, any measure which will reduce the hazard of infection is of supreme value, but, when the course and outcome of the battle of mankind versus tubercle bacilli are envisaged, it would not be realistic to fail to give first place to the statistically much more significant problems of the infected Paradoxically, it is here that our knowledge, and its practical application, are relatively deficient

The Infected

As is the case with many other host parasite relationships, the carrier state between man and tubercle bacilli is much the most common consequence of infection It is usually achieved following primary infection, but is also quite often seen in post primary and in adult-type disease All of these tuberculous states are examples of unstable equilibrium, and adaptation may fail at any time, but the reasons for this failure are very incompletely understood To put the same point into other words, we do not know at all accurately why primary infection is followed by progressive tuberculosis in one case but by healing in another Similarly, in post-primary and adult type disease, progression, remission, and relapse are not predictable with any certainty Furthermore, the part played by superinfection at any of these stages of tuberculosis is very imperfectly appreciated We do know that human beings vary in their biological response to infection, and in part at least this response is determined by constitution Thus, primary infection leads to progressive tuberculosis far more often in some relatively unexposed races, because the susceptible stock has not been removed as has happened in other races during centuries of exposure to infection A similar argument presumably also applies to individuals and their families Likewise, clinical observation shows that physical and mental fatigue, and certain diseases (some constitutional, others acquired), modify the course of tuberculous infection More important, however, is the effect of nutrition Wherever this has been studied, it has been shown that an inadequate food-supply is associated with enhanced tuberculosis morbidity and mortality, and that both these rates fall as food-supply is increased to an optimum level This is true irrespective of age and race and under widely differing climatic conditions For many years, fatigue, nutrition, and consecutive disease have been in some degree within human control and from this knowledge developed the basic therapy of tuberculosis

Finally, the age of the host is important Rich (1944) has summarised the position in adolescence thus "The sharp rise in mortality that follows the childhood period of relative safety is associated with the following circumstances

> (i) a progressive increase in the incidence of infection,
>
> (ii) apparently a specific adverse effect of the state of pubescence on resistance, and,
>
> (iii) the beginning of exposure to the stresses and strains associated with a struggle for existence and with childbearing"

That other less evident factors may be operative cannot be denied In infancy certainly, and possibly in old age, resistance to infection and to the progression of tuberculosis is relatively low

Primary Infection

For these reasons, in the early years of this century, the view was widely held that primary infection in childhood was a useful asset it rarely progressed to a serious degree, and the children developed some immunity which was thought to be of considerable benefit in adolescence and young adult life For the inhabitants of an English industrial city in the latter half of the 19th century, for example, it was in all probability an advantage to have thus acquired some immunity, since they were heavily exposed to infection for the rest of their lives in their homes and in the factories where they worked In much of the world today the epidemiological position is still the same, but in many countries, including our own, it has vastly improved in that exposure to repeated gross infection is uncommon, and the standard of living is high enough to secure for the vast majority a fair degree of natural resistance to tuberculosis which ensures their survival as they grow up Moreover, the risks of primary infection are in actual fact considerable, for dissemination may soon follow, or after a latent period which is often considerable the quiescent infection may flare up and progress Indeed, for these reasons, and from the results of many follow-up studies, it is now recognised that the prevalence of tuberculosis in any generation is determined during the early years of life (Dubos 1956) Thus, the mortality-rates from tuberculosis can be accounted for statistically by the assumption that every generation has the same pattern of mortality at various ages in other words, its level of mortality from this disease is determined early in life, and remains peculiar to it thereafter This epidemiological law is probably valid today for those countries which have a relatively low and falling tuberculosis mortality, and it emphasises that in these circumstances one of the most effective methods of prevention of tuberculosis is to attack the disease during infancy and childhood

Infants and young children as a rule experience their first infection without clinical or radiological evidence of disease, so that detection of the event depends upon serial tuberculin skin-testing, and, however true it may be that we still lack proper understanding of the scope, limitations, and value of this test, it remains our most sensitive diagnostic procedure Heaf (1956) has suggested that tuberculin testing should be done in the first, second, fifth, ninth, and twelfth years of life as a practical routine—ideally, of course, much more frequent testing is desirable—and that health visitors and nurses should be trained in this technique and use it, as in fact they do in Scandinavia The discovery of a positive tuberculin test will permit full investigation not only of the infected individual but also of the contacts, among whom—as Gedde Dahl (1952) and McDougall et al (1953) showed —there is a considerable probability of discovering an infectious person requiring treatment Furthermore, the epidemiological considerations outlined above lead logically also to the conclusion that recent primary infection, irrespective of apparent health or disease, is an indication for treatment with antimicrobial drugs What in this connection may be called chemoprophylaxis, in type and duration adapted to the particular features of each case, is already widely used in America, and has the advantage that, for the great majority, interference with the normal routine of life is unnecessary There would seem to be no reason why the same argument and management of the situation should not apply to primary infection acquired later in life If chemoprophylaxis is widely adopted and succeeds in its aim, the population of today which carries living virulent tubercle bacilli in the latent form—that is to say lives in a state of uneasy neutrality with its tuberculous parasites—will in time be replaced by a population in which these organisms have been largely destroyed by the combined effect of natural defence mechanisms and chemotherapy No one would belittle the theoretical and practical difficulties of such a programme, but until much more exact knowledge of the mechanism of antituberculous immunity is achieved—until we can as a practical procedure measure, and if necessary fortify, the state of immunological resistance of an infected individual—it is both logical and imperative to do the best we can to destroy the organism at a time when it is most accessible

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* The Marc Daniels lecture for 1957, given to the Royal College of Physicians on Jan 15

Post-primary and Adult-type Disease

In much of the world, tuberculosis mortality was falling fast before the introduction of chemotherapy and surgical resection During the past twenty years, with increasing momentum, these two therapies have greatly improved prognosis in post-primary and adult-type disease, and have undoubtedly saved or greatly extended many thousands of lives in this country alone To estimate their significance in terms of preventive medicine is much more difficult, because usually, neither together nor singly, do they produce a bacteriological cure We may reasonably expect that for many years a considerable population in constant need of supervision lest relapse should occur will be with us, and it will be the larger because of the very success of the methods used

When we add to this the disturbing fact that drug-resistant forms of tubercle bacilli are isolated increasingly often, even after several different drugs have been used simultaneously in treatment, we are again brought back to the fundamental fact that, once it has been infected, it is the human body itself, through its own defence mechanisms, which determines the issue As has been said, little is known of these mechanisms

Vaccination of the Uninfected

Although for more than fifty years it has been known that the resistance of animals to tuberculosis can be raised with vaccines consisting of either dead or attenuated living bacilli, only one of very many attempts to produce immunity has so far proved of practical value in man B C G, today widely used among the previously uninfected, derives directly from the parent strain developed by Calmette and Guérin at the Pasteur Institute at the turn of the century, and an important disadvantage in its use arises from the inevitable divergence of the characteristics of its many descendants Thus, a method for its biological standardisation is much needed, and we also lack the means of measuring the level and duration of the immunity to which it gives rise Unfortunately, too, all forms of tuberculosis vaccine, including that prepared from vole tubercle bacilli, render the vaccinated person tuberculin positive to skin tests, and therefore eliminate our most sensitive diagnostic method—one which is of increasing value as the average age of primary infection rises All this would be insignificant if B C G or vole bacillus vaccine did provide complete, or even considerable, protection against tuberculosis, but it is certain that the degree of immunity they induce is of a moderate order and probably temporary Thus, there is no evidence that immunity acquired in this way can ever prevent infection or superinfection by virulent organisms There is, however, evidence (Medical Research Council 1956) that progression from infection to disease is retarded, so that acute forms of tuberculosis occur less often in the vaccinated The value of these vaccines in preventing the epidemiologically and socially much more important chronic pulmonary tuberculosis seems less certain (Daley loc cit) Some recent work by Strom (1955) in Sweden and Pasquier (1955) in Paris, using B C G and tubercle bacilli in which radioactive isotopes (^{32}P and ^{14}C respectively) were incorporated, is of importance in this respect They have shown that virulent bacilli injected into a previously vaccinated animal are not disseminated as quickly or widely as are the same organisms injected into a normal unvaccinated animal—proving that vaccination does retard the spread of infection They have also shown that the vaccinated animal can destroy injected bacilli more rapidly than can the unvaccinated animal. This method of investigation, using labelled B C G, has been repeated in man and has given the same result It is a very important method of research, and will probably be developed extensively

A review of the advantages and disadvantages of B C G suggests that in countries such as New Zealand Canada, the United States of America, Scandinavia, and our own, where the risk of infection is relatively small and the resistance of the native population relatively high, its use should be limited to certain groups These include those known to incur a considerable risk of infection, such as contacts (whatever their age), hospital workers, and seamen They also include, because of their known susceptibility, adolescents and young adults and immigrants of (for example) Irish and Negro stock On the other hand, in countries such as India, China and much of the Middle East, where the risk of infection is comparatively high, all uninfected persons would derive benefit from vaccination, and this also applies to immigrants and travellers who have occasion to go there for any appreciable length of time

The Prevention of Infection

The uncertain outcome of events after infection by tubercle bacilli clearly indicates that prevention of infection is the most important measure for the preservation of health To achieve this, it is necessary to discover and then eliminate sources of infection Much has been done in this respect in some parts of the world, little in others

Bovine Tuberculosis

Fifteen years ago in this country, Wilson (1942) estimated that infection with bovine tubercle bacilli was responsible for 1500–2000 deaths every year At that time there was evidence from the United States and Scandinavia that a policy of drastic eradication of bovine tuberculosis and pasteurisation of milk led to direct and rapid prevention of this type of tuberculosis in man The adoption of a somewhat comparable policy here has had similar results, and the disease is now very rare The prevalence of bovine tuberculosis probably varies widely in different parts of the world, and in many countries nothing is known of its extent

Human Sources of Infection

From person to person pulmonary tuberculosis is spread by droplets and dust The use of masks for those especially exposed to risk of infection (e g , nurses) and the training of infectious patients in the control of sputum and coughing, are sound preventive measures. The latter training is especially important, since for a variety of reasons it is impracticable, in this and in many other countries, to isolate every known infective patient until either cure or death results. In addition, when isolation is impossible, it should be remembered that infants, adolescents, and young adults are likely to be the most susceptible of those coming in contact with the patient, and therefore merit priority in any measures of prevention which may be practicable (Daniels et al 1948).

The proper treatment of patients, their rehabilitation, and the provision of financial assistance to them and their families are all important measures in preventing the spread of the disease to others. They are also much the most costly. Indeed, Benjamin (1955) has estimated that to provide for the treatment of tuberculosis in India on the scale commensurate with its known extent would cost more than three times the sum now available for the entire public health and medical relief services of that country. The authorities there are wisely concentrating at first on more directly effective and less expensive preventive measures. None the less, in the prevention of the disease, therapy for known cases is not to be despised. Indeed, it is essential.

The major problem, however, is the detection of infectious and potentially infectious cases before they have spread infection to others and then to treat these patients so that they become uninfectious. The traditional method of detection is to examine those who have clinical evidence of the disease, and it is an effective method if to clinical investigation bacteriological and radiological investigations are added. If the public were educated to expect these last two investigations as a matter of course when respiratory illness is suspected, examination of patients would become an even more useful preventive method than it is at present. This would imply the provision of better facilities for X-ray and bacteriological investigation on behalf of the general practitioner. Such facilities exist in this country, but they could be improved with advantage.

Similar methods of examination, when applied to contacts of known post-primary and pulmonary tuberculosis, also yield a considerable harvest of cases, and a proportion of these will be inapparent in the sense that there will be no clinical evidence of disease. Since in tuberculosis the interval from infection to disease varies, and may extend to two, three, or even more years, re-examination of contacts is very desirable.

Unsuspected cases of pulmonary tuberculosis are also often discovered if routine X-ray examination of the chest is used as a condition of employment and emigration. In these circumstances a problem in ethics may well develop, for the rights of the individual may conflict with the rights of population groups or of nations to protect their health. The level at which this conflict will arise—and, still more, that at which it will be settled—will largely depend on public opinion about the significance of tuberculosis. As a nation, we are today far less demanding in respect of examination to exclude tuberculosis than are several other Commonwealth countries or the United States.

A most important preventive measure for hospital workers and patients, and one used increasingly in the United States and Canada in the last decade, is the routine chest X-ray examination of *all* patients admitted to general hospitals. Those found to have radiological evidence of pulmonary tuberculosis may then be segregated in special wards for further investigation and treatment. This has been done in St Mary's Hospital for the past four years. The considerable extent of unsuspected tuberculosis and of other intrathoracic disease thus disclosed, as well as the benefit for hospital personnel, is being published elsewhere. There is little doubt that this procedure should be used in every general hospital in this country.

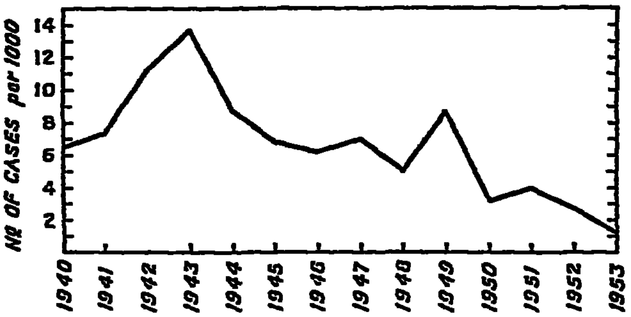

Fig 1—Incidence of pulmonary tuberculosis number per 1000 fluorographed Royal Navy, men new entry 1940–53

Miniature mass radiography (fluorography), made practicable by the work of D'Abreu (1936), has been widely adopted throughout the world as the least costly procedure for finding otherwise inapparent cases of pulmonary tuberculosis in various population-groups. It gives a much more accurate picture of the prevalence of the disease than any other method. For our purposes today, its epidemiological value may be illustrated by some experience in the Royal Navy, where it was first used and developed in this country—largely through the efforts of the late Sir Sheldon Dudley—and where it has become an annual event for every sailor.

Fig 1 shows the incidence of pulmonary tuberculosis (revealed by fluorography) in men newly entering the Royal Navy from 1940 to 1953. It thus shows the incidence of inapparent tuberculosis in these years in men, mostly young who had previously been physically examined, coming fresh from civilian life. A well-marked trend is evident indicating a decrease in incidence over the fourteen-year period. This tendency was twice interrupted—in the years 1941–43 and again in 1949. The first rise in incidence took place after civilian sanatoria and chest hospitals had been largely emptied of their patients and air-raids had imposed a "shelter life"—the interval being compatible with what is known of the usual incubation-period of the disease. The second rise, in 1949, correspondingly followed the worst phase in the shortage of beds for the treatment of pulmonary tuberculosis. At this time (1946–48) large numbers of infectious patients waited at home many months for treatment, thereby increasing the risk of infection for the general population. I know of no better or clearer illustration of the relationship between risk of infection and resultant disease.

The most important and easily understood index of the consequence of repeated fluorography upon the incidence of pulmonary tuberculosis in the Royal Navy is to be found in the attack-rate of the disease in those

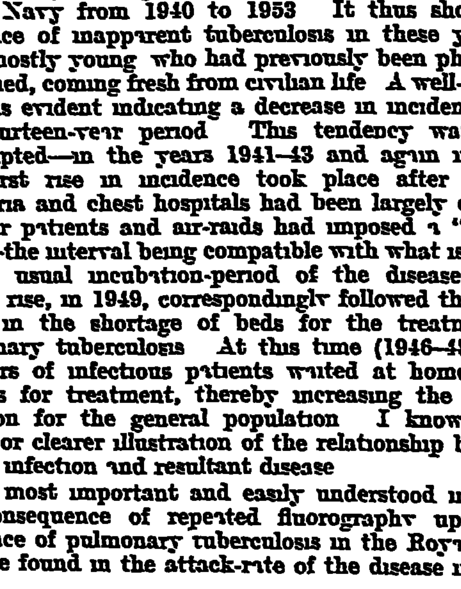

Fig 2—Incidence of pulmonary tuberculosis number of new cases per 1000 fluorographed, in those previously normal to fluorography Royal Navy, men. 1944–53

established personnel previously found to be normal to fluorography This is measured by the aggregate of the incidence of new cases disclosed by fluorography, and of new cases diagnosed through disease becoming clinically evident The latter had been shown by Dudley (1938) to have remained fairly constant at 2 per 1000 per annum for many years before the war It had fallen (Brooks and Frazer Roberts, unpublished) by 1945 to 1·1 per 1000 per annum, and in 1953 was 0 54 per 1000 The former incidence is shown in fig 2 and covers the period 1944–53 There were relatively slight fluctuations until 1949, and thereafter a dramatic fall to about a ninth of the previous incidence—a fall which seems to be related to the consecutive decrease in the mean intervals between examinations Taken in conjunction with the fall in incidence of clinically disclosed disease, it seems probable that, if annual fluorography is maintained, tuberculosis following infection within the Royal Navy will be controlled and kept at a minimal level

How variable is the extent of inapparent tuberculosis over the world may be illustrated by quoting, the experience of a fluorography unit working in the Persian Gulf, with Arab employees who had been clinically examined previously An incidence of pulmonary tuberculosis of 22 per 1000 fluorographed was found This figure is the more remarkable because where racial resistance is low, as it is in Arabs, the proportion falling ill with tuberculosis (and so not fluorographed in this survey) will be relatively high With a diminishing incidence of disease in this country, on the other hand, mass radiography will prove more and more costly—where cost is measured by the yield of cases in relation to the money and time spent Increasingly strong arguments will therefore arise for the concentration of the procedure upon certain population groups—e g , the elderly—whose incidence of undisclosed disease is known to be high They will be justified only if iatrogenic neurosis does not then prove too serious an obstacle for what is, and I hope will remain, a voluntary examination in a civilian population Where everyone is examined, such an objection does not arise Mass radiography, and indeed all the other preventive measures we have discussed, if they are to be used successfully in a free society to preserve health, depend fundamentally upon public opinion about the disease in question Education, and less certainly propaganda, may influence this, but both are slow processes Health legislation has always been found ineffective if not backed by public sentiment, even in a disciplined fighting service such as the Army—as *Pringle* indicated as long ago as 1752 when he said

> "The prevention of disease cannot depend on the use of medicine or anything which the soldier shall have in his power to neglect, but upon such orders as he himself shall think not unreasonable and which he must necessarily obey"

In the last analysis, the prevention of tuberculosis, by those methods we know today as well as by those methods we may find tomorrow, depends on the will of the people

I am indebted to the Medical Director General for permission to publish statistics relating to the Royal Navy

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HÆMATOGENOUS OSTEITIS IN THE NEWBORN

J Boyes
F R C S E , F D S R C S E
NUFFIELD PROFESSOR OF ORAL SURGERY IN THE UNIVERSITY OF DURHAM

A E Bremner
M B St And , F R C S E
ASSOCIATE ORTHOPÆDIC SURGEON, ROYAL VICTORIA INFIRMARY NEWCASTLE UPON TYNE

G A Neligan
B M Oxfd, M R C P
SENIOR LECTURER IN CHILD HEALTH IN THE UNIVERSITY OF DURHAM

Hæmatogenous osteitis is still an important cause of crippling deformity, and a potential cause of death in the newborn This fact tends to be obscured by the surprising mildness of many of the cases (Dillehunt 1935, Cass 1940)

The recognition of two grades of severity (Greengard 1946) was an important step towards clearer understanding of this disease For this reason neonatal osteitis requires to be treated as a separate entity from the osteitis of older infants, which is almost invariably mild and has an excellent prognosis

Unfortunately no criterion other than personal impression has been suggested for distinguishing between the mild and the severe cases (Dennison 1955a), and we cannot suggest a better, because a precise clinical definition of severity appears unattainable and because the ultimate severity of certain cases can be so much influenced by the promptness with which effective treatment is started The difficulty of clinical assessment is illustrated by the fact that it is usually impossible to decide even how long the disease has already lasted when the patient is first seen

Any attempt to describe the clinical picture and treatment has to be set against this unsatisfactory background of extreme variability and lack of clear clinical definitions, but the attempt seems worth while because Dennison's (1955a) authoritative contribution leaves room for further discussion of the all-important questions of early diagnosis and treatment with antibiotics

Material

40 cases of neonatal osteitis have been treated by us at some stage (not necessarily the acute stage) of the disease in the past eight years 21 were classified as severe and 19 as mild A *Staphylococcus aureus* was recovered from the pus in 24 cases, a *Streptococcus hæmolyticus* in 5, a pneumococcus in 2, and an *Escherichia coli* in 1, no pus was available in the remaining 8 Of the 24 strains of *Staph aureus* 16 were resistant to penicillin in vitro, 7 were sensitive, and 1 was not tested (but the patient responded well to penicillin) All the strains of streptococcus and pneumococcus were sensitive to penicillin, and the *Esch coli* to streptomycin Where possible we relied on the bacteriologist's report of the in-vitro sensitivity when deciding which antibiotic was most suitable for each case, and we had no reason to regret any decision based on this information

Early Diagnosis

The natural history of the disease covers a remarkably wide range of severity The mildest cases show a strong tendency towards spontaneous recovery without complications of any kind, but the most severe cases are characterised by rapid dissemination through the blood stream, with formation of metastatic abscesses elsewhere in the skeleton or in vital organs, such as the lungs and the kidneys

It seems to us impossible to judge the potential severity of any case when it is first seen; what at first appears a mild infection may become really severe within a few days in the absence of effective treatment (see case 4, under "Failures"). We have therefore come to regard it as a matter of great urgency to make the correct diagnosis and to start effective treatment.

The rewards which can be won by successful application of this policy are illustrated by the 5 patients in this series in whom the upper end of the femur was involved. In 4 of them there was considerable delay—5, 8, 20, and 27 days—between the first recognisable signs of osteitis and the start of effective treatment. In all 4 the hip-joint was destroyed, and they were left with an absent, hypoplastic, or greatly distorted femoral head (as were the 3 patients in whom a hip-joint infection originated in the pelvis).

Case 13, however, was admitted to the Babies' Hospital for treatment of a large abscess in the left cervical and axillary groups of lymph glands. During his routine examination on admission he moved his left leg less than his right, and thickening and tenderness round the upper part of his left femur were detected (although his mother had not noticed anything abnormal). He was immediately started on treatment with intramuscular penicillin, at first 3 hourly and later 6 hourly, and after 11 days was sent home to continue with a single daily injection of procaine penicillin for a further 11 days.

The pus aspirated from the gland abscess grew a *Staph aureus* fully sensitive to penicillin. The femoral lesion required no local intervention, and the hip joint remained free from infection. The left leg was clinically normal on the 7th day of treatment and remained so thereafter.

The radiological changes were severe by 2 months from the start of treatment, with well marked patchy rarefaction in the femoral neck and slight raising of the periosteum over the upper two thirds of the shaft. By 3 months both femoral heads were visible in the radiographs, however, and by 9 months the left femoral head was as good as the right, and the shaft appeared to be completely healed.

The attainment of this objective—correct diagnosis and effective treatment as early as possible—depends on appropriate action being taken by one or more observers (mother, nurse, family doctor, and hospital) as soon as the first signs of disease appear. In our 40 cases the following were the first signs noted by one or other of these observers: swelling, with or without discoloration of the skin (14 cases), excessive irritability, often increased by handling (13 cases), relative immobility of a limb ("pseudoparalysis") (9 cases), and signs of severe general infection with or without fever (4 cases). The last of these signs was recorded only in severe cases, but the other three signs were noted as the first sign of disease in mild and severe cases with about equal frequency. In most cases two or more of these signs were already present when the patient reached hospital, and the cardinal sign of tenderness over the bone was clearly elicited.

The average delay between the appearance of the first sign and the start of effective treatment in the 21 severe cases was 8 days. In 5 of the 6 cases where the delay exceeded 10 days it was largely explained by the doctor's failure to make the correct diagnosis in the first instance: 3 had been treated as soft tissue infections, 1 as a severe generalised infection without specific localisation, and 1 had not been treated. In the 19 mild cases the average delay was a little more than 8 days; but in 3 of the 6 cases where it exceeded 10 days the greater part was due to the mother's failure to call the doctor sooner.

Consideration of the causes of any delay in arranging appropriate action, on the part of either the doctor or the nurse who first saw the cases in this series suggests that nearly all of it could have been avoided if the following points had been appreciated:

(1) Any tenderness or relative immobility of a limb during the first few weeks of life, with or without swelling of the overlying soft tissues, is more likely to be due to infection than to any other cause except trauma. Attention may often be drawn to the local signs by the fact that the baby cries excessively, especially when the affected part is handled—e.g., when the legs are handled during napkin changing. If the effects of birth trauma can be *confidently* excluded, the case should be regarded as one of infection until proved otherwise.

(2) The primary site of the infection is much more likely to be in bone than in the subcutaneous tissues. Although primary bloodborne abscesses of the subcutaneous tissues can, of course, occur in the newborn they are relatively very rare; in this series of 40 patients who, between them, had 70 known lesions of osteitis, only three primary abscesses of the subcutaneous tissues were detected, in 2 patients.

(3) The prognosis and possible complications of a bone infection in a young baby are so serious that the patient should be referred at once to a hospital where the necessary special types of clinical experience and laboratory facilities are available. The differential diagnosis from trauma, other forms of infection, and poliomyelitis (rare as it is in the newborn) may be very difficult or impossible on clinical grounds alone, as in the case of a baby who, born at home and cared for by a resident private nurse, developed a painful swelling over the lower end of the right femur at the age of 14 days and became irritable. The patient was admitted to the Babies' Hospital and started on treatment with penicillin until the routine radiograph (which should always be taken as soon as possible) showed a fracture. Within a few weeks further fractures occurred, and the diagnosis of osteogenesis imperfecta was established.

Surgical Treatment

Our policy as regards surgical treatment has been to try to remove pus, by aspiration through a short large-bore needle, in any case where there is appreciable swelling of the soft tissues overlying the lesion. In most such cases (including all the severe cases) pus has been obtained; but considerable perseverance, including the use of gentle expression of pus through the needle, may be necessary to achieve adequate emptying of the abscess. The aspiration is repeated as often as the local signs suggest that pus has reaccumulated. In case 4 (who weighed 8 lb.) 320 ml. of pus was aspirated from a single lesion during the baby's first 10 days in hospital. In cases where the joint is infected we inject either penicillin 50,000 units or streptomycin 50 mg. after aspirating the pus and washing out the joint cavity with isotonic saline solution. In 2 cases repeated removal of sequestra was necessary (cases 30 and 33 reported under "Failures").

No immobilisation was used in most of the cases. When the humerus was involved nursing was made easier by strapping the baby's forearm to his trunk. When either the knee or the ankle-joint was involved, a well-padded plaster splint was applied over the front of the limb to obtain the best possible support for the proximal part of the splint. Where the hip-joint was involved, however, we found no really satisfactory method of immobilisation in the acute stage. After finding plaster casts of various kinds quite unpractical, we experimented with a modified form of gallows suspension using weight and pulley traction and tried to hold the hips in moderate abduction and flexion. We cannot yet say anything about the long-term results of this method, which can be successfully applied by the average mother at home after the need for penicillin injections and aspirations is over; but we doubt if any method can do much to prevent, or even *modify*, permanent damage to the joint in cases where the hip is already severely infected when treatment is started.

After the infection is controlled the extent to which satisfactory remodelling of the affected bone can take place in some cases has to be seen to be believed; but, in our experience, no such satisfactory recovery takes place in cases where the hip joint has been seriously damaged by the initial infection. In 5 of our 7 cases of this kind we gave prolonged treatment on conservative lines as for congenital dislocation of the hip, keeping the patients in plaster for 3, 7, 10 11, and 12 months The results did not justify the effort, and we now doubt if the attempt to prevent these deformities by these means is really in the patients' best interests

Antibiotic Treatment

The importance of early diagnosis and immediate treatment with an effective antibiotic has already been emphasised The selection of the best antibiotic with which to start treatment, before the results of any bacteriological tests are available, has been made much more difficult by the emergence of a high proportion of penicillin-resistant strains of *Staph aureus* during the past few years, at least in babies born in hospital We still regard penicillin as the drug of choice and start treatment with it in a dosage of 25,000–50,000 units intramuscularly every 3 hours, reducing to 6 hourly administration when it is clear that a good clinical response is being obtained, and finally changing to oral administration in some cases to enable the mother to take her baby home for the completion of his treatment

It would be foolish to rely on penicillin alone until the sensitivity of the organism is known ; In selecting the most suitable partner to penicillin for this purpose of initiating treatment, when the need for such a partner was first appreciated, we rejected streptomycin largely because we expected that the emergence or resistance to streptomycin would soon overtake, in frequency, the resistance to penicillin which we had observed, but we were wrong Only two of the twenty three strains of *Staph aureus* recovered from our cases and appropriately tested were resistant to streptomycin in vitro

This fact is causing us seriously to reconsider our policy, which has been to use aureomycin (chlortetracycline) routinely as the partner to penicillin until the results of sensitivity tests are available (or throughout the course of treatment if no organism is available for testing) Unfortunately there are practical difficulties about using streptomycin in certain cases for instance, a suitable injection site may not be available for a drug which causes considerable local reactions, as in case 4, where the left leg was involved in the osteitis and the right thigh was occupied by a chronic ulcer resulting from a nikethamide injection given in the Maternity Hospital We are therefore at present exploring the possibility that a tetracycline may be effective if given in larger than standard dosage at the start of treatment, and this point is discussed in relation to the clinical history of case 15, reported under "Failures" In the end it may seem wiser to start with a combination of penicillin and streptomycin, as suggested by Dennison (1955a), and to rely on a tetracycline only for continuation of treatment in those cases where the organism is resistant to penicillin

The proper duration of the antibiotic treatment is the one subject of real controversy (Dennison 1955a and b, Neligan 1955) Far from being unduly optimistic about the control of the ' unconquered staphylococcus " in neonatal osteitis by modern methods of treatment, we believe that the extreme seriousness of the disease, and of its potential local and systemic complications, demands that we give the natural processes of resistance and repair the greatest possible assistance, in the shape of effective antibiotics and that we continue to give this assistance until uninterrupted recovery is assured by complete elimination of the infection In severe cases where the start of effective treatment has been delayed, with the result that the pathological changes in the bone are already very extensive it seems to us advisable to prolong the antibiotic treatment correspondingly for many weeks or months, until revascularisation and absorption are complete In the 18 severe cases whose initial course of antibiotic treatment was given by us the average length of this course was 41 days (range 21–116 days) and with increasing experience we have tended to increase the length of the course

But we do not base our policy solely on theoretical arguments , nor is our strong opposition to the advice of Dennison (1955a), that "whichever antibiotic is used treatment with it should be discontinued as soon as the blood infection appears to be controlled," explained only by our inability to accept the theoretical arguments which he puts forward in its support We prefer to depend on the difference between the subsequent courses of two groups of cases whose initial antibiotic treatment differed much in duration

Of our 40 patients 1 died (case 2, under "Failures") and 1 was not adequately followed up , 31 of the remainder had an initial course of a suitable antibiotic lasting 3 weeks or more (average 34 days, range 19–116 days) 25 of these patients (12 severe and 13 mild) appear to have recovered completely from the infection after this initial course, judged by satisfactory clinical and radiological progress thereafter 6 had one or more recurrences of infection and are discussed under "Failures" (cases 4, 19, 21, 25, 30, and 33) These results give little enough cause for undue optimism (particularly since, as stated, they take no account of the fact that 10 of the patients were left with one or more abnormal joints), but at least they compare very favourably with the results in the remaining 7 cases, the length of whose initial course of treatment with an antibiotic to which their organism was sensitive was quite inadequate by the standards which we have adopted

The initial course of antibiotic treatment in these 7 cases averaged 7 days (range 4–13 days) 1 case showed no recurrence of infection after a week's treatment with chloramphenicol for a mild osteitis of the maxilla, from which an infected tooth-bud was removed on the same day as the antibiotic was started, 14 days after the first sign of the disease had appeared The remaining 6 patients had, between them, twelve recurrences of infection after twelve short courses of antibiotic treatment, administered either at home or in other hospitals, for what were thought to be infections of the soft tissues or of the blood The treatment was stopped in each case when the clinical response was regarded as satisfactory The average delay in starting treatment was less than 3 days In all 6 cases (3 mild and 3 severe) the organism causing the osteitis was sensitive to the antibiotic used for the initial course, and all of them eventually responded completely to a more prolonged course of treatment with the same antibiotic (average duration 43 days, range 21–58 days) In 2 of them pus was aspirated once at the start of this final course of treatment, but the others required no additional measures of any kind In 1 of these 6 cases the story was not quite so straightforward as this summary suggests, and it is reported in greater detail under "Failures" (case 15)

These results (see table) provide clear cut evidence in favour of using a suitable antibiotic for at least 3 weeks, and much longer if necessary, from the time when the patient is first admitted to hospital The same conclusions about the need for prolonged antibiotic treatment

EFFECT OF DURATION OF INITIAL COURSE OF APPROPRIATE ANTIBIOTIC

	Adequate duration *		Inadequate duration	
	Severe	Mild	Severe	Mild
Average duration (days)	43	26	8	7
No of cases	17	14	3	4
No with recurrences	4	1	3	3

* Adequate is defined as lasting for at least 3 weeks

had been reached by Disney et al (1956) as regards staphylococcal pneumonia in young babies But we are much concerned with trying to understand the reason for the failures which can still occur, and they are briefly reported and discussed below

Failures

Under this heading are discussed the 1 death, the 6 patients who had one or more recurrences of infection after an initial course of antibiotic treatment lasting 3 weeks or more, and case 15 mentioned above

Case 2 (severe) died at the age of 27 days, after 11 days' treatment with chloramphenicol He had become ill, at the age of 11 days, in a maternity hospital and was at first treated with penicillin After 5 days the clinical response had been most unsatisfactory, and the organism recovered from the pus aspirated from his right shoulder was resistant to penicillin but sensitive to chloramphenicol in vitro (this finding was repeatedly confirmed in pus from other sites obtained later) When he was transferred to the Babies' Hospital at the age of 16 days he already had overt lesions of osteitis in both humeri, both hands, and the right mandible His response to chloramphenicol was never encouraging, blood culture still being positive on the 6th day of treatment, and he died with gross signs of heart failure Necropsy revealed, in addition to the bony lesions, well developed abscesses in the lungs with several small encysted empyemas (whose presence had been suspected some days before death but had not been confirmed on aspiration)

Comment—We attribute this baby's death, and the failure of treatment with chloramphenicol, to our not draining collections of pus within the chest when treatment was started

Case 4 (severe) developed an abscess of the right thigh at the site of an injection of nikethamide given at birth, and osteitis of the middle phalanx of a finger was diagnosed at the age of 12 days She was started on treatment with penicillin at once, but 4 days later she was sent home from the Maternity Hospital without the visiting pædiatrician's knowledge

At the age of 20 days she developed an abscess over the upper part of the left tibia, which the family doctor treated with penicillin for the next 6 days, he also incised the abscess

By the age of 31 days, when she was first admitted to the Babies' Hospital, she was seriously ill, with further lesions over the left clavicle and over the left ilium and hip joint 340 c cm of pus was aspirated from her lesions during the next 10 days

Three days after admission the *Staph aureus* cultured from her pus was reported as being resistant to penicillin but sensitive to chloramphenicol She was treated with chloramphenicol for the next 21 days, when we stopped it because of the potential toxic effects There was no part of her body into which we felt we could inject streptomycin, and no other antibiotics were available at that time

6 weeks later she had a recurrence of infection over the clavicle, a year later she had a recurrence over the left tibia, at the age of 4 years she had a further minor recurrence, and at the age of 5 years she had a recurrence over the left ilium, which has not completely healed yet a year later

Her left hip joint is dislocated and the femoral head very abnormal, in spite of 10 months' treatment in plaster during the first year of life as for congenital dislocation of the hip

Comment—Although this case is included as a failure of prolonged treatment, we did not consider the 21-day course of chloramphenicol really adequate in view of the length of her history, but we can only speculate about the likely result of a more prolonged course of treatment given at that stage There is little doubt in our minds, however, that an adequate course of an effective antibiotic, given when she had only a mild osteitis of one phalanx, would have produced a very different result

Case 21 (severe) was admitted to hospital 2 days after developing signs of osteitis in his right humerus Penicillin was stopped 3 days after admission when his *Staph aureus* was reported to be resistant to penicillin but sensitive to aureomycin He was treated with aureomycin for 43 days after admission, and three aspirations during the first 10 days in hospital produced 9 c cm of pus He had a recurrence at the age of 8 months, and another mild one at the age of 2 years

Comment—In this case the duration of the initial antibiotic treatment was regarded as adequate, but the radiological changes which developed, with wide separation of the periosteum from the cortex of the shaft suggested that the aspiration of the subperiosteal abscess had been inadequate and ineffective

Case 19 (severe) developed multiple lesions of acute osteitis in a maternity hospital at the age of 8 days, with involvement of the left foot, left index finger, left mandible, and right lower femur He was started on treatment with chloramphenicol at once, and after 3 weeks aureomycin was substituted and was continued until the total course of antibiotic treatment was 53 days A few days after the onset crepitus was detected over the right lower femur, and radiographs subsequently showed that the lower femoral epiphysis had been displaced about an inch backwards, leaving the lower third of the shaft protruding through the anterior wall of its periosteal sheath

Various methods of immobilisation were used to try to prevent further displacement during the next few weeks, and the bone has shown remarkable powers of reconstruction and longitudinal growth The boy walked unsupported at the age of 16 months and since then has led a normal active life But at the age of 8 months he had a recurrence over the lower end of the femur, with spontaneous discharge of a flake sequestrum measuring $^1/_4 \times {^1/_{16}}$ inch, and at the age of $3^1/_2$ years he had a superficial swelling in the scar, from which a bead of sterile pus was aspirated

Comment—The only lesion which caused any further trouble in this case was the one in which there must, initially, have been extensive interference with the blood-supply of the affected bone This fact suggests that it would have been wiser, and possibly more effective, to continue the initial course of treatment for longer than 53 days

Cases 30 and 33 (both severe) are reported together because they have many features in common In case 30 there was a delay of 14 days after the first sign of osteitis of the mandible before admission to hospital, and in case 33 the delay was 19 days after the first signs of osteitis of the right parietal bone of the skull Both were draining pus freely, in large quantities, on admission In both cases the *Staph aureus* was resistant to penicillin, and aureomycin was used for initial courses of 55 days and 116 days respectively In both cases sequestra had to be removed and further prolonged courses of aureomycin given Now, about $1^1/_2$ years after the onset, neither case can yet be regarded as completely healed, but the most striking feature of both patients is their magnificent physique and healthy appearance

Comment—We feel that in both these cases the failure of the initial course of treatment to eliminate the infection completely was probably due to the long delay in starting treatment, together with the unusual structure and blood-supply of the bones affected, which led to extensive sequestration We also regret that the first operation for removal of sequestra and tooth-buds from the mandible of case 30 was delayed until 30 days after admission to hospital, by which time the initial satisfactory clinical response to the antibiotic had been shown to be illusory by the appearance of a further spontaneous discharge of pus It seems probable that this operation could have been done much sooner, with safety and benefit, had the need for it been appreciated sooner

Case 25 (mild) was admitted 2 days after developing signs of osteitis of the right maxilla She was treated with aureomycin from the start, and within 4 days of admission 8 c cm of pus had been aspirated from the right orbit, and there had been a spontaneous discharge of pus into the mouth from the right bucco alveolar sulcus The *Staph aureus* cultured was partially resistant to penicillin but sensitive to aureomycin, with which drug treatment was continued in diminishing dosage for 67 days

3 weeks later, however, she developed swelling of the right cheek and lower lid and was given a second course of aureomycin, which lasted 106 days During the subsequent $1^1/_2$ years all has been well, apart from the fact that the right

upper first premolar is poorly enamelled and has only partly erupted

Comment —In this case the reason for the failure of the *first course of treatment is less clear Probably it would have been wiser to explore the spontaneous sinus into the mouth when it first developed, with a view to removing* any infected tooth-buds, but this was never seriously contemplated, because the opening healed in a few days

Case 15 (mild) received three short courses of antibiotic treatment during the first 4 weeks of life (penicillin for 5 days, and chloramphenicol for 6 days and again for 3 days) The indication was an inflammatory swelling over the chest wall which was first seen in the Maternity Hospital at the age of 7 days and thought to be a primary soft tissue abscess The course of penicillin was started at the age of 8 days, and the swelling was also incised twice during the first month After each course of treatment the local signs recurred, but it was not until the baby was nearly 6 weeks old that an underlying osteitis was suspected when the abscess recurred for the third time and burst spontaneously She was then treated with aureomycin for 3 weeks, but 3 weeks later there was a further recurrence, and this time aureomycin treatment was continued for 6 weeks

About 6 weeks later, however, she had yet another recurrence (her fifth) A *Staph aureus* sensitive to penicillin and aureomycin was recovered from the pus in her first recurrence (at the age of 17 days), her third (at the age of 32 days), and her fifth (at the age of 6 months), in her fourth recurrence, however (at the age of 3 months), the *Staph aureus* was resistant to penicillin Since no penicillin had been used since the 2nd week of life, this organism was thought probably to have been a contaminant, and the fifth recurrence was treated with penicillin for 6 weeks During the subsequent 4 years there has been no further trouble

Comment —This case is included as one of those in which a short course of the appropriate antibiotic did not eliminate the infection Penicillin was used at the start but for only 5 days, and a whole series of recurrences followed, yet, about 6 months later, when the same antibiotic was used again but this time for 6 weeks, an apparent cure followed But there is the complicating factor that in the interval two long courses of aureomycin had been given, lasting 3 weeks and 6 weeks, without success This may be a simple question of a bacteriostatic drug's being less effective than a bactericidal one, but we have wondered whether it was partly a question of dosage In treating acute osteitis with penicillin it it has long been the practice to use much larger doses, and greater frequency of administration, than in treating soft tissue infections This practice is based on sound theory and supported by experience Yet with other antibiotics the standard dosage has been routinely used even in acute osteitis, both by ourselves in the past and by others (Dennison 1955a, case 1) We have more recently adopted the practice, when using a tetracycline antibiotic, of starting with a dosage of about 50 mg per lb of body weight daily, administered 3 hourly by mouth and later reducing the frequency of administration and the dosage if a favourable clinical response is achieved We have not yet had enough experience of this method to judge its effectiveness in preventing recurrences

The anomalous bacteriological findings in this case represent the only possible example of a change of antibiotic sensitivity during the course of observation in any case in this series

Summary

Evidence from the case histories of 40 cases of neonatal osteitis (21 "severe" and 19 "mild") confirms that this disease can still produce death or crippling deformity

It also confirms that really early antibiotic treatment, in a suitable hospital may prevent these serious complications The earliest signs of the disease are, in order of frequency local swelling excessive irritability, pseudo paralysis of a limb, and the signs of a severe general infection

Prolonged antibiotic treatment (for a minimum of thre weeks, and an average of five weeks) is shown to b effective in preventing recurrences, as compared wit *short courses of treatment Of 31 cases* "adequately" treated, 5 had one or more recurrences of 7 case inadequately treated, 6 had one or more recurrence

We are most grateful to our colleagues, who allowed us to treat their cases so that we might gain greater experience of this disease and to Dr C A Green, in whose department was done the bacteriological work on which we relied so heavily in deciding which antibiotics to use

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PITUITARY NECROSIS DUE TO IMPLANTS OF RADIOACTIVE GOLD AND YTTRIUM

Stretton Young
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From the Clinico Pathological Laboratories of the Imperial Cancer Research Fund

It is well known that some cases of mammary and prostatic carcinoma respond favourably to removal of the steroid-producing endocrine glands When these cases relapse, a further period of improvement can sometimes be induced by removal or destruction of the adenohypophysis Other cases may be treated by hypophysectomy without previous ablation therapy, and in some of these also the disease is arrested

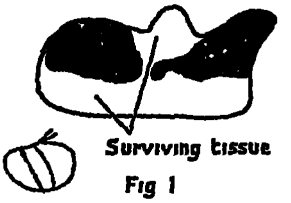

Fig 1

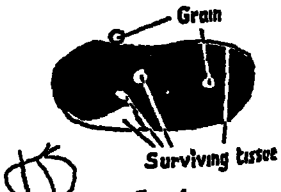

Fig 4

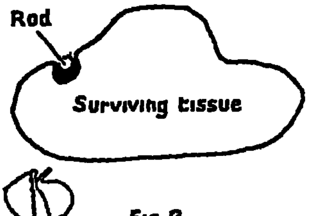

Fig 2

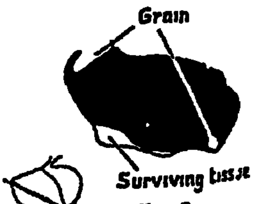

Fig 5

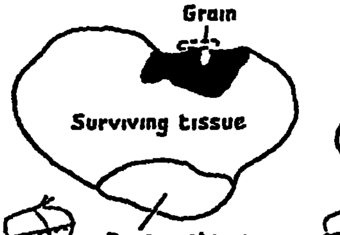

Fig 3

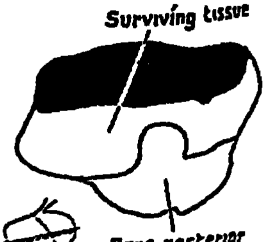

Fig 6

Fig 1—Effect of two 5 7 mC grains for 21 days (×2½)
Fig 2—Effect of one 9 03 mC grain for 31 hours (×2½)
Fig 3—Effect of one 3 8 mC grain for 119 days (×2½)
Fig 4—Effect of two 9 8 mC grains for 8 days (×2½)
Fig 5—Effect of two 6 75 mC grains for 27 days (×2½)
Fig 6—Effect of two 8 33 mC grains for 32 days (×2½)

TABLE I—RESULTS OBTAINED WITH RADIOACTIVE GOLD GRAINS

Fig no	Radon equivalent per grain (mC)	No of grains	Duration of action	Effective activity (mC)	γ r at edge of necrotic area	Radius of necrosis (mm)
1	5 70	2	21 days	5 70	93 600	2 40
2	9 03	2	31 hours	2 64	313,750	0 90
3	3 80	1	119 days	3 80	68,150	2 30
4	9 80	2	8 days	8 55	> 70,000	1
5	8 75	2	27 days	8 75	75,900	3 34
6	8 33	2	32 days	8 23	72,650	3 34

In successfully treated cases it is believed that the tumour is stimulated to proliferate by one or more of the protein hormones from the pars anterior of the pituitary gland, and deprivation of these hormones leads to arrest of tumour growth or even to its regression

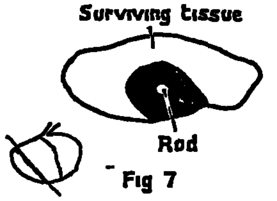

Fig 7

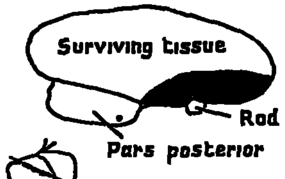

Fig 9

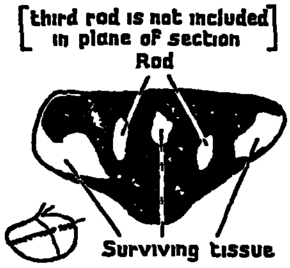

Fig 8

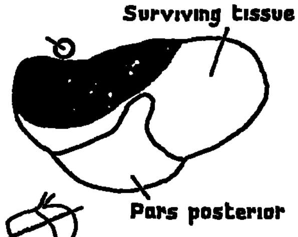

Fig 10

Fig 7—Effect of one 1 58 mC rod for 33 days (×2½)

Fig 8—Effect of three 0 81 mC rods for 105 days (×2½)

Fig 9—Effect of one 4 57 mC rod for 95 days (×2½)

Fig 10—Effect of one 4 5 mC implant for 28 days (×2½)

The difficulties encountered during the operation of hypophysectomy have led to the introduction of techniques for destroying the pituitary In one of these the destructive material is a radioactive isotope which is introduced into the pituitary through a cannula passing through the nose and the sphenoidal sinus

This paper contains a description of structural changes in the pituitary gland following implantation of the two radioactive isotopes ^{198}Au and ^{90}Y

Materials and Methods

Pituitary glands were obtained at autopsy from 14 patients who had previously received radioactive pituitary implants for mammary or prostatic carcinoma The glands were usually fixed in Helly's fluid, but cold formol saline solution followed by secondary fixation in Helly's fluid was also employed

Drawings were made of the shape of the gland and of the position and orientation of any visible implants The implants were then removed and the tissue trimmed so that the plane of the section would cross the axis of the implant at right angles

Three types of radioactive material had been used

(1) Radioactive gold (^{198}Au) grains cylindrical in shape measuring 0 8 × 2 5 mm The outer 0 1 mm is a non-radioactive screen of platinum which reduces the β irradiation

(2) Radioactive gold (^{198}Au) rods, cylindrical in shape and measuring 0 8×5 mm No platinum screen was present, thus the ratio of β to γ irradiation was considerably greater than in the screened variety

The activity of these implants is given in equivalent millicuries (mC) of radon, and the dose of γ irradiation in r units

(3) Yttrium oxide pellets, cylindrical in shape and measuring 1 3×3 95 mm (but subject to slight variations in size) These emit β irradiation only

TABLE II—RESULTS OBTAINED WITH RADIOACTIVE GOLD RODS

Fig no	Radon equivalent per rod (mC)	No of rods	Duration of action (days)	Effective activity (mC)	γ r at edge of necrotic area	Radius of necrosis (mm)
7	1 58	3	33	1 58	80 000	1 34
8	0 81	3	150	0 81	77 100	1 00
9	4 57	3	95	4 57	197,400	1 50

Results

Histological sections in a plane at right angles to the long axis of the implants were photographed at low magnification The photomicrographs were used to prepare line drawings in which necrotic areas are shown in black The plane of the section is indicated in the diagram accompanying each drawing Only ten of the fourteen pituitary glands examined have been illustrated by line drawings, the remaining four were technically unsuitable for presentation in this manner

TABLE III—RESULT OBTAINED WITH RADIOACTIVE YTTRIUM

Fig no	Activity (mC of ^{90}Y)	No of pellets	Duration of action	Effective activity (mC)	Radius of necrosis (mm)
10	4 5*	1	28 days	4 5	4

* This is the absolute activity of the pellet in mC of ^{90}Y as determined by 4π counting

The sections have been chosen to show the result of individual implants rather than their combined effect, and no attempt has been made to measure the total amount of destruction

Figs 1–6 illustrate the necrosis obtained in six cases in which grains of radioactive gold (^{198}Au) screened by 0 1 mm of platinum were used These results are summarised in table I

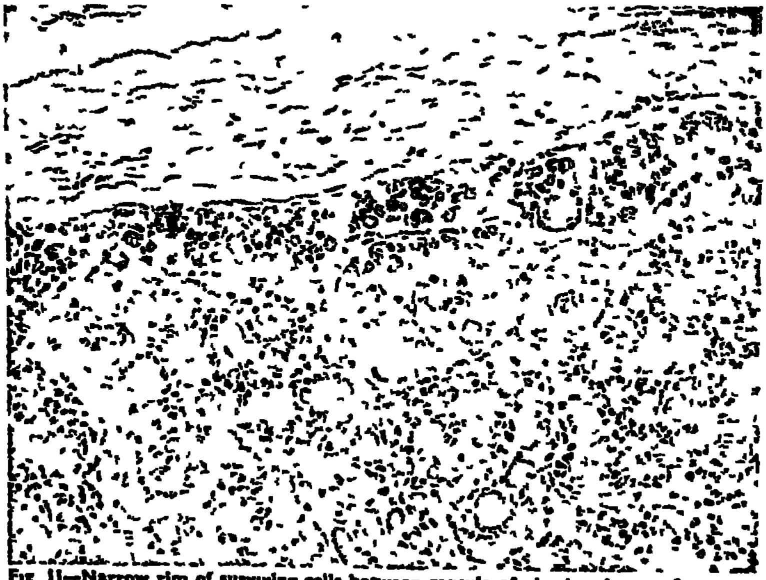

Fig 11—Narrow rim of surviving cells between capsule of gland and area of necrosis (Hæmatoxylin and eosin 200)

It would be of great value if some estimate could be made of the capacity of surviving pituitary tissue to regenerate Mitotic activity has been reported in the pituitary glands of animals after injury and hormone interference, and replacement may be complete if destruction be not too extreme (Cameron 1952) In numerous sections of irradiated pituitary glands, ranging from slight to almost total destruction, and from 31 hours' to 150 days' duration, I have not observed any evidence of mitosis

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Conclusions

In this series of 14 cases, implants of radioactive gold (^{198}Au) and yttrium (^{90}Y) did not cause complete necrosis of the pituitary

A minimum of about 70,000r of γ irradiation appears to be necessary to cause necrosis in most parts of the pituitary gland

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5-HYDROXYTRYPTAMINE DEFICIENCY IN PHENYLKETONURIA

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Phenylketonuria is an inborn error of metabolism characterised by a severe degree of mental deficiency, by the excretion of phenylpyruvic acid in the urine, and by certain bodily features, of which fair hair is the most noticeable

There are several excellent accounts of the condition (Jervis 1937, 1938, Penrose 1946, Cowie 1951a and b), so only a brief survey will be given here Of mental defectives admitted to institutions about 0 5% suffer from the disorder, which is transmitted by a single recessive gene Fundamentally, there is a failure of hydroxylation of phenylalanine to tyrosine in the liver (Jervis 1947, 1953, Udenfriend and Bessman 1953, Armstrong and Shaw 1955) This results in a high plasma concentration of phenylalanine and the presence of many abnormal metabolites in the urine, of which phenylpyruvic acid is the best known (for biochemical review see Dalgliesh 1955) Although the defective hydroxylation of phenylalanine to tyrosine may account for the deficient pigmentation, it has provided no explanation for the other main clinical finding of mental deficiency The intelligence quotient (I Q) in these patients correlates neither with the level of phenylalanine in the blood nor with phenylpyruvic acid excretion in the urine (Borek et al 1950, Jervis 1950) It has been claimed that there is a correlation between the I Q and the amount of phenylpyruvic acid in the plasma , but this correlation is a positive one plasma levels of phenylpyruvic acid increasing with I Q and is probably an indication of the state of nutrition (Jervis 1952) Nevertheless various workers have treated affected children with a low-phenylalanine diet for long periods and in general have reported some improvement both in intelligence and in physical condition (Bickel et al 1953, Armstrong and Tyler 1955, Woolf et al 1955) Armstrong and Tyler (1955) conclude that " it seems probable that unknown and possibly complex factors other than the known defect in phenylalanine oxidation operate in conjunction with it and contribute to the mental defect "

Recently, Armstrong and Robinson (1954a and b) have offered evidence of abnormal indole metabolism in phenylketonuria, demonstrating the presence of indolelactic acid (I L A) in the urine of affected patients They also claimed, from paper-chromatographic studies, that there was a decreased urinary excretion of 5-hydroxyindoleacetic acid (5 H I A A) in some of their patients Their findings were confirmed by Ferrari and his colleagues (1955)

5-H I A A is known to be a metabolite of 5-hydroxytryptamine (5-H T , serotonin, enteramine) (Titus and Udenfriend 1954, Erspamer 1955), which is normally present in the central nervous system and may be functionally important It therefore occurred to one of us (M S) that a quantitative examination of the 5-H T. pathway in phenylketonurics might demonstrate a failure of hydroxylation of tryptophan similar to that of phenylalanine This anomaly, if present, might throw some light on the nature of the mental defect hitherto unexplained

Methods

Serum 5-H T—The use of platelet-rich plasma provides a more accurate measure of the amount of 5-H T in blood than does serum (Hardisty and Stacey 1955), but for reasons of convenience it was necessary to use serum for our investigations When blood clots, part of the 5-H T liberated from platelets passes into the red cells (Stacey 1956) and the amount lost in this way depends on the conditions during clotting (Sharman and Sullivan 1956) These must therefore be standardised In the estimations reported here, venous blood was allowed to stand in an incubator at 37°C for an hour without being disturbed and serum was then separated by centrifugation 5-H T was extracted using 95% acetone and assayed on the rat uterus In order to test for the presence of other smooth muscle contracting substances a specific antagonist was applied to the uterus Brom-lysergic acid diethylamide (brom-L S D) in a concentration of 50 ng per ml was found preferable to lysergic acid diethylamide as it caused less spontaneous activity in the uterus

Urinary 5-H I A A excretion was measured by the method of Udenfriend et al (1955) and expressed as mg per g creatinine Creatinine was measured by a Lloyd's reagent adsorption method (Hare 1950) The ferric chloride test (Folling 1934) was used to detect phenylpyruvic acid in the urine and paper chromatographic

Figs 7–9 illustrate the necrosis obtained in three cases in which unscreened radioactive gold rods 0 8 × 5 mm were implanted These results are summarised in table II

Fig 10 shows the necrotic effect of one pellet of radioactive yttrium oxide measuring 1 3 × 3 95 mm, and the result is given in table III

The dose of γ irradiation received at the periphery of the necrotic area, expressed in r, is given in tables I and II In six of the nine cases the dose lay between 68,000 and 93,000 γ r In case 2 (with over 300,000 γ r) the irradiation had acted for only 31 hours, and many of the cells outside the radius of 0 9 mm would probably have died if the patient had lived longer In case 4, on the other hand, the whole of the pituitary in the plane illustrated appears to have received more than 70,000 γ r (derived from two sources) The only surviving cells in this plane are those adjacent to the capsule and surrounding some of the blood-vessels (see below) In case 9 the dose of γ irradiation at the edge of the necrotic area appears to have been more than 190,000r The case has been carefully reconsidered, but no satisfactory explanation has been found for this unusually high value

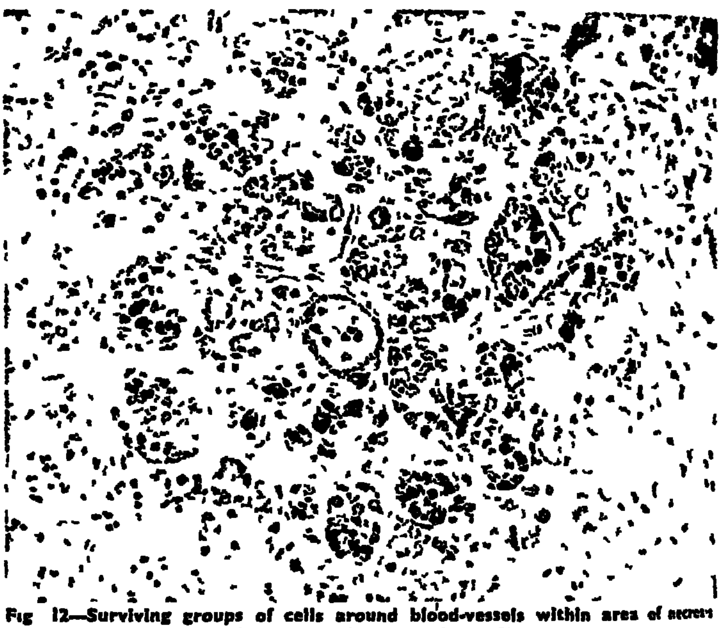
Fig 12—Surviving groups of cells around blood-vessels within area of necrosis (Hæmatoxylin and eosin ×200)

Destruction was incomplete in all fourteen pituitary glands examined One of the four not illustrated contained surviving tissue in spite of the implantation of six grains on three occasions in 7 months, with a total activity of more than 30 mC of radon It is tempting to assume that the small remnants of pituitary found in some of these cases would not be capable of much functional activity This is not necessarily true, for Gomez and Turner (1937) have shown that in animals, in the presence of œstrogens, pituitary remnants as small as 2% of the whole gland can continue to cause considerable breast stimulation There is ample experimental evidence that, after incomplete hypophysectomy, the injection of œstrogens and progesterone will induce a substantial growth reaction in the mammary gland, whereas no mammary response can be induced with these hormones when hypophysectomy has been proved to be total by serial histological examination of the operation site (Folley 1952)

Histology

The histological appearances in the necrotic tissue are those of coagulative necrosis The tissue outlines are preserved, but cytoplasmic staining is entirely eosinophilic, and nuclear staining is lost Pyknotic nuclei are not common and are only seen around the periphery of the necrotic area The nuclei usually undergo karyolysis, but a minority show karyorrhexis A few weeks after the implant, necrotic cells are still clearly defined and the area contains numerous phagocytes, but there is no hyperæmia Later the cell remains are lost and phagocytes disappear, but the reticulin framework persists almost unchanged for a long time Shrinkage of the necrotic area is slight and fibrosis has not developed even after 150 days Granulation tissue has not been seen

On several occasions a narrow rim of surviving cells has been found in close contact with the capsule of the gland, between it and the main area of necrosis (fig 11) The appearance of this rim is similar to that described by Russell (1956) after section of the pituitary stalk and by Wolman (1956) in pituitary necrosis following raised intracranial pressure The distance between the radioactive material and this rim of cells has been found to be less than the distance to the edge of the necrotic area elsewhere (see figs 1, 4, 5, and 8) It follows that these cells possess a greater resistance to radioactivity than do others which have already undergone necrosis from the same dose of irradiation Similar surviving groups of cells have been seen surrounding blood vessels (fig 12) In areas of the pituitary tissue adjacent to necrosis, including those described above, chromophobe and chromophil cells are present The latter may have a granular cytoplasm, and eosinophils sometimes have cytoplasmic vacuoles in addition There is no evidence, however, that one type of cell differs much from another in sensitivity to radioactivity. In fig 13 a section from case 10 has been stained to differentiate eosinophil and basophil cells, both types (together with chromophobe) can be seen in the surviving rim of tissue

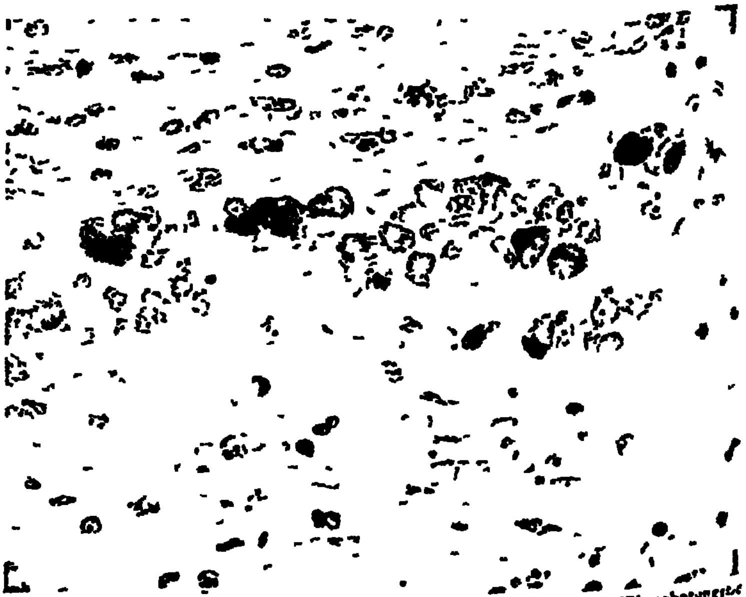
Fig 13—Chromophobe and chromophil cells in surviving rim of tissue (Phosphotungstic acid hæmatoxylin ×450)

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Urinary 5-H.I A.A excretion was measured by the method of Udenfriend et al (1955) and expressed as mg per g creatinine Creatinine was measured by a Lloyd's reagent adsorption method (Hare 1950) The ferric-chloride test (Folling 1934) was used to detect phenylpyruvic acid in the urine and paper chromatographic studies of urinary indoles were carried out by the method of Jepson (1955).

The intelligence tests used (kindly carried out by Mrs. L. Mundy, M.SC., and Miss M. Woodward, PH.D.) were the Stanford Binet (Terman-Merrill revision), the Merrill Palmer, and the Vineland Social Maturity scale.

Results

Four groups of children were investigated.

Group 1.—Twelve normal children, 3–12 years of age, living at home. We thought it unjustifiable to take venous blood samples from them, so that in this group only 5-H.I.A.A. excretion has been determined.

Group 2.—Fifteen children admitted to hospital from a tonsillectomy waiting list and awaiting operation.

Group 3.—Ten phenylketonurics (table I (*a*)), all of whom had a positive ferric chloride test and had chromatographic evidence of P.P.A. in the urine.

Group 4.—Nine mentally defective children, without phenylketonuria, living in the same hospital as the phenylketonurics (table I (*b*)).

All the mentally defective children had been in hospital for at least 12 months and were in a good state of health and nutrition.

The means of the urine and blood estimations are summarised in table II together with results from normal adults. There is a conspicuous difference between the means of the different groups. The phenylketonurics show significantly lower values than all others both with respect to serum 5-H.T. ($P < 0.01$) and urine 5-H.I.A.A. ($P < 0.02$). The difference between the serum 5-H.T. of the phenylketonurics and the other mental defectives is particularly striking; only one phenylketonuric had a serum-5-H.T. above 100 ng. per ml. and only one of the other mental defectives was below this. Similarly, 5-H.I.A.A. levels overlapped in only two patients.

One cause of a low level of 5-H.T. in blood and serum is thrombocytopenia (Bigelow 1953, Hardisty and Stacey 1957). There is no evidence that this is common in phenylketonuria; platelet counts in patients no. 13 and 18 were within normal limits (378,000 and 500,000 per c.mm. respectively).

No correlation was found between the I.Q. of patients with phenylketonuria and their serum-5-H.T. and 5-H.I.A.A. excretion.

The 5-H.I.A.A. excretion of children awaiting tonsillectomy was considerably higher than that of normal children at home. This has not yet been further investigated.

Some of the non-phenylketonuric mentally defective children had surprisingly high serum 5-H.T. When these were repeated after an interval of 6 months substantially similar results were found in each case. In some of the sera in both groups of mentally defective children traces of another smooth-muscle-contracting substance, not antagonised by brom-L.S.D., was found. The amount of this other substance was in all cases small and cannot be the sole cause for high 5-H.T. figures as in some of the sera with high values (e.g., no. 14) all activity was antagonised by brom-L.S.D.

TABLE I—TO ILLUSTRATE CLINICAL FEATURES, SERUM-5-HYDROXYTRYPTAMINE (5-H.T.) LEVELS, AND URINARY 5-HYDROXYINDOLEACETIC ACID (5-H.I.A.A.) EXCRETION IN PHENYLKETONURICS AND MENTAL DEFECTIVE CONTROLS

No.	Sex	Age	Weight	I.Q. (%)	Serum 5-H.T. (ng. per ml.)	Urinary 5-H.I.A.A. (mg. per g. creatinine)
(*a*) *Phenylketonuria*						
1	F	27	7 st. 3 lb.	7	8	2·2
[illegible]	M	8	3 st. 9 lb.	13	66	1·[illegible]
9	F	25	[illegible] st. [illegible] lb.	6	72	3·0
10	M	6	3 st. 0 lb.	11	15	1·[illegible]
11	M	17	7 st. 0 lb.	13	61	2·8
12	M	13	[illegible] st. 13 lb.	10	120	
13	M	8	4 st. 4 lb.	30	76	3·6
15	F	[illegible]	2 st. 3 lb.	18	61	2·0
18	F	11	3 st. 7 lb.	10	80	2·[illegible]
19	F	6	3 st. 8 lb.	[illegible]3		1·6
(*b*) *Mental defective controls*						
2	M	12	4 st. [illegible] lb.	14	131	4·7
4	M	12	4 st. 4 lb.	Idiot	270	1·6
[illegible]	M	11	9 st. 6 lb.	21	77	1·9
6	M	8	4 st. 8 lb.	12	2[illegible]9	6·2
7	M	7	[illegible] st. 7 lb.	25	146	[illegible]
8	M	13	4 st. 12 lb.	27	144	5·[illegible]
14	F	5	3 st. 0 lb.	44	604	[illegible]·0
16	M	9	3 st. [illegible] lb.	Idiot	[illegible]	5·0
17	F	7	2 st. 11 lb.	42	240	5·2

TABLE II—SUMMARISING MEAN VALUES AND STANDARD ERRORS OF THE MEAN (S.E.M.) OF SERUM 5-H.T. AND URINE 5-H.I.A.A. IN PHENYLKETONURIC AND CONTROL GROUPS

Group	—	Serum 5-H.T. Mean ± S.E.M. (ng. per ml.)	Urine 5-H.I.A.A. Mean ± S.E.M. (mg. per g. creatinine)
I	Normal children (12 subjects)		6·6 ± [illegible]
II	Children awaiting tonsillectomy (15 cases)	124 ± 14	11·0 ± 1·3
III	Phenylketonurics * (9 cases)	57 ± 11	2·9 ± 0·[illegible]
IV	Other mental defectives (9 cases)	270 ± 51	4·9 ± 0·[illegible]
	Normal adults	99 ± 16	4·4 ± 0·5

* The phenylketonuric group includes two patients in whom either 5-H.T. or 5-H.I.A.A. estimations alone were performed.

Discussion

Tryptophan has been demonstrated by isotopic studies with ^{14}C-labelled compounds to be the precursor of 5-H.T. (Udenfriend et al. 1956a). It is presumably hydroxylated to 5-hydroxytryptophan (5-H.T.P.) (Smith et al. 1957), decarboxylated to 5-H.T. (Clark et al. 1954), and metabolised by monoamine oxidase to be excreted in the urine as 5-H.I.A.A. (Blaschko 1952, Sjoerdsma et al. 1955). The finding of a low serum-5-H.T. and a diminished 5-H.I.A.A. excretion in patients with phenylketonuria is compatible with the view that there is in these patients a disturbance in tryptophan metabolism which results in a diminished production of 5-H.T. During the past few years evidence has accumulated that 5-H.T. plays an important part in the central nervous system. It has been shown, for example, that the ability to synthesise 5-H.T. from its immediate precursor, 5-H.T.P., and to store it occurs in particular regions of the grey matter (Amin et al. 1954, Gaddum and Giarman 1956); further, Feldberg and Sherwood (1954) in animal experiments, have described characteristic changes in behaviour following the injection of 5-H.T. into the cerebral ventricles. In view of this it seems possible that impaired 5-H.T. synthesis may contribute to the causation of mental deficiency in patients with phenylketonuria.

Two lines for further investigation suggest themselves. The administration of 5-H.T. is unlikely to benefit these patients because it is rapidly destroyed in the circulation and because it does not easily pass the blood-brain barrier (Bogdanski et al. 1956). If phenylketonurics have an impaired capacity to hydroxylate tryptophan, as seems likely, the administration of 5-H.T.P. might overcome this deficiency. Moreover, 5-H.T.P. readily passes the blood-brain barrier and in animal experiments has been shown to raise brain 5-H.T. concentration (Udenfriend et al. 1956b).

In the second place it has been observed that the mental condition of some patients with phenylketonuria improves on a low-phenylalanine diet (Bickel et al. 1953, Armstrong and Tyler 1955, Woolf et al. 1955). Could such a diet improve 5-H.T. synthesis? Any answer must at the moment be guesswork; but if phenylalanine competes with tryptophan for hydroxylation, a reduction in blood-phenylalanine would favour hydroxylation of tryptophan and result in a raised serum-5-H.T. level and raised 5-H.I.A.A. excretion. We are pursuing both these lines of investigation.

Summary

The levels of 5-hydroxytryptamine in the serum and of 5 hydroxyindoleacetic acid in the urine were assayed in children with phenylketonuria and in controls Abnormally low levels of both were found in the phenylketonuric group The relation of these findings to the mental deficiency in phenylketonuria is discussed

We are indebted to Dr L T Hilliard and Dr B H Kirman of the Fountain Hospital, for the facilities which they gave us We are grateful to Dr D N Baron for his constructive criticism We should like to thank Miss Joan Wise, B SC, for technical assistance and the Royal Free Hospital Endowment Fund for defraying her salary and for apparatus Messrs Roche Products kindly supplied 5 hydroxytryptamine

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DEFECTIVE ORGANIC BINDING OF IODINE BY THE THYROID IN HASHIMOTO'S THYROIDITIS

M E MORGANS
M B Lond, M R C P
W R TROTTER
D M Oxfd, M R C P
From the Medical Unit University College Hospital Medical School, London

IN normal circumstances labelled iodide is rapidly bound by the thyroid gland and incorporated in organic compounds If the formation of hormone is interfered with, as it is when a person is given an anti thyroid drug of the thiouracil series, much of the labelled material remains concentrated within the thyroid in the form of inorganic iodide Stanley and Astwood (1948) showed that this state of affairs could be easily demonstrated by administering a large dose of thiocyanate When the person was under the influence of an anti-thyroid drug, thiocyanate caused most of the labelled iodine to be discharged from the thyroid into the general circulation In untreated subjects labelled iodine was not discharged by thiocyanate, but no more was taken up

A similar technique has been used to show that the action of other drugs, such as *p*-aminosalicylic acid (Edwards et al 1954) and phenylbutazone (Morgans and Trotter 1955), on the thyroid gland is similar to that of thiouracil In these studies the place of thiocyanate was taken by perchlorate, which has a similar though more potent effect (Stanbury and Wyngaarden 1952)

It is possible that anti thyroid substances known to be present in some foodstuffs may be a contributory cause of simple goitre (Astwood 1949, Clements and Wishart 1956) If so, it might be expected that the technique of Stanley and Astwood (1948) would reveal defective organic binding of iodine in some patients with this condition

During the past few years we have investigated some cases of simple goitre in this way With a single exception (see below) these cases of simple goitre have reacted in an entirely normal fashion, perchlorate has failed to discharge any of the radio-iodine taken up by the thyroid, and hence it can be assumed that organic binding of iodine was proceeding normally But, when the investigation was extended to include cases of Hashimoto's thyroiditis (lymphadenoid goitre), it was found that the administration of perchlorate was often followed by a considerable loss of radio-iodine from the thyroid

Clinical Material

12 patients believed to have Hashimoto's thyroiditis were studied 6 of them had undergone thyroidectomy, and histological sections showed the typical appearances of Hashimoto's thyroiditis 4 of the remainder had positive serum-flocculation tests and raised serum-gamma globulin levels (Fromm et al 1953, Skillern et al 1956, Luxton and Cooke 1956), and in 2 of these the diagnosis was further confirmed by a precipitin reaction against thyroglobulin (Roitt et al 1956) Of the remaining 2 patients one had clear signs of myxœdema with a small firm diffuse goitre, the other presented with a fairly large firm diffuse goitre, which disappeared after X ray therapy with the simultaneous development of symptoms of myxœdema Serum has not yet been obtained from these 2 cases for confirmatory tests

The 26 cases classed as simple goitre included both those with diffuse and those with nodular glands, thyroid function being normal in all cases

Method

The patients came for their tests at least five hours after the last meal 20-40 µC doses of radio iodine ^{131}I were given by mouth, and counts were made simultaneously over the thyroid and thigh regions with a standard Geiger counter at fifty and sixty minutes after the dose Immediately after the sixty-minute count the patients drank a solution of potassium perchlorate containing either 200 mg or 400 mg with 25 or 50 ml of water respectively The counting-rate opposite the neck and thigh was measured at ten, twenty, thirty, and forty minutes after the administration of perchlorate

In calculating the results half the thigh count was subtracted from the neck count, because previous experience with subjects in whom the thyroid was absent or temporarily out of action showed that, with the particular geometrical arrangement of counters used by us, the extrathyroid radioactivity in the neck amounts to about half the thigh count This gives an approximate estimate of the radioactivity in the thyroid gland The values thus calculated for thyroid radioactivity at ten, twenty, thirty, and forty minutes were then expressed as a percentage of the thyroid radioactivity present immediately before the perchlorate was given

EFFECT OF PERCHLORATE ON THYROID RADIOACTIVITY

Diagnosis	No of cases	Dose of perchlorate (mg)	Thyroid count as percentage of initial value (mean and S E)			
			Interval after perchlorate (min)			
			10	20	30	40
Healthy	7	200	116(±13)	117(±12)	114(±7)	113(±2)
Thyrotoxicosis	5	200	116(±3)	119(±6)	120(±8)	115(±4)
Simple goitre	19	200	124(±4)	126(±3)	121(±4)	128(±5)
Hashimoto's thyroiditis	5	200	99(±1)	85(±7)	82(±10)	71(±13)
Simple goitre	7	400	111(±8)	111(±8)	109(±7)	114(±7)
Hashimoto's thyroiditis	7	400	80(±7)	65(±15)	57(±10)	43(±9)

The thyroid count has been expressed as a percentage of the thyroid count immediately before perchlorate was given—i e the count at 1 hour after the tracer dose of radio iodine

Results

In the earlier cases in this series the dose of potassium perchlorate was 200 mg We later suspected that this dose might not be sufficient to give the maximal response, and therefore we doubled it Although this suspicion was never proved, it is worth noting that the mean values of the relative thyroid count from the cases of simple goitre were lower in the group given 400 mg than in the group given 200 mg at all time intervals after the administration of perchlorate (see table) The same is true of the cases of Hashimoto's thyroiditis when they are subdivided according to the dose of perchlorate. In neither case, however, is there a significant difference between the mean values obtained with the two doses There would therefore be formal justification for assuming that the dose of perchlorate given was immaterial and for using the combined results from both doses in a comparison of the responses of patients with simple goitre and of patients with Hashimoto's thyroiditis It is, however, possible that the higher dose was really more effective, but that the significance of the effect was obscured by the high variance and small numbers in the groups In view of this possibility we thought that it would be prudent to consider the results with the two doses separately

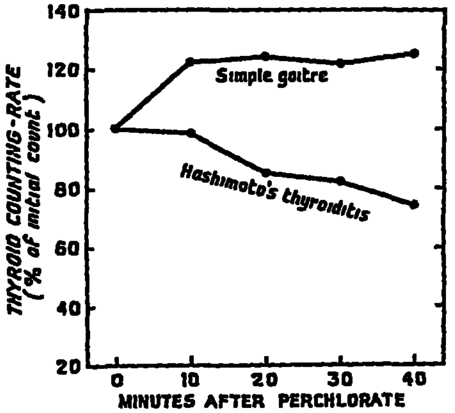

Fig 1—Mean values of thyroid counting rate at intervals after administration of potassium perchlorate 200 mg

Figs 1 and 2 and the table show that in normal subjects and in patients with simple goitre or thyrotoxicosis the thyroid counting-rate tends to rise slightly during the first ten minutes and then remains level The initial rise represents the continued fixation of radio iodine before the perchlorate reaches the thyroid in adequate quantities Thereafter, the iodide concentrating mechanism being out of action, the thyroid can no longer bind appreciable quantities of radio iodine, so the thyroid count remains steady The mean values for the patients with goitre or thyrotoxicosis did not differ significantly from those of the normal subjects at any time-interval

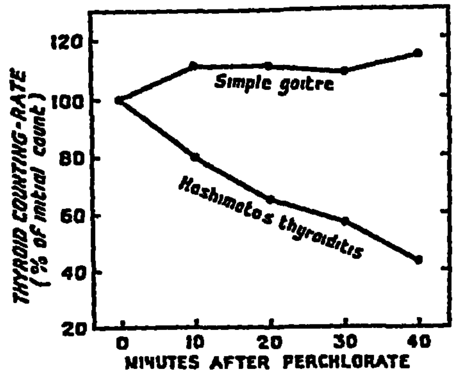

Fig 2—As fig 1 after 400 mg of potassium perchlorate

The relative thyroid counting-rate at forty minutes after perchlorate can conveniently be used as a rough measure of the defect in organic binding of iodine These values are shown in figs 3 and 4 as histograms for each of the groups studied With only 1 exception, all the subjects with normal, goitrous, or thyrotoxic thyroids, who were given 200 mg of perchlorate, retained 90% or more of the radio iodine in their glands There was therefore no detectable quantity of free radio active iodide present in the thyroid and organic binding *is assumed to be complete*

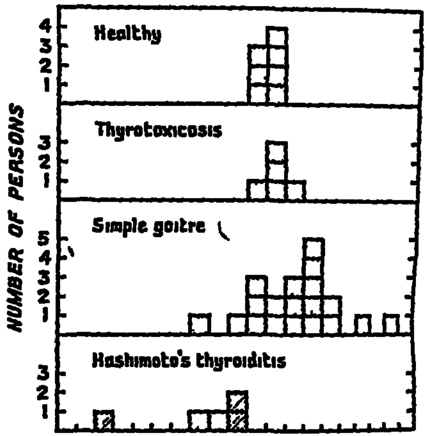

Fig 3—Frequency distribution of thyroid counting rate at 40 minutes after 200 mg of potassium perchlorate hatched squares indicate cases of histologically proved Hashimoto's thyroiditis

This conclusion does not apply, however, to our patient with simple goitre, who retained only 78% of the radio iodine in her thyroid She had what appeared to be an ordinary nodular goitre, with typical histological appearances and no excess of lymphoid tissue The perchlorate test was repeated after the operation, with almost identical results The patient is, however remarkable in that her mother and all her four siblings also have goitres Of these, only one sister has so far been investigated, her response to perchlorate was quite normal

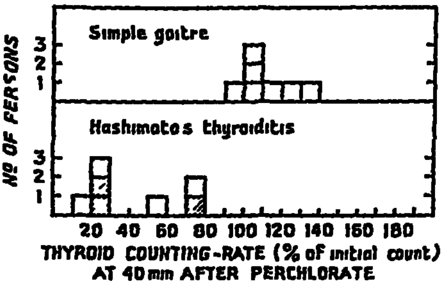

Fig 4—As fig 3 after 400 mg of potassium perchlorate

The 5 patients with Hashimoto's thyroiditis who had been given 200 mg of perchlorate all retained less than 91% of the radio iodine initially present in the thyroid *The mean value for the percentage retained at forty minutes is significantly different from the mean value for the groups* with normal goitrous, or thyrotoxic thyroids (P<0·005)

When 400 mg of perchlorate was given, all the patients *with simple goitre retained 90% or more of the* radio iodine initially present in the thyroid In contrast all the 7 with Hashimoto's thyroiditis retained less than 80% (fig 4) As we have no proof that 400 mg of per chlorate was more effective than 200 mg, it may well be that this sharp differentiation between the two groups was fortuitous, and that overlap would become apparent if more cases were studied

As there was necessarily some doubt about the diagnosis in those cases in which thyroidectomy was not performed, it is necessary to consider the histologically proven cases of Hashimoto's thyroiditis separately The mean relative thyroid counting-rate at forty minutes for this group differs significantly from the mean value for the combined cases of simple goitre (P <0 001)

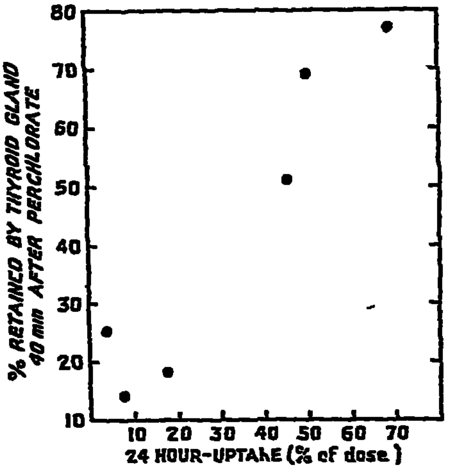

Fig 5—Relation between 24-hour uptake of radio-iodine by thyroid gland and proportion retained in thyroid gland 40 min after perchlorate in 6 cases of Hashimoto's thyroiditis in which both tests were made

Discussion

When perchlorate was given to patients with Hashimoto's thyroiditis, labelled iodine tended to leave the thyroid This is taken to mean that the portion discharged by perchlorate was in the form of inorganic iodide Hence organic binding of iodine was still incomplete at one hour after a tracer dose of radio-iodine There was nothing to suggest that these patients had been consuming anti-thyroid substances, or iodides, in their food or as drugs It seems equally unlikely that they had a congenital enzyme defect, such as Stanbury and Hedge (1950) postulated for their goitrous cretins, since Hashimoto's thyroiditis usually starts in middle age

A possible explanation of the defective binding of iodine is provided by recent evidence (Roitt et al 1956, Rose and Witebsky 1956) which suggests that Hashimoto's thyroiditis is the result of an auto-immune response to thyroglobulin This interesting hypothesis will require further confirmation, and there is at present no indication of the anatomical site at which the presumed antigen-antibody reaction occurs A plausible guess might be that thyroglobulin is formed within the epithelial cells of the thyroid, and that the antibody might unite with it soon after its formation If thyroglobulin were incompletely iodinated at this stage, it is possible to conceive that the antibody might actually cover up some of the available tyrosine radicles and so prevent the first stage of hormone formation This would result in defective organic binding of iodine and so allow inorganic iodide to accumulate in the thyroid This suggestion is put forward as a possible way of bringing together our observations and recent immunological work, but, as it is based on no more than guesswork, its only function is to serve as a pointer to further investigations

The existence of a partial block to iodination helps to explain the very varied results obtained in studies of twenty four-hour uptake of radio iodine in patients with Hashimoto's thyroiditis These may be low, normal, or high The histological evidence suggests that the thyroid in this condition is under strong stimulation by the pituitary The combination of various degrees of iodination defect, with attempted compensation by the pituitary, would go some way to explain these diverse results The degree of iodination defect appears to be correlated with the twenty-four-hour uptake of radio-iodine (fig 5)

We have found the perchlorate test of some practical use in diagnosis, although it will not necessarily differentiate all cases of Hashimoto's thyroiditis from other types of goitre, and there may be exceptional cases of simple goitre which do show some discharge after perchlorate Our experience with the precipitin test of Roitt et al (1956) is that it is usually but not invariably positive in Hashimoto's thyroiditis The flocculation tests are also useful but less specific We feel that a combination of all three tests—perchlorate, precipitin, and flocculation—will give a high degree of diagnostic accuracy and thus obviate the need for biopsy in most cases

Summary

When potassium perchlorate is given to normal subjects one hour after a tracer dose of radio-iodine, the thyroid counting-rate rises slightly and then remains constant This is taken to mean that, by this time, almost all the labelled iodine in the thyroid gland is organically bound

25 patients with simple goitre reacted in the same way

1 patient with simple goitre and an exceptionally strong family history of goitre showed some discharge of thyroid radioactivity after the administration of perchlorate

In 12 cases of Hashimoto's thyroiditis there was a significant tendency for thyroid radioactivity to be discharged after the administration of perchlorate These observations are taken to mean that an appreciable proportion of the administered radio-iodine was still present in the thyroid in the form of iodide at the time the perchlorate was given This is presumptive evidence of a partial defect in the organic binding of iodine by the thyroid in Hashimoto's thyroiditis

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' In a competitive society like ours, almost every formative influence to which we are subjected from the cradle to the grave conspires to persuade us to seek worldly success and to avoid failure, to be proud of achievement and to be ashamed of defeat or weakness But these utilitarian standards by which we are being measured are sub personal standards The only emotions they encourage in us are variations on the themes of fear and ambition, both of which make it almost impossible for us either to give or to accept the inner freedom and self-possession that go with emotional maturity The instability of modern marriage is not an isolated phenomenon that can be explained and remedied by attention to local conditions or individual cases It is one of many social disorders stemming from a single cause namely, the determination of modern man to make material prosperity the chief aim of his life I see no hope of man being able to liberate himself from this enslavement to the economic machinery he has invented until he sees clearly, and with conviction derived from his own personal experience, that the price he is paying for his aim is a deterioration of his spiritual integrity, emotional maturity and happiness.' —PETER FLETCHER in *Marriage and the Community* (published by the British Social Biology Council, Tavistock House South, Tavistock Square, London, W C 1, at *1s 6d*)

A METHOD FOR EVALUATION OF HYPNOTIC DRUGS

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IN comparing hypnotic agents in man two major difficulties are encountered. (1) standardisation of the environmental conditions, and (2) measurement of the depth of sleep induced In the present study the first difficulty was overcome by using as subjects normal *medical students rather than hospital patients, and by* conducting the tests in their own homes The depth of sleep was measured by a new method which is simple and objective

Principle of the Method

Just before retiring to bed, the subject swallowed special capsules of the drug under test, emptied his bladder, and drank a large volume of water Because of this "water load," much urine was secreted during sleep, and the subject was sooner or later roused by the discomfort of his full bladder Rising to micturate, he noted the duration of sleep and the volume of urine passed When, because of the action of a hypnotic drug, sleep was deeper than usual, waking was delayed and a larger volume of urine was voided on waking Both the duration of sleep and the volume of urine passed on waking were taken into account in assessing the average depth of sleep during the night This was represented by the equation

$$D = \log t \times \log v$$

where D was the mean depth of sleep, t the time in minutes from retiring to first waking, and v the volume of urine in millilitres passed on first waking The use of this expression is discussed below Comparison of the values for log t × log v after taking various hypnotic drugs gave a measure of their relative hypnotic potency

Experimental Details

Design of the Experiment

The subjects were healthy male medical students Each man volunteered to take part in four tests at intervals of a week He was asked to perform a test on the same night each week after an evening spent at home In each test unknown capsules were taken on retiring, and at the same time a water load was drunk The capsules which were tasteless and indistinguishable in appearance, comprised

(i) Inert capsules
(ii) and (iii) A standard with which the new drug was to be compared—e g, pentobarbitone in two doses
(iv) The drug to be evaluated

The method of interpreting the data is considered here, the findings with glutethimide are presented in the accompanying article

Measurement of the Depth of Sleep

A method of representing the depth of sleep was sought which would remain uninfluenced by unavoidable differences in the rate of urine flow in different tests To test the suitability of the parameter D = log t × log v, 91 students drank a water load and *took inert capsules on retiring to bed* They recorded the duration of sleep and the volume of urine passed on waking The value of log t × log v from each test was plotted against the corresponding value of t (fig 1) and of v (fig 2) When t was less than 200, log t × log v was low but increased as t increased When t was greater than 200, log t × log v tended to increase only slightly with v, but the two measures were nearly independent of one another

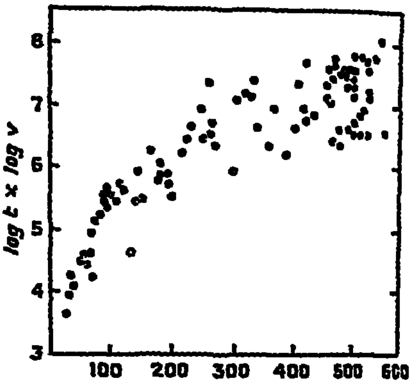

Fig 1—Values of log t × log v plotted against the corresponding sleeping time

The interpretation of these results is that, in general, high waking-volumes of urine were associated with short sleeping-times, and vice versa The value of log t × log v gave a reasonable estimate of the mean depth of sleep which was independent of the rate of urine flow, provided that sleep lasted for more than three hours

When sleep was short it was usually light, and low values of *log t × log v were to be expected with low* values of t But this expression gave unduly low values when the rate of urine flow was high

Suppose, for example, that the subject slept for sixty minutes and that the waking volume of urine was 500 ml The high rate of urine flow represents a strong waking stimulus and indicates moderately deep sleep We have

$$t = 60 \qquad \log t = 1.78$$
$$v = 500 \qquad \log v = 2.70$$
$$\log t \times \log v = 4.81$$

which is an erroneously low estimate of the depth of sleep

Such high rates of urine flow were not aimed at in this test, and a correction was required when they occurred It was decided to reject from the experiment records in which the waking stimulus was "excessive," defined as one which resulted in the subjects' waking less than sixty minutes after retiring, when the mean rate of urine flow exceeded 5 ml per minute Such records were unsuitable also because one hour might not be sufficient time for a hypnotic drug, taken on retiring, to exert its full effect

Difficulties might also be introduced from an unduly low rate of urine-flow

Suppose that a subject slept for eight hours and passed 400 ml of urine on waking We have

$$t = 480 \qquad \log t = 2.68$$
$$v = 400 \qquad \log v = 2.60$$
$$\log t \times \log v = 6.97$$

This value is higher than the average for log t × log v, and such a result is consistent with lighter than average sleep But the same figures might have been obtained after deep *sleep, since the subject would waken after eight hours*

As the effect of a low rate of urine-flow is to obscure *differences between light and deep sleep, it was desirable*

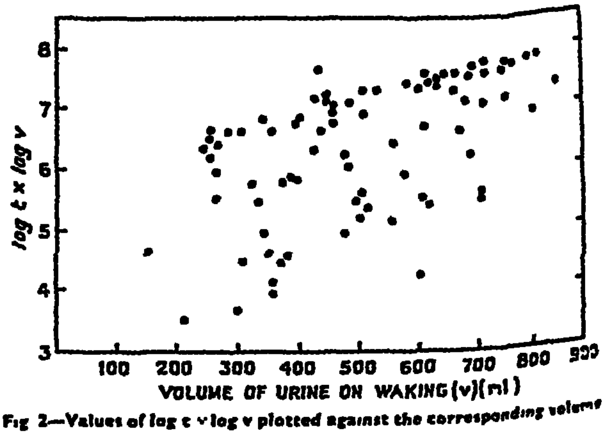

Fig 2—Values of log t × log v plotted against the corresponding volume of urine on waking

to exclude from the experiment records in which the stimulus was "inadequate," defined as one which resulted in sleep lasting for more than seven hours, and in which the subject passed less than 400 ml of urine on waking These figures were based on an experiment in which 20 students recorded the duration of sleep and the volume of urine on waking after an ordinary night's sleep when no water load had been taken In 18 students, sleep lasted for more than seven hours, and in 15 of these the volume of urine on waking was less than 400 ml

Provided that unsuitable records were rejected, it was considered that log t × log v gave a reasonable estimate of the depth of sleep

Choice of a Suitable Water Load

Preliminary studies suggested that 500 ml taken immediately before retiring was a suitable water load This volume was used at first in the main experiment, but almost a third of all records had to be rejected because the waking stimulus was "inadequate" as defined above (table I) During the remainder of the experiment a larger water load was used—500 ml an hour before bedtime and another 500 ml at bedtime This proved more suitable, but several records had to be rejected because the waking stimulus was "excessive" as defined above

It was necessary to determine whether altering the water load during the experiment affected the values of log t × log v Table II shows that the values obtained after hypnotic drugs were the same with both water loads After inert tablets, the values were lower with the high than they were with the low water loads This was because, with the higher water load, the subject often awoke in the second hour after retiring, when values of log t × log v were low

TABLE I—INFLUENCE OF THE MAGNITUDE OF THE WATER LOAD ON THE RATE OF URINE FLOW

(For definitions of "inadequate" and "excessive" see text)

Water load	Adequate	Inadequate	Excessive
500 ml once	85	49	5
500 ml twice	133	10	17

Because of the cross over design of the experiment, changing the water load during it did not invalidate comparisons between drugs In future experiments, however, other water loads should be tried It seems unwise to give water an hour before retiring

Effect of Drugs on Water Diuresis

To make sure that the drugs tested did not themselves influence water diuresis, an experiment was undertaken

12 convalescent hospital patients each drank 500 ml of water and swallowed the active or placebo capsules used in this study The course of the diuresis was followed at half hour intervals for three hours No alteration in the pattern of diuresis attributable to the drugs was detected The results however varied widely, both between subjects and between drugs To be certain that the hypnotic drugs had no antidiuretic effect, these studies would have to be made on a much larger scale

Previously glutethimide had been shown to have no such effect (Gross 1956), and pentobarbitone has not been shown to affect diuresis except in large doses in dogs (de Bodo and Prescott 1945)

Statistical Considerations

TABLE II—INFLUENCE OF THE WATER LOAD ON THE MEAN VALUE OF LOG t × LOG v AFTER THE VARIOUS DRUGS

(Records classed as "inadequate" or "excessive" are not included)

Drug	Water load	No of experiments	log t × log v	
			Mean value	Standard error
Control	500 ml once 500 ml twice	31 35	6 69 6 26	0 15 0 16
Pentobarbitone gr 1½	500 ml once 500 ml twice	23 42	7 04 7 06	0 18 0 10
Pentobarbitone gr 3	500 ml once	20	7 34	0 18
Glutethimide 500 mg	500 mg once 500 ml twice	25 45	6 88 6 96	0 18 0 14

It was decided to obtain four values of log t × log v for each subject in the experiment, one value corresponding to each of the four sets of capsules If for any reason one record from any subject had to be rejected, then the other results from that subject could not be used *in the analysis* Our experience suggests that valid results could probably be obtained if 20 subjects entered the experiment

The results were examined by a two-way analysis of variance This showed that variation between subjects contributed more to the total variance than did variation between drugs Values could be obtained for the probability of the significance of observed differences between the active drugs and the placebo, and between the different active drugs

Discussion

This method of evaluating hypnotic drugs assumes that they increase the resistance of the sleeping brain to arousal stimuli from the filling bladder No assumption need be made about the site or mechanism *of such an* action The expressions "mean depth of sleep" and "resistance to waking impulses" are used because they are convenient in the context of this experiment It is not claimed that those terms have true physiological meaning

Several other methods have been used for the quantitative evaluation of hypnotic agents in man Many of these depend in part on the patient's own report of the duration and quality of sleep (Lasagna 1954, Foltz et al 1955, Rushbrooke et al 1956) or on the reports of nurses or technicians (Lasagna 1954) In another method the doses which produced comparable degrees of depression of the central nervous system (Foltz et al 1955) were determined for different hypnotic drugs Electro encephalographic studies of sleep after hypnotic drugs have also been made (Ladwig 1955) but these are of limited application No one method used alone can give a satisfactory objective measurement of the hypnotic properties of drugs

The following advantages are claimed for the method proposed here

1 Normal healthy subjects are used

2 The tests are performed in the subjects' own homes

3 Repeated tests with different drugs or different doses are performed on the same subjects, and a cross over experimental design can be used in which the subjects act as their own controls

4 No elaborate apparatus and no observers are needed

5 The method of measuring the depth of sleep is objective and free from bias, and observer error is slight

6 Only physiological stimuli are employed

7 *Statistically* valid results can be obtained with relatively few subjects

The method has the following disadvantages

1 It is not used in patients who actually require hypnotic drugs

2 It gives no information about the time of onset of the drug's action or its duration of action

3 It gives no information about side effects or after-effects

4 It can provide only comparative information against drugs of known potency

5 It assumes that the drugs tested have no action on the bladder or on water diuresis

Some of the disadvantages are common to other methods of evaluating hypnotic drugs

This method can be applied in the evaluation of new hypnotic drugs, and in measuring the hypnotic side-effects of drugs such as anti-histamines, provided that an effect of the drug on water diuresis or on the bladder can be excluded

Summary

A method is described for the evaluation of hypnotic drugs in man The method depends on determining the resistance of the sleeping subject to waking impulses from the filling bladder Before retiring, and at the time of taking the drug under test, the subject drinks a large volume of water On waking he records the duration of sleep (t minutes) and the volume of urine passed on waking (v ml.) It is shown that the expression log t × log v can then be used as an empirical measure of the mean depth of sleep, and thus of the relative potency of hypnotic drugs

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HYPNOTIC EFFECT OF GLUTETHIMIDE IN NORMAL HUMAN SUBJECTS

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GLUTETHIMIDE (α-phenyl α-ethylglutarimide, 'Doriden') is a new non-barbiturate hypnotic (Gross et al 1955) Experimental and clinical studies suggest that it may be a useful substitute for barbiturates (Ladwig 1955, Müller and Rohrer 1955, Rushbrooke et al 1956). I record here an attempt to measure its action in normal people

Material and Methods

The majority of a class of medical students volunteered for the trial The women took part in a subjective study designed to give information mainly on side effects The men (average age 21) took part in an objective study designed to give quantitative information on the hypnotic potency of the drugs tested Each student undertook, in his own home, a series of four tests on himself, as described in the previous article For each test he received a pair of capsules which, he was told, might or might not contain a hypnotic drug The capsules were tasteless and indistinguishable in appearance, and contained one of the following (the doses are the total for two capsules)

1	Lactose	500 mg
2	Pentobarbitone	100 mg (gr 1½)
3	Pentobarbitone	200 mg (gr 3)
4	Glutethimide	500 mg

All students were to receive the four different sets of capsules, one kind each week *The order in which they* were given differed at random for each student, all 24 possible sequences being used The women were given the following questionary to be completed on the day after the test

1 Did you sleep (A) the same as usual ?
(B) more soundly than usual ?
(C) less soundly than usual ?

2 Did you fall asleep (A) less easily than usual ?
(B) as usual ?
(C) more easily than usual ?

TABLE I—ANSWERS TO THE QUESTIONARY

Question	Answer	Numbers providing each answer after taking			
		Control	Pentobarbitone gr 1½	Pentobarbitone gr 3	Glutethimide 500 mg
1	A	24	22	4	21
	B	2	8	6	5
	C	2	0	0	0
2	A	2	1	0	3
	B	26	27	8	23
	C	0	2	2	3
3	A	1	7	3	3
	B	3	2	0	0
	C	24	21	7	26
4	A	25	18	3	24
	B	3	1	1	0
	C	0	11	6	5
5	A	0	8	9	9
	B	2	0	0	0
	C	26	22	1	20

3 Did you waken during the night (A) less than usual ?
(B) more than usual ?
(C) as usual ?

4 Did you waken in the morning (A) as usual ?
(B) with less difficulty than usual ?
(C) with more difficulty than usual ?

5 On waking did you feel (A) unusually tired ?
(B) unusually fresh ?
(C) as usual ?

6 During the day did you notice any unusual symptoms and if so what were they ?

The male students were issued with a record form and a plastic cylinder for urine collection

In the subjective study, the women took their capsules on retiring to bed, but did not alter their usual bedtime habit Next morning they answered questions 1-4 of the questionary by ringing A, B, or C, questions 5 and 6 were answered in the evening 34 students entered the experiment, but a few withdrew in the course of it

TABLE II—SIDE EFFECTS

Symptom	Number complaining after taking			
	Control	Pentobarbitone gr 1½	Pentobarbitone gr 3	Glutethimide 500 mg
Unusually tired, sleepy	0	5	5	6
Dizzy, light headed	0	5	7	3
Ataxia slurred speech	0	2	8	[illegible]
Headache	0	1	1	0
Nausea	0	0	3	0
Lack of concentration	0	0	1	2
Argumentative	0	0	1	0
Confused as though drunk	0	0	3	4
Irritable	0	0	2	0
Apathetic	0	0	1	1

All the results obtained were used in the analysis but the numbers in the different drug groups differ slightly

In the objective study, using male students, the method described in the accompanying paper was adopted It measures the ability of the drug to maintain sleep despite the waking stimulus of a full bladder

Results

The studies were run simultaneously When the results for the first week came to hand, it was apparent that in the majority of students pentobarbitone gr 3 had caused drowsiness and mental confusion on the day after the test This dose was therefore withdrawn from the trial In all experiments with male students with the dose of pentobarbitone the water load was therefore 500 ml only

Subjective Trial (Women)

The answers to the questionary are presented in tables I and II and the statistical analysis in table III After taking placebo capsules almost all students described their sleep as "usual," and none complained of after-effects This apparent lack of suggestibility contrasts with the findings of other studies on the subjective effects of drugs on "sophisticated" observers, such as medical students (Glaser 1953, 1954, Glaser and Whittow 1954)

Questions 1–3 provide little information about the drugs, because normal students fall asleep rapidly, sleep soundly, and do not waken during the night Only after pentobarbitone gr 3 did increased depth of sleep become apparent From questions 4 and 5 it is seen that in about a third of the students pentobarbitone gr 1½ caused increased difficulty in waking and drowsiness next morning Fewer subjects noted difficulty in waking after glutethimide 500 mg , but the same proportion, about a third, complained of drowsiness next day Other after effects were rare with these two drugs, but pentobarbitone gr 3 caused a large number of unpleasant after effects (table II), and is clearly unsuitable for administration to young ambulant subjects

TABLE III—SIGNIFICANCE OF DIFFERENCE BETWEEN DRUGS (χ^2 test)

Question	Drugs compared	Probability (P) that observed difference is not significant
1	C and P3 G and P3	<0 001 <0 02
2	No significant differences	
3	No significant differences	
4	C and P1½ C and P3 P3 and G	<0 01 <0 001 <0 05
5	C and P3 C and G P1½ and P3 P3 and G	<0 001 <0 02 <0 01 <0 01

All other differences not significant

C = control.
P1½ = pentobarbitone gr 1½
P3 = pentobarbitone gr 3
G = glutethimide 500 mg

Objective Study (Men)

109 students entered the experiment, but complete records for all four drugs were obtained from only 9 Satisfactory records for three substances (excluding pentobarbitone gr 3) came from 30 others Many records were rejected because the stimulus was either "inadequate" or "excessive" as previously defined, or for other reasons listed in table IV The gr 3 dose of pentobarbitone was given to only a quarter of the subjects These were all during first tests, and with the smaller water load This departure from the original experimental plan must be borne in mind in interpreting the results, but it is unlikely to have introduced serious error Incomplete sets of records could not be used in the final analysis

TABLE IV—CAUSES OF INCOMPLETE RECORDS

No submitting at least one return	109
No returning complete set of four acceptable results	9
No returning set of three acceptable results (i e other than for pentobarbitone gr 3) excluding the above	30

Cause of default	Control	Pentobarbitone gr 1½	Pentobarbitone gr 3	Glutethimide 500 mg
No return submitted	20	19	75	16
Doubt about capsule issued	1	3	0	0
Water load inadequate	15	19	12	17
Water load excessive	6	1	3	6
Rash after pentobarbitone (one subject)	1	1	0	1
Total	43	46	90	40

TABLE V—RESULTS FOR FOUR TEST SUBSTANCES IN 9 SUBJECTS

Subject	Sequence of drugs	Value (log t × log v) after			
		1 (Control)	2 (Pentobarbitone gr 1½)	3 (Pentobarbitone gr 3)	4 (Glutethimide 500 mg)
1	3–1–2–4	4 63	5 07	7 40	7 41
2	3–2–1–4	5 44	8 04	8 67	5 60
3	3–2–4–1	5 56	7 38	7 21	6 92
4	3–1–2–4	5 49	5 52	5 66	5 98
5	3–1–2–4	7 45	7 63	7 44	7 74
6	3–4–1–2	7 80	8 00	8 10	7 74
7	3–4–1–2	7 39	7 58	7 69	7 81
8	3–2–1–4	5 21	5 27	6 03	7 27
9	3–1–4–2	5 62	7 59	8 22	7 57

The full data obtained from giving four test substances to 9 subjects are set out in table V, and table VI shows the analysis of variance It is seen that differences between individuals contributed more to the total variance than did differences between drugs A significant difference between the effects of the drugs was apparent (P = 0 01) When the drugs were compared in pairs, it was found that there were significant differences between each of the drugs and the placebo and between the two dose-levels of pentobarbitone The difference between 500 mg of glutethimide and pentobarbitone gr 1½ was not significant The difference between glutethimide 500 mg and pentobarbitone gr 3 just failed to reach the 5% level of significance in this small series

In the analysis of 39 sets of results (including these 9) in which the placebo, pentobarbitone gr 1½, and glutethimide 500 mg were compared (table VII) a significant difference between the drugs was again found (P = 0 001) A comparison by pairs showed that both drugs differed significantly from the placebo, but not from one another

TABLE VI—ANALYSIS OF VARIANCE—SMALLER SERIES

Source of variation	Sums of squares	Degrees of freedom	Mean squares	Ratio
Between drugs	8 71	3	2 90	Drugs to residual
Between individuals	20 59	8	2 57	
Residual	15 18	24	0 63	F = 4 72
Total	44 48	35		

F 0 01 = 4 72

TABLE VII—ANALYSIS OF VARIANCE—LARGER SERIES

Source of variation	Sums of squares	Degrees of freedom	Mean squares	Ratio
Between drugs	8 50	2	4 25	Drugs to residual
Between individuals	50 85	38	1 34	
Residual	45 38	76	0 60	F = 7 08
Total	104 73	116		

F 0 001 = 7 70

Discussion

The response of normal subjects to a hypnotic cannot give a complete picture of what is to be expected from the drug in clinical practice But the subjective and objective appraisal of glutethimide in different subjects lead to the same conclusion—that this drug in a dose of 500 mg was equivalent to pentobarbitone gr 1½ in hypnotic effect, and was slightly less liable to cause difficulty in waking Clinical studies of glutethimide have led to rather similar conclusions, and Rushbrooke et al (1956) said that their patients in general practice found that glutethimide 500 mg was comparable to cyclobarbitone 200 mg

Summary and Conclusions

A subjective test in 34 female students showed that glutethimide 500 mg had about the same effect as pentobarbitone gr $1^1/_2$ in increasing the depth of sleep, and was slightly less prone to cause difficulty in waking

An objective study in male students, based on the measurement of resistance to waking from bladder stimulation, showed that glutethimide 500 mg was about as potent a hypnotic as pentobarbitone gr $1^1/_2$

This trial supports the validity of the method of comparing the potency of hypnotic drugs proposed in the preceding paper

I wish to express my sincere thanks to the students who took part in these experiments I also thank Miss Sheila Grace for her help and Dr S D Silvey for advice on the statistical analysis Glutethimide was supplied by Messrs Ciba Laboratories, Horsham, and the special capsules were prepared by Messrs John Tye & Sons

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PENICILLIN IN THE TREATMENT OF LACTATIONAL BREAST ABSCESS

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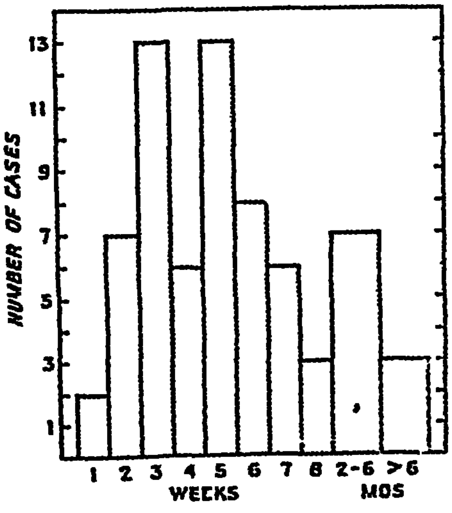
Breast abscess remains one of the more disabling forms of sepsis For the mother it may mean a prolonged illness, a maimed breast, and one or more ugly scars, and for the child, an unfortunate interruption of breast feeding

The high hopes of controlling this distressing illness raised by the advent of antibiotics have not been realised, and the number of cases treated annually at the London Hospital remains approximately constant In an attempt to assess the effect of antibiotics, especially penicillin, in modifying the course of the illness, 68 consecutive cases treated at *the London Hospital between 1953 and 1955* were analysed, and the results are presented here



Interval between parturition and breast abscess

Of these 68 lactating women, 35 were delivered in hospital and 33 at home The intervals elapsing between delivery and the *onset of the* breast abscess are shown in the accompanying figure, from which it will be seen that, as previously noted by Walsh (1949), a substantial number of abscesses developed when the patients had left hospital and were under the care of their general practitioner During the same period the surprisingly large number of 32 non-lactational cases of breast abscess were also treated

TABLE I—ANTIBIOTICS USED

Antibiotic	No of cases
Penicillin only	36
„ and other antibiotic *	8
Other antibiotics only †	4
No antibiotic	20
Total	68

* Aureomycin 7 cases chloramphenicol 1 case
† Oxytetracycline, aureomycin chloramphenicol and streptomycin 1 case each

Bacteriology

The infecting organism was cultured from the pus in all except 3 cases In 64 cases *Staphylococcus pyogenes* was grown and its sensitivity in vitro to penicillin determined A non hæmolytic streptococcus was cultured in 1 case When delivery took place in hospital 90% of the staphylococci cultured were resistant to penicillin, whereas when *delivery took place at home* 71% were resistant

Antibiotics

These patients were treated by a number of general practitioners and several surgical and obstetric firms, hence there was no general policy for the use of antibiotics The cases were divided into two groups those in which antibiotics were given before incision of the abscess and those in which they were not Table I shows that 48 cases were treated with *antibiotics* and 20 not Penicillin was used in 44 cases, but in 8 of these another antibiotic, usually aureomycin, was also given Of the 48 cases treated with antibiotics only 4 were not treated with penicillin The number of cases treated with other antibiotics was too small for any conclusions of value to be drawn

TABLE II—COMPARISON OF AVERAGE NUMBER OF INCISIONS *AND HEALING TIME IN ANTIBIOTIC TREATED AND UNTREATED* CASES

Treatment	No of cases	Average no of incisions	Average healing time (wk)
1 No antibiotic	20	1·0	3·9
2 Penicillin (organism resistant)	10	1·7	6·3
3 Penicillin (organism sensitive)	4	1·2	4·7
Difference between 1 and 2		0·7 (s e ±0·4)	2·4 (s e ±1·0)

s e standard error of difference between means

Criteria of Comparison

Two criteria were used to assess the effect of penicillin on the course of the illness the total duration of the illness from first symptom to final healing, and the number of incisions necessary before this took place The results are shown in table II

In the 20 cases not treated with antibiotics before drainage the average healing time was 3·9 weeks and the average number of incisions 1·0

In 4 cases the organism was subsequently proved to *be sensitive to penicillin, in them the healing* time was 4·7 weeks and the average number of incisions 1·2 In the 10 cases treated with penicillin in which later examination showed the organism to be penicillin resistant the average healing time was 6·3 weeks and the average number of incisions 1·7

Case-reports

Certain cases were of particular interest as illustrating *the effect of antibiotics on the course of the illness*

Case 1 —The patient, aged 19, developed painful red flushed breasts with pyrexia (102°F) on the 10th day after a normal delivery in hospital. After a 4-day course of soluble penicillin 500,000 units b.d. the pain settled and the temperature fell to normal. The child was weaned, and the patient was discharged home. She was referred to hospital 14 days later with an abscess in her right breast, and an "enormous multilocular cavity" was drained. 2 days later she developed further abscesses in her left breast, and two large cavities were drained on this side. A month later the abscess recurred in the left breast, requiring two further incisions. In every specimen a staphylococcus resistant to penicillin was grown. The total period of disability in this case was 10 weeks.

Case 2.—The patient, aged 26, complained of pain and tenderness in her left breast on the 7th day after a normal delivery in hospital. A localised area of tender induration was palpable, and she was given a course of soluble penicillin 500,000 units b.d. with little improvement. Aureomycin was substituted on the 3rd day, and the condition appeared to resolve. She was discharged home and continued breast-feeding. 2 weeks later, however, pain recurred, and she was readmitted with an abscess in her left breast. This was incised and a staphylococcus insensitive to penicillin was grown. 5 days later a further abscess required drainage and then healed. The period of disability was 5 weeks.

Case 3.—The patient, aged 30, developed pain and swelling in her right breast two weeks after normal delivery in another hospital. After a 4-day course of penicillin the pain and swelling subsided, and she was discharged home to continue breast-feeding. A week later she was referred to the London Hospital and admitted. Her right breast was extremely tense and tender, but after expression of milk no definite lump was felt. Pus, however, was aspirated from the lower medial quadrant, and on incision a large single cavity was found deep in the breast. A penicillin-resistant staphylococcus was cultured. Lactation was suppressed with stilbœstrol. 16 days later a further small abscess in the right breast required incision. The total period of invalidism was 5 weeks.

Case 4.—The patient, aged 28, developed pain and swelling in her left breast 3 weeks after a normal delivery of a second child at home. She was treated by her doctor for 12 days with procaine penicillin without improvement and then referred to surgical outpatients. She had an extensive tender indurated area deep to her left nipple and extending out in all quadrants. A large multilocular abscess was incised, and its wall was noted to be thick and very hard. Pus grew *Staph. pyogenes* insensitive to penicillin. The period of disability was 5 weeks.

Case 5.—The patient, aged 23, was treated by her doctor for right flushed breast, which developed a month after normal delivery in the London Hospital. After a 3-day course of soluble penicillin 500,000 units b.d. the condition gradually subsided and she continued breast-feeding. 2 months later pain recurred and lactation was suppressed with stilbœstrol. A lump then appeared in her right breast, and she was referred to the London Hospital, where a large indurated non-tender mass was found in the lower inner quadrant of her right breast. After application of a kaolin poultice for 24 hours fluctuation was found, and two incisions produced nearly half a pint of pus. The abscess wall was very vascular and bled briskly, an abnormal ooze persisting for 48 hours. Surprisingly a staphylococcus sensitive to penicillin was grown. The total period of disability was 2 months.

Case 6.—The patient, aged 23, developed a painful right flushed breast with pyrexia (102 F) on the 9th day after a normal delivery in the London Hospital. After a 3-day course of soluble penicillin 300,000 units daily the condition appeared to resolve, the patient's temperature fell to normal, and she was discharged home. 15 days later a painful lump reappeared and she received a further 5-day course of soluble penicillin 300,000 units b.d. without improvement. She was then referred to the London Hospital, and a tender, very hard and non-fluctuant mass was found in the upper outer quadrant of her right breast with redness of the overlying skin. Penicillin was discontinued, and kaolin poultices were applied daily. The condition remained indolent until 3 weeks later, when it was considered that fluctuation was present, and an incision was made into "a large fibrous mass" containing a small cavity but no pus. 2 weeks later a fluctuant area developed here and was incised, a small quantity of pus being evacuated. A profuse growth of *Staph. pyogenes* insensitive to penicillin was cultured. The residual indurated area in the breast was treated with short-wave diathermy, and the condition eventually healed 6 weeks later. The period of disability was 3 months.

Discussion

Today many of the dreaded complications of uncontrolled sepsis have been eliminated or at least mitigated. Mutilated hands resulting from severe finger infections, useless joints after septic arthritis; fulminating septicæmias, the sequel of osteomyelitis, no longer fill septic wards. Nevertheless, every therapeutic advance poses its own set of problems, and antibiotics are no exception. When penicillin became generally available it was thought that its use would greatly lessen both the duration of breast abscess and the need for surgical incision (Florey et al. 1946).

It is indeed remarkable that penicillin continued in the present series to be the antibiotic favoured by both general practitioner and in hospital treatment, despite the handicap of its having to be used parenterally and despite the availability of a variety of other potent antibiotics. The evidence presented above, however, suggests that neither healing-time nor the number of surgical incisions has been lessened. Where the organism is insensitive, the healing-time is lengthened and the number of incisions increased. Several factors may be responsible for this.

Firstly, the conditions in the lactating breast are peculiarly favourable to the rapid multiplication of pathogenic organisms and the early formation of an abscess.

Secondly, the chance of the responsible organisms being insensitive to penicillin is always considerable and, when the patient has been delivered in hospital, almost certain. Barber and Burston (1955) found that, in 89% of babies leaving a maternity unit, a penicillin-resistant staphylococcus could be grown from the anterior nares. Not only is there, therefore, a considerable chance of penicillin being useless from the start, but also, once pus is formed, there is little likelihood of cure without drainage, whatever the antibiotic used. Moreover, apart from penicillin therapy's being often pointless, its injudicious use may complicate treatment of the established abscess.

Some of the disadvantages are illustrated in the cases cited above. In cases 1, 2, 3, 5, and 6 the symptoms and signs of infection completely disappeared after treatment with penicillin, only to recur later, by which time large abscesses had formed.

Case 5 was of particular interest. When the patient eventually presented as an outpatient, a large, indurated, and notably non-tender mass was found which clinically resembled a carcinoma. This difficulty has been noted by Stammers (1953) and is due to the masking of the signs of inflammation.

The findings in case 6 were somewhat similar, and it was only after the discontinuance of penicillin and the daily application of kaolin poultices for 3 weeks that fluctuation became evident. When the breast was finally incised, a hard fibrous mass was found surrounding a small cavity but little pus. Healing was considerably delayed by this fibrotic reaction, which eventually disappeared after a course of short-wave diathermy.

The excessive formation of vascular granulation tissue too may lead to excessive hæmorrhage when the abscess is incised, as in case 5. These features have also been noted by Mills (1953).

The masking of the signs of inflammation may lead to serious delay in instituting drainage, with the result that an excessive amount of breast tissue is destroyed, amounting in some cases to functional mastectomy.

A further consequence of this destruction of breast tissue is the increased liability to further breast abscesses, particularly after later pregnancies.

It therefore seems reasonable to restrict the use of penicillin to early cases of acute mastitis, and then only when the mother has not been delivered in hospital and there is therefore a reasonable chance of dealing with an organism sensitive to penicillin If there is no response within 48 hours, its use should be discontinued because of the difficulties already mentioned If a satisfactory response is obtained, the patient must still be kept under close supervision to ensure that the condition has been cured and not merely masked When an abscess has already formed, early and effective drainage is the surest way of obtaining early healing

Summary

Of 100 consecutive cases of breast abscess treated at the London Hospital between 1953 and 1955 32 were non lactational The 68 lactational cases were analysed with particular reference to penicillin therapy

In this series penicillin continued to be the antibiotic most commonly used both by general practitioners and in hospital

Where the patient had been delivered in hospital 90% of the staphylococci cultured were insensitive to penicillin, and in other cases 71% were insensitive

Where the organism was insensitive to penicillin both the number of surgical incisions required and the healing-time were increased in comparison with the cases in which no penicillin was given

I wish to thank the surgical and obstetric staff of the London Hospital for permission to cite their cases, and Mr A R Anscombe for much helpful criticism and encouragement

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BRONCHIAL LAVAGE

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BRONCHIAL lavage, as a means of obtaining material for the culture of tubercle bacilli, has already been described several times (Lees et al 1955, Spencer Jones 1956) The present work, which confirms previous findings, has led to a much simpler technique which can be quite easily used by nurses

All patients admitted to this hospital for investigation of respiratory disease and who had no sputum were subjected, as soon as possible after admission, to three daily gastric residue and three daily bronchial lavage examinations As all specimens were collected within a week and usually within three days, the two series are comparable

Technique

The technique is simpler than previous methods and carries less risk to the operator For half an hour before examination the patient sucks an amethocaine hydrochloride ('Decicain') 100 mg lozenge (two half tablets, at quarter hour intervals, is most effective) He sits in a chair leaning backwards and to one side (fig 1) The operator stands behind the patient and with the left hand holds the patient's tongue The patient is told to breathe slowly and deeply and not to cough or swallow while 10 ml of normal saline is poured slowly on to the tongue so that it trickles back through the larynx and down the trachea The patient now coughs into the wide mouthed jug which was placed in his hands at the beginning The procedure is then repeated for the second side It is very important to acquire a technique of pouring the saline slowly and steadily, otherwise the patient will cough The saline should be poured as fast as is possible without producing cough—usually ten to twenty seconds for 10 ml The best method is to hold a syringe as in fig 2 The operator should, of course, be protected by gown and mask, but risks of infection are less when standing behind the patient than with the other methods of bronchial lavage described previously The specimen is then transferred to a bottle A satisfactory specimen always contains some solid particles, and they may be plentiful even from a healthy chest The specimen is then cultured in the laboratory in the same way as a gastric residue specimen, except that neutralisation is omitted

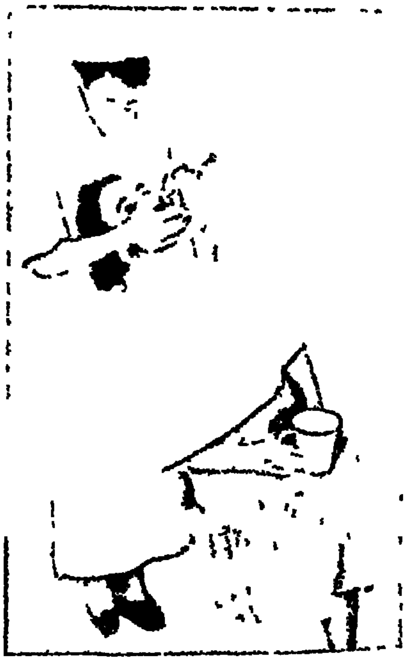

Fig 1—Position of patient.

Results

70 patients took part in this trial, and all had three bronchial lavage and three gastric residue examinations 41 had pulmonary tuberculosis, active or inactive, 9 had pleural effusions, and the remaining 20 had other respiratory conditions Table I shows the number of patients in each group from whom positive cultures for tubercle bacilli were obtained by bronchial lavage and gastric residue examinations No case was positive on gastric residue which was not also positive on bronchial lavage

To determine the most reasonable number of examinations to which a patient should be subjected, the proportions of patients first found to be positive by each of the three tests was recorded The bronchial lavage and gastric residue series have here been regarded as separate investigations, but the cases of pulmonary tuberculosis and pleural effusion have been added together (table II

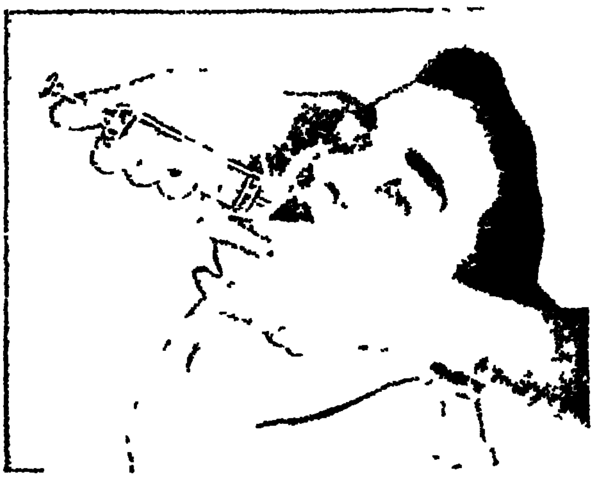

Fig 2—Position of syringe

TABLE I—RESULTS OF EXAMINATIONS

Diagnosis	No of cases	No of cases with positive cultures	
		Bronchial lavage	Gastric residue
Pulmonary tuberculosis	41	14 (*34%*)	3 (*7%*)
Pleural effusion	9	2 (*22%*)	1 (*11%*)
Other respiratory conditions	20	0	0

TABLE II—THE FIRST POSITIVE CULTURE

Examination giving first positive culture	No of patients	
	Bronchial lavage	Gastric residue
1st	9 (*18%*)	4 (*8%*)
2nd	6 (*12%*)	0
3rd	1 (*2%*)	0
Total	16 (*32%*)	4 (*8%*)

From these tables it is apparent that bronchial-lavage examination was four times as efficient as gastric residue examination in the recovery of tubercle bacilli, and that the majority of positive cases can be found by two bronchial lavages

The results of this trial suggested the possibility that tubercle bacilli contaminating a healthy respiratory tract might be recovered by bronchial lavage giving a false positive result It was therefore decided to try the test in healthy volunteers who all had normal chest X-rays and no past history of pleural or pulmonary tuberculosis The tests were arranged at times when it was thought that maximum contamination was likely—e g, after bed-making 105 lavages were made in 30 nurses, but there was not one positive result

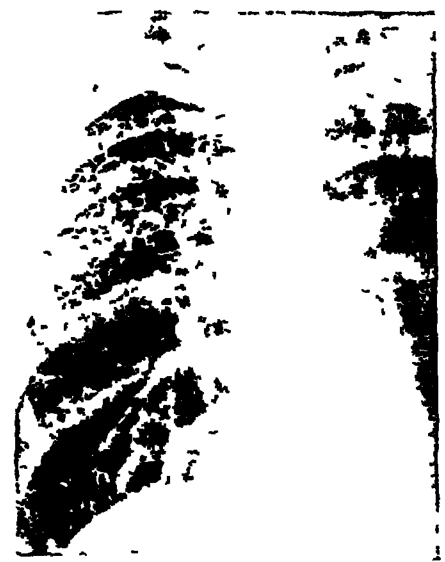

Fig 3—Bronchogram

The negative results in healthy volunteers and non tuberculous patients show that false positives from contamination of the air-passages by tubercle bacilli are unlikely, and that a positive result means active disease (apart from very rare laboratory errors)

During these examinations it was suggested that the saline went no further than the larynx Accordingly, after a normal bronchial lavage and without further anæsthesia, one of the volunteers had 20 ml of propyliodone (' Dionosil ') poured over the back of the tongue (straight from the bottle) Positioning was carried out as for bronchography, fig 3 shows the bronchogram obtained This also demonstrates the efficiency of the anæsthesia, which has since been used in obtaining satisfactory routine bronchograms in coöperative patients without any other premedication

Conclusions

In this hospital we have been so satisfied with the ease and accuracy of the tests that bronchial-lavage has now replaced gastric-residue examinations The ward sisters carry out the tests without difficulty Cases under treatment may seem to remain positive a little longer when bronchial-lavage examinations are used, but this is due to increased sensitivity of the test

At least two lavage examinations are necessary for accuracy, there is no doubt that the second examination is more thorough than the first, because the patient cooperates better

The great majority of those who underwent the examinations, and of those who performed them, preferred bronchial-lavage to gastric-residue examinations

Summary

A parallel comparison of bronchial-lavage (by a simplified method), and gastric-residue examination showed that bronchial lavage was four times as efficient in isolating tubercle bacilli

A control series of healthy volunteers yielded no false positive results

A simple technique for bronchography, suitable for certain patients, has resulted from this work

I wish to thank Dr R L Midgley for encouragement and advice, Dr B Moore who did the bacteriological work, and all the volunteers who made this investigation possible

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RELIEF OF ŒDEMA AND HIGH BLOOD-PRESSURE BY CONCENTRATED HUMAN SALT-POOR SERUM-ALBUMIN

IN ELLIS TYPE-II NEPHRITIS

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THE value of concentrated human serum-albumin has been extensively studied in the U S A, mainly by Cohn et al, Eckhardt et al (1948), and Janeway et al (1944), and as far back as 1942 the first standard preparation for the Armed Forces was tested In the U K it has been studied by Martin (1954) Most of the early work was directed towards the treatment of shock and burns, and its value in hypoproteinæmia was mainly in the treatment of malnutrition and hepatic cirrhosis Recorded cases of its use in the nephrotic syndrome are relatively few (Janeway et al 1944, Martin 1954, Ferguson 1955)

Case-report

A girl, aged 19, was seen for the first time on June 14, 1955, complaining of œdema of the face and trunk for two days, œdema of the ankles for three weeks, and severe headaches for six months There was no previous history of either scarlet fever or renal disease

On examination she was pale and had gross anasarca, her heart sounds were normal and blood pressure was 130/90 mm Hg, there was no retinopathy Laboratory investigations showed plasma proteins 3 91 g per 100 ml (albumin 1 25 g per 100 ml, globulin 2 66 g per 100 ml), cholesterol 610 mg per 100 ml, non protein nitrogen 33 mg per 100 ml, and hæmoglobin 86% The urine contained many red blood cells and epithelial casts and an average of 12 g of albumin (Esbach's method) per litre in 24 hr

Treatment —The patient was treated with high protein salt free diet with restricted fluids, and both mersalyl and acetazolamide were tried with some effect

Readmission —Four months later she was readmitted with similar symptoms, her urine containing 15 g of albumin per litre on admission Other investigations showed plasma proteins 3 72 g per 100 ml (albumin 1 52 g per 100 ml, globulin 2 20 g per 100 ml), albumin globulin ratio 0 7, non protein nitrogen 27 mg per 100 ml Urine contained granular casts and some red blood cells

Treatment —To encourage absorption of peripheral œdema, 400 ml of double strength plasma was transfused, with only slight improvement The induction of malaria pyrexia was contra indicated owing to the presence of red blood cells in the urine Treatment with cortisone 300 mg initially, followed by 50 mg daily was started, but the patient developed pyrexia and bilateral pneumonic consolidation with effusion and pericarditis So the cortisone therapy was abandoned, and after prolonged antibiotic treatment she gradually improved During the high pyrexia the peripheral œdema subsided, but there was no coincident change in electrolyte or in serum protein levels The patient was discharged on a high protein diet

Readmission —The patient was readmitted on April 13 1956, with anasarca, which had been increasing for two weeks

On examination her blood pressure was 170/120 mm Hg and her heart rate showed a gallop rhythm at the apex There were slight exudates in the fundi The amount of albumin in the urine was 14 g per litre in 24 hr Other investigations showed serum proteins 3 94 g per 100 ml (albumin 1 45 g per 100 ml , globulin 2 49 g per 100 ml), albumin globulin ratio 0 7, non protein nitrogen 22 mg per 100 ml No casts were found in the urine

Treatment —Given 1000 ml of triple strength plasma the patient had a diuresis of only 90 oz in 24 hours It was then decided to transfuse human serum-albumin set up in 100 ml transfusion bottles containing 25 g of albumin per 100 ml 200 ml was transfused in $1^1/_2$ hours, and during the next 12 hours the patient passed 227 oz of urine containing about 12 g of albumin per litre Her condition was much improved serum proteins 3 01 g per 100 ml (albumin 1 23 g per 100 ml , globulin 1 78 g per 100 ml), albumin globulin ratio 0 7, non protein nitrogen 18 mg per 100 ml Since there was still slight residual peripheral œdema 100 ml more of the albumin was transfused in 20 minutes, followed by a diuresis of 132 oz in 24 hours, when no œdema could be discovered (blood pressure 150/100 mm Hg) There was no symptom of overloading the circulation , nor did the blood pressure rise Her serum proteins were 6 12 g per 100 ml (albumin 2 29 g per 100 ml globulin 3 83 g per 100 ml), albumin globulin ratio 0 6, non protein nitrogen 28 mg per 100 ml , Hb 83% On April 24 the patient started a 250 g protein salt free diet and was given a further 200 ml of albumin intravenously in 45 minutes, the only side effect being a slight headache, and the diuresis being 101 oz in 24 hours Her serum proteins were 4 96 g per 100 ml (albumin 2 88 g per 100 ml , globulin 2 08 g per 100 ml), albumin globulin ratio 1 4, non protein nitrogen 23 mg Four days later, the total serum protein level had risen to 6 59 g per 100 ml though the albumin globulin ratio was still 0 9 Another transfusion of 100 ml of serum albumin in half an hour was given, producing a slight headache and a slight change in the serum protein level There was a further diuresis of 170 oz She was discharged without œdema and with a blood pressure of 130/90 mm Hg There was no change in the retinopathy

Follow-up —The patient returned a week later when œdema of her ankles had returned Her urine still contained about 12 g of albumin per litre and her blood pressure had risen to 150/110 mm Hg, but exudates were no longer present in her fundi Her serum protein level was 3 63 g per 100 ml (albumin 2 08 g per 100 ml , globulin 1 55 g per 100 ml), albumin globulin ratio 1 3, non protein nitrogen 26 mg per 100 ml Her urine contained epithelial debris and a few red blood cells

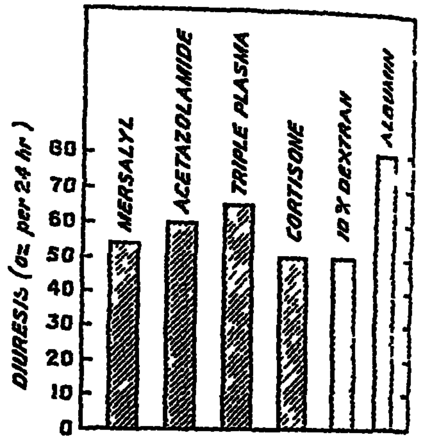
Readmission —A week later she was readmitted for further treatment , her blood pressure having risen to 170/120 mm Hg and œdema having appeared again Her serum proteins were 3 96 g per 100 ml (albumin 1 34 g per 100 ml , globulin 2 62 g per 100 ml) and albumin globulin ratio 0 5

Treatment —Double strength 10% salt free dextran was transfused but had to be discontinued because of severe headache and vomiting The diuresis was only 90 oz in 24 hours Later 300 ml of the serum albumin was transfused without causing headache , it did not give so dramatic a diuresis as previously (103 oz in 24 hours) but relieved the œdema The blood pressure on discharge was 130/90 mm Hg serum proteins 3 12 g per 100 ml (albumin 1 25 g per 100 ml globulin 1 87 g per 100 ml), albumin globulin ratio 0 7, and non protein nitrogen 33 mg per 100 ml

Follow up —The patient has since visited for examination and her blood pressure was found to have returned to 170/130 mm Hg and much of the œdema had returned The accompanying figure shows the relative diuretic values of the various diuretics used

Discussion

Characteristically, Ellis type II nephritis occurs in young patients without previous history of any severe streptococcal infection The onset is insidious, often with vague malaise followed by facial or ankle œdema, which although undergoing remissions and exacerbations gradually increases to anasarca Hypertension may or may not be present, and retinopathy, apart from macular œdema, is uncommon There is much albumin in the urine, often well over 20 g per litre in twenty four hours and the amount of urine excreted is small Casts are common in the urine However, there is no general renal insufficiency, the non-protein nitrogen, urea clearance and urea concentration being usually normal The blood shows a low total protein level with a reversal of the albumin globulin ratio and a raised blood cholesterol level



Diuretic values of diuretics used

The main feature of the present case was anasarca, but the mild hypertension and slight renal exudates are also of note because they are uncommon in Ellis type II nephritis *On each occasion that the human serum albumin was used there was a dramatic relief of œdema* because the corrected osmotic pressure of the plasma caused a diuresis unsurpassed by that due to standard diuretics , *also the blood-pressure was lowered*, and overloading symptoms were extremely mild This is interesting because other workers have found the use of human serum albumin to produce such symptoms as severe headache, gross venous engorgement, and a slight rise in blood-pressure But it appears that their patients were treated with human serum-albumin together with a diluent, usually dextran, whereas the present patient was treated with concentrated human serum albumin I feel that this is of significance because it is only necessary to replace lost protein (essentially the albumin fraction of the plasma), additional fluid causing only circulatory embarrassment The rapidity of transfusion had no untoward effect on the patient, probably owing to the small volume transfused at a time It was also extremely difficult to correct the reversal of the albumin globulin ratio, and the effect of the human serum albumin was transient, lasting only a few days

Summary

In a case of Ellis type II nephritis concentrated human salt poor serum albumin produced a much better diuresis than did plasma and dextran The blood pressure was lower after this treatment on each occasion

Concentrated human serum albumin has only a transient effect , for this reason it is of no use in maintenance therapy

I wish to thank Dr C M Miller for permission to publish, Dr L Horwich for much helpful advice, and the [illegible] officer at the U S A A F base at Sealand for the gracious gift of 1200 ml of serum albumin

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Preliminary Communication

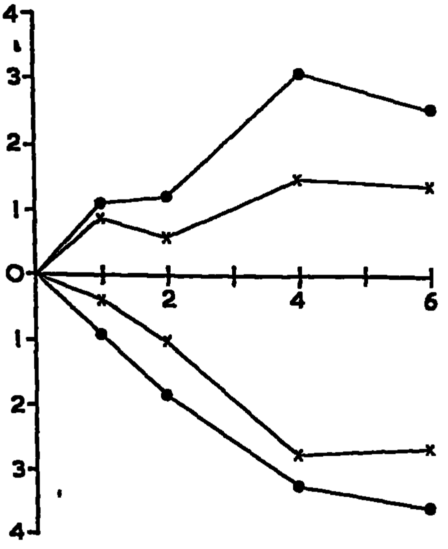
THE EFFECT OF QUINIDINE ON POTASSIUM FLUX

QUINIDINE has been known since the work of Frey in 1918 as a substance which arrests atrial (auricular) fibrillation Recently fibrillation has been produced in the atria of the rabbit heart suspended in a bath To produce fibrillation three things were necessary (*a*) acetylcholine in concentrations from 3 to 8×10^{-4} g per ml , (*b*) electrical stimulation at a rate from 600 to 800 per minute , and (*c*) a reduction of the K^+ in the bath to 1 4 mM per litre When fibrillation was produced, it persisted after the stimulation was stopped [1]

Holland [2] has measured the net amount of K^+ leaving the atria He changed the bath fluid to one containing 0 35 mM per litre of K^+ and left the atria in it for five minutes He removed the fluid and measured the K^+ by a flame photometer He found that when stimulation was applied at increasing rates in the absence of acetylcholine the net K^+ loss rose very little In the presence of acetylcholine, however, an increasing rate of stimulation produced an increasing potassium loss, and when it reached a certain figure, fibrillation occurred

When the isolated atria are beating spontaneously, quinidine (10^{-5} g per ml) slowly reduces the rate and amplitude until the beats stop Armitage [3] has recently observed that when the amount of potassium in the solution bathing the atria was reduced, the contractions started again These observations suggested that quinidine affected the permeability of the cell membrane to potassium, perhaps diminishing the potassium flux

We have therefore carried out experiments to test this, and have used human red cells When blood is freshly drawn, the cells are rich in K^+ and poor in Na^+ Blood was therefore cooled to 0°C, and kept at this temperature for 3–5 days during which the cells lost K^+ and gained Na^+ The blood was then incubated at 37°C for several hours , at this temperature the metabolic processes which drive Na^+ out of the cell and which raise the concentration of K^+ within the cell were active To some of the blood quinidine was added (25–250 µg per ml), and the rate of rise of K^+ in the cells in blood containing quinidine was compared with the rate of rise in control blood Ten experiments were carried out in six heparin was added to the blood , in three the blood was defibrinated , and in one the cells were separated from plasma and suspended in Ringer's solution In each experiment it was observed that the presence of quinidine diminished the uptake of potassium A similar result was obtained in two experiments in which chloroquine was used The accompanying graph shows the mean results The observations also showed that sodium was driven out of the cells more slowly in the presence of quinidine



The abscissa is time in hours The ordinate for the two curves above is the mean increase in potassium (mM per 100 g hæmoglobin) of red cells incubated at 37°C. The black circles represent control figures the crosses represent figures in the presence of quinidine The ordinate for the two curves below is the mean decrease in sodium (mM per 100 g hæmoglobin) of red cells Black circles are control figures the crosses represent figures in the presence of quinidine

This finding makes it seem likely that the action of quinidine in arresting fibrillation is due to a reduction of the permeability of the cell membrane to potassium, and probably to sodium also

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Medical Societies

HEBERDEN SOCIETY

THE society met in London on Feb 22

Shoulder-hand Syndrome

Dr R P HICKEY showed a case of bilateral shoulder hand syndrome The involvement on the right side, which included the right elbow, followed a traumatic right hemiplegia, while the involvement of the left side followed herpes zoster of the cervical 5th–7th nerve distributions

Lupus Erythematosus

Dr A. BEARDWELL, Dr A G BECKETT, and Dr C FELDMAN each showed patients with probable disseminated lupus erythematosus associated, respectively, with lung changes and pneumothorax, with hepatitis and peripheral neuropathy, and with polyarthritis and leg ulceration

Polymyositis

Dr A T RICHARDSON described the diagnostic features of polymyositis based on his findings in twenty one patients The histological findings in the muscles in polymyositis included patchy muscle fibre degeneration and widespread cellular infiltration, and contrasted with the focal infiltration of rheumatoid arthritis or the widespread degeneration without much infiltration in the myopathies It could not be differentiated from the changes seen in dermatomyositis Clinically, too, there was no clear dividing line between polymyositis and dermatomyositis , indeed, one of his myositis cases showed a scaly erythema, another had calcinosis, and a third developed scleroderma like changes In three other cases where there was no suggestion of skin involvement, symptoms included dysphagia One case was notable for the extreme rapidity with which muscular contractures developed Seven of his cases had been previously diagnosed as "myopathy of late onset" Polymyositis was usually thought of as involving mainly proximal muscles , but he had found that the forearm muscles were usually involved as well, and were often a suitable site for testing electromyographically There was evidence of impairment of action potentials on voluntary contraction of affected muscles, but in addition the electromyogram showed rheobase changes of denervated muscle and also evidence of spontaneous lower motor neurone activity The combination of muscle wasting with both a muscle fibre and a lower motor neurone lesion was diagnostic of myositis, and it was interesting that, as testing was proceeding, most of the cases which had been referred to him as myopathy of adult life were proving to have a myositis

Serum-proteins

Dr J H JACOBS and Mr R L MARKHAM showed a two dimensional zone electrophoresis of serum proteins They had used albumin impregnated paper (to minimise absorption of the test proteins) and, after making a conventional separation at pH 8 6, transferred the albumin, α globulin, and β globulin fractions to another paper and ran the separation at pH 4 5 at right angles to the original direction On staining for polysaccharides they obtained clear and isolated spots representing the α_1 and α_2 glycoproteins, which could be estimated semi quantitatively These spots were sometimes oval and sloping, especially in rheumatoid arthritis, suggesting they were not single substances The estimate of α_2 glycoproteins in rheumatoid arthritis correlated quite well with the clinical condition of the patient as judged by the erythrocyte sedimentation rate, but the α_1 glycoproteins seemed to vary independently of both Somewhat similar changes had been found in various other diseases

Sheep-cell Agglutination Tests

Dr E V HESS had found that sheep cell agglutination tests for rheumatoid arthritis had given positive results in 48% of cases of lupus erythematosus, 33% of cases of polyarteritis nodosa, 26% of cases of scleroderma, and one out of five cases of myositis Using a modification of Ziff's euglobulin precipitation technique she had examined both precipitate and freeze dried supernatant for agglutinating activity In rheumatoid arthritis this activity usually remained in the precipitate, but in some positive cases of lupus the activity remained in the supernatant The distinction was not completely reliable but might be helpful where the diagnosis between rheumatoid arthritis and lupus was in doubt She had been impressed with the tendency for lupus patients to have a positive agglutination test if they had joint involvement It seemed likely, also, that this group gave biological false positive results on Wassermann testing somewhat more commonly than the cases of lupus in which the agglutination test was negative In rheumatoid arthritis the agglutinating factor was associated with the gamma globulins In a positive case of lupus, however, she had found that the activity lay in the β globulin zone

SOCIETY OF UNIVERSITY SURGEONS

THE 18th annual meeting of the Society of University Surgeons was held on Feb 7–9 at Columbus, Ohio, under the presidency of Dr HAROLD A ZINTEL Of the 40 papers 12 were concerned with anomalies and diseases of the heart or great vessels and 7 with acute or chronic disease of the pancreas

Congenital Dislocation of Hip

In order to decide whether the changes in the head of the femur and the acetabulum in congenital dislocation of the hip are due to the dislocation or the cause of it, W S SMITH (Columbus) dislocated one hip joint in each of 22 puppies In 6 of the animals the dislocation was reduced at once, but in 16 it was allowed to persist Examination after six months showed that normal development had continued in the 6 control animals, but in each of the 16 animals in which the dislocation had persisted the acetabulum was shallow and the changes in the head and neck of the femur resembled those in congenital dislocation of the hip These findings suggest that the bone and joint changes in congenital dislocation are due to the dislocation and raise the possibility of birth injury as the primary cause of the condition

Obstructive Jaundice in the Newborn

A McDONALD jun (Columbus), pointed out that 60% of cases of obstructive jaundice in the newborn are due to atresia of the bile ducts and 25% to intrahepatic disease especially hepatitis The difficulty in distinguishing between these two causes commonly leads to delay in operation for up to six months until hepatitis has been excluded He has found that early biopsy of the liver through a small incision under local or cyclopropane analgesia will safely provide an accurate diagnosis within one or two months of birth and thus permit early exploration of biliary atresia before the liver is irreversibly damaged.

Exstrophy of the Bladder

O SWENSON (Boston) said that it used to be thought that continence could not be achieved in children with exstrophy of the bladder, and the standard treatment was by transplantation of the ureters Following Sweet s lead Swenson has been repairing the bladder and urethral defects at an early age but has not initially attempted to provide an artificial sphincter Of 16 children treated by early closure within a few weeks of birth, 9 have achieved continence He believes that early closure is better than early transplantation of the ureters followed by delayed closure of the bladder

Splenectomy

B K WISEMAN (Columbus) reviewed the use of splenectomy during the past twenty five years in the treatment of blood dyscrasias in 822 patients, in 745 of whom splenectomy was done with a 4% mortality Accessory spleens were present in 28% No evidence was found of the high incidence of infection which many believe accompanies the surgical treatment of hypersplenism, infection occurred in only 1% of his cases About a quarter of the cases of acquired hæmolytic anæmia did not respond either to operation or to steroids alone or in combination Only a quarter of the patients with thrombocytopenic purpura responded to steroids alone as a primary treatment, but nearly all responded well to the combination of operation and steroid therapy Congenital hæmolytic anæmia responded well to operation unless an accessory spleen was present There were twice as many complications when steroids were used

Operations on the Aorta

R N WATMAN (Columbus) had observed oliguria and sometimes anuria after resection of aortic aneurysms which was associated with a reduction in renal plasma flow of 0–60% In dogs it was found that reduction in renal plasma flow to 0–6 ml per minute from the normal of about 12 ml per minute followed clamping of the aorta, but not when the aorta was dissected out without being clamped After resection of a segment of aorta and replacement by a vena cava graft and release of the clamps the renal plasma flow rose to normal and it remained normal after three months even although the vein graft had now become an aneurysm Slow clamping and slow release of the aorta alone did not reduce renal plasma flow, and bilateral splanchnicectomy protected the animal from the renal effects of rapid release after clamping the aorta By operating under high spinal analgesia they have avoided changes in renal plasma flow in 2 further patients subjected to aortic resection

In one year S R POWERS (Albany, N Y) encountered 4 deaths after resection of aortic aneurysms, which were due largely to distal tubular necrosis By inserting a T shaped cannula into the left renal vein through a lumbar incision it was possible to divert the whole of the renal venous blood to a collecting vessel, urine also was collected, and aortic pressure was recorded When the aorta was clamped, although the renal arterial pressure was maintained the renal blood flow was much reduced and the response to a water load was poor Trimetaphan ('Arfonad') reduced both systemic blood pressure and renal blood flow, but clamping the aorta did not now further reduce renal blood flow, which began to return to normal as the effect of the trimetaphan passed off He concluded that a nervous mechanism is concerned in the reduction of renal blood flow which follows clamping of the aorta and hopes to avoid this by the use of trimetaphan Powers also recommended, however, that in the patient who is fully under the influence of trimetaphan, distal aortic blood flow should be slowly restarted the aortic clamp being replaced by manual compression which is slowly relaxed over a period of about four minutes

Paradoxical hypertension may be a serious and even fatal complication after resection of coarcted aorta In 31 patients W C SEALY (Durham N C) observed an immediate response during the first thirty six hours after operation in 7 but subsequent progress was satisfactory In 14 patients the onset of the response was delayed for more than thirty six hours and it lasted for seven to ten days in patients aged 4–32 years In 6 of these there was severe generalised cramping abdominal pain with vomiting anorexia and gaseous distension In 2 patients the symptoms were so severe that the abdomen was explored and patchy necrosis of the small intestine was found in 1 case the terminal ileum was resected and on histological examination he found thrombosis of the arteries of the intestine and also in the rectus muscle Reduction of the blood pressure by hydrallazine ('Apresoline') relieved the abdominal pain In the delayed type of disturbance the changes are localised to the regions supplied by the aorta distal to the obstruction

F Lewis (St Paul, Minn) had found abdominal pain in 18 out of 80 patients after resection of coarcted aorta, and in 5 it was severe enough to lead to abdominal exploration—1 patient survived extensive gangrene of the small intestine He thought the pain was worst in those who had had the greatest and most sustained fall in blood pressure after operation and wondered whether the changes in the small vessels were similar to those of periarteritis nodosa Sealy thought they were more like those of experimental renal hypertension, he had observed that the onset of symptoms was related to diastolic hypertension

Oxygenators

The difficulties besetting those who are trying to devise satisfactory apparatus for maintaining blood flow when the heart has been shunted were discussed in several papers

C M Maloney (Los Angeles, Calif) had found experimentally that a high rate of blood flow was followed by a large mortality which appeared to be related to the rate of flow through the bubble oxygenator, this mortality could be reduced by using two oxygenators, each with a slow rate of flow, thus allowing the high rate of inflow to the animal to be maintained Although no serious changes were observed in the recipient dog's blood chemistry the mortality rate remained high

C Dennis (Brooklyn, N Y), who had abandoned the bubble oxygenator because of the risk of air embolism, had found that when air is injected into the carotid artery the heart will survive a degree of air embolism which the brain cannot tolerate, such dogs look fine for ten to fourteen hours and then become comatose and die Moreover survival does not exclude the occurrence of air embolism.

G Clowes (Cleveland, Ohio), who uses a membrane-oxygenator, thinks that fibrin, not air, emboli are the probable cause of death, and that these are avoided by his type of apparatus

C W Lillehei (Minneapolis, Minn) has, however, treated 317 patients using a bubble type of oxygenator and thinks that the fundamental problem in cardiac surgery is not the type of oxygenator and by-pass which is used but the methods of dealing with the anatomical lesion The mortality in dogs is high regardless of the type of apparatus used One of the commonest reasons for this may be the priming of the oxygenator with blood from an anæsthetised dog, which may double the dose of anæsthetic to the recipient dog If the adaptors are not streamlined and polished the resulting turbulence may cause fibrin emboli In the helix type of debubbling apparatus which he uses turbulence is avoided Another important factor is the rate of flow, oxygen consumption rises as the flow rate is increased, and the optimum rate appears to be 50–55 ml per kg per minute in patients aged 2–15 years, but these values should be reduced by 20% in adults and increased by 20% in cyanotic disease

Septal Defects

C W Lillehei described his technique of closing ventricular septal defects with an 'Ivalon' plaque and mentioned the value of lung biopsy as a means of assessing the risk of operation in the presence of high pulmonary arterial pressure The number of vessels with intimal hypertrophy in a piece of lung removed through a small intercostal incision gives an indication of the secondary effects of the pulmonary hypertension, such changes may regress after treatment Of 14 patients with only minor vascular disturbance none died after operation, but there were 11 deaths in 14 patients with severe changes These patients died of either cardiac or respiratory failure, and he emphasised that, whereas before operation the left ventricle plays a large part in the maintenance of the circulation through the partially obliterated pulmonary vessels, after operation this depends on the right ventricle alone which in addition now has a long sutured wound in its wall

Only 25 cases of aortico pulmonary septal defect have been described, but D A Cooley (Houston, Texas) encountered his 3 cases in six weeks during 1956 Diagnosis is very difficult because of variation in the clinical signs A catheter may pass into the innominate artery or medium may be seen passing out of the aorta, especially in a retrograde aortogram, a lateral radiograph may then assist in distinguishing this defect from a persistent truncus arteriosus Only 8 patients have ever been operated on and 5 have survived, the first was operated on by Gross in 1948 This anomaly is a wide defect between two vessels and is not a duct, it should therefore be dissected clear and each opening closed by sutures If it is diagnosed before operation hypothermia should be employed, but if it is first discovered only at operation and hypothermia is not being used it is probably wise to stop the operation and reopen the chest later under hypothermia

Coronary Circulation

It has been thought that when the coronary circulation is arrested survival of cardiac muscle is short because of its continuing metabolic demands When the heart is excluded from the circulation for thirty minutes the capillaries become plugged with small clots which stop the blood flow when this is restarted, recovery can be obtained when the coronary blood is first heparinised By removing all the blood from the coronary vessels E F Webb and J D Howard (Jackson, Miss) were able to occlude the coronary circulation experimentally for ninety minutes with resumption of normal function and a resting work-load The dogs did not survive because normal respiration could not be re established.

W H Spencer (Philadelphia, Pa) described a method of perfusing the coronary arteries in order to extend the range of tolerance of hypothermia After clamping the aorta proximal to the arch, blood is injected into the root of the aorta and so perfuses the coronary circulation The heart is subsequently able to maintain a normal range of blood pressure without a latent period of hypotension such as occurs without coronary perfusion

Hypothermia and the Adrenals

The effect of hypothermia on the three phases of adrenal steroid function—secretion, conjugation, and excretion—have been studied by H E Swan (Denver, Colorado) In the uncooled subject there is an early rise in the free blood-corticoid substances followed by a later and smaller rise in the conjugates The urinary content of conjugates rises early during operation, continues to rise after operation, and falls during the next twenty four hours During cooling, which stimulates the adrenal cortex, free corticoids rise in the blood, but once cooling has been achieved no further rise occurs until the patient is warmed when the level of free corticoids rises to that found in uncooled patients The blood-level of conjugates rises slowly during cooling, changes little in the cooled state, and does not rise as the free corticoids do after rewarming The urinary output of corticoid material is delayed and does not rise significantly until after rewarming, renal clearance of creatinine also is depressed during the cooled state Thus in hypothermia not only is the output of free corticoid reduced but conjugation and excretion also are depressed, and the two later phases remain subnormal for some time after rewarming, but all three functions gradually return to normal in the course of a day or so

J D Hardy (Jackson, Miss) has found that some conjugation of adrenal steroids occurs in the hepatectomised dog, and that some other organ is concerned in this aspect of corticoid metabolism but possibly accounts for only a small part of the normal conjugation

Pancreatic Carcinoma

In carcinoma of the pancreas external irradiation is of limited value When 10 μC ^{198}Au was injected experimentally into the head of the pancreas (R J Ireton, Columbus) most of the gold remained in the region of the injection site, but some was found in adjacent lymph nodes, little was excreted, no effects were observed on other organs, and there was no pancreatitis This isotope may therefore be of value in the treatment of carcinoma of the pancreas in man

Pancreatitis

Although 50–75% of patients with pancreatitis have also disease of the biliary tract it is believed that bile does not enter the pancreatic duct system, because of the high secretory pressure in the pancreas D W Elliot (Columbus) cannulated the pancreatic duct and produced localised hæmorrhagic pancreatitis by the injection of 10 ml of bile after forty eight hours of obstruction of the duct Accidental obstruction of the main pancreatic duct showed that despite extensive pancreatic obstruction only the area affected by the bile injection became hæmorrhagic The acute hæmorrhagic process is more rapidly induced, and the animals are more ill when the gall bladder is first filled with pancreatic juice before bile is withdrawn for injection into the pancreas

CENTRAL SURGICAL ASSOCIATION

THE 11th annual meeting of the Central Surgical Association was held on Feb 21–23 at Chicago, Illinois, under the presidency of Dr **ROBERT M ZOLLINGER** (Columbus, Ohio) The 46 papers presented at the meeting will be published in the *Archives of Surgery*

Analysis of Lung Tissue

Spectrographic analysis of lung tissue resected from patients with industrial lung disease has shown the presence of manganese, silicon, thorium, iron, zinc, and silver (in a patient who had used nasal drops for a prolonged period) **R JENSIK** (University of Illinois) in reporting these observations suggested that this method of analysis might be profitably applied to lung tissue which showed no evidence of malignant disease or infection

Colostomy

In order to avoid the fluid losses which follow the establishment of a double barrelled colostomy after resection of an irreducible ileocæcal intussusception, **J A ROONEY** (Loyola University) has devised a T shaped anastomosis About 2 inches of the end of the ileum is denuded of mesentery and is pushed into the lumen of the transverse colon The proximal stump of colon is then brought out as a single barrelled colostomy through a separate incision This allows the small intestine to drain freely into the colon, but there is little loss of intestinal contents from the colostomy

Pancreatitis

Recurrent pancreatitis often improves if any associated disease of the biliary system is relieved **C PUESTOW** (University of Illinois) believes that progression or recurrence of the pancreatitis is related to constriction of the proximal part of the main pancreatic duct When only the tail of the gland is involved local resection is often satisfactory Pancreatitis confined to the head of the gland can be treated by excision with anastomosis of the distal part of the gland to the jejunum, but this carries a fairly high mortality rate He therefore recommends cutting slices off the tail of the gland until the main duct is seen to be dilated, the duct is then slit to open it more widely and the proximal stump of the gland is inserted into the side of a Roux Y limb of jejunum for 2 inches and the wall of jejunum is sewn to the serosa of the pancreas This type of procedure has been employed in 15 patients, 13 of whom subsequently gained weight, were relieved of pain, and passed normal stools Since all these patients had constrictions of the proximal part of the main pancreatic duct of up to 6 cm in length no benefit would have followed division of the sphincter of Oddi, and prolonged drainage or anastomosis of the common bile duct would probably have been of little value

Lumbar Sympathectomy

In order to determine directly at operation the area affected by lumbar sympathectomy **W C RANDALL** (Loyola University) applied wide bands of starch paper to the lower limbs after these had been painted with iodine A very wide variation in anatomical arrangement of the lumbar sympathetic chain was found, preganglionic fibres entering at any level from L1 to L5 Since there is no way of predicting the effects of sympathectomy apart from the sweating test, either this should be done routinely on the operating table or the conventional excision of L2–3 should be extended to L1–5 No evidence of sweating in the opposite limb was found, so it seems unlikely that fibres cross the midline

Carcinoma of Breast

The surgical treatment of 230 patients with carcinoma of the breast between 1946 and 1951 was reviewed by **S P** [illegible] (University of Chicago) Radical mastectomy was employed in 90% of cases with 2 postoperative deaths, 56% survived for five years, but not all without further evidence of the disease These patients did not represent a true sample of the population of the country as a whole

Aganglionic Megacolon

Intestinal obstruction unrelieved by conservative treatment affects only a minority of infants with aganglionic megacolon but in these the mortality rate varies from 25% to 60% **W K SIEBER** (Pittsburgh, Penn) reported 30 such cases in infants under 6 months of age only 6 were females Of 16 less than a month old 7 died, 2 survived without colostomy, and in the remainder colostomy led to rapid improvement Of the 12 older patients, 3 died, and in 2 survival followed colostomy, 3 died of peritonitis, which in 2 cases was due to perforation of the bowel following enemas, 4 died after prolonged ineffectual "medical management," 2 of pseudomembranous colitis, and 1 after colostomy had failed to relieve obstruction when the entire colon was affected by the aganglionic lesion. It is dangerous to delay colostomy proximal to the affected segment, which results in prompt recovery except in the presence of pseudomembranous colitis or severe disturbance of body fluid equilibrium

Arterial Grafting

H B SHUMACKER (Indianapolis, Ind) reviewed the fate of 80 plastic grafts applied to large vessels In only 1 instance was failure due to the graft Nylon filter fabric seems to be suitable for replacement of the distal part of the aortic arch and thoracic and abdominal aorta and the bifurcation, braided nylon grafts do well between the aorta and the iliac and femoral arteries

D E SZILAGYI (Detroit, Mich) examined by serial angiograms and histologically the results of 200 arterial homografts Various grades and types of degenerative change were found in about 20% of the grafts, but there was no evidence of thrombosis attributable to defects of the graft itself Rupture of the graft, with the formation of an aneurysm may be commoner than has been suspected Though there seem to be grounds for preferring plastic grafts to homografts he believes that the life of plastic materials is limited

Portal System and Liver

Percutaneous splenoportography was discussed by **M S DE WEESE** (Ann Arbor, Mich) The procedure was attempted 134 times in 120 patients, with 85% successes 30 ml of 70% 'Urecon' was injected in four seconds, the first film being taken half way through the injection A good shadow of the portal venous system appeared after twenty seconds The procedure was complicated by bleeding in 6 patients, pneumothorax in 3, and subcapsular extravasation of blood in 3 In 9 cases the needle did not enter the spleen Collateral vessels may be shown in portal hypertension and cirrhosis, but not in normal patients Useful information of the state of the portal vein may be obtained A filling defect in the liver was seen in 5 cases of primary hepatic neoplasm, and neoplasms of the body (but not the head) of the pancreas may be shown by venous filling defects This method of investigation should not be used if laparotomy is indicated anyway

W A ALTEMEIER (Cincinnati, Ohio) described 3 examples of cholangioma, a rare type of carcinoma of the intrahepatic bile ducts It progresses slowly over years, sometimes in young subjects, resembling an inflammatory rather than a malignant neoplastic process, ultimately it causes stenosis of the bile ducts, progressive jaundice, and impaired liver function Histological examination usually leads to a diagnosis of sclerosing cholangitis 2 of his patients were repeatedly subjected to operation during several years Though the ultimate prognosis is bad, survival is usually much longer than with other carcinomas of the bile ducts

Lung Function

W E ADAMS (Chicago, Ill) and his group compared the response to exercise of dogs whose lung volumes had been acutely reduced by 75–85% with others in which a similar reduction had been made six or seven years earlier In the first group, the average resting pulmonary arterial pressure was 90% above normal, but in the second group the pressure was only 20% above normal Exercise caused only a [illegible] further increase in pressure in the first group, but an [illegible] increase in the second In both groups of animals the oxygen saturation and systemic blood pressure differed only slightly from normal Although some compensation occurs as more time elapses after pneumonectomy the capacity for response to exercise remains poor clearly the less lung removed the better and lobectomy should be preferred to pneumonectomy

Postoperative Nitrogen Balance

J C PEDEN (St Louis, Mo) described the anabolic effect of 17 α ethyl 17 hydroxy androsterone ('Nilevar') in women after hysterectomy and similar operations They were given 75 g protein and 900 calories daily, by intravenous infusion for four days and by mouth for three days On this inadequate intake the controls remained in negative nitrogen balance throughout the fourteen postoperative days for which they were observed, whereas the patients given the [illegible] remained in positive nitrogen balance, even during the second week when the steroid was not given

Parotid Tumours

O H Beahrs (Rochester, Minn) reviewed all the cases of mixed tumour of the parotid gland seen at the Mayo Clinic between 1907 and 1954, and concluded that any tumour which, after a long period of slow growth, begins to grow more rapidly should be suspected of having become malignant, especially if there is also facial palsy If necessary the diagnosis should be confirmed by biopsy When the facial nerve is already damaged or has to be sacrificed at operation an immediate nerve-graft using the auriculotemporal nerve should be used E S Judd remarked that it might be ten to sixteen months before any restoration of function was evident, but that ultimately the functional result was quite good.

The Œsophagus

F S Cross (Cleveland, Ohio) described the use of cinefluorography in the study of neuromuscular abnormalities in the œsophagus In combination with study of the intraluminar pressure it has been found that such neuromuscular disturbances as segmentation and cardiospasm are not separate entities but degrees of a similar kind of disturbance, and are often seen together Their relation to the formation of diverticula and hiatus hernia was shown in a film

In acquired short œsophagus D B Effler (Cleveland, Ohio) moves the cardio œsophageal junction forwards through an incision dividing the crus and the adjacent portion of the diaphragm, then closes the diaphragm behind the œsophagus so that the cardio œsophageal junction lies below the diaphragm, finally the phrenic nerve is crushed

E R Maurer (Cincinnati, Ohio) pointed out that the size of a hiatus hernia was often not related to the severity of the disturbance it caused, or the complications which are associated with it H C Fisher (Denver, Col) believes that the treatment of œsophagitis is more important than the cure of a hiatus hernia Œsophagitis may respond to a holiday or require gastric resection, but he recommended gastrojejunostomy and vagotomy W E Adams (Chicago, Ill) pointed out that simply crushing the phrenic nerve may give lasting relief to elderly or debilitated patients with hiatus hernia He suggested that in obstructed lesions the œsophagus should be drained above the obstruction by lateral gastro-œsophageal anastomosis, and the stomach below the diaphragm by gastrojejunostomy J K Berman (Indianapolis, Ind) reminded the meeting that good access to the hiatus could be obtained by dividing the left coronary ligament, and that only an abdominal approach to the hiatus allowed an adequate examination of the stomach, duodenum, pancreas, and gall bladder, in which he has found associated lesions in 17% of his cases

R A Mustard (Toronto, Ont) reviewed 381 cases of primary carcinoma of the hypopharynx and œsophagus treated in the Toronto General Hospital in 1937–53 The results of high-voltage irradiation were not good Surgical excision led to a longer survival, but the operative mortality rate was 36% With ^{60}Co, swallowing is often much improved and symptomatic relief is achieved more certainly and readily than with high voltage irradiation or operation The ultimate outlook seems no better He suggested that radical surgery should be reserved for patients in good physical condition with early localised lesions and the remainder treated with ^{60}Co

Reviews of Books

Official History of the Canadian Medical Services, 1939–1945

Vol I *Organization and Campaigns* Edited by W R Feasby, B A, M D, lieutenant colonel, R C A M C, supplementary reserve Ottawa Edmond Cloutier 1956 Pp 566 $5

THIS beautifully produced book appears some months after the second volume, which dealt with clinical and professional aspects (see *Lancet*, 1955, ii, 1373) This one describes the organisation, development, and campaigns of the medical and dental services From a corps consisting in 1939 of 40 medical officers and of other ranks in proportion, the medical services of the three Armed Forces grew into sister-organisations containing 5219 medical officers, 4172 nursing sisters, and 40,112 other ranks and ratings, and more than 2 million casualties passed through their hands The record is as factual as painstaking research could make it, and, like most official histories, it is based mainly on reports submitted by smaller field units to headquarters In such reports events tend to fall into a more orderly and deliberate pattern than they had in reality but even those with no personal memories to revive will find this an exciting record, and to the professional historian and medical administrator—both military and civilian—it will prove an invaluable source of reference and a fund of useful information

Enzyme, Antigen and Virus

A Study of Macromolecular Pattern in Action F Macfarlane Burnet, KT, F R S F R C P, director, Walter and Eliza Hall Institute of Medical Research, Melbourne London Cambridge University Press 1956 Pp 193 18s

IN this fascinating monograph, Sir Macfarlane Burnet has taken three biological phenomena—the formation of adaptive enzymes, the production of specific antibodies, and the multiplication of influenza viruses—and has discussed their basic similarities In each case there is growing evidence that ribonucleic acids are intimately connected with directing the synthesis of new protein and the evidence with regard to tobacco-mosaic virus (which has been published since this monograph was written) is even more direct Burnet's theme, which is most clearly stated in the concluding chapter, is that physico-chemical concepts cannot be expected to have much value in explaining how such highly complex macromolecules are synthesised and that the methods by which the cell transfers information about protein synthesis are best understood in terms of communications theory The nucleic acid is thought of as analogous to the coded instructions which are fed to a computing machine, and Burnet has grave doubts whether orthodox chemical methods will be capable of decoding the instructions

The author has never been deterred from putting forward a hypothesis by the thought that it might be wide of the mark, and the success of his policy has been amply justified by his brilliant prediction of the recent work of Medawar and his colleagues on immunological paralysis If this monograph has the effect of stimulating people to new experiments it will have satisfied its author's purpose Certainly biologists in many fields, and physicists and chemists with an interest in biology, will find this monograph highly provocative

The Care of the Expectant Mother

Josephine Barnes, M A, D M, M R C P, F R C S, F R C O G, assistant obstetrician and gynæcologist, Charing Cross Hospital and Elizabeth Garrett Anderson Hospital London Pitman Medical Publishing Co 1956 Pp 270 30s

THIS book has been written primarily for those whose principal contribution to the maternity services is the conduct of antenatal care

In the first section a brief description of anatomy and physiology is followed by chapters on clinical examination, special investigations, advice to the mother, and preparation for childbirth The last chapter in this section gives very useful information about the maternity services in Britain In the second section the author deals with complications of pregnancy, and in the third describes the general diseases which may complicate pregnancy

Rather more dogmatic teaching would have been of advantage in a book of this scope In particular, more detailed advice might have been given about the types of case which should be referred for hospital confinement or for specialist opinion This work does not pretend to be a textbook of obstetrics, but it will meet a definite need for a short readable guide to those who look after women during the antenatal period

Changes in Body-water Compartments during Growth

BENT FRIIS HANSEN, clinical assistant in the Department of Pediatrics, Rigshospitalet Copenhagen Copenhagen Munksgaard 1956 Pp 68 Cr 25

THIS monograph, which is also available as supplement 110 of *Acta Pædiatrica*, gives the results of the author's observations on 93 infants and children

By supplementing his own results with others that have been reported, he has built up a very complete account of what is known of total body water, and of extracellular and intracellular fluid, throughout fœtal life, infancy, and childhood While intracellular fluid, as a percentage of body weight, stays almost constant, there is a striking fall in extracellular fluid, and it is this change which is mainly responsible for the decline in the proportion of body weight accounted for by body fluid Although these conclusions are familiar to many, it is convenient to have the evidence for them collected in one publication, and this should prove a useful work of reference The text is in English, with summaries in English and Danish

Religious Factors in Mental Illness

WAYNE E OATES London Allen & Unwin 1955 Pp 239 16s

CHAPLAINS to mental hospitals have a difficult task for which as a rule they have had little or no special preparation In this little work the problems they will encounter are described and illustrated from hospital practice, of which the author has had considerable experience both as chaplain and as teacher of pastoral counselling to missionary and other students He gives advice which will enable psychiatrist and clergyman to work helpfully together

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New Inventions

AN ADJUSTABLE GUIDE-DIRECTOR FOR TRIFIN NAIL INSERTION

THE insertion of cannulated nails and nail-plate appliances has become standard surgical practice in treatment of fractures about the femoral neck Whilst it is true that experienced surgeons sometimes dispense with mechanical aids in these operations, for the majority one or other of the many guide-wire directors is often helpful

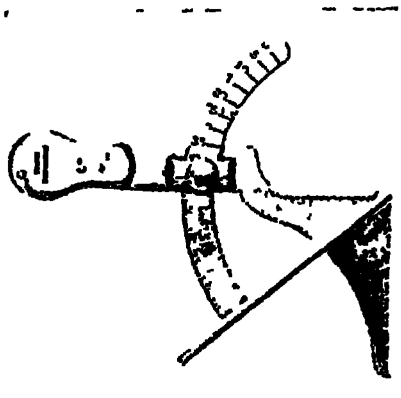

Fig 1—Adjustable guide-wire director, which is sterilised

For Smith-Petersen nail insertion, the technique requires estimation of an angle which will take the guide-wire into position in the head from a selected point on the femoral cortex Insertion of a fixed-angle nail-plate, on the other hand, entails finding a suitable point of entry on the cortex for a nail whose angle of insertion is predetermined in manufacture (130–135°) Where a long low nail technique is favoured for sub-capital fractures, a line from the centre of the head passing just above the calcar femorale determines both the point of entry in the cortex for the nail and its angle of insertion To be of practical value, a guide-wire director should provide this information simply and quickly

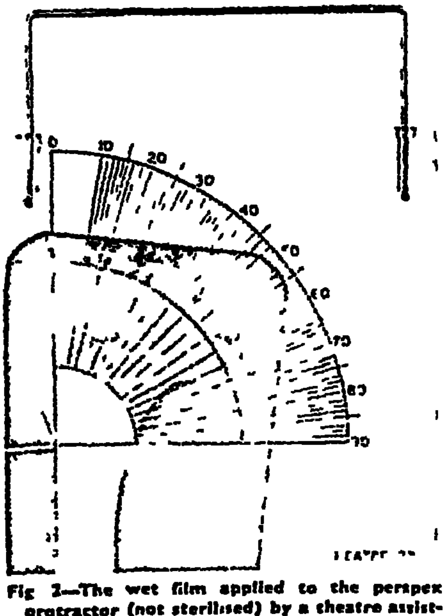

Fig 2—The wet film applied to the perspex protractor (not sterilised) by a theatre assistant slid into proper register and held up to the operator for selection of angle

A protractor type of director, which has proved reliable and simple in use, has come to be adopted in nailing technique in our unit during the past four years

The director is designed on a principle similar to that described by King in 1939 [1] and aims to provide accurate placing of the nail in the anteroposterior radiographic projection, leaving the position in the lateral projection to be estimated by the surgeon Two pieces of equipment are required as illustrated—a metal adjustable guide-wire director (fig 1) and a 'Perspex' sheet protractor The desired angle of nail-insertion from a fixed point on the femur, or the suitable point of entry for a fixed angle nail-plate is determined, after manipulative reduction of the fracture and exposure of the femur, by taking an anteroposterior radiograph with a marker held against the femoral cortex This wet film is applied to the perspex sheet and, by sliding it into register with the protractor (fig 2), the particular angle and point of entry can be chosen and then transferred to the femur by the suitably adjusted guide-wire director As shown in the illustrations, a bradawl marks the selected entry point for ordinary Smith-Petersen nailing For nail-plate and long low nail insertion, the director itself is held against the femur as the marker, and the particular notch on its straight edge is chosen which will carry the appliance into correct position in the femoral head and neck The femoral cortex is drilled at the point of entry in the usual way, the director set to the selected angle, and the guide wire passed with the director held firmly in position against the femur (fig 3) The same technique has also been used for convenient selection of site and direction of cut in performing McMurray osteotomy

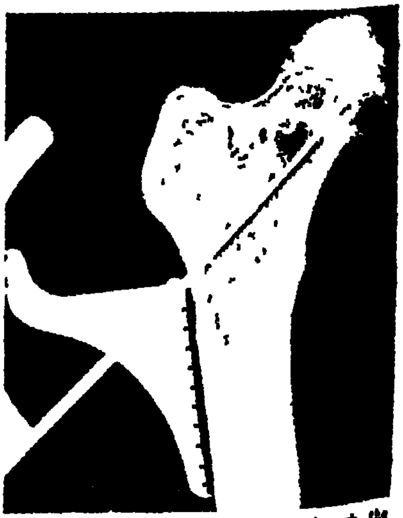

Fig 3—A guide-wire inserted through the director which has been set to the angle indicated and held firmly against the femur

Acknowledgment is due to Mr A MacDonald for making the original prototype and to Mr G Donald for the photographs The present instrument has been made for me by Messrs Down Bros and Mayer & Phelps London

Western Infirmary
Glasgow

J T BROWN
M B Glasg F R C S

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[1] King T *Brit J Surg* 1939 26 721

THE LANCET

LONDON SATURDAY, MARCH 16, 1957

Lung Cancer in Women

LUNG cancer is increasing among women, but the tenfold rise in the past forty years has been overshadowed by the far more dramatic change in men. In England and Wales for the years 1911–15 the age-specific death-rate for women was 9 per million living, and by 1951–53 it had risen to 96; in the same time the rate for men had increased from 15 to 569.[1] The changes are most profitably visualised in cohort analyses of the mortality-rates, and CASE[2] has lately emphasised the great value of this method of analysis as a narrative or historical technique. It allows the changing pattern of the recorded mortality to be seen in temporal relation to the changing structure and environment of the population; and knowledge derived from social and medical history can be used to interpret it. Cohort analysis follows the development of some attribute, in this case the rate of dying from lung cancer, in a group of people born within a defined period. Thus, for lung cancer, the age-specific death-rates of women in England and Wales born around the year 1871 was 0.026 per thousand living when the group had reached the age of 50 to 54; but the cohort born around 1901 were subject at the same age to a rate five times as great (0.135). For men, the comparable rates were 0.066 and 1.231—almost a twenty-fold increase. CASE[3] analysed the death-rates for cancer at 21 sites during the period 1911–54 in England and Wales. He found that the male death-rates at ages over 60 were always higher than the female for the sites common to both, and in all but 5 sites the male rate was higher at all ages studied. The death-rate from cancer at all sites in both sexes has fallen between 1911 and 1954; on the other hand, the rate for all sites in men is rising; but, if lung cancer is excluded, the trend, as in women, is downwards, and the mortality-rates for all sites except lung at the age of 50–54 in persons born around 1901 are, for men, 70%, and, for women, 80% of the rates that affected those born thirty years earlier. In women, as in men, the mortality-rates for lung cancer show a steady rise with each succeeding cohort.

The histological pattern of the disease differs in the two sexes. In necropsy material the adenocarcinomas have been reported to be divided almost equally between men and women, with in some cases a slight predominance of men.[4–7] In material obtained by biopsy the reported ratio of men to women has in general been higher, up to 3.3 to 1 and 4.4 to 1 in this country.[8 9] Adenocarcinomas undoubtedly form a higher proportion of all lung tumours in women than in men.[6–12] Because of the varying criteria of classification, it is hard to estimate changes in the pattern of histological types throughout the period of the disease's increase. There is no convincing proof that adenocarcinomas have not increased at all; but there is suggestive evidence that the increase has been least in this type of tumour.[13] For this and other reasons, many people believe that there are two types of lung cancer, exogenous and endogenous in origin. The adenocarcinomas, bronchiolar-cell carcinomas, adenomas, and salivary-gland tumours form the endogenous tumours, which have an equal sex incidence and no connection with known external irritants.[14]

In both men and women, the close connection between tobacco-smoking and lung cancer has been conclusively demonstrated. DOLL and BRADFORD HILL,[8] for instance, found that 37% of 108 women with lung cancer were non-smokers, compared with 55% of their paired controls; 11% of those with lung cancer had been smoking 25 cigarettes or more a day, compared with only 0.9% of the controls. The relationship of smoking to the development of particular histological types of lung cancer has also been investigated.[8 14–17] From a study of 300 patients in Norway, KREYBERG[14] concluded that tobacco-smoking was not an important cause in the development of the adenocarcinoma group of tumours in either men or women. In the U.S.A., WYNDER and his colleagues[17] studied the smoking habits of 105 women with lung cancer and compared them with those of 1304 women with cancer or benign tumours at other sites. Of the 41 with adenocarcinomas 29 were non-smokers; the number expected on the assumption that the smoking habit of these 41 women was the same as that of the patients without lung cancer was 32. On the other hand, only 16 of 41 women with squamous carcinomas were non-smokers, compared with the expected number of 30; and there were 5 non-smokers among the 14 with anaplastic carcinomas, the expected number being 10. A high proportion of adenocarcinomas would be expected in women if this type were not caused by smoking, for fewer women smoke and fewer of those who do smoke heavily. A social survey in this country in 1951 showed that 53% of women did not smoke and only 6% smoked 15 or more a day.[8] In the U.S.A., WYNDER et al. found that about half the women under 50 and most of those over 50 in their control group were non-smokers and that less than 2% of the women over 50 smoked as much as a packet a day. The differences in the mortality-rates for lung cancer in men and women have been used in the past to try to refute the unwelcome conclusion that smoking causes lung cancer. In fact, the pattern of the disease and the smoking habits of women add further support to an already overwhelming case. From an investigation of lung cancer in non-smokers,

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[1] Case, R. A. M., Pearson, J. T. Cancer Death Rates by Site, Age and Sex, England and Wales 1911–53. London Institute of Cancer Research Royal Marsden Hospital 1955. Unpublished tables.

[2] Case, R. A. M. *Brit. J. prev. soc. Med.* 1956, 10, 159.

[3] Case, R. A. M. *Ibid.* p. 172.

[4] Christiansen, T. *Brit. J. Cancer*, 1953, 7, 428.

[5] Jakobsen, A. *Ibid.* p. 423.

[6] Bryson, C. C., Spencer, H. *Quart. J. Med.* 1951, 20, 173.

[7] Galluzzi, S., Payne, P. M. *Brit. J. Cancer*, 1955, 9, 511.

[8] Doll, R., Bradford Hill, A. *Brit. med. J.* 1952, ii, 1271.

[9] Mason, G. A. *Lancet*, 1949, ii, 587.

[10] Harnett, W. L. Survey of Lung Cancer in London 1952. British Empire Cancer Campaign, 1952.

[11] Bignall, J. R., Moon, A. J. *Thorax*, 1955, 10, 183.

[12] Nicholson, W. F., Fox, M., Bryce, A. G. *Lancet*, Feb. 9, 1957, p. 296.

[13] Womack, N. A., Graham, E. A. *Amer. J. Path.* 1941, 17, 645.

[14] Kreyberg, L. *Brit. J. prev. soc. Med.* 1956, 10, 145.

[15] Wynder, E. L., Graham, E. A. *J. Amer. med. Ass.* 1950, 143, 329.

[16] Breslow, L., Hoaglin, L., Rasmussen, G., Abrams, H. K. *Amer. J. publ. Hlth*, 1954, 44, 171.

[17] Wynder, E. L., Bross, I. J., Cornfield, J., O'Donnell, W. E. *New Engl. J. Med.* 1956, 255, 1111.

DOLL[18] concluded that the proportion of men and women among them was consistent with the hypothesis that in the absence of smoking and exposure to industrial carcinogens the death-rates are equal in the sexes, and HAENSZEL et al,[19] in the U S A, found that the known difference in smoking habits could be expected to lead to an incidence among men approximately four times that in women—which is approximately the present sex-ratio in the mortality statistics of that country

There is some evidence that relatively fewer women than men with lung cancer are seen at hospitals The sex-ratio from death certificates in 1951–53 was 5 9 to 1, and from a necropsy series from eight hospitals in London during 1948–52 it was 4 7 to 1 [7] But the ratios in most series compiled from the records of attendance at or admission to hospitals have been higher In the group reported by DOLL and BRADFORD HILL [8] from several general and special hospitals in 1948–52, the ratio was as high as 13 to 1, and ratios of a similar order have been recorded in thoracic surgical centres, special hospitals, and radiotherapy departments [9 11 12 20 21] In a large series from hospitals in Birmingham [22] during the years 1936–52, the ratio was 7 to 1, and among those treated surgically it was 15 to 1 Differences between the sexes are also seen in the pattern of histological types The proportion of differentiated tumours in necropsy series seems to be much the same in the two sexes,[6 7] but among hospital admissions and attendances [8–10 12] and in surgically treated patients [11 20] not only have there been relatively fewer women but also relatively fewer with differentiated tumours Little has been reported about differences between the sexes in the evolution and modes of presentation of the disease The pattern of survival in untreated patients, however, has been said to be broadly similar in men and women [23], and it seems likely that proportionately fewer women have been operated on in the past In the series of 910 patients described by NICHOLSON and his colleagues [12] there were 70 women, and only 5 (7%) had a resection "with any hope of cure" A significantly better prognosis after operation has, however, been recorded in women BIGNALL and MOON [11] found two-year and five-year survival-rates of 65% and 57% among 41 women, compared with 46% and 31% among 412 men, more of the women had undifferentiated tumours, but fewer had enlarged mediastinal nodes

Lung cancer in women has in general received less attention than the disease in men It has been estimated [24] that the male death-rate in England and Wales may increase from its present level of 687 per million to 1350 per million before it stabilises, and the incidence of lung cancer in women will also increase It may rise more rapidly than it has done in the past, since the fashion of heavy cigarette-smoking evolved more recently in women than in men and its effects may only now be starting to influence the national death-rates from this partly preventable disease

Effects of Fœtal Anoxia

THE adjustment from intra-uterine to extra-uterine life is one of the most important and difficult changes in any individual's life Fortunately, for most of us it is a physiological process, but for too many it still carries a mortality and morbidity of its own While perinatal mortality remains challengingly high, it naturally receives more attention than perinatal morbidity, but it should not be forgotten that many infants who survive the perinatal period do so only with a severe handicap The recent work on perinatal mortality by BOUND and his colleagues [1] has shown that even when accurate clinical data are matched with careful pathological examinations, it is hard to correlate clinical cause with pathological effect This is not altogether surprising in view of the infinitely variable complications of late pregnancy and labour, the poor definition of many neonatal syndromes, and the limitations of even expert pathological examination of stillbirth and neonatal deaths

If this is true of severe lesions which cause death and which can be studied in recent necropsy material it shows how formidable is the task of delineating the influence of birth hazards on surviving infants Over a century ago, LITTLE [2] suggested that cerebral anoxia caused spastic diplegia, and much work has been done since then Methodological difficulties have made much of this evidence hard to interpret and there are many contradictions Many workers have favoured the retrospective inquiry, in which groups of abnormal children were selected and their birth histories investigated It has been shown [3–7] without doubt that many children with cerebral palsy, mental retardation, epilepsy, and behaviour disorders have a history of prematurity, difficult birth, or neonatal anoxia There is a very strong case for blaming trauma or anoxia for the cerebral palsies not due to kernicterus, but it is not so certain that mental retardation is a common sequel of perinatal lesions YANNET,[8] surveying 2500 admissions to a school for the mentally retarded, could attribute only 3% to mechanisms associated with the process of birth Some of the objections to retrospective techniques have been eliminated in a series of studies by LILIENFELD and his colleagues [9–12] They selected a group of abnormal children born between certain dates, and the birth certificates of these children were extracted The next birth certificate relating to a child of the same sex, race, maternal age, and parity was then taken as a control, and the birth history of the abnormal child was then compared with his matched control [9] A highly significant association was demonstrated between complications of pregnancy and labour and the development of cerebral palsy,[10] epilepsy,[11] and mental deficiency [12] There was a lesser association with behaviour [13] and reading disorders, and some association with tics[14] but none with speech difficulties[15] Conditions associated with a sustained intra-uterine hazard, such as pre eclamptic toxæmia or bleeding in late pregnancy, seemed to be a greater threat than short-lived anoxic states or difficult labour

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[18] Doll R Brit J Cancer 1953 7 303

[19] Haenszel W, Shimkin M B, Miller H P United States Department of Health Education and Welfare Public Health Monograph no [illegible] 1956

[20] Holmes Sellors T Brit med J 195[illegible] i 445

[21] Brown P F M Brit J Radiol 1952 25 172

[22] United Birmingham Hospitals Annual Cancer Report 1951 vol 2 p 14

[23] Bignall J R Lancet 1955 ii 210

[24] Mackenzie A Quoted by Doll R in Advances in Cancer Research vol 3 New York 1955

[1] Bound J P, Butler N R, Spector W G Brit med J 1[illegible] ii 1191 1260

[2] Little W J Lancet 1843 i 319

[3] Schreiber F J Amer med Ass 1938 111 1263

[4] Preston M I J Pediat 1945 26 353

[5] Rosenfeld G B, Bradley C Pediatrics 1948 2 74

[6] Evans P R Arch Dis Childh 1948 23, 213

[7] Plum P Dan med Bull 1956 3 99

[8] Yannet H J Pediat 1957 50 226

[9] Lilienfeld A M, Parkhurst E Amer J Hyg 1951 53 [illegible]

[10] Lilienfeld A M, Pasamanick B Amer J Obstet Gynec 1955 70, 93

[11] Lilienfeld A M, Pasamanick B J Amer med Ass 1955, 155, 719

[12] Lilienfeld A M, Pasamanick B Ibid 1955 159 155

[13] Pasamanick B, Rogers M E, Lilienfeld A M Amer J Psychiat 1956 112 613

Important as these findings are in assessing the contribution made by perinatal events to the total number of handicapped children, they give little guidance to the doctor who is trying to predict the course of a particular child whose independent existence has been achieved only with difficulty. This guidance can be gained only from longitudinal studies of many closely observed pregnancies The pioneer work has not given a definite answer some investigations[16–18] revealed considerable deviations from normal, whereas others[19–22] detected little harm from adverse birth conditions But direct comparison of these results is not altogether justifiable some are based on a study of babies slow to start breathing, others on children born after difficult or long labour, and the assessment of normality is hardly a standardised procedure It is clear, however, that many babies can survive long periods of asphyxia without damage to the nervous system or the intellect—a tribute to the infant's powers of withstanding hypoxia,[23] as well as an encouragement to those who plead for more active resuscitation of the newborn Nevertheless, these results must lack precision because of the many variable factors in normal birth, for example, the clinical state of the newborn infant is only a rough guide to the degree and duration of intra-uterine anoxia Recoverable lesions of nerve-cells cannot be distinguished on clinical grounds from permanent destruction, and independent genetic and cultural influences may affect both the fœtus and the process of birth, giving rise to a spurious causal association

Some, but by no means all, of these difficulties may be lessened by adopting a specific objective measure of the infant's condition at birth as a basis for follow-up studies, and the most readily accepted measure is that of oxygen saturation The normal infant achieves an arterial oxygen saturation of over 90% in the first hour of life, and infants who fail to do so may be considered hypoxic It is of obvious interest to relate their later development to the degree of hypoxia at birth, and three such inquiries[24–26] are in progress It is still too early to say whether they will solve the main problem it seems unlikely that they will, since hypoxia at birth is only one of many variables that may affect development, and it may be a sign only of some underlying disorder which may itself vary considerably in its effect on the infant Thus, anoxia at birth may be due to a temporary interruption of fœtal oxygen supply caused by traction on the umbilical cord, or to a mild depression of the infant's respiratory centre by anæsthesia given to the mother again, it may be the result of severe intracranial hæmorrhage or long-continued exposure to an unfavourable uterine environment, as in pre-eclamptic toxæmia Clearly, all these factors cannot be eliminated in planning and controlling such investigations APGAR and her associates[25] found no correlation between the blood-oxygen levels measured in the first three hours after birth and intelligence as tested in early childhood PENNOYER's work[26] has not reached the stage of providing follow-up data, but *there are some* interesting preliminary findings Anæsthesia other than pudendal block and analgesia if given in moderate doses within four hours of delivery, produced *some* reduction in oxygen saturation The cord oxygen saturation was low in 54 complicated deliveries, and these babies and those subjected *to* prenatal complications both had difficulty in reaching normal saturations within one hour It does seem, therefore, that oxygen saturation in the first hour of life is some guide to perinatal hazard This extends the work of MONTGOMERY et al[27] and ROOTH and SJÖSTEDT,[28] who have examined the influence of cæsarean section on the oxygen saturation of cord blood and shown that cæsarean section, especially if performed under inhalation anæsthesia, leads to hypoxia Whether the measurement of oxygen saturation is a better measure of the clinical state of the baby than careful observation, duration of apnœa,[29] *or measurements of* respiratory volume,[30] is difficult to say, but it is less vulnerable to subjective impressions and, with accurate techniques, it is reproducible

The last words on the prognosis of fœtal anoxia remain to be written Until then, it is essential to remember that reduction of *mortality is not* the only goal physiological parturition must be *the* aim and the infant must not, without very good reason, be exposed to anything that may conceivably be harmful While awaiting the results of further investigations, we must do everything possible *to help infants to recover* from an abnormal birth and adapt themselves successfully to extra-uterine life

Remuneration

THE members of the Royal Commission to inquire into the remuneration of doctors and dentists were made known on Tuesday The chairman is SIR HARRY PILKINGTON and the names of the other members appear on p 583 The terms of reference were announced earlier[31]

At a meeting with the PRIME MINISTER this week, the joint chairmen of the Negotiating Committee, SIR RUSSELL BRAIN and DR TALBOT ROGERS, discussed the possibility of an interim adjustment, to which MR MACMILLAN had earlier referred A statement issued afterwards on behalf of the Negotiating Committee said that there had been no fundamental change in the situation The PRIME MINISTER had now agreed to make a statement at some later but as yet indefinite date about the nature of the adjustment MR MACMILLAN later told the House *that* the pay of junior hospital medical and dental staff, up to *and* including senior registrar, would be increased by 10% from April 1, and as reported on p 583, MR THORNEYCROFT announced plans for raising the salaries of university staff

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[14] Pasamanick, B, Kawi A *J Pediat* 1956 48 596

[15] Pasamanick B Constantinou F K Lilienfeld A M *Amer J Dis Child* 1956 91, 113

[16] Russ J Strong R A *Amer J Obstet Gynec* 1946, 51 643

[17] Darke R A *J Pediat* 1944 24 148

[18] Stevenson S S Stuart H C *Amer J Dis Child* 1950 79, 931

[19] Keith H M Norval M A *Proc Mayo Clin* 1950 25 11

[20] McPhail F L Hall F L *Amer J Obstet Gynec* 1941 42 656

[21] Campbell W A B Cheeseman E A Kilpatrick, A W *Arch Dis Childh* 1950, 25 351

[22] Usdin G L Weil M L *Pediatrics* 1952 9 387

[23] Cross K W Killick E M Huggett A St G *Amer J Obstet Gynec* 1954 68 81

[24] MacKinney L G Ehrlich, F E Chase, H C *Amer J publ Hlth* 1955 45 653

[25] Apgar V Girdany, B R, McIntosh R, Taylor H C *J Pediatrics* 1955 15 653

[26] Pennoyer M M Graham, Frances K, Hartmann A F *J Pediat* 1956, 49, 685

[27] Montgomery, T L Brandfass R T First H E *Amer J Obstet Gynec* 1956 71, 1

[28] Rooth G Sjöstedt S *Acta obstet gynec scand* 1955, 34, 442

[29] Ozinsky, J Harrison G G *Brit med J* 1956 i, 725

[30] Roberts, H Kane K M Percival N, Snow, P, Please N W *Lancet* Jan 19 1957 p 128

[31] See *Lancet* March 9, 1957 p 535

Annotations

OSTEITIS IN THE NEWBORN

THE fall in neonatal mortality has concentrated attention on infection as the most important single cause of death after the first week of life Particular concern has been expressed about hæmatogenous osteitis, for although the mortality of this condition is now low, the results of inadequate treatment can be crippling Dennison[1] pointed out that it is hard to compare the results achieved in different series nevertheless it is encouraging to note the improvement on previously published results recorded in the paper by Professor Boyes and his colleagues on p 544 Their frank discussion of failures is particularly informative

Most instances of osteitis in the newborn are caused by the obtrusive staphylococcus, and the invasion of the antibiotic-resistant organism has been nowhere more threatening than in the care of newborn infants, particularly those born in hospital The osteitis is a local manifestation of a generalised infection and its clinical course varies considerably It can be quite mild, and has usually been so described in the past, or it can be rapidly fatal Any bone may be affected, and the region of the hip is a common site and one where the effects can be serious Bones developed in membrane are often among those attacked, and many infections involve the maxilla, in these flat bones where the resistance is low the infection is specially virulent

It seems that the severe form is a new and violent manifestation of an old disease, and, since it is an eminently treatable condition, its early diagnosis is of prime importance Any swelling of the soft tissues, any signs of irritability in a child that is being moved or washed, any suggestion of immobility, or any generalised infection associated with an apparently superficial lesion, must raise the suspicion of this severe underlying condition Tenderness over bone is the sign to look for One important lesson is that soft tissue infections are not at all common in the newborn and all suspicious lesions should be treated as arising in bone until the contrary is proved As in the now rare osteomyelitis of older children, the radiographs are slow to reflect the bone changes and they never give the full picture of the havoc, since much non-opaque cartilage may be destroyed

The first line of treatment is vigorous, uninterrupted, and long continued chemotherapy Penicillin and streptomycin are given at once, and the sensitivities of the organism determined if possible Once the infection is well under control, treatment by injection can give way to an appropriate drug by mouth One of the important points that has emerged is that treatment must be continued for a long time The average length of treatment in the series described by Professor Boyes and his colleagues was five to six weeks, and experience has tended to lengthen rather than shorten the course Pus should be aspirated, and here again it is necessary to needle repeatedly and at the slightest provocation Even the keenest supporters of bone drilling for infection could hardly say that it was the treatment of choice in patients of this age Sequestra should be removed and it is important to think of loose teeth as sequestra

Even with the sustained care and interest which Professor Boyes and his associates devoted to their treatment, a quarter of the children were left with a crippling deformity of one or more joints The analysis of these failures discloses some valuable facts Apart from late diagnosis, the two big causes of failure were inadequate length of treatment and failure to aspirate pus Where the infection was in the neighbourhood of the hip, the results were really bad in spite of long-continued chemotherapy and orthopædic treatment, the destruction was severe, except in one case diagnosed early

How can this damage be prevented? Doctors and midwives should always be on the lookout for "minor sepsis," and be ready to seek a second opinion if they have any doubts whether it is truly minor And they should urge mothers not to hesitate to seek advice for such conditions When it comes to antibiotic treatment, it must be assumed that the organism is hardy if not immune, and large doses must be given for a long time But all rests on early diagnosis, and early diagnosis depends on suspecting osteitis when the bone changes are still slight

NERVE-GAS POISONING

THE nerve gases are organic phosphorus compounds which powerfully and irreversibly inhibit cholinesterase They were first synthesised in Germany in the 1930s by Schrader, who was searching for new insecticides Except for their greater potency, they have the same pharmacological and toxicological action as the rapidly expanding group of organic phosphorus insecticides[1]

The nerve gases can enter the body through the lungs, the intact skin, or the eye In the conscious animal a lethal dose causes muscular fasciculation, followed by incoordination, convulsions, prostration, gasping respirations, "air hunger," engorgement of veins, and often precipitate micturition and defæcation The animal falls unconscious and stops breathing, the heart slows, cardiac output and blood pressure fall, and the pupils may contract (miosis is an early sign if the eyes are directly exposed) Finally, the skin capillaries collapse and the heart stops beating In all species so far studied the general post-mortem appearance is that of asphyxia Respiration can fail because of paralysis of the respiratory centre (the most important factor), bronchoconstriction or paralysis of the muscles of respiration by neuromuscular block The degree of bronchospasm and muscular paralysis depend on the compound used and the species poisoned Breathing is made even harder by the profuse secretion of mucus from the bronchial glands and the abolition of the cough reflex

Normally, acetylcholine is hydrolysed almost as soon as it is released, but when cholinesterase is destroyed, acetylcholine accumulates where it is produced The symptoms of poisoning are the result of excessive parasympathetic stimulation (muscarine action), neuromuscular block (nicotine action), and paralysis of the vital centres in the brain stem (central action) The parasympathetic and central effects of acetylcholine are prevented and reversed by atropine, which is the most effective antidote to poisoning by organic phosphorus compounds Large doses must be given early and must be continued, more atropine being given as indicated by bradycardia or miosis Cullumbine[2] emphasises that there should be no hesitation in giving more doses if the patient's condition demands it, since acetylcholine is continually being released But atropine does nothing to combat the nicotine action, so that peripheral neuromuscular paralysis persists Since death is due to respiratory failure caused by central paralysis, bronchoconstriction, or neuromuscular block, the efficacy of atropine in different species depends on the relative importance of these three mechanisms In man and the monkey, respiratory failure is central in origin and the response to atropine is good Certain oximes and hydroxamic acids can reactivate inhibited cholinesterase They and hasten the destruction of absorbed nerve gas but they promise to be useful adjuncts to atropine, but the compounds of this type so far investigated are too toxic for general use and the search for better ones continues

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[1] Dennison W D *Lancet* 1955 ii 474

[1] See annotation *Lancet* Feb 2 1957 p 260

[2] Cullumbine H *J R Army med Cps*, 1957 103 [illegible]

Early treatment is vital, and it has been recommended that, in war, the individual Serviceman should be responsible for his own treatment. But the first signs and symptoms of poisoning are vague, and it is hard to know when atropine is really needed. The dose to be self administered must therefore be a compromise between one of therapeutic value in nerve-gas poisoning and one which can be given safely to a normal person. Trials under different conditions have shown that 2 mg. (gr. $^1/_{30}$) of atropine sulphate intramuscularly is a reasonable dose.

In severe poisoning, positive-pressure artificial respiration will support the action of atropine by improving oxygenation of the tissues (in asphyxia atropine is a less effective stimulant of the respiratory centre). Positive pressure is needed to overcome the resistance due to bronchospasm, but ordinary manual methods of artificial respiration should form part of first-aid, preferably by the Holger-Nielson (arm-lift/back-pressure) method. A manually operated positive pressure respirator, such as a bellows resuscitator or a mask-to-mask device, is being considered for field use.

TETANUS AFTER OPERATION

THE power of tetanus to strike a hospital with sudden ferocity is again evident in recent events at the North Staffordshire Royal Infirmary, Stoke-on-Trent. Tetanus attacked 5 patients lately operated on in the main surgical block at the infirmary: 2 have died and the latest information about the others is that they are "unchanged and still very ill." All operations at the infirmary have been suspended for the time being and work is being transferred to other hospitals in the group. The source of the infection has not yet been identified. Those concerned will have in mind particularly previous disasters in which tetanus has been attributed to dust entering the operating-theatre,[1] to infected hair used in repairing plaster walls,[2] to infected talc powder,[2] to catgut,[3] and to the use of other imperfectly sterilised materials.[4 5]

EPIDEMIC VERTIGO

IN the study of the more benign diseases of short duration, the general practitioner has advantages over his colleagues in hospital; and this is well illustrated by what has been written about epidemic vertigo. In 1949 Walford[6] described a case of vertigo during an epidemic of influenza. In the following year Meulengracht[7] pointed out that what was thought to be an example of drug toxicity was in all probability a disease known in Denmark as "vertigo epidemica," or "neurolabyrinthitis epidemica." Subsequently Rogers[8] described 3 further patients, and Stewart[9] suggested that the cause might be a virus labyrinthitis. Since then rather more than 50 cases have been reported from general practice in different parts of the country. Further attention has lately been drawn to this condition by Charters,[10] who, in a paper from Kenya, discusses 13 cases that he has seen in the eight years between 1947 and 1955.

The clinical picture of epidemic vertigo seems to be reasonably clear. The patient has a sudden attack of severe vertigo accompanied by nausea and vomiting. The vertigo may last from one day to two weeks and then gradually ease (being brought on at this stage by movements of the head) until it subsides entirely. There is, however, considerable variation in the recorded duration of vertigo, Worster Drought[11] stating that it gradually improves in six to nine weeks, rarely lasting as long as twelve months. The vertigo is accompanied by nystagmus, and sometimes by headache, generalised pains, and slight fever for a day or two at the onset. Tinnitus and deafness, though not the rule, do affect a small proportion of patients. Leishman[12] mentions that 3 of his patients had diplopia, and this symptom was present in 2 of Dalsgaard-Neilsen's series[13] of 21 cases in Copenhagen and in 2 of Charters's patients. The disease may affect either sex and the patient may be of any age, the youngest described being three years old; but it is generally mild in children and is more common as well as more severe in those over twenty.

There has been much discussion about the ætiological agent, its infectivity, and the site of damage, but many more facts are needed. Cases have occurred during epidemics of influenza, but vertigo as a direct result of influenza is usually accompanied by deafness. Moreover, epidemic vertigo may appear at any time of year, and often it is unassociated with pyrexia. It is tempting, therefore, to consider this disease as an infection by a distinctive virus, though Alcock[14] takes the view that there are several different causes. In Charters's series of 13 cases, 10 appeared between May, 1954, and August 1955. There was no special predilection for any particular month, and the cases were widely scattered throughout Kenya. He supports Burrowes's view[15] that the disease may be spread by carriers. This point might be settled by wider study of the condition in general practice and a comparison with other diseases prevalent at the time.

In most infections the labyrinth and cochlea are often involved together. Since tinnitus and deafness are relatively uncommon in epidemic vertigo, it seems unlikely that the end-organ itself is affected (virus infections very rarely attack this structure).

The electro-encephalogram showed a "mild abnormality" in 6 of Dalsgaard-Neilsen's 13 cases, but it was normal in the remaining 7. Moreover, the cerebrospinal fluid has been normal almost every time it has been examined. It also seems unlikely that a brain-stem encephalitis would confine itself to the labyrinthine nuclei, with occasional involvement of the cochlear nucleus and even more rare damage to one oculomotor nucleus; what is more, it would have to do so without causing any general upset in most patients (Dalsgaard Neilsen mentions slight changes in reflexes or sensibility). On the other hand, it is hard to explain in any other way the involvement of the oculomotor nerves if this condition is to be attributed to one cause.

Embryologically and phylogenetically, the vestibular nerve and ganglion develop before the cochlea, and this may be a factor in the localisation of the damage. If so, then epidemic vertigo would be one variety of vestibular neuronitis. The disease does, in fact, show many points of resemblance to vestibular neuronitis as described by Dix and Hallpike,[16] in particular the age distribution, the onset associated with a febrile illness, and the localisation to the vestibular apparatus. It differs from vestibular neuronitis in its short course and in the possible involvement of the auditory apparatus. These differences, however, may well be differences of pathology rather than of anatomy. Charters suggests that the condition is a ganglionitis and that spread might be occasionally expected from Scarpa's ganglion to the cochlear nerve. This is an interesting postulate, and, while the analogy he draws with herpes zoster cannot be pushed very far, it is not an unreasonable hypothesis.

Aschan and Stahle[17] have lately described 10 cases of vestibular neuritis (neuronitis) some of which might well be epidemic vertigo. By means of nystagmography and the more usual investigations, they support the view that the lesion is in the peripheral vestibular neurone or the brain stem nuclei. Although nystagmography could not be generally applied, it would be interesting to refer more patients thought to have epidemic vertigo for caloric tests, audiometry, electro encephalography, and possibly galvanic tests at an early stage of their illness, for none of these investigations is very burdensome to the patient.

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[1] See *Lancet* 1956 ii 29
[2] Sevitt S *Ibid* 1949 ii 1075
[3] Dalrymple Champneys W *Proc R Soc Med* 1936 29, 35 see *Lancet* 1937 ii 559
[4] Pulvertaft R J V *Brit med J* 1937 i 441
[5] Cane L H *Lancet* 1938 ii 1059
[6] Walford P A *Brit med J* 1949 i 821
[7] Meulengracht, E *Ibid* 1950 ii 1493
[8] Rogers E C *Ibid* 1951, i 1301
[9] Stewart M *Ibid*
[10] Charters A D *East Afr med J* 1957 34 7
[11] Worster Drought C *Lancet* 1952, i, 371
[12] Leishman A W D *Ibid*, 1955 i 228
[13] Dalsgaard Neilsen T *Acta psychiat*, *Kbh* 1953 28, 263
[14] Alcock, N S *Lancet* 1952 i, 467
[15] Burrowes, W L *Ibid* 1955 i, 408
[16] Dix, M R, Hallpike, C S *Proc R Soc Med* 1952 45, 341
[17] Aschan G Stahle J *J Laryngol.* 1956 70, 497

Treatment must clearly be empirical. The distressing vertigo can usually be relieved by rest in bed for a short period, and simple sedatives are usually sufficient until the trouble subsides. Nevertheless, the disease remains a challenge, and more energetic efforts to explain what it is may yield results which have a bearing on virus infections as a whole.

PULMONARY FUNCTION AFTER PNEUMONECTOMY

AFTER pneumonectomy without thoracoplasty it might reasonably be expected that the volume of the remaining lung would increase, and that the consequent over inflation would impair respiratory activity. In fact, lung volume does tend to increase, but there is often little change in the various criteria of respiratory efficacy. Thus, Cournand et al[1] made a survey of ventilation perfusion relationships and gas exchange in 16 patients after pneumonectomy, and found that distension did not inevitably follow, even with some degree of over inflation and hyperventilation, the respiratory performance was in the lower part of the normal range. Friend,[2] who examined 15 men before and after pneumonectomy, found evidence that the remaining lung increased in volume, but that the over-inflation did not progress for more than three months. Over-inflation of itself had "no demonstrable adverse effect on ventilation", Friend also demonstrated post-operative respiratory insufficiency only in those patients who had chronic bronchitis, and he concluded that the maximum breathing capacity test could predict post operative dyspnœa.

McIlroy and Bates[3] examined 10 men, aged between 39 and 63, who had had a pneumonectomy from eight months to eight years before, all operations had been done, without thoracoplasty, for carcinoma of the bronchus. They measured intraœsophageal pressure (as an index of intrathoracic pressure), so that lung compliance and flow resistance could be estimated, and the pulmonary diffusing capacity (by the carbon-monoxide method) both at rest and during exercise on a treadmill. In 6 patients with little evidence of over inflation of the lungs the results were what would be expected with a halving of the tissue available for respiration. In about half the patients, the compliance was less than that expected for one normal lung (i e, there was a smaller increase in volume than normal for a given increase in pressure) and in most cases the compliance decreased more rapidly than normal as the lung volume increased. The respiratory work on exercise was greater than normal even when the lung was not over inflated, and much greater when it was over inflated, this might be expected since the ventilation of one lung alone is about double that of two lungs, for a given exercise rate, hence there would be a bigger resistive pressure component across the lung for a given rate of air flow than there would be if there were two lungs to share the flow, with the correspondingly lower flow resistance offered by two sets of airways in parallel instead of one. This was in accordance with the finding of a mean inspiratory resistance greater than normal in all the patients. In 3 patients there was over inflation (evidenced by a low intraœsophageal pressure and grossly increased functional residual volume), but normal gas diffusion was maintained. 1 patient, [illegible] years after operation, had a much over inflated lung but normal end-expiratory pressure, indicating a loss of elastic recoil, and considerable impairment of gas diffusion with a ventilation higher than normal for a given oxygen uptake, he could be considered to have emphysema.

Thus, the absence of one lung may result in very little change in the function of the other, but, since only one lung is left to bear the respiratory burden, there is a tendency to over inflation. A low intrathoracic pressure leads not only to over inflation but also to a fall in compliance. The tendency then is for the lung to lose elasticity, with a consequent rise in intrathoracic pressure and functional residual capacity, and a relative fall in diffusing capacity, gas distribution, however, is little deranged, differentiating the condition from classical emphysema secondary to long standing bronchitis.

McIlroy and Bates began their investigation with three questions in mind. The first was whether over inflation led to dyspnœa through changes in the mechanical properties of the lungs, they presume that postoperative dyspnœa is due to the necessary over ventilation of the remaining lung, and that over inflation accentuates the dyspnœa by a further reduction in compliance. The second question was whether the diffusing capacity was lowered, and if so what were the results, they found it was generally half the value in normal people, and this reduction means a greater ventilation for a given oxygen uptake. The relation between over inflation and emphysema constituted the third question, and the results suggested a clear distinction between these two conditions, for "over inflation results in an increased lung volume with a low intrathoracic pressure level and normal gas diffusion. Emphysema, on the other hand, is characterised by an increased lung volume with a normal intrathoracic pressure level and impaired diffusion."

POLIOMYELITIS VACCINE

THE colour change in a few vials of poliomyelitis vaccine during storage[1] has been traced to contamination. In a letter to medical officers of health, Sir John Charles, chief medical officer of the Ministry of Health, says that faulty containers were to blame and the contaminant was a non pathogenic *Pseudomonas fluorescens*. Repeated sterility tests on the remainder of the batch have been negative. After incubation at 37°C, 25°C, and room temperature, normally coloured vaccine showed no discoloration. It has therefore been decided to proceed with the issue of this batch of vaccine.

THE Q J M

IN 1907, at the first meeting of the Association of Physicians of Great Britain and Ireland, plans were made to establish a medical journal to publish "papers which, though scientifically important, were not suitable for the Journals, nor for the clinical or pathological societies." The name first chosen was *Archives of Medicine*, but there must have been objections to this title, for it was soon changed to one now familiar wherever medical journals are read—*The Quarterly Journal of Medicine*. The energy of William Osler, for 12 years its editor, gave the new venture a flying start, and in the succeeding 50 years of vigorous life it has been ably served by a distinguished line of editors. We congratulate them and all who have helped them to attain this anniversary. To mark the occasion an attractive jubilee number has just been published, and in an opening article Sir Russell Brain recounts the history of the association and the journal and mentions some of the memorable names connected with them.

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[1] Cournand, A., Riley, R. L., Himmelstein, A., Austrian, R. *J. thorac. Surg.* 1950, 19, [illegible]
[2] Friend, J. *Lancet*, 19[illegible], ii, [illegible]
[3] McIlroy, M. B., Bates, D. V. *Thorax*, 1956, 11, 303.

[1] See *Lancet*, March 9, 1957, p. [illegible]

Special Articles

OPERATION SESAME*

EDWARD S STERN
M.A, M D Camb, M R C.P, D P M
MEDICAL SUPERINTENDENT,
CENTRAL MENTAL HOSPITAL, HATTON

ON June 5, 1956, I opened the last closed ward at Hatton, so that now any of our 1380 patients is free to walk out of the place if he wants to do so This could not have been achieved without the cooperation of the staff, and many physical difficulties have had to be surmounted

In the first place we have no main gates (our visiting anæsthetist and his car saw to that eleven years ago) there is not even a porter at the place where the gates were We are surrounded by farmland with ordinary hedges and fences and twenty open gateways in them We are close to a canal and a main railway line Our buildings are mostly a century old, with wards opening out of each other and many other antiquated inconveniences We have overcrowding of over 40% That we are short of nurses is, I believe, immaterial, for our staff turnover is low, and that is far more important Our patients are unselected, and include short order cases under sections 20 and 21 of the Lunacy Act, 1890, for we act as our own observation wards

THE FIRST STEPS

It is fitting that we should be among the earliest to unlock our wards, for Hatton was the first asylum in which no patient was ever put under mechanical restraint It was opened in 1852 during an enlightened period Unfortunately the beginning of the 20th century was a period of recession in psychiatry, marked by a flight from the patient into the study of pathology, psychobiology, biophysics, biophysiology, biometry, biochemistry, binovular twins, even the binomial theorem, and other byways of the physical sciences

When I was a junior medical officer two events made me resolve to open the doors of the hospitals The first was when my old chief, the late Dr A O'Neill, told me with compunction that, in the twenty-five years that Napsbury Hospital, St Albans, had been opened, more patients had been placed under observation and more wards had been locked The second was when I found that a patient of mine had recovered after many years in the hospital I proposed his release, only to be told by the senior nurse that he had been so long detained that he was now institutionalised and unfit ever to leave I am glad to say that I did secure his discharge and I believe that he did well But what a reflection on the mental hospital it was, that prolonged stay there should unfit a man for normal life I resolved that I would, if ever I had the chance, reverse the process, open more wards, and make mental treatment fit the patient to live the good life outside

When I arrived at Hatton as medical superintendent in 1942, I found 3 of 14 female and 4 of 11 male wards open Throughout the hospital were many peremptory notices "Lock this Door" As an immediate first step I unlocked the door between two open male wards The staff did not know that this was only the thin end of the wedge, but I now literally had my foot in the door

Other reforms were started Chronic sick were collected together in one ward, and epileptics in another The use of suicidal caution cards was discontinued We have never regretted this as the pink tickets have died our patients have lived

STEADY PROGRESS

But until the Appointed Day I was able to open only one more ward On that day, however, the dual medical and lay control, which had been a peculiarity of Hatton for 13 years, was ended The result was electric In a single day there was an immense rise in morale which has continued ever since The progress in unlocking wards is shown in the table

Sometimes there was a long pause between openings This was because the staff could not accept it unless patients who were regarded as likely runaways were transferred to closed wards The advent of such ill-reputed people to wards where the new freedom was already feared naturally further delayed their own opening But even the most conservatively minded staff eventually wanted to be in the swim and asked if their wards, too, could not be opened It became U to have one's ward unlocked and non-U to keep it closed Occasionally a change in charge-nurse led to the rapid opening of a ward

PROGRESS IN UNLOCKING WARDS

—	Men					Mixed	Women						
	Clean and healthy	Disturbed and excited	Sick	Recent admissions	Convalescent	Insulin	Clean and healthy	Epileptic	Disturbed and excited	Senile and infirm	Sick	Tuberculosis and isolation	Recent admissions
Already open in 1942	31, 44			23	46		28 31						40
Opened in													
1947	48												
1948						12	72						
1949	75							76	73	47	66		
1950									80				
1951													
1952							32						
1953													
1954							65					28	
1955		80 89	83	85						88			58
1956		53		*38*	*38*								

Each ward is shown by a figure giving the number of patients at the time of opening New wards are shown in italics

The disturbed wards were not always the last to be opened It often proved more difficult to liberate senile and demented patients who are inclined to wander and get lost Indeed the only serious accident we have had was with one of these

Since 1942 the total number of wards has been increased by 3, and these have been open from the beginning Altogether the 28 wards have over 100 open and unguarded doors

HOW WE DID IT

The male and female sections of our main building can largely be shut off by locking central doors, and on the women's side we opened the wards at first behind these closed doors It was, in fact, possible to walk out of the building without a key, but only if one had an intimate knowledge of the design of the women's side —a knowledge that even many nurses did not possess A few months later we quietly opened the section doors quietly because we did not wish to upset the doubters among the staff—we knew that the patients could take it and would be all right On the men's side we opened

be epidemic vertigo By means of nystagmography and the more usual investigations, they support the view that the lesion is in the peripheral vestibular neurone or the brain stem nuclei Although nystagmography could not be generally applied, it would be interesting to refer more patients thought to have epidemic vertigo for caloric tests, audiometry, electro-encephalography, and possibly galvanic tests at an early stage of their illness, for none of these investigations is very burdensome to the patient

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* Based on a paper read at the annual general meeting of the Royal Medico-Psychological Association on July 19, 1956

Treatment must clearly be empirical The distressing vertigo can usually be relieved by rest in bed for a short period, and simple sedatives are usually sufficient until the trouble subsides Nevertheless, the disease remains a challenge, and more energetic efforts to explain what it is may yield results which have a bearing on virus infections as a whole

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Opened in 1947	48												
1948						12	72						
1949	75							76	73	47	66		
1950									80				
1951													
1952							32						
1953													
1954							65					28	
1955		80 89	83	85						88			53
1956		53		38	38								

Each ward is shown by a figure giving the number of patients at the time of opening New wards are shown in italics

The disturbed wards were not always the last to be opened It often proved more difficult to liberate senile and demented patients who are inclined to wander and get lost Indeed the only serious accident we have had was with one of these

Since 1942 the total number of wards has been increased by 3, and these have been open from the beginning Altogether the 28 wards have over 100 open and unguarded doors

HOW WE DID IT

The male and female sections of our main building can largely be shut off by locking central doors, and on the women's side we opened the wards at first behind these closed doors It was, in fact, possible to walk out of the building without a key, but only if one had an intimate knowledge of the design of the women's side—a knowledge that even many nurses did not possess A few months later we quietly opened the section doors quietly because we did not wish to upset the doubters among the staff—we knew that the patients could take it and would be all right On the men's side we opened the section door before the wards I think that, on the whole, this was the more difficult method

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* Based on a paper read at the annual general meeting of the Royal Medico-Psychological Association on July 19, 1956

In 1949 we were so short of women nurses that we stationed a male nurse in our disturbed women's ward by day to quell any possible outbreak of violence The result was unexpected There was no violence, but the patients began to use cosmetics and take a renewed interest in their appearance We discovered that we could improve each side by the introduction of the opposite sex

We have opened the dormitories so that patients can go to bed when they like, and can use the sanitary annexe which is open at night This has done away with the use of chamber-pots, dangerous both as weapons and as a means of spread of intestinal infection The bathrooms are open and we dispense with key-taps But we lock the outer doors of the hospital at night just as in our own homes

I think it important not only to unlock the doors but also to give the appearance of freedom To that end we have opened as many doors into each ward as we safely can, having regard to the danger of falls by old people down steep stairways Since we unlocked our ward garden-gates we are finding that the airing-court is a thing of the past, and this will free land for other purposes The railings which surrounded our cricket field and home paddock have been taken down The latter is now a park

SOME USEFUL PRINCIPLES

In carrying out the operation we found the following principles useful

The patients must be happily occupied Their occupations should be outside the wards, which are used mainly for eating and sleeping, and so regarded by the patient as his home We began occupations on a large scale for chronic disturbed patients in 1945 The resulting improvement, though slow, has been sure and has exceeded all my expectations

Recreations must be provided away from the wards These should generally be of a high class, for if you give the patients only trivial fare you show that you think they have trivial tastes and trivial minds Games and dancing are valuable, especially if they are provided by outside bodies Our constant aim is the resocialisation of the patient for his eventual discharge

The patient must be respected as a person All his complaints and requests, and those of his relatives too, must be considered There must be infinite patience and gentleness in all our dealings with him It may be wondered how we manage with the chronic paranoid individual who is continually trying to escape We have found that the hostility of such people can be worn down by constant kindness After all why should a patient leave the only place where he can always be sure of a kind word and a sympathetic ear?

The patient's clothes should be improved

Holidays and visiting should be encouraged We allow visiting at any time while retaining our regular visiting days

The staff must be continually stimulated and supported, for the mental hospital must be a happy and confident place and opening the doors is a matter of staff confidence

SOME DIFFICULTIES

The sort of opposition we met from the nurses was "The patients will escape What shall I do?", and finally, "Who will be responsible?" Our answer was, "Don't worry, nurse, we'll be responsible" In fact, when a ward is first unlocked, nothing at all usually happens Perhaps a patient finds the door is unlatched and hastily closes it again, the next patient to discover this draws the sister's attention to the irregularity The patients have to be encouraged to take a stroll outside For they are threatened with the loss of the security of chronic psychosis

Shortages of staff sometimes led nurses to give keys to patients Whenever the matron discovered this, she would say "Nurse, I have just found a patient with your key, so you cannot tell me if the ward is locked or not You had better leave it open, for then at least you will know" Now we find that those who were most doubtful at first are as enthusiastic as the rest of us Of course we all had some anxiety then, and I sometimes feared that Operation Sesame might become Operation Pandora But we never opened a ward until the staff was ready for it, and always left the final decision to the sister or charge-nurse

At first we had more escapes after we opened our wards, now we have fewer They did not give rise to such anxiety as formerly, for they were no longer antisocial To prevent them we need a new technique in mental nursing, known absconders must be constantly occupied and interested This is not as formidable as it sounds, for they soon learn to engage themselves contentedly at all times We have not had any notable trouble with local residents or police, nor do the patients pester staff or visitors at the hospital

ADVANTAGES

On the other hand, the advantages have been abundant and increasing, and no-one at Hatton would care to return to the days of imprisonment for mental illness The whole staff-patient relationship is transformed Nurses are no longer regarded as turnkeys On the day that we opened the admission ward for men, the duly authorised officer said, "This is the best thing you have ever done Now you have made it easy for me to persuade patients to enter the mental hospital"

Seclusion of patients in a locked room, formerly common, has almost ceased and is practically confined to patients who have just been admitted Violence, resistance, and hostility have virtually disappeared, and so has forced feeding Wards that were previously disturbed have become the most popular with staff, for they are full of recovering chronic patients many of whom have already been discharged and are known to be doing well at home

Patients have learnt to be independent and responsible Their behaviour with strangers or at a party is exemplary—i e, better than that of the general public

At the end of June our Hospital League of Friends gave a garden party Patients decided for themselves whether they wished to go and then went out and enjoyed themselves without supervision At the end of the day they all returned to their wards at the right time No nurses were on point or supervisory duty and this freed them so that they could give their time to helping the halt, the lame, and the blind round the gardens But all that is the usual thing for us

They are out of the wards so much that overcrowding is less serious But we have had to provide more open garden space and seats, as well as a comfortable library where patients can read or write quietly

The strain of nursing has been less since patients have been removed from the wards for periods of the day When they were massed together in a locked room it was common for fights and window smashing to occur, especially in bad weather To return to closed wards would require more nurses than we have

But the open door system does not mean merely undoing locks It means the provision of interests and re education for the patient, respect for his dignity as a person, and friendliness to him in all his needs

Public Health

ATMOSPHERIC POLLUTION, TEMPERATURE INVERSION, AND DEATHS FROM BRONCHITIS

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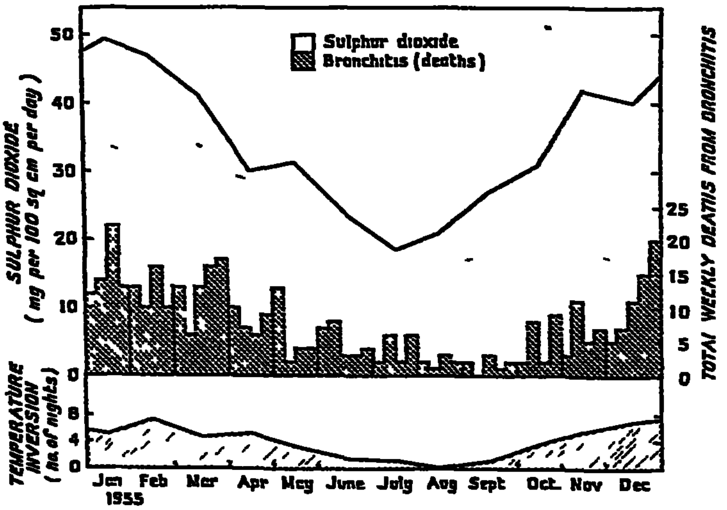
It is common knowledge that the number of deaths from bronchitis tends to rise when the weather is cold and foggy, and it has often been assumed that there is a direct association between the mortality and the climatic conditions. Looking for a more precise association, we have found (see graph) similar trends in

(1) The sulphur-dioxide content of the atmosphere;
(2) The number of days showing "temperature inversion"; and
(3) The number of deaths recorded as being caused by bronchitis.

In the graph, the figure for sulphur dioxide was a monthly total of the readings of thirteen gauges placed in different parts of the city.

An "inversion" was recorded on any night when the minimum temperature (in Weston Park, half a mile from the centre of the city) was at least 5°F lower at ground level than it was four feet above the ground, provided that the cloud cover was less than half during most of the night and the wind not more than force two on the Beaufort scale.



Graph showing total sulphur-dioxide readings, temperature inversion, and deaths from bronchitis in Sheffield, 1955.

The number of deaths was obtained from the list of registered deaths reaching the public-health department.

One could expect an increase of sulphur dioxide in the air in winter because of the increased amount of fuel burnt. It may, however, be true that this increased amount of sulphur dioxide produced is concentrated at ground level on days when there is temperature inversion, because there is then less dispersion of the gases. There are more such days in winter.

Mr J. Barwick, F.R.MET.S., A.M.A., supplied the meteorological data.

Points of View

A STUDY OF WAKE

AN APPROACH TO THE PROBLEMS OF INSOMNIA

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SLEEP and wake are the alternating modes of life, but how differently we view them. We assume that "sleep is a temporary cessation of the waking state" (Carter 1955) and study its cause and nature. To study the cause and nature of wake seems foreign to our nature, for we do not find the word "wake" in the index of any textbook. Yet surely arousal is the most spectacular phenomenon in life.

The reason for this prejudice is obvious but not generally recognised. We must be awake to study any problem including that of sleep-wake. It is therefore only natural to take wake for granted and to argue from wake to sleep. But in the same way we must be on the Earth to study any problem including the allied night-day problem, and it was only natural to take the Earth for granted and to argue from Earth to Sun. But that was pre-Copernican error, and science has proved that we must alter our egocentric ideas and argue from Sun to Earth. Is there any justification for thinking that our assumptions over sleep and wake are also erroneous, and that we should change our ideas on this problem and assume that "wake is a temporary cessation of the sleeping state"? Such a change of view is not a mere playing with words. It is a fundamental reorientation of thought and seems to have been under consideration by some students of the subject (Jefferson 1954, Kahn 1916, Wright et al. 1952a).

Sleep as Basic State of Life

If we study objectively the relation of wake and sleep we must first note that life begins in an inert fœtal state that may well be termed "sleep," and that the embryo seems incapable of arousal in its early life. Barcroft's (1946) experiments, however, have shown that in later fœtal life anoxic and tactile stimuli can rouse the embryo while "asleep," so that temporarily it "will wake to activity." But fœtal life is a sleeping life and it is amazing that the fœtus continues its sleep even during labour unless aroused by threatened asphyxia. (Freud [1933] stated that, in adult life, when we try to go to sleep "we try to bring about quite similar conditions to intrauterine life.")

At birth the baby awakes for a short time but, when anoxic and tactile threats have been removed, reverts to sleep. Unlike the fœtus it is now no longer nourished by a kind of perpetual drip-feed through the umbilical vein and it will starve if it sleeps perpetually. It is accordingly awakened at regular intervals by hunger, but as soon as it has fed it is asleep again. (This need for regular feeds remains the fundamental cause for waking throughout life.) At a slightly later age the young baby can also be temporarily aroused by pain, noise, and light but sleep again recurs when these stimuli cease. Like the fœtus the very young baby lives mostly a sleeping life.

The pattern so far, therefore, is quite plain. Sleep is the original and basic state of life. At first it is continuous, but, as development proceeds, this perpetual sleep may be interrupted temporarily by an increasing number of causes which we may term "arousal stimuli."

Nevertheless, throughout this fœtal and very early baby life of sleep, wake is but a briefly temporary cessation of the sleeping state We certainly could not say that the sleep of this period was a temporary cessation of the waking state

But what of the later stages of life ? As development proceeds, this clear-cut pattern alters profoundly We find in the growing baby that the polyphasic waking episodes are prolonged In the young child they gradually merge together into a triphasic and then a biphasic pattern, and finally, with the abolition of the afternoon nap, there is one long monophasic wake period With growing age this increases until the waking hours (sixteen or more) exceed the hours of sleep (eight or less) This long daily vigil continues for many years, but with increasing age there is a gradual return to the baby pattern The afternoon nap of "forty winks" (usually after food) is the first sign of the return of biphasic wake, and in old age triphasic and polyphasic modes are found In extreme senility there is sometimes a return to the almost perpetual sleep of the fœtus, and it may be that the arousal stimuli disappear from life in the reverse order of their appearance

Wake Maintainers

Can we fit this changing picture into the simple pattern mentioned above ? Yes, it seems that we can It is most significant that, as the young baby grows, the period of wakefulness begins to persist after the waking stimulus has apparently been withdrawn For instance, instead of falling asleep immediately after its feed, it will remain awake for a time, interested in a bright light or coloured object or playing with its hands We must therefore postulate the emergence of "wake maintainers" which continue the alert reaction after the arousal stimuli have ceased—cf Kleitman's (1939a) "wakefulness of choice"

These wake maintainers take the form of investigation of, and play with, the environment And their brief and rudimentary origins in the young baby gradually enlarge with age as the awareness of the environment widens, until the broad horizons of adult perception claim the long monophasic period of wake As age increases, however, this zest for investigation and play lessens until, in the apathy of senility, wake maintainers may disappear almost completely Throughout life wake maintainers are less evident in the more vegetative members of society (such as the Fat Boy of Pickwick), and more evident in the more active

Development of Sleep-wake Relationship

Three phases in the development of the sleep-wake relationship may therefore be recognised (1) undisturbed sleep (in the early fœtus), (2) sleep briefly disturbed by arousal stimuli (in the later fœtus and the very young baby), and (3) sleep increasingly disturbed by arousal stimuli supplemented by wake maintainers But, although wakefulness lengthens with the growing need for alertness and diminishes with the diminuendo of old age, sleep is always our perpetual background and is "there" whenever the cause of wake disappears, just as the analogous state of nakedness is "there" whenever we undress Even in adult life wake is still a temporary cessation of the basic sleeping state The acceptance of this view of sleep should be of fundamental help in agrypnophobia

How does wake cease ? Initially wake ceases when the arousal stimulus is removed, witness the infant's relapse into sleep after feeding or having a wet nappie changed (Illingworth 1953) But when wake maintainers supplement the arousal stimuli, what then ? The dominant waking urge may either be abolished by satisfaction, like hunger by food, libido by coitus, and labour by delivery, or fade away through fatigue or adaptation In either case drowsiness and sleep recur

Of course wake maintenance may be suppressed by circumstances If, for instance, we are trapped in the inescapable boredom of a dull lecture or sermon, the removal of the possibility of any kind of purposive activity leads to drowsiness and sleep (Compare the sleep occurring in volunteers submerged in body temperature water, in the experiments of the National Institutes of Health in the U S A) (*British Medical Journal* 1956) The picture is therefore always one of sleep disturbed by a waking agent and automatically recurring when this is removed How similar to its physiological counterpart where the relaxed muscle of the nerve muscle preparation (Wright et al 1952b) contracts with stimulation and relaxes when the stimulus is removed—a picture in miniature of the sleep wake life and of the levator palpebræ superioris muscle in particular

If wake is a temporary disturbance of the basic state of sleep (and it seems that we must accept this unorthodox view), there is no "cause" for sleep but only cause for wake And what is this cause ? We have enumerated the arousal stimuli, tactile and anoxic threats, hunger, pain, noise, and light, in this order of appearance In addition, "exogenous" training (where the parent wakes the infant for excretion, &c) and later "autogenous" training (where the individual trains himself to awake, often with such an aid as an alarm clock) should be added to complete the list of arousal stimuli Why do all these stimuli cause arousal whereas other types of stimuli do not ? Is there any single factor common to the former which is absent from the latter ? Yes, it seems that arousal stimuli all partake of a "threat to well being" which can only be met by the alert reaction, whereas the non-waking stimuli and sleep associated states are devoid of this threat We may cite hunger (not satiety), nightmare (not idyllic dream), arousing shake (not rocking cradle), the smell of burning (not the scent of flowers), bugle (not lullaby), work to be done (not task completed) It is this affective nocuous and therefore prepotent (Wright et al 1952c) element which is required to disturb the placid equilibrium of sleep Perhaps this is the subconscious reason for calling the instrument that awakes us the "alarm" clock Threats below threshold level presumably cause disturbed sleep (sleep movements, sleep noises, dreams, and modification of the sleeping electro-encephalogram) If they reach threshold level they produce the extreme disturbance of wake, the speed of arousal being proportional to the degree of threat The threat of a very loud noise will cause almost instantaneous arousal, whereas minor threats (Kleitman 1939b) whose summation causes our ordinary morning awaking (daylight, minor sounds, hunger-pains, bladder distension, and training) produce a more gradual arousal It is obvious that when wake maintainers contain a large element of threat, as in anxiety, they will prolong the alert reaction in the unwanted wakefulness of insomnia, for which psychotherapy, religion, and relaxing techniques are more rational treatments than is the use of depressive drugs for blocking the pathways to the arousal centres (Arduini and Arduini 1954)

Because they contain this element of threat arousal stimuli are a form of stress I am therefore tempted to suggest that arousal corresponds to Selye's (1954) "alarm reaction," the ensuing period of wake to his stage of "resistance," and the final drowsy fatigue to his stage of "exhaustion," but perhaps this is oversimplifying the sleep wake problem But there is certainly some evidence to suggest that corticotrophin may play a part in waking Polley (1956)

In arousal the placid unconsciousness of sleep is disturbed by nocuous afferent impulses into a conscious awareness of the challenge which the arousal stimulus contains. The first stage of arousal is the introduction of the conscious state by the "open-sesame" of the threat element in the stimulus. But, according to Magoun (1953), modality is unrecognised in the arousal centres, and the second stage therefore is the conscious (cortical) activity which recognises the modality of the arousal stimulus and orients it in time and space. In this connection three observations in the phenomena of awaking may be noted.

(1) Possibly the purposeless athetoid movements of its early stages may be due to the opening of the thalamo cortical circuits by the removal of the suppressor bands (Wright et al. 1952d).

(2) Certainly the mental confusion, fantasy, or hallucination described by Grotjahn (1932) shows the gradualness of waking awareness.

(3) The quasipurposive movements of closing the eyes (often with a frown) after their first brief opening, and of grimaces of displeasure and turning over in bed, all may be connected with the nocuous nature of the arousal stimulus.

Complete awakening leads to action designed to deal with the arousal stimulus, after which wakefulness may continue with pleasurable affect.

Conclusion

The orthodox approach to the sleep-wake problem is due to an obvious (but generally unrecognised) prejudice—i.e., the subject can only be studied when we are awake. If we clear our minds of this prejudice and look at the problem objectively, it appears that sleep is the initial basic mode of life. Wake is a temporary disturbance of the sleeping state. The cause of wake lies in an increasing variety of arousal stimuli which all have the nature of a threat to well being and are therefore forms of stress. The lengthening duration of wake with age is due to the emergence in early life of wake maintainers which "tag on" after the arousal stimuli have ceased. Whenever the arousal stimuli and wake maintainers disappear, the temporary disturbance of the sleeping state ceases.

This conclusion provides a firm foundation for the further study of the physiology and pathology of wake. It entirely reorients the problem of insomnia, the secret of which lies not in the study of sleep but in that of wake (especially the wake maintainers). In particular the acceptance of this basic view of sleep should be of fundamental help to sufferers from agrypnophobia, and the "threat" nature of arousal underlines the importance of anxiety in the maintenance of unwanted wake.

The importance of insomnia and dyssomnia in the production of unhappiness and ill health cannot be exaggerated. It is along the lines described above that we shall reach a solution of the problem.

I am indebted to the late Prof. Samson Wright for helpful criticism.

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Parliament

Taxation and Public Expenditure

THE burden of taxation which this country carries and its pressure on the professional classes was one of the main themes of the debate in the House of Lords on March 6. It was recognised that if taxation was to be eased it could only be done by a reduction in public expenditure, and this led several noble Lords to a reconsideration of our social services.

Indeed if we were to achieve any big saving in domestic expenditure we must, Lord BALFOUR OF INCHRYE maintained, do "some basic re-thinking." He readily agreed that the Welfare State must continue to safeguard citizens against such unavoidable hazards as sickness and old age. But he believed that we must throw over the idea which had crept upon us that a Government could do better for the citizen and could spend better for the citizen than a citizen could do for himself if he were released from the present rapacious tax system. The practical application of a revolt against the Government as the spending agent for the citizen would be no subsidised rents for four-figure incomes, no food subsidies, and no free health-service benefits for those who could afford to pay for their own doctors. Against this could be set a level of personal taxation which would allow a man to order his affairs as he wished, to order his own housing, to feed his own family, to doctor as he wished and to educate his children as he wished.

The EARL OF CROMER suggested that the Welfare State was designed against the background of the past but had to be paid for at the cost of the present. Too much of the cost of the Welfare State was devoted to relieving wage-earners of what unhappily they could not afford twenty five years ago, but today in general happily could afford. It was absurd and unrealistic to expend too much of our energies trying to mitigate the hardships of the past. We needed them all to overcome the problems of the present, of which undoubtedly the paramount one was our economic survival, and he reminded noble Lords that of the total Government expenditure of £6000 million a third was on the Welfare State. If a man was working his wages should be at a level to provide him with a decent standard of living. Such funds as the nation could make available for welfare should be devoted primarily to the care of those who could not care for themselves, and to protect those whom society could not look after in the normal sense. Lord Cromer could see no justification in this day and age for large-scale largesse to the population as a whole—such as, for example, family allowances. He suggested that the Welfare-State costs might be divided into two categories: the first covering those items which the normal Christian morality demanded of the State—such as National Assistance and the like—which should be left as a charge against the Budget as at present. The second category, covering other items of the Welfare State, might come under an entirely separate social-security budget which would not have recourse to the general Exchequer, but be financed by National Insurance contributions and by part of the proceeds of purchase tax or a special sales tax. This scheme would have the merit of disillusioning those who believed that they were getting something free, and would produce an awareness of the truth of the situation, which was that the Welfare State had to be paid for, not by someone else, but by every working member of the community.

A less drastic reform, put forward by Lord MOYNIHAN, was for some relief from taxation for people who saved to send their children to schools outside the State system of education, or who chose to go to their own private doctor. Why should not a citizen spend a little of the money he might have in having just a little more than the State would give him? But in doing that, why should he be forced to pay for his medicines, whereas other people who did not take the trouble got it all free? These two were surely blatant attempts at bringing the standard of the people down to a level, rather than trying to raise it.

In replying for the Government VISCOUNT HAILSHAM showed a demure pre-budget reticence which happily

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If wake is a temporary disturbance of the basic state of sleep (and it seems that we must accept this unorthodox view), there is no "cause" for sleep but only cause for wake And what is this cause ? We have enumerated the arousal stimuli, tactile and anoxic threats, hunger, pain, noise, and light, in this order of appearance In addition, "exogenous" training (where the parent wakes the infant for excretion, &c) and later "autogenous" training (where the individual trains himself to awake, often with such an aid as an alarm-clock) should be added to complete the list of arousal stimuli Why do all these stimuli cause arousal whereas other types of stimuli do not ? Is there any single factor common to the former which is absent from the latter ? Yes, it seems that arousal stimuli all partake of a "threat to well being" which can only be met by the alert reaction, whereas the non-waking stimuli and sleep-associated states are devoid of this threat We may cite hunger (not satiety), nightmare (not idyllic dream), arousing shake (not rocking cradle), the smell of burning (not the scent of flowers), bugle (not lullaby), work to be done (not task completed) It is this affective nocuous and therefore prepotent (Wright et al 1952c) element which is required to disturb the placid equilibrium of sleep Perhaps this is the subconscious reason for calling the instrument that awakes us the "alarm" clock Threats below threshold level presumably cause disturbed sleep (sleep movements, sleep noises, dreams, and modification of the sleeping electro encephalogram) If they reach threshold level they produce the extreme disturbance of wake, the speed of arousal being proportional to the degree of threat The threat of a very loud noise will cause almost instantaneous arousal, whereas minor threats (Kleitman 1939b) whose summation causes our ordinary morning awaking (daylight, minor sounds, hunger pains, bladder distension, and training) produce a more gradual arousal It is obvious that when wake maintainers contain a large element of threat, as in anxiety, they will prolong the alert reaction in the unwanted wakefulness of insomnia, for which psychotherapy, religion, and relaxing techniques are more rational treatments than is the use of depressive drugs for blocking the pathways to the arousal centres (Arduini and Arduini 1954)

Because they contain this element of threat arousal stimuli are a form of stress I am therefore tempted to suggest that arousal corresponds to Selye's (1954) "alarm reaction," the ensuing period of wake to his stage of "resistance," and the final drowsy fatigue to his stage of "exhaustion," but perhaps this is oversimplifying the sleep wake problem But there is certainly some evidence to suggest that corticotrophin may play a part in waking Polley (1956)

In arousal the placid unconsciousness of sleep is disturbed by nocuous afferent impulses into a conscious awareness of the challenge which the arousal stimulus contains The first stage of arousal is the introduction of the conscious state by the "open-sesame" of the threat element in the stimulus But, according to Magoun (1953), modality is unrecognised in the arousal centres, and the second stage therefore is the conscious (cortical) activity which recognises the modality of the arousal stimulus and orients it in time and space , In this connection three observations in the phenomena of awaking may be noted

(1) Possibly *the purposeless athetoid movements of its* early stages may be due to the opening of the thalamo cortical circuits by the removal of the suppressor bands (Wright et al 1952d)

(2) Certainly the mental confusion, fantasy, or hallucination described by Grotjahn (1932) shows the gradualness of waking awareness

(3) The quasipurposive movements of closing the eyes (often with a frown) after their first brief opening, and of grimaces of displeasure and turning over in bed, all may be connected with the nocuous nature of the arousal stimulus

Complete awakening leads to action designed to deal with the arousal stimulus, after which wakefulness may continue with pleasurable affect

Conclusion

The orthodox approach to the sleep-wake problem is due to an obvious (but generally unrecognised) prejudice —i e , the subject can only be studied when we are awake If we clear our minds of this prejudice and look at the problem objectively, it appears that sleep is the initial basic mode of life Wake is a temporary disturbance of the sleeping state The cause of wake lies in an increasing variety of arousal stimuli which all have the nature of a threat to well-being and are therefore forms of stress The lengthening duration of wake with age is due to the emergence in early life of wake maintainers which "tag on" after the arousal stimuli have ceased Whenever the arousal stimuli and wake maintainers disappear, the temporary disturbance of the sleeping state ceases

This conclusion provides a firm foundation for the further study of the physiology and pathology of wake It entirely reorients the problem of insomnia, the secret of which lies not in the study of sleep but in that of wake (especially the wake maintainers) In particular the acceptance of this basic view of sleep should be of fundamental help to sufferers from agrypnophobia, and the "threat" nature of arousal underlines the importance of anxiety in the maintenance of unwanted wake

The importance of insomnia and dyssomnia in the production of unhappiness and ill health cannot be exaggerated It is along the lines described above that we shall reach a solution of the problem

I am indebted to the late Prof Samson Wright for helpful criticism

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Parliament

Taxation and Public Expenditure

THE burden of taxation which this country carries and its pressure on the professional classes was one of the main themes of the debate in the House of Lords on March 6 It was recognised that if taxation was to be eased it could only be done by a reduction in public expenditure, and this led several noble Lords to a reconsideration of our social services

Indeed if we were to achieve any big saving in domestic expenditure we must, Lord BALFOUR OF INCHRYE maintained, do "some basic re-thinking" He readily agreed that the Welfare State must continue to safeguard citizens against such unavoidable hazards as sickness and old age But he believed that we must throw over the idea which had crept upon us that a Government could do better for the citizen and could spend better for the citizen than a citizen could do for himself if he were released from the present rapacious tax system The practical application of a revolt against the Government as the spending agent for the citizen would be no subsidised rents for four-figure incomes, no food subsidies, and no free health-service benefits for those who could afford to pay for their own doctors Against this could be set a level of personal taxation which would allow a man to order his affairs as he wished, to order his own housing, to feed his own family, to doctor as he wished and to educate his children as he wished

The EARL OF CROMER suggested that the Welfare State was designed against the background of the past but had to be paid for at the cost of the present Too much of the cost of the Welfare State was devoted to relieving wage-earners of what unhappily they could not afford twenty five years ago, but today in general happily could afford. It was absurd and unrealistic to expend too much of our energies trying to mitigate the hardships of the past We needed them all to overcome the problems of the present, of which undoubtedly the paramount one was our economic survival, and he reminded noble Lords that of the total Government expenditure of £6000 million a third was on the Welfare State If a man was working his wages should be at a level to provide him with a decent standard of living Such funds as the nation could make available for welfare should be devoted primarily to the care of those who could not care for themselves, and to protect those whom society could not look after in the normal sense Lord Cromer could see no justification in this day and age for large-scale largesse to the population as a whole—such as, for example, family allowances He suggested that the Welfare-State costs might be divided into two categories the first covering those items which the normal Christian morality demanded of the State—such as National Assistance and the like—which should be left as a charge against the Budget as at present The second category, covering other items of the Welfare State, might come under an entirely separate social-security budget which would not have recourse to the general Exchequer, but be financed by National Insurance contributions and by part of the proceeds of purchase tax or a special sales tax. This scheme would have the merit of disillusioning those who believed that they were getting something free, and would produce an awareness of the truth of the situation, which was that the Welfare State had to be paid for, not by someone else, but by every working member of the community

A less drastic reform, put forward by Lord MOYNIHAN, was for some relief from taxation for people who saved to send their children to schools outside the State system of education, or who chose to go to their own private doctor Why should not a citizen spend a little of the money he might have in having just a little more than the State would give him ? But in doing that, why should he be forced to pay for his medicines, whereas other people who did not take the trouble got it all free ? These two were surely blatant attempts at bringing the standard of the people down to a level, rather than trying to raise it

In replying for the Government VISCOUNT HAILSHAM showed a demure pre-budget reticence which happily left him free to turn to the broader issues raised in the debate We were admittedly living in difficult times—he later described them as "abounding prosperity and extreme economic precariousness"—but he thought it wrong to paint the picture in too gloomy tones When he went about the streets and saw the children vigorous, straight-limbed, well clad, with bright faces and obviously never under-nourished, he could not regret the changes of recent years

We were spending, he continued, about £1600 million on social services, and as far as education was concerned he did not think we were spending extravagantly—£514 million or less than 3% of our national product But he admitted that many of the evils against which we planned our social services had not come about The Beveridge report and the white-papers which succeeded it were all based on the belief that we were going to have about 10% unemployment He believed that the social services could have been designed more economically if it had been fully apprehended that we were going to have for fifteen years at least (and he hoped it would last much longer) full employment

The health service plan was based on an expenditure of £175 million a year Sir Stafford Cripps thought that he would limit it to £400 million a year At the latest figures it was running at something like £690 million a year These were startling figures As Lord Hailsham saw it, the National Health Service, if not properly controlled, would run away with a great deal of our national resources Pension funds would be in the red somewhere about the middle of next year, to the tune of £40 million By about 1970 the cumulative deficit would be about £380 million Unless fairly stern measures were taken the budgetary situation for our social services would face a serious financial crisis much sooner than we expected What then were we to do? Abandon the social services for which many people had spent part of their lives? He thought that would not be the right course but he thought that some greater charge for them must be made if they were to be maintained, and if honest finance was to be retained

In a system of full employment a country was entitled to look to wages and salaries as primary sources out of which the ordinary necessities of life ought to be met It was true that needed to be qualified by the insurance principle We had learned to pay while we were well for what we might suffer when we were sick At the same time, we had all to be on guard against the belief that we, as a nation or as individuals, had a right to a gradually expanding standard of life always at the expense of other people As he saw it, inflation was nothing more or less than a large number of individuals making on the cumulative resources of the country a large number of demands, amounting, in fact, to a bigger total than the cumulative resources were able to meet We must remember that in times like this it was not only Governments but countries and systems of government which were on trial If we would not face the necessity for spending enough on investment and education, but continued to spend more on enjoyment than we spent on the true necessities of life, we should find that the dictatorships would beat us in the race for the control of the world

QUESTION TIME

Hydrogen Bomb Tests

Mr Frank Allaun asked the Prime Minister if, in view of the cumulative danger of nuclear explosions to this and future generations, he would consider postponing the hydrogen bomb explosion over Christmas Island for six months, during which period Her Majesty's Government would take the initiative in seeking international agreement to stop all future tests —The Prime Minister replied I understand that the Medical Research Council have no evidence that the amount of strontium 90 and other radioactive particles released by hydrogen bomb explosions which may become sources of internal radiation has reached a potentially dangerous level The present and foreseeable hazards, including genetic effects, from external radiation due to fall out from the test explosions of nuclear weapons, fired at the present rate and in the present proportion of the different kinds, are considered to be negligible Accordingly I am not prepared to postpone the forthcoming test in the Pacific

So far, however, as long term policy is concerned, the policy of Her Majesty's Government has been clearly defined I would add that various proposals on nuclear and conventional disarmament will be considered when the Disarmament Subcommittee, of which Her Majesty's Government is a member, meets on March 18

Mr W N Warbey When did the Medical Research Council give the Prime Minister this information?—Did the council take into account the new evidence produced by Dr Libby, the American Atomic Energy Commissioner, which according to a report in *The Times*, shows that the level of strontium 90 in the bones of Americans will reach, by 1970, a level which will already be as dangerous as that laid down in the standards of the Medical Research Council? In view of the great importance of this matter to human beings now living, including children, and to the future of the human race will the Prime Minister look into this matter again?—The Prime Minister Yes, Sir The Medical Research Council's report was, of course, published last June The Council is in continuous touch with this matter All I can say is that the information which I have given is that which is supplied to me I would point out that the banning of tests is quite a different question from that of their possible limitation All these matters Her Majesty's Government are always ready to consider What I am not prepared to do is to postpone the the tests which we are about to make and which put us as a nation in the position in which we have a right and a duty to be Mr Allaun Since the new American evidence shows that we are in real danger of visiting the sins of the fathers on the children, not only to the third and fourth generations but far beyond that, will the right hon Gentleman have another look at the proposal of postponement?—The Prime Minister Of course, we keep all these matters under consideration, but when I am told that the dangers are negligible, as at present, it is not a reason why we, of all countries, should deprive ourselves of a weapon necessary for our safety

Mr Hugh Gaitskell The Prime Minister will recall that Sir Anthony Eden gave us an undertaking that the Government were prepared to try to bring about a separate agreement on H-bomb tests May I ask the Prime Minister, therefore, whether it is the intention of Her Majesty's Government, when the Disarmament Subcommittee meets on March 18, to put forward definite proposals for abolishing these tests, independently of any other disarmament agreement?—The Prime Minister That is a question we would certainly consider The banning of the tests is one thing and their limitation is another What I am not prepared to do, and I do not think the country or the House would wish, is that we alone should deprive ourselves of the tests at this particular moment thus leaving ourselves in a position of inferiority to others Mr Gaitskell Will Her Majesty's Government put forward separate proposals, at any rate for limiting, with a view to their eventual abolition, such tests, independently of any general disarmament agreement?—The Prime Minister We would rather have a comprehensive agreement dealing with the reduction of armaments both in the unconventional and the conventional fields That is what we would like and what we have been working for Short of that, if we cannot get that, we should be anxious to get any limitation of tests agreement

Dr Edith Summerskill Is the right hon Gentleman aware that the statement which he has just made is considered out of date by authorities, and that it cannot be reconciled with the statement which was made within the precincts of this House last week by Professor Haddow, who is regarded as the greatest authority in this country on this subject?—The Prime Minister Governments can only rely upon the best authorities that they can find The best authorities available to Her Majesty's Government are the authorities which we normally consult and whose opinion I have quoted These are not individual experts here and there, but the Medical Research Council which, I think the right hon Lady will admit, comprises the best organised and the most efficient research on this matter that can be found

North Staffordshire Infirmary

Mr Ellis Smith asked the Minister of Health when it was intended to implement the promises made to the hon Member for Stoke on Trent, South, that the urgently required extensions would be made to the North Staffordshire Infirmary —Mr Dennis Vosper replied The regional hospital board has included in its capital programme a new casualty and accident department, which it is hoped to start building next year Mr Ellis Smith While attributing no responsibility in the matter to the present Minister, will the right hon Gentleman see that this matter is now given super priority ? Is he aware that the hut which is now housing a great surgeon and a very fine staff of nurses, together with disabled miners and others, was built in the first world war and was used for a soldiers' sports centre ? Is it not disgraceful that we should have expected these very fine people to have carried on for so long in these appalling conditions, and will he not give the matter super priority ?—Mr Vosper I am aware of what the hon Gentleman says, and that is why this project is in the 1958–59 programme In fact, I understand that some preliminary work is in the 1957–58 programme

Mr Ellis Smith What representations has the Minister received during the past years about the urgent need for extensions at the North Staffordshire Infirmary, Stoke on Trent , what kind of facilities exist there in the huts built of wood , is the accommodation satisfactory ?—Mr Vosper Representations have been received during the past three years from the hon Member for Stoke on Trent, Central (Dr Stross), and the hon Member for Newcastle under-Lyme (Mr Swingler), as well as from the hon Member himself A large wooden hut is in use for the accident follow-up clinic, and a similar one for the skin department The accident accommodation is not satisfactory, and it will be replaced by the proposed new casualty department Comprehensive treatment facilities are provided for the injured in the main hospital building

Prison Doctors

Dr Barnett Stross asked the Home Secretary how many medical practitioners are employed full time in prisons in England and Wales , and of these how many hold the diploma of psychological medicine —Mr J E S Simon replied 49 and 6, respectively Dr Stross Would it not be reasonable to ask that when any improvements are made in the service a special point should be made of ensuring that as many medical men as possible who serve full time in the prisons should have the diploma and that outsiders coming in to assist should also, where possible, be skilled in psychological medicine ?—Mr Simon In the case of applications relating to the prison service, the diploma is regarded as an advantage but not a prerequisite or essential, because the posts do not involve full time psychiatric work When an outside consultant is brought in, he is always a specialist

The Royal Commission on Remuneration

The Prime Minister announced on March 12 that Sir Harry Pilkington, a company director, a director of the Bank of England, and a former president of the Federation of British Industries, has been appointed chairman of the Royal Commission The other members are

Mrs Baxter (aged 54), secretary, Cambridge University Women s Appointments Board

Mr A D Bonham Carter (51), a director of Unilevers

Mr J H Gunlake (53), vice chairman Institute of Actuaries

Prof John Jewkes (54), professor of economic organisation, Oxford

Mr I D McIntosh (49) Headmaster, George Watson's College Edinburgh a member of the Committee on Recruitment of Dentists

Sir David Hughes Parry (64), professor of English law, London University

Sir Hugh Watson (54) deputy keeper of Her Majesty's Signet

Mr Samuel Watson (59) Secretary Durham Miners' Association , chairman of an N H S executive council

The Prime Minister said that the pay of junior hospital medical and dental staff, up to and including the grade of senior registrar, will be increased by 10% from April 1 " We are also considering," he added, " what should be done by way of interim adjustment for other doctors and dentists covered by the commission's terms of reference I shall make a further statement on this matter in due course "

University Salaries

Parliament is to be asked to vote additional funds allowing universities, as from August 1 next, to pay higher salaries to full time staff The necessary increase in the recurrent grant is estimated at £3 million initially For non-medical and preclinical professors the salaries will be £2300 to £3000 a year, according to post For clinical professors they remain at £2500 to £3100, with increases for juniors

In England Now

A Running Commentary by Peripatetic Correspondents

Hurrah for the deep, deep peace of a flat in town in place of the hurly-burly of the weekend cottage, as Mrs Patrick Campbell might have said Not having lived in the real country since I was a boy, I had forgotten what a ceaseless war has to be waged against its denizens in fact, except for mining it's the nearest thing to war in peacetime that there is Up in the night to stop the rats moving the furniture around until you won't recognise the room in the morning Then the dawn patrol against the rabbits, who, like the enemy on most dawn patrols, aren't there " Born and bred in a briar patch " they may be but the local Ole Doc Bunny evidently prescribes the choicest treasures of the rock garden as a diet for convalescent myxomatosists Round the house to take the mice out of their traps and dispose of them After breakfast, out against the pigeons, who can distinguish a gun from a stick at 50 yards with the sun in their eyes But I can still put a shot in a grey squirrel's drey and get a fircone on the head—and no squirrel Then the moles, who have made the lawn look like a lunar landscape The moles ! Some say worms baited with arsenic or strychnine but we do not hold these views Others say cyanide, but we have tried this and it doesn't work Some advocate running the exhaust from the car into the runs for twenty minutes but who, except spivs, has got twenty minutes' petrol to spare ? And the chap from whom we borrow the mole-traps never seems to be at home When all else fails there are the slugs which (are slugs which or who ?) have eaten the primula seedlings, the moths in the carpet, the worm in the chairs, and—by Monday—the bats in the belfry

* * *

Into the E N T *outpatients department* of this large Canadian hospital walked a rather elderly gentleman with his hands clapped to his mouth

" Zzzzz," he said, urgently, to the sister in charge

" Comment, Monsieur ? "

" Aaah ! "

" What is it that you want ? "

" Rrrrrr "

This history, though somewhat lacking in detail, secured entry to the surgeon On examination, a piece of something about the size of a grape was discovered grasped somewhat insecurely between the fingers, and most securely between the teeth Nor would the patient release his grip until it was safely held by forceps Endoscopy then revealed the object to be a nasal polyp which had attempted to enter the glottis It was promptly rejected with such explosive force that it was hurled through the mouth, and out of the lips, until arrested by reaching the end of its somewhat elongated pedicle At this stage, the patient, finding the pedicle between his teeth, had fixed it firmly, and sought help

* * *

How long is a piece of string ? My wife is worried about our pigs We seem to be rearing some curiously elastic variety In case you do not know all the undertaking secrets of the mortuary, the patient is measured up by two official ghouls, one being a gentleman from the National Pig Progeny Testing Board, and the other a grader from the Ministry of Fish and Chips, none the less gentlemanly in the silent presence of those little darlings who pay our rent We could never fathom how there was always about 1 in between them Now we know The grader measures the length of the pig while the carcase is hanging, his colleague while flat on the slab One regards our dear departed as just another hunk of meat The other shows true professional delicacy Bacon factories contain a curious mixture of hopes and fears

Such anomalies strike at the very foundations of anthropometry For many years my wife has made our pyjama-clad little figures stand bolt upright against the bedroom door, with *Price's Medicine* on their heads, while I searched for a scalpel to scratch on the paint Ought we to have looped a dressing-gown cord over the clothes hook and measured them downwards? Would some less weighty tome than *Price* have affected their compression? I doubt if we shall ever know We have long suspected that boarding-schools practise some such expansion-and-contraction technique to puff up their catering claims Even their own figures suggest that our children must shrink in the holidays Maybe we too should keep a rack in the cellar

But the diversionary art of London's escalators asserts that whatever may have slipped in the way of anthropometry can be adequately compensated by the one-way linear stretch, the two-way area stretch, or the three-way cubic s-t-r-e-t-c-h in our new foundation garments Measurements are becoming so relative that before long we must expect another set of little brackets to augment those elementary metric conversions sprinkled all over our journal I can see no limits to tension, short of disruption, and might not some of the world's present troubles be due to one set of people measuring an object hanging and the others measuring it flat, when they are both really measuring the same thing?

* * *

Time off in February or March is often useless Where can one go in this climate? Staying at home to paint the house is tolerable only in small doses and is apt to be interrupted by calls from hospital This year I discovered the Isles of Scilly I went by boat from Penzance (about 3 hours) but those anxious to escape more quickly from civilisation and avoid a possibly stiff dose of the Atlantic can get there in 15 minutes in a tiny aeroplane from Land's End

On arrival there is certainly a feeling of being abroad and a sense of surprise to find English spoken The oldest inhabitant told me of the days when wrecks were common, and on Tresco I saw an interesting Valhalla full of figureheads and odd objects collected from wrecks Many TV aerials are to be seen, but the chance of meeting a car on a nine-mile tramp round St Mary's is slight and the drone of an aeroplane engine is only heard for a brief period On the off islands of St Martin's, St Agnes, Bryher, and Tresco one can really escape completely from the sounds of modern civilisation

The flowers, mostly daffodils, grow in small fields protected from the south-west wind by evergreen hedges But anyone expecting to see bright fields of colour will be disappointed, for the flowers are picked as soon as buds appear Only those spared by an uneconomic price are left to blossom in the field I don't think there is much soil in the Scillies and many of the 140 islands which are uninhabited have none Even grass does not grow on them and by this criterion (Leland's test) they are mere rocks or sandspits the others make up for their Cornish ruggedness by their Mediterranean climate

* * *

Theatre Sister to *Staff Nurse* "Mr Phillips will not be turning up till 9 30 tomorrow, but Simpson is starting at 9"

Not very illuminating, perhaps, unless you happen to know that Phillips is the theatre porter and Simpson the consultant surgeon

* * *

We, in Scotland now, who try to maintain high educational standards, have always looked with a little suspicion at the apparent ease with which Sassenachs can obtain the degrees of M B, CH B at English universities Imagine our surprise then, when on looking through the *Occupational Tables, England and Wales, 1951 Census* (H M S O 1956, and costing *£7 7s mark you*!) we discover there were in England and Wales four medical practitioners whose age last birthday was 15, three aged 16, one aged 17, and four between the ages of 18 and 19 years Can it be that, having failed the 11+ examination, instead of going up to the much vaunted public school, English children are now being sent up to medical schools?

* * *

News from School—As Lent has begun we ought to give something up which we have always said, before, was essential for us. I wonder what would happen if I gave up my food? So far I have'nt given anything up especially sweets, because people are more ready to give them away now, as lots of people have given them up

Letters to the Editor

GOVERNMENT AND PROFESSION

SIR,—Age having caused my retirement just one year before the National Health Service came into action, it is quite impossible for me to assess, in pounds, shillings, and pence, what are the right amounts for the various services and ranks to receive as annual emoluments, yet would I implore all my brethren in our profession to refrain from taking any further part in that strike which is-not-a strike On three former occasions this has failed because the partakers in it realised at the last moment that they could not possibly be parties to so disloyal an action

Today we are in as grave a position as the country ever has been since the end of the Napoleonic wars, and are entering in that second decade after the death of Hitler which corresponds with that which after the fall of Bonoparte preceded the Reform Bill We have been through two wars that have drained us of our wealth, and since then have had Korea to pay for and now there is Suez In this next decade we shall need all the spirit of fraternity that human nature is composed of to get through without grave disturbances

Everyone is feeling the strain, from those who live in great houses and wonder how they can keep them up, to those in the little ones whose daily dread is that they may again be driven down to the standard of living of the first years of this century when the food of many of our children was "bread and marg" for breakfast, dinner, and tea This is not the time for us to take any action, other than by the accepted methods of discussion

Much as many of us may think its methods need amending, trade-unionism has become the accepted means for those who work primarily with their hands This does not mean that anything resembling it should be the means for those that work primarily with their minds—as it has been made since 1911 by those who have claimed to be our leaders Even setting up the organisation is harmful, as it clogs the machinery of proper discussion

It has done so in the past, it will do so again As a private individual, therefore, I beg everyone in the profession to refrain from signing any documents that they may very soon have cause to regret, and will feel bound to repudiate

London, W 1 T B LAYTON

TOWARDS PREVENTING SUICIDE

SIR,—One of the medical members of the Samaritans has drawn my *attention to* Mr A Watney's letter last week The service he envisages has been in operation since November, 1953, when, on my appointment as rector of a City church with minimal parochial responsibilities, I secured the kind cooperation of the national press in inviting anyone who was in *despair* to use MAN 9000 as a sort of spiritual "999"

The calls began coming in at once, and over *650 troubled* people, of whom some 300 appeared to be potential suicides have been persuaded to come and discuss their problems, the commonest of which are lack of a faith to live by, psychological disturbance, marital or other sexual *maladjustment*, and loneliness in the world's most populous city In addition to our "clients," over 150 people have offered to help, and more than half of these are still as active as their circumstances allow Some of the most effective first came as *clients* Our only full time staff apart from myself are a secretary and a telephonist (our telephones ring over 100 times a day)

Our experience has proved the truth of Mr Watney's contention that many suicides can be prevented by "a sympathetic listener and counsellor" Few of our members are armed with anything more than compassion and common sense plus the training we are able to give at our meetings, yet their intervention in the spirit of the Good Samaritan may make all the difference. Only two of our clients have so far committed suicide, though another half-dozen are still in danger of this.

I cannot agree that "helpers should not belong to medical or religious bodies, nor should they be trained social workers or psychiatrists" if Mr Watney means that these should be excluded. The collaboration of medical and lay psychotherapists is essential in many cases, and where there is serious mental disturbance we feel a heavy burden of responsibility until we have won the sufferer's confidence sufficiently to persuade him or her to allow us to obtain a *qualified* opinion. The collaboration of one or two trained social workers has pointed the way to avenues of practical help we might otherwise have been unaware of, and if we were to exclude members of religious bodies we should be reduced to about ten volunteers who give invaluable help but obviously cannot be expected to deal with the many theological difficulties and problems of conscience which come our way. But if Mr Watney means that astonishing successes can be achieved in this work by "ordinary people," especially if they have "been through it themselves" I can assure him that this has been proved up to the hilt.

The broadcast about our work by Stephen Grenfell in the Light Programme last month, and its discussion by the Critics on the Home Service, have not only inundated us with calls from the London telephone area which we regard as our "beat," but have also greatly added to the number of letters from other parts of the country and from abroad. It is clear that a similar service ought to be in operation in all the great centres of population. I am in touch with the work that has started in the last year or so in Berlin (where a psychiatrist who is also a Lutheran pastor is in charge) and in Sweden, but if anything of the kind is going on elsewhere in this country I am unaware of it. I have had inquiries from people in the Provinces willing to help if we will extend, but whilst close links and exchange of experience would be indicated if there were "Samaritans" in all the big towns, it would be undesirable and indeed impossible to organise them from London. We should naturally be willing both to invite leaders to work with us for some weeks, and also to visit other towns to help a newly formed branch to avoid our past mistakes. An active part would need to be taken by a clergyman who did not regard clients as conversion-fodder, a psychiatrist who took people's spiritual needs seriously, a lay psychotherapist working under medical supervision, someone in addition to the clergyman with experience of marriage guidance, a social worker, and a lawyer, and these "experts" would need to be surrounded by a devoted band of people of all religious faiths and none to do that most vital work without which all the rest may be in vain, and which we call "befriending."

I should like to warn anyone who is thinking of starting this work that once it has begun there will be no time to raise the money necessary to keep it going. We innocently imagined that sooner or later (and we hoped not *too* late) someone would notice that we were working understaffed in appalling conditions, and would consider that 3½ years on a shoestring had proved that the idea was sufficiently promising to be worth financing properly. This has not happened, and I would advise prospective anti suicide squads to make sure of adequate premises and funds before committing themselves to anything up to 100 hours a week of the most exacting (if also the most rewarding) work imaginable.

St Stephen's Church
Walbrook, London, E.C.4

CHAD VARAH

NEW DRUGS, OLD DANGERS

SIR,—Your editorial warning (Feb. 9) rightly draws attention to the dangers of toxic reactions to drugs but, as Dr Fraser and Dr Doniach say (Feb. 23), it is unfortunate that a drug of such proven efficacy and safety as carbimazole should be stigmatised by association with the amidopyrine derivatives or even phenylbutazone.

In neither of the above communications was a further interesting point mentioned. In the treatment of other than the mildest degree of thyrotoxicosis, three alternatives are open—radio iodine, surgery, and anti-thyroid drugs. It is not yet certain whether therapeutic radio iodine may eventually have a carcinogenic effect. Surgery has a mortality-rate of at least 0.24%[1] and an appreciable morbidity. Anti-thyroid drugs occasionally cause toxic reactions, but carbimazole appears to be the safest at present available;[2] though many thousands of patients must have been treated with carbimazole, the third fatal case has only just been reported.[3]

Without discussing their relative merits, I would point out that treatment by thyroidectomy has a higher mortality than treatment with anti-thyroid drugs.

Cardiff Royal Infirmary

CRAIG BURRELL

BRONCHIAL CARCINOMA

SIR,—Many of us will find the plea put forward by Mr Thompson (Feb. 23) unacceptable as a rational step towards improving the treatment of this condition. It is true that, as Mr Thompson says, "the difficulties in diagnosis are the real problem" but it is unfortunate that the stress in his comments should focus attention on an aspect of delay that does little justice to his colleagues' efforts, particularly as it has yet to be shown that the earliest possible diagnosis of this condition is, in fact, early enough to justify considering surgery as the treatment of choice.

Without planning especially for any lung condition the hospital service in this area has, for over seven years, provided general practitioners with both X-ray and pathological services, which are freely available, as is access to the thoracic surgeon. The conditions which Mr Thompson advocates have, in fact, existed for a good while, and it is interesting that the almost invariable step of the general practitioner, after getting his X-ray, is to turn either to the consultant physician or to the chest clinic for further investigation. Reports on chest X-rays from hospital departments, though frequently worded in such a way as to indicate probable pathological conditions, are nevertheless commonly couched in terms which cannot indicate to the general practitioner a clear need to turn to the thoracic surgeon. It is presumably at this juncture that Mr Thompson desires a "cancer differentiation clinic" and, although, with suitable rearrangement of the radiologists' phraseology and the general practitioners' habits, new referrals might be less than some of your correspondents forecast, they would necessarily have to be numerous to make any impact on mortality, as I think the following figures indicate.

In this area, of a population of roughly 140,000, during 1956 24 cases of bronchial carcinoma were diagnosed at the chest clinics. Of these, 8 arose in patients already under supervision on account of tuberculosis and/or pneumoconiosis, while 16 were new cases. In 15 others bronchial carcinoma was provisionally diagnosed, and 9 of these were bronchoscoped. 1 patient deemed tuberculous was found to have a neoplasm after ten weeks—the diagnosis was missed in fact. Of the proven group of 24, 11 died during the year. 4 patients had obvious metastases when first seen, 4 others were found to have metastases within two weeks of first attendance, 5 others had bilateral pulmonary tuberculosis (sputum positive in 2), a further 3 had complicated pneumoconiosis category B (Pneumoconiosis Research Unit classification), 2 more refused admission to hospital for either bronchoscopy or deep X-ray therapy, 4 were deemed inoperable by the surgeon by virtue of respiratory insufficiency or advanced age, and 2 were submitted to pneumonectomy and survive. The operability-rate was thus about 8%, and the patients found suitable for operation came from *symptom free* attenders for mass miniature radiography.

Now for the delay: of 17 bronchoscoped the average time between first interview at the clinic and admission for bronchoscopy (always after consultation with the surgeon) was 16 days—a figure materially influenced by 4 patients who, despite every encouragement, held back for 49, 30, 26, and 24 days before agreeing to bronchoscopy. 4 patients (none of them submitted to bronchoscopy) had, in fact, attended hospital for X ray previously, the report going to the general practitioner, and as this is the procedure Mr Thompson favours, their fate is worth following The time which elapsed between the hospital X ray report and referral to the chest clinic was 332 days 71 days, 40 days, and 39 days In the *1st case the patient failed to reattend hospital for further* X rays as requested and there was inadequate follow up by the X-ray department, in the 2nd, delay appears to have been the general practitioner s procrastination, and in the 3rd and 4th cases a firmly made but incorrect radiological diagnosis from the hospital gave the practitioner no hint of the possibility of neoplasm, and a routine appointment at the chest clinic was thus asked for

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[1] Cattell R. B *J clin Endocrin* 1949 9, 999
[2] Burrell C D, Fraser R, Doniach, D *Brit med J* 1956, i, 1453
[3] Tait, G B *Lancet* 1957, i 303

If Mr Thompson will accept 16 days as a reasonable practical interval, to what extent will more speedy diagnosis reduce mortality ?

Workington Infirmary,
Cumberland
R HAMBRIDGE

YOGURT IN GASTRO-ENTERITIS OF INFANCY

SIR,—I have read with interest the correspondence on this subject Yogurt seems to be established as a remedy In eastern parts of India (Bengal and Assam) yogurt is used by village women who regard it as a specific treatment for gastro enteritis in infants and adolescents

Edinburgh
A K CHATTERJEE

A NEWSPAPER FOR THE PARTLY SIGHTED

SIR,—Dr Atkinson's letter of Feb 2 raises the problem of helping the partially sighted to read He suggests the solution may lie in the provision of reading matter printed in type large enough for them to decipher This possibility has already been examined carefully by the educationalists in regard to school books for the partially sighted and found impracticable at present on the grounds of cost of production and limited demand

There are now many devices in the form of hand lens, lens mounted on stands, telescopic lenses, and high power spectacle lenses giving various degrees of magnification up to 15 A special clinic exists at Moorfields Holborn Branch, in London, for providing these aids The aims of the clinic are to find out the needs of the patient and supply the most appropriate aid Some training and encouragement in the use of the appliances in the higher ranges of magnification is found to be necessary Visual aids successfully prescribed give the patients much wider scope than could ever be obtained by the limited production of reading matter in the larger type which would be required

I hope Dr Atkinson will not take it amiss if I suggest that he refers his partially sighted patients to his ophthalmic colleagues, who are fully aware of these appliances and can obtain them for their patients from their local dispensing opticians

London, W 1
P McG MOFFATT

SIR,—Dr Atkinson has drawn attention to the misfortune of those many and often elderly people whose visual acuity is so impaired that they can read type only of newspaper headline size He suggested a special newspaper composed wholly of headline typefaces —a suggestion which poses many problems of which expense is not least

The difficulties of the partially sighted have been prominent in the activities of members of the Association of Dispensing Opticians for many years Telescopic spectacles were produced a half century ago, special magnifiers have been manufactured since the 1920s and made known to ophthalmic surgeons Since 1950, telescopic spectacles of increased power and improved magnifiers of greater field of view have been made available, more recently dispensing opticians have devised reading spectacles permitting magnifications of 4×, 6×, and 8× to be used, and these can be obtained through ordinary trade channels

A system of quantitative assessment of the degree of magnification necessary has been advanced by one of my members and this is the subject of systematic tests for patients at the Westminster branch of the Moorfields, Westminster and Central Ophthalmic Hospitals in London The same member has produced ingenious combinations of illumination and magnification extending the range from 8× to 20×

The Oxford Ophthalmological Congress in July, 1956, made the question of aids to the partially sighted one of its principal subjects for discussion, and the important part to be played by the dispensing optician was recognised when the president and the vice-president of this association were invited to contribute to the opening papers

The problem voiced by your correspondent is therefore being met by ophthalmologists and dispensing opticians, and its solution will render newspapers of enlarged type unnecessary

The Association of Dispensing Opticians,
London, W 1
M G AIRD
Secretary

ÆTIOLOGY OF PRE-ECLAMPSIA

SIR,—May I answer certain criticisms that time did not allow me to deal with at the meeting at the Royal Society of Medicine on Feb 22, reported in your columns last week ?

Renal ischæmia, Pappenheimer's study has shown,[1] can remain undetected it can provoke a rise in blood pressure, and Wilson[2] draws attention to the possibility of an undetected renal mechanism underlying essential hypertension, it can account for *all* the signs of toxæmia and be provoked by the uterorenal reflex,[3] which is the primary and effective, *but not the sole*, stimulus for its production in toxæmia

Professor Browne's experience of serious deterioration of toxæmia after surgical induction is thus accounted for by the excitement of operation, the anæsthetic, the cervical manipulation, and the heightening uterine tension of incipient labour (a supreme adverse factor), which can all increase the renal ischæmia and often help to outweigh the benefit conferred by reducing the intra uterine *pressure* by amniotomy

Renal ischæmia is more likely in pregnancy complicated by essential hypertension—a clinical state where I *suspect* it already exists undetected by our hitherto incomplete appreciation of renal hæmodynamics measured biochemically Renal ischæmia is reflected in the reduced uterine circulation—a change noted also in the pregnant woman suffering from essential hypertension Its occurrence and extent depend on the responsiveness of the kidney, which occasionally varies greatly from patient to patient, thereby largely explaining the also occasional apparent exceptions to the thesis, when even a small fœtus can evoke the renal ischæmic reflex, though a larger one may fail to do so Similarly, as Dr Morris pointed out, a pregnancy complicated by twins or by acute hydramnios is not always a toxæmic one In these circumstances the adaptation of the uterus to its contents also affects the extent of the renal ischæmic response Such adaptation is the measure of the uterine tension (the stimulus of the reflex), and is not to be confused with the intra uterine pressure, which is a minor factor in the production of the tension

The foregoing helps to explain the difference in the incidence of toxæmia when these identical pressure factors (twins and hydramnios) complicate either the primigravid or the multiparous state

Dr Morris raised another point of peculiar interest by citing that toxæmia is not an invariable accompaniment to pregnancy in a rudimentary horn I would like to offer the following explanation Grunewald[4] found an association between the failure of development in the uterine horn on one side and absence of the kidney on *the same* side There may be a physiological counterpart to *this* embryological connection each uterine horn may exert its reflex ischæmic action on the corresponding kidney alone Thus the kidney on the side of the normally developed and non pregnant *horn* would *not* have been subjected to reflex ischæmic stimulation. It would therefore be free to neutralise the humoral hypertensive substances produced by its ischæmic partner and also to deal with the additional salt and water load. Experimental parallels are provided by Kolff and Page[5] and by White.[6]

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[1] Pappenheimer, J R, Kinter, W B *Amer J Physiol* 1956 185 377

[2] Wilson C Ledingham, J M *Brit med J* 1956 ii 1236

[3] Sophian, J *Toxæmias of Pregnancy* London 1953

[4] Grunewald W J *Anat Rec* 1939, 75 237 *Ibid* 1943, 86, 321

Finally, Franklin's[7] "hæmex" effects responsible for renal ischæmia may well underlie the association of toxæmia with extra uterine pregnancy, since blood and certain other substances spilled on the peritoneum can provoke a renal shutdown.

The correct appreciation of the thesis I have advanced is therefore sufficient to explain these apparent exceptions. Its main themes are that the primigravid uterus by resisting stretch imposes renal ischæmia, and that this change is responsible for the pre-eclamptic syndrome. Both remain unshaken is my submission.

London, W 1 JOHN SOPHIAN.

ACETAZOLAMIDE IN THE TREATMENT OF CYSTIC DISEASES

SIR,—We have made an observation which we find quite appealing but are unable to pursue because of lack of suitable patients in our military practice. It is with the hope that readers with suitable patients will investigate the effects of acetazolamide ('Diamox') on cysts of various organs that these superficial observations are presented.

For about a year we have been caring for a 37-year old white woman whose only complaints have been referable to chronic cystic mastitis. Shortly after hysterectomy for "abscessed uterus" in 1949, she first noticed swelling, tenderness, and spherical nodules in both breasts. Over the years the breasts became larger and more tender, and their very weight caused pain in spite of reinforced supporting devices. Progesterone therapy seemed to provide some temporary relief, but at the time of her first visit to the clinic she was quite miserable most of the time. The breasts were enormous, turgid, hyperæmic, and too tender to palpate adequately. There was no other evidence of disease; and urinalysis, blood counts, and chest X-ray were normal. She was examined by a surgical consultant, who was willing to defer surgical intervention.

Progesterone therapy was reinstituted, but no definite improvement ensued and after four months it was apparent that some other measure was mandatory. Because of a possible analogy between secretory cysts and glaucoma, acetazolamide (2 acetylamino-1, 3, 4-thiadiazole-5 sulphonamide) 250 mg was prescribed for each eight hours for three days twice a month. A few days later the patient telephoned joyfully that the pain and tenderness had subsided completely, that her breasts felt light and buoyant, and that the size had so diminished that she could wear comfortably a brassiere several sizes smaller than had been possible for years.

When she returned the following month she described a gradual refilling and increasing tenderness of the breasts after the first detumescence and an equally striking response after the second course of acetazolamide. At this time the breasts were pale, flaccid, wrinkled, and pendulous, and palpation revealed grape like clusters of firm nodules about 1 cm. in diameter, which were non tender. Her weight was 2 lb less than the previous month, and she believed that her feet and ankles were slimmer, although the first examination had revealed no œdema. The regimen was changed to three days of acetazolamide therapy each week, and in the past nine months the patient has had no recurrence of her symptoms.

It was unknown whether the improvement from acetazolamide was a result of reduction of generalised œdema which was apparent only in the breasts and for which there was no obvious cause, or whether there was a specific effect on the cysts themselves. If, like the ciliary body of the eye,[8] the cysts secreted bicarbonate to increase their osmolar, and hence their water, content, inhibition of carbonic anhydrase might cause a reduction in cyst volume. To investigate this possibility, cyst fluid and plasma from a second patient, who had a solitary breast cyst of some 50 c cm volume, were examined before and after a three-day course of acetazolamide with the results shown in the accompanying table.

BIOCHEMICAL FINDINGS IN A CASE OF SOLITARY BREAST CYST

—	Plasma		Cyst fluid	
	May 17, 1956	May 21, 1956	May 17, 1956	May 21, 1956
Na (m.eq per litre)	135.6	142.7	148.5	62.4
K (m.eq per litre)	4.8	3.3	10.0	99.9
CO_2 (m.eq per litre)	27.3	20.2	15.5	31.3
Cl (m.eq per litre)	104.6	110.7	93.0	32.4
pH			7.39	7.18
Milli-osmols per litre*	309.7	288.4	286.2	285.4

* By freezing point depression

We would not dare attempt to interpret these surprising results until they are confirmed in additional cases, but neither this same patient nor any other suitable one has been available to us. Serious analytical errors are uncommon in this laboratory, and the comparability of the 90 m eq per litre gain in potassium and the 86 m eq per litre loss of sodium by the cyst fluid suggests that a true change has occurred. The initial discrepancy of 50 m eq per litre between cations and anions in the cyst fluid, rising to 100 m eq per litre, with no change in total osmolar concentration, indicates a large and increasing concentration of an unmeasured anion.

Although we have been anxious to find patients with cysts of the breast, we are even more interested in the possibility of a favourable response in cysts of the kidney, where slight relief of pressure might have profound effects on function and viability of the renal parenchyma and, hence, the patient. In the one patient whose renal cyst fluid, obtained by percutaneous needle aspiration, was examined before and after acetazolamide therapy, there were no changes from plasma except those expected from the lower protein content. In retrospect, it might have been predicted that a renal cyst, which is derived from the proximal portion of the nephron and presumably lacks secretory capability, would resemble an ultrafiltrate of plasma. However, this too should be confirmed, and the rarity of such clinical material in a military practice makes it unlikely that we will be able to pursue this project.

Walter Reed Army
Institute of Research
Washington 12 D C
U.S.A.

WILLIAM H MERONEY
WILLIAM B BLYTHE
IVAR WERNER
MILTON E RUBINI

POLYNEURITIS AS A CAUSE OF "AMYOTONIA CONGENITA"

SIR,—It is certainly true, as Dr Woolf points out in his letter last week, that amyotonia congenita is a term originally proposed by Oppenheim to identify a condition in which generalised hypotonia of skeletal muscles is present at birth and in which spontaneous improvement occurs. On the other hand, the fact that progressive infantile spinal muscular atrophy (Werdnig-Hoffmann disease) could begin at or before birth was not generally recognised when Oppenheim wrote his original description.[1] Furthermore, it soon became apparent that many cases in which Oppenheim and others diagnosed amyotonia congenita showed steady deterioration and eventually proved to be instances of the progressive disease.[2] Whether or not this was Oppenheim's original intention, it soon became the custom to describe all cases showing severe hypotonia at or soon after birth as amyotonia congenita and few have reserved this name for that small proportion of cases which show spontaneous improvement. Indeed it is now a common practice amongst pædiatricians and neurologists to use the term amyotonia congenita for all cases with muscular weakness and hypotonia developing in the first year of life, even when the condition is obviously one of progressive spinal muscular atrophy Hence I would agree with Brandt[3] that this title is now generally utilised to describe a syndrome which can be produced by many disease entities

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[5] Kolff W J Page I H *Amer J Physiol* 1954 178 69

[6] White H L Transactions 2nd Josiah Macy Conference New York 1950 p 128

[7] Franklin K J *Irish J med Sci* May 1955 p 214

[8] Becker B *Amer J Ophthal* 1954, 37 13

[1] Oppenheim H *Mschr Psychiat Neurol* 1900 8 232

[2] Greenfield J G Stern R O *Brain*, 1927, 50 652

In my view, Dr Chambers and Dr MacDermot (Feb 23) were therefore justified in saying that their cases of infantile polyneuritis had presented with the syndrome of amyotonia congenita While I do not wish to deny the importance and validity of Oppenheim's original observations, I would submit that the term amyotonia congenita has become unsatisfactory and is better discarded It is for this reason that I have suggested[4] a new name—"benign congenital hypotonia"—to identify that group of cases which carry a good prognosis

Neurological Unit,
Royal Victoria Infirmary,
Newcastle upon Tyne

JOHN N WALTON

DEPOT TUBERCULIN

SIR,—Dr Hall's letter (March 2) regarding the disadvantages of depot tuberculin prompts us to record our own experience with this substance

Eleven months ago it was given to a group of 42 elderly people who were negative to 100 T U of Old Tuberculin The difference between the reactions to the P P D (purified protein derivative) and to the control oily vehicle was quite definite in those who reacted, but we find that almost a year later the dusky red indurated area persists in a substantial number of patients It matters little in the elderly, but it is understandable how unpopular it would be in younger people

Another curious feature is that the indurated area becomes more red and angry-looking if the patient has an intercurrent infection We have been unable to explain this

Bournemouth

J KOLCAN
O D BERESFORD

BURNS AND SCALDS

SIR,—We regret having delayed our comment on the letter from Mr Watson and Mr McLaughlin[5] At any rate this delay will have given them the opportunity of saying, "There, I told you so, he does graft immediately"

In the past year, more than eighty patients with burns were admitted to our clinic and only one was grafted, this was a little girl who developed, while in hospital and as had long been forecast by us, a contracture beneath the chin Because of their position and her habit of slobbering food over the raw surface, we were never able to keep the granulations dry

Professor Wells is quite right in his evaluation of the Baghdad granulations, and many others of the experienced visiting surgeons who have examined these cases have commented that they have never seen anything quite like them before But we are especially grateful to Professor Wells because he persuaded his colleague, Mr J H Johnston, to visit us in Baghdad and we had the privilege of his criticism and help over an all-too-short period of weeks Working in the middle of a vast desert, it is easy to develop the belief that all one's geese are swans, and a little deflation has a salutary effect

We are grateful for the dogma on the pathology and repair of burns but should like to refer you to what Shakespeare *might* have said in the matter "There are more things in heaven and earth than are dreamt of in your pathology"

For the information of your correspondents, it is theoretically possible to leave London Airport in the early morning and arrive in Baghdad early the same evening

Baghdad

W E M WARDILL
KHALID NAJI

COLDS IN RELATION TO THYROID ACTIVITY

SIR,—The connection between the thyroid gland and the nose has been recognised for several decades[1] Proetz[2] and Hollender[3] reported an increased tendency to upper respiratory disease in their hypothyroid patients, which could be diminished by giving thyroid hormone

I have compared thyroid function, in patients having diagnostic radioactive iodine (^{131}I) tests for suspected thyroid diseases, with the incidence of upper respiratory infections

Patients referred for these tests were asked the following questions

(1) Do you get colds ?
(2) Have you had a cold or influenza in the past two years ?
(3) Do you suffer from sinusitis or catarrh ?
(4) Do you suffer from hay fever ?
(5) Do you suffer from asthma or bronchitis ?

A patient who replied "yes" to any of these questions was classified as positive, and one who said "no" to every question was classified as negative

A tracer dose of ^{131}I, either 50 μc or 100 μc, was then given by mouth on a fasting stomach After twenty-four hours the thyroid uptake of ^{131}I was estimated, and after forty-eight hours the serum protein bound ^{131}I The second test was omitted in 16 hyperthyroid patients who had an elevated basal metabolic rate or well-developed clinical signs Diagnosis was made by methods other than ^{131}I tests in 4 hyperthyroid patients Patients with a high uptake but low protein bound ^{131}I did not suffer from hyperthyroidism[4] The results in 4 euthyroid patients who had had a previous partial thyroidectomy and in a pregnant patient have been excluded, for falsely high values are found in these cases

All the patients in the hyperthyroid group were clinically hyperthyroid, the majority were suffering from toxic nodular goitres The age distribution is shown in table I

The hyperthyroid patients were remarkably free from upper respiratory infection Only about 13% of them had a positive history, compared with 85% of those without hyperthyroidism (see table II, $\chi^2 = 49\ 5$)

TABLE I—AGE-DISTRIBUTION OF PATIENTS

—	Age (years)					
	0–30	30–40	40–50	50–60	60–70	> 70
Hyperthyroid	2	3	3	6	13	3
Not hyperthyroid	9	14	14	17	16	4
High uptake but low protein bound ^{131}I	2	2	0	2	3	2

Hyperthyroidism may affect the nasal mucosa in two ways

(1) Vitamin A has been shown to be present in greater amounts than normal in hyperthyroid persons[5] owing to the direct action of thyroid hormone on its absorption and conversion from carotene Vitamin A is concerned in the maintenance of mucous surfaces[6] and has been

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[3] Brandt S Werdnig Hoffmann s Infantile Progressive Muscular Atrophy Copenhagen 1950
[4] Walton J N *Lancet* 1956 i, 1023
[5] Watson J McLaughlin C R *Ibid* 1956 ii 685

[1] Osler W, McCrae, T A System of Medicine London 1909 vol 7, p 459
[2] Proetz A W *Ann Otol &c St Louis* 1947 56 328
[3] Hollender, A R *Arch Otolaryng, Chicago* 1956 63 135
[4] Bell G O Eisenbeis C H jun *New Engl J Med* 1955 253 812
[5] Moore T *Biochem J* 1937 31 155
[6] Fell H B *Brit med Bull* 1956 12 35

called the *General Practitioner* ran a campaign to persuade those in practice not to allow themselves to be described as doctor unless they held a university doctorate My father, who subscribed to this journal and held the Conjoint diploma, regarded this advice as an unnecessary interference with the wishes of his patients, who had always considered him their family doctor and often their adviser on matters outside medicine

London, W 1 **PEARSE WILLIAMS**

PEDICULOSIS CAPITIS

SIR,—The investigation described by Dr Nelson and Mr Cromie (Feb 23) is full of interest and the observations will be of value to medical officers of health, all of whom must still be concerned with the prevalence and difficulty of eradication of *Pediculus capitis* The authors very rightly call attention to the part played by reinfestation within the family circle and the desirability of treating other members of the household The issue of dicophane preparations to adult members of families in which recurrent cases of *P capitis* infestations occurred among the children has, in my experience, proved worth while

Is there not, however, a tendency to forget that the outstanding property of the new contact insecticides is their *persistence*? If the application is not allowed to remain on the hair long enough (about a week) its value in killing successive batches of lice as they are hatched is lost The instructions supplied by the makers of certain insecticidal preparations, which advise that the hair should not be washed for at least 24 hours after treatment, seem therefore open to question

In a series of cases in which the hair was untouched for a week after treatment no living lice were found, and all the "nits" were empty Possibly if this practice became more general fewer cases of "reinfestation" would occur

Camberwell, London, S E 5 **H D CHALKE**

A NEW CLINICAL ENTITY ?

SIR,—In a series of letters to your journal in the past few months, epidemics of aseptic meningitis, often associated with rubella-like exanthema, have been discussed These outbreaks have occurred mostly in England, but epidemics were also reported from Belgium and Holland, where ECHO virus type 9 has been isolated from such cases[1] In Sweden this syndrome has been very common since September, 1956

The syndrome does not appear to be altogether new Thus Gabinus[2] has described an outbreak of meningo-encephalitis combined with rubella-like exanthema in Sweden in 1946, and Parry and Good[3] reported the occurrence of a similar clinical picture in 1948 in England

The outbreaks of aseptic meningitis in Sweden during September and October, 1956, were usually not associated with a rash. However, during November and December the combination of aseptic meningitis with exanthema was much more common

The familial occurrence of cases with and without exanthema was quite typical of the outbreaks, and the clinical picture was similar to that described in your columns In about 70% of a total of 64 patients examined over the period from September to January, agents which were cytopathogenic for monkey-kidney cells and human embryonic lung cultures were isolated These were obtained from fæces, throat swabs, or cerebrospinal fluid (C S F) Virus was *found in* C S F *in* 13 cases In several cases virus was isolated from fæces, throat swabs, and C S F from the same patient Fæcal extracts inoculated into suckling mice did not provoke symptoms On the other hand the cytopathogenic agents produced flaccid paralyses in suckling mice in 7 of 20 isolations examined thus far after one or two passages in tissue culture The virus was neutralised in tissue culture by ECHO type 9 antiserum, which type was found in association with the above mentioned syndrome in an outbreak described by Crawford et al[4,5] during an outbreak in England in 1954 In the majority of our cases examined there was a distinct increase of antibody titre against ECHO type 9 virus during the acute phase of the disease

There is an indication, however, that a similar syndrome can be caused by another agent Thus in a third outbreak we have isolated a virus in approximately 65% of 20 cases examined This virus differs from ECHO type 9 *in several* ways and resembles the agent described by Neva and Enders[6] in connection with the so called Boston exanthema In 3 cases we isolated virus from the C S F One of the agents was neutralised by an anti ECHO-virus type 4 serum kindly supplied by Dr Krech, of Berne, who has isolated this type from cases of aseptic meningitis Our strain seems not to be related immunologically to the strains isolated by Neva and Enders

State Bacteriological Laboratory,
Stockholm, Sweden **TORSTEN JOHNSSON**

Obituary

EVARTS AMBROSE GRAHAM

M D Rush, LL D Leeds and Glasg , Hon F R C S

Prof Evarts Graham died on March 4 at the age of 73 at the Barnes Hospital, St Louis, where he had carried out much of the work on thoracic and biliary surgery which won him an international reputation A former president of the American College of Surgeons he was also an honorary fellow of the English college and he held honorary degrees from an English and a Scottish university

He was born in Chicago, where his father, *Dr David W Graham*, was a surgeon on the staff of the Presbyterian Hospital In 1900 he entered Princeton University, and after graduating in 1904 with credits in chemistry and biological sciences he began a concentrated medical course at Chicago University and Rush Medical College Before he graduated M D in 1907 he had already published his first medical paper—a joint report on generalised blastomycosis After his intern year at the Presbyterian Hospital he "withdrew from surgery," as a friend later put it, for *further* and wider studies He joined the Chicago Pathological Society, which at that time included a distinguished group of men who were studying the integration of morbid anatomy with physiology and chemistry He spent two years at the Sprague Institute for Medical Research and a further two years as a postgraduate student of chemistry at the university

The 1914–18 war brought him firmly back to clinical surgery His work for the Empyema Commission on the physiological principles that underlie methods of removing pus from the chest not only clarified the Army's problem in dealing with this complication of measles and influenza in its training camps but also charted a course for thoracic surgery in the years that followed the war But this laboratory work left Major Evarts Graham unsatisfied, and he at length persuaded the Surgeon-General to send him to France in command of an evacuation hospital After the Armistice there was a frustrating period of inactivity in a small French town, and in a moment of depression he confided to the friend with whom he shared a cramped billet over a byre "I don't know what will happen to me when I get back. I have no home, no practice no hospital or teaching position, no money" His friend replied

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1 Nihoul E Quersin Thiry, L *Lancet* Feb 2 1957 p 260
2 Gabinus O *Svenska Läkartidn* 1947 44, 835
3 Parry S C Good R A *Publ Hlth Lond* 1949 62 163
4 Crawford M Macrae, A D , O'Reilly J N *Arch Dis Childh* 1956 31 182
5 Macrae A D Personal communication
6 Neva F , Enders J F *J Immunol* 1954, 72, 307

Graham when you get home you will be offered things n a silver tray," and his heartening prophecy came true

In 1919, after Graham's return to the United States ut before he was demobilised, the Washington University ommittee came to interview him, and the day after s discharge from the Army he arrived at St Louis o take up the Bixby chair of surgery At that time ll-time clinical chairs were an innovation, and Graham elcomed the opportunity the appointment would give m for research and teaching He planned to spend the ornings with the patients and the afternoons in the aboratory, but when he arrived at the Barnes Hospital, he teaching school of the university, he found that there ere only 40 surgical patients 'It was obvious' s he used to relate "that somebody would have to estir himself to increase the number of patients in the ain teaching hospital of the newly reorganised medical chool Somehow or other, much of that job seemed o fall on the new professor of surgery" Graham met he prejudice aroused by a hospital with a closed staff y "barnstorming trips" to county and State medical ocieties Gradually patients began to come new buildngs were soon needed, and the hospital easily met the school's need

Dr Graham's reputation and stature grew with the school till he became one of the acknowledged leaders of his specialty and his profession Of these years of achievement C F W I, a British colleague, writes

Thirty years ago when I first knew him, Evarts Graham was already a notable figure in world surgery His introduction of cholecystography had brought new interest to the diagnosis of biliary disorders while his earlier researches on empyema and his growing interest in lung cancer had earned him a wide reputation in thoracic surgery As the acknowledged leader at Barnes Hospital he had already begun to gather about him the team of young men who were later to extend the range of his influence to many medical schools throughout the country, and already he had begun the zealous advocacy of surgical research which became one of his main interests In later years he took an increasing part in the direction of surgical services and research, served on many scientific commissions and held office as chairman of the American Board of Surgery and as a regent of the American College of Surgeons.

But, important as these things are, it may well be claimed that Graham's greatest contribution was a moral one, through the impact of his powerful personality and fine example A man of high integrity and deep convictions, he expected equal standards of others, and did not hesitate to do battle with those who seemed to fall short Especially he was an unsparing critic of any deviation from a strict code of ethics

Evarts Graham will be remembered with affection and respect by the many British surgeons who, during these thirty years have visited St Louis to work under him They will remember his massive physique his deep melodious voice his slow careful speech, his warm humanity And especially they will remember with gratitude his friendliness towards this country his tolerant understanding of our way of life, and his personal kindness to every one of them

The affection and respect which he won from his British surgical visitors led to more formal contacts with' his colleagues in this country, many of whom already knew him as editor of the *Year Book of Surgery* In 1943 he was elected an honorary fellow of the Royal College of Surgeons of England, which had already the previous year, awarded him the Lister medal He did not come to this country till 1947 to receive these honours and to deliver the Lister oration, later published in the *Annals* of the college, in which he described his first pneumonectomy for malignant disease in 1933 Graham received the honorary degree of LL.D from the University of Leeds in 1951, and he also held the honorary LL.D of Glasgow University In 1953 he was president of the International Congress of Surgeons His own country was of course not behind in recognising his achievements and worth, and he was well furnished with American medals, lectureships, and degrees The admiration and warmth which lay behind these orthodox tributes could be measured by the number of friends colleagues, and students who attended a two-day scientific meeting held at St Louis in 1952 to honour him on his retirement. In his speech at this gathering, Dr Graham looked forward eagerly to further opportunities for research and to getting back "to the laboratory in the afternoons and maybe even some mornings" Unfortunately the time that was left him was short, and his contribution to the surgery of bronchial carcinoma was insufficient to save his own life

DUDLEY WILLIAM CARMALT-JONES

M.A, D.M Oxfd, F R C.P, F R.A C.P

Dr Carmalt-Jones who died on March 5 in his 83rd year, was one of that small group of physicians who early this century were using the new knowledge of physiology and bacteriology for more systematic diagnosis and treatment of disease Born in 1874, the son of T W Carmalt-Jones, F R C S.E, he was rather late in taking up the study of medicine, for going from Uppingham to Corpus Christi College, Oxford, he studied the classics as a preliminary to the medical career His clinical work was done at St Mary's Hospital Paddington, and he qualified in 1903 Almroth Wright had but recently arrived at St Mary's, where he was beginning his stimulating work on vaccine therapy Carmalt-Jones, after holding house-appointments at his own hospital and elsewhere, joined the eager band of research students whom Wright had gathered round him

He was appointed assistant physician to the Seamen's Hospital Greenwich, in 1908 and to Westminster Hospital soon after, and in 1912 he acted as dean of the Westminster Medical School In 1911 he published his *Introduction to Therapeutic Inoculation*, which embodied the principles he had learnt from Wright But, just when he seemed set for the life of a distinguished consultant in this country, the first world war broke out, and Carmalt-Jones joined up and served in France and Egypt, finishing as consulting physician to the Egyptian Expeditionary Force and a temporary colonel in the Army Medical Services In the last year of the war he changed his plans and decided to apply for the chair of systematic medicine, which was then being established at the University of Otago, Dunedin Appointed to this post, he was at first a little disappointed with the conditions under which he worked, but soon he entered into the life of the growing medical school and identified himself with its aims and aspirations so that at the end of his time as professor he declared that his election was "the greatest piece of good fortune which has ever befallen me" For twenty years he worked hard, and inculcated the principles of medicine into the minds of many generations of students. Also he gave time and thought to the affairs of the British Medical Association and of the Royal Australasian College of Physicians, of which he was vice-president

[Zenith Studio Dunedin

Carmalt-Jones was suited to the academic manner of life and probably would not have been happy in competitive consultant practice His knowledge was great and his opinions sound, but he was a little diffident in manner, he did not seek private practice but gave all his time to his professorial duties He was a ready writer, for besides the book mentioned above he produced several others of which perhaps the best known was *Elementary Medicine in Terms of Physiology* (1929) On his retirement from the professoriate he was elected emeritus professor and he occupied some of his time writing the annals of the University of Otago Medical School which contain a great deal of information about the early days of medical development in New Zealand Another pursuit during retirement was painting and in his middle 70s he still had the energy and courage to go sketching in London *coram populo* In his 30s he had joined the Athenæum and it gave him pleasure when, a few months ago, he was elected an honorary member of the club

Dr Carmalt-Jones married in 1907 Mabel, daughter of Captain F L Tottenham. She died in 1935, leaving a son and a daughter

CHARLOTTE ALICE KING

M D Lond , M R C P , D P H

Dr Alice King, late physician to the Queen Elizabeth Hospital for Children, London, died at her home in Hampstead on Jan 11 in her 77th year

She was born in Fifeshire, but her family soon moved to London and she was educated first in a day school there, and later at Exeter High School From school she went to the London School of Medicine for Women and then to the Royal Free Hospital. After graduating in 1905, she held house-posts at her teaching hospital and the New Hospital for Women, now the Elizabeth Garrett Anderson Hospital She was appointed medical registrar at the Royal Free Hospital, and worked with Dr Sydney Owen at the Queen's Hospital for Children (now, since amalgamation with the Princess Elizabeth of York Hospital, the Queen Elizabeth Hospital for Children) In 1921 she joined the staff of " The Queen's " as assistant physician, and gave the hospital whole-hearted service for 24 years She was also for a number of years on the visiting staff of the South London Hospital for Women, until she decided to confine her work to pædiatrics For many years she was secretary of " The Queen's " medical committee She was due to retire in 1940, but as the hospital's staff was depleted as the result of the war, she stayed on despite failing health and attended with unfailing regularity to give her help until the end of the war

H. M M M writes

Dr King was one of a large and closely knit family of five brothers and four sisters, and as her nephews and nieces grew up in different parts of the world she took a keen interest in their doings and achievements and they found a warm welcome from herself and her sister when they visited her home She was quiet and unassuming in manner, methodical in her work, and kindly and tolerant in her outlook Her outpatient clinics were crowded, and during the inter war years of poverty and unemployment and the disruption of the war years, her kindness and sympathy gained her affection from many of the people of East London The kindness of herself and her sister was exemplified in the warm hospitality they gave when my flat was blasted by a bomb in 1941, and two bedraggled individuals presented themselves in the small hours of the morning at their house

Alice King was a member of the London Natural History Society, and was interested in ornithology and in archæology She and her sister took much pleasure in music and were great walkers, spending many holidays together in the Lake District, or, on Sundays enjoying strenuous tramps in Surrey or Sussex

FRANCIS GEORGE FRANCE

M B Lond

Dr France, who had been a general practitioner in Bromley, Kent, for thirty years, died at his home there on Feb 22, at the age of 58 He was born at Ludlow and was always proud of his Shropshire birth and boyhood He was educated at Ludlow Grammar School and Bromsgrove School In 1917 he joined the Welch Regiment and served in France where, at the age of 19, he was severely wounded in the chest by shrapnel He was invalided from the Army, and after he had recovered from his wounds he began his medical studies at St Bartholomew's Hospital He qualified in 1924 and then, in turn, was house-physician at Brompton Hospital and resident surgical officer at Leicester Royal Infirmary

In 1926 he joined Dr McArthur in one of the oldest practices in Bromley, and practised from the house that had at one time been the Manor House of Bromley He became honorary physician to Bromley Hospital and served in this capacity until, shortly before the start of the National Health Service, the hospital was enlarged and its staffing reorganised to include visiting consultants from London

A colleague writes

Though severely handicapped by the cardiac disability left by his wounds Dr France lived an active life as a general practitioner, caring diligently and conscientiously for a wide spread practice and earning the esteem and devotion of his patients His pleasures were those of the study, and he drew lifelong enjoyment from his reading of the Greek classics, Shakespeare, Proust, and other great writers in English and French literature He played chess for his county, and he was a founder member of the Bromley chess club and later its president

Dr France leaves a widow, two daughters, and a son His elder daughter was the first woman to win an open scholarship to St Bartholomew's She has now qualified from her father's hospital, and her brother is a student there

Dr. WILLIAM STOBIE

N J E writes

Dr William Stobie had many endearing characteristics that will long be remembered by those who worked with him He had a great zest for life The activities of youth and sport of all types, but particularly rugby, were certain to engage his interest In consequence he usually had a keen following of the more energetic students and it was not surprising to find him acting as a referee in his 50th year

[illegible]

Despite his leaning towards the youthful way of life, he was essentially a traditionalist A stickler for medical etiquette, he deplored any slackness in the formal relationship both with colleagues and patients As might be expected these virtues helped to make him a good committee man, an excellent chairman, and carried him to senior honours in local authority administration, as mayor of Oxford and latterly chairman of the Oxford bench.

Always full of energy, striding along away ahead of his followers, his familiar figure with a flower in his buttonhole and his " come along, doctor " will be sadly missed

Births, Marriages, and Deaths

BIRTHS

WOLFSON —On Feb 17, at Dudley Road Hospital Birmingham to Nancy wife of L J Wolfson, F F A R C S —a third daughter Barbara Hilary

Appointments

BAIRD, G M M B Edin , M R C P E consultant psychiatrist St George's Hospital Morpeth

COOPER J R O, M R C S , L D S honorary dental surgeon Hospital of St John and St Elizabeth London

FAULKNER, G E M B Birm D P M deputy physician-superintendent Kingseat Hospital Newmachar, Aberdeenshire

GIORDANI A , M R C S D M R D honorary assistant radiologist, Hospital of St John and St Elizabeth, London.

HELSBY, C R , M B Lpool, F R C S consultant surgeon Liverpool Royal Infirmary

IRVINE R E , M D Camb M R C P assistant physician (S H M O) geriatric unit, Sunderland area group of hospitals

MARSHALL L J , M B Lond assistant M O , public health department Leeds

East Anglian Regional Hospital Board

BERGIN M M , M B , D A registrar in child psychiatry and mental deficiency Little Plumstead Hospital Group

MERRITT T J K M B Lond D P M senior registrar department of child psychiatry Ipswich and East Suffolk Hospital

MILLAR K J M B Melb surgical registrar, West Suffolk General Hospital

SOOTHILL E F M B Camb , F R C S senior surgical registrar United Norwich Hospitals

Leeds Regional Hospital Board

PUGH R J M B Birm M R C P D C H part time consultant in pædiatrics Hull and East Riding Hospitals

REYNELL, P C D M Oxfd M R C P part time consultant in general medicine Royal Infirmary and St Luke's Hospital Bradford

STREET D R K M B Leeds D P M assistant psychiatrist (S H M O) Broadgate Hospital Beverley, and associated clinics at Beverley, Driffield and Hull

Notes and News

AGEING BUSMEN

SOME occupations offer the elderly worker a longer welcome an others As Mr Le Gros Clark in his report on ageing in dustry has already pointed out[1] a clock maker can continue make clocks long after a miner has had to leave the coal face et the miner though he can no longer hew coal may still be le to do a useful day's work These elderly men who have ven the community years of arduous physical work deserve e opportunity to change to less strenuous work in their late fties and early sixties To talk glibly of a light job is, however, ne thing, to find it seems to be another, and Mr Le Gros Clark as already shown that many of these men have great difficulty finding alternative employment

In his latest report[2] he has examined the problems of usmen, a group who for their own health and the community's afety should be encouraged to retire when they feel the pproach of old age In a group of 150 London bus drivers he ound that 38 retired between the ages of sixty and sixty four nd a further 55 at the age of sixty five when they became ligible for a pension For a group of 150 conductors the igures were 53 and 61 respectively Though some 80% of hese men left for reasons of health some of them were prepared o go on working and went in search of other jobs, but it is ncertain how many found work.

About three quarters of the men who left the buses before eaching pensionable age were given lighter work in the arages and offices of the service, but no work could be given o those who left after they were sixty-five Moreover men ransferred to light work are compulsorily retired when they each the age of sixty five, for the number of light jobs is imited and they have to make way for the next batch of men who have had to give up driving or conducting The bus service, though clearly anxious to help its elderly employees, is thus unable to provide enough lighter jobs This is a difficulty shared by most arduous occupations, and it is unfair and ineffective to leave these undertakings to meet it alone In Mr Le Gros Clark's view the problem will only be solved by " nationally widening the range of alternative jobs "

CHRONIC BRONCHITIS

LAST year the National Association for the Prevention of Tuberculosis changed its charter to include interest in other lung and heart diseases, and last December a meeting was held under its auspices at which eleven London doctors spoke Each dealt with those aspects of chronic bronchitis in which he was expert The ætiology, diagnosis, and treatment were discussed, and the consequences of the disease when social care and chest surgery are considered The lectures have now been published in a well illustrated booklet[3]

THE PUBLIC HEALTH IN LAGOS

IN former years the report of the inspector general of medical services covered the whole of Nigeria, but the division of the country into three regions, each with its own director of medical services, has meant that the report of Sir Samuel Manuwa, the chief medical adviser to the federal government, is now restricted to an account of the problems and services in the urban area of Lagos His first report[4] in the new form is a clear and far sighted account and evaluation of a complex and developing situation

Sir Samuel at once makes the important point, which must be grasped by all administrators—medical and other—that in such tropical cities the chief difficulties relate not so much to tropical diseases as to those found in large towns everywhere He classifies the major problems as provision of hospital facilities (at present almost 1000 beds for a population of 350,000, with proposals for construction involving 750 further beds), shortage of staff, tuberculosis, mental health, sanitation (water supply, slum clearance, sewage), and health education 0 5–1 0% of the population have active tuberculosis as discovered by mass radiography, and if the experience of some other African cities is a guide, this high rate may be expected to increase, though steps are being taken vigorously to control the disease An infant mortality rate of 80 8 per 1000 live births is recorded The chief causes of death at all ages are dysenteries and diarrhœas, malaria, pneumonia, cardiovascular disease, tuberculosis, malnutrition, and tetanus The federal government controls the University College Teaching Hospital, Ibadan,[5] and the Pharmacy School, Yaba, and it trains many nurses and other workers

OUTSTAYING THEIR WELCOME

DURING the period Jan 1 to Dec 15, 1956, 1289 patients were admitted to the infectious diseases wards of Neasden Hospital, as many as 739 cases were refused One reason given for this large number of refusals is the fact that many patients overstay their discharge date 677 bed days (about 1½% of the total) were lost in this way In many cases the child had been admitted from a hostel in Fulham for mothers and children, and the mother had become homeless because she was not allowed to stay there without a child Sometimes the parents were ill or vagrant or could not be traced Eventually most of the children were claimed by their parents, but a number were adopted and others placed in residential nurseries or homes In the hope of detecting such " problem cases " early, an almoner is to be employed for two and a half days a week at the hospital

PREPARATION FOR GENERAL PRACTICE

IN 1955 the University of North Carolina made a field study of the family doctor, hoping thereby to identify some of the strengths and weaknesses of the system of medical education under which he is trained According to the Rockefeller Foundation,[6] " one of the most important conclusions was that training in internal medicine for periods longer than three months, during either the internship or hospital residency of a young M D, leads to better performance in his later years as a general practitioner No other factor was found to be more consistently correlated with good performance "

University of Oxford

On March 2 the following degrees were conferred

D M—M G Ellis, M A Peyman, Sabine J Strich
B M—D H G Ogg

University of London

The title of professor of hæmatology has been conferred on Dr J V Dacie in respect of his post at the Postgraduate Medical School of London

Dr Dacie took the M B Lond from King's College Hospital in 1935 and the M R C P the following year He has held a Medical Research Council research studentship and a Will Edmonds clinical research fellowship and he has also acted as resident pathologist at King's During the war he was for a time a pathologist in the E M S and later he served in the R A M C with the rank of major In 1946 he became senior lecturer in hæmatology at the Postgraduate Medical School, and two years later was promoted to a readership In 1956 he was elected F R C P His published work includes papers on familial hæmolytic anæmia nocturnal hæmoglobinuria and blood loss in battle casualties His *Practical Hæmatology* appeared in 1950 and *The Hæmolytic Anæmias* in 1954 He is editor of the *British Journal of Hæmatology*

The title of professor of clinical endocrinology has been conferred on Dr T Russell Fraser in respect of his post at the school

Dr Fraser graduated M B with distinction at Otago in 1932 and he has held a New Zealand University travelling fellowship In 1935 he was awarded the Hallett prize and three years later a Rockefeller travelling fellowship He has also worked as a research fellow at Harvard University In 1940 he was appointed psychiatrist at Mill Hill E M S Hospital where for the next two years he was in charge of a team investigating for the Ministry of Home Security the psychiatric effects of bombing, and he reported the results in a paper to the Royal Society of Medicine In 1943 he became investigator in charge of a team for the Industrial Research Board and in 1946 he joined the staff of the Maudsley Hospital The same year he became registrar and lecturer in medicine at the Postgraduate Medical School of London and in 1947 he was appointed to a readership in medicine there He was elected F R C P in 1948 He has published papers on insulin therapy Simmonds's disease and the urinary excretion of radioiodine as a test of thyroid function

University of Liverpool

On Tuesday, March 26, at 5 15 P M, Prof B Uvnäs, of the department of pharmacology of the Karolinska Institute, Stockholm, will deliver a lecture on the sympathetic vasodilator system

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[1] See *Lancet* 1955 ii, 1126

[2] Bus Workers in their Later Lives 1957 Pp 26 A limited number of copies available free from the Nuffield Foundation Nuffield Lodge Regent's Park, London N W 1

[3] Chronic Bronchitis—an N A P T Symposium Obtainable from Tavistock House North Tavistock Square London W C 1 Pp 44 6s

[4] Federation of Nigeria Annual Report on the Medical Services of the Federal Territory of Lagos for the Year 1955 Lagos, 1956

[5] See *Lancet* 1956 i 628

[6] Rockefeller Foundation annual report for 1955 From 49, West 49th Street, New York, N Y, U S A

Auxiliary Royal Army Medical Corps Funds (1939)

The annual general meeting of the funds will be held at 11, Chandos Street, London, W 1, on Monday, April 1, at 5 P M

Collegium Internationale Allergologicum

This association will hold a symposium at 1, Wimpole Street, London, W 1, from March 25 to 29, under the presidency of Dr David Harley

Marjory Stephenson Lecture

Dr A Lwoff, of the Institut Pasteur, will give this lecture on Monday, April 15, at 6 P M at the Royal Institution, 21, Albemarle Street, London, W 1 The title of his lecture is The Notion of Virus

United Hospitals' Choir

The choir, conducted by Dr Buxton Orr, is to give Mozart's requiem mass at 8 30 P M on Thursday, April 4, at the Church of St George the Martyr, Queen Square, London, W C 1 Admission will be by programme (3*s* 6*d*) to be obtained from Miss J Magrath, 18, West Side, Clapham Common, S W 4

International Conference on Hepatology

This conference will be held in Perugia from June 18 to 20 under the auspices of the medical clinic of the university and its director, Prof Giorgio Dominici Further information may be had from Dr G Menghini, Clinica Medica (Policlinico), Perugia, Italy

St. John Ambulance Brigade

A weekend conference for surgeons of all ranks will be held at the Cairn Hydro Hotel Harrogate, from Friday to Sunday, May 3 to 5 Further information may be had from the surgeon in chief's department, 8, Grosvenor Crescent, London, S W 1

Association of Psychiatric Social Workers

The annual general meeting of this association is to be held at the Middlesex Hospital, London, W 1 on Saturday, March 30, at 2 30 P M, when Mr Kenneth Robinson, M P, will give his presidential address on public attitudes toward mental disorder

Royal Medico-Psychological Association

Child Psychiatry Section—A meeting of this section will be held at the Bristol Royal Hospital for Sick Children, St Michael's Hill, Bristol, 2, on Thursday, May 2, at 5 30 P M when Dr Gaynor Lacey will open a discussion on young children with recurrent abdominal pains

Instruments used in Industrial Hygiene

The British Occupational Hygiene Society is holding a *conference on this subject* in London on April 16 and 17 It is open to non members, and further particulars may be had from Dr D Turner, M R C Laboratories, Holly Hill, Hampstead, N W 3

Medical Society of London

At the 177th anniversary dinner on March 7, Lord Evershed remarked that the society's early records included no mention of the Napoleonic wars on land or at sea, yet perhaps this was not so singular, for in the whole of Shakespeare's works there figured but one Spaniard—and he a fantastical figure Lord Evershed was convinced that his friend the president (Dr T C Hunt) would soon be making fun of the law, and for his own part he recalled *Voltaire's definition of* a physician as one who pours drugs of which he knows little into bodies of which he knows less Replying for The Society, the President likened Lord Evershed's *life as Master of the Rolls to that of* a consultant in John Lettsom's day, when the apothecaries brought news of cases to him in a coffee house Nowadays of course the news came from Savile Row, usually gently through *Prescribers Notes*, but occasionally in harsher tones Turning to the society's affairs, the President said that the number of fellows had increased to nearly 700, and the society's rooms were proving too small The subscription had remained at 2 guineas for many years, indeed it had no more than doubled since Lettsom's time Dr J S Richardson dealt kindly with The Guests, and Dr Macdonald Critchley, though himself a fellow, responded as master of the Society of Apothecaries, observing without rancour that, whereas this year he was seated among the mighty, next year he would be in the body of the hall among the scornful

C M F /M E F. Physicians' Dinner

This dinner will be held at Simpson's in the Strand London, W C 2, on Saturday, March 30 Particulars can b had from Dr Arthur Willcox, 59, Harley Street, W 1

Doctors who wish to watch the Boat Race on March 30 from the Bemax premises should make early application to Dept B E J Vitamins Limited, Upper Mall, London W 6

Diary of the Week

MARCH 17 TO 23

Monday, 18th

UNIVERSITY COLLEGE LONDON, Gower Street, W C 1
5 P M Dr George Popjak Biochemistry of Fatty Acids and Cholesterol (Third of three lectures)

HUNTERIAN SOCIETY
8 30 P M (Talbot Restaurant, London Wall, E C 2) Dr Raymond Greene, Dr Eric Scowen Hormonal Treatment of Disease

POSTGRADUATE MEDICAL SCHOOL OF LONDON, Ducane Road W 12
4 P M Prof G. M Wilson Thyrotoxicosis and Heart-disease.

INSTITUTE OF DERMATOLOGY, Lisle Street, W C 2
5 30 P M Dr I A Magnus Respiratory Activity of the Skin.

Tuesday, 19th

INSTITUTE OF DERMATOLOGY
5 30 P M Dr F R Bettley Industrial Dermatitis

WEST END HOSPITAL FOR NEUROLOGY AND NEUROSURGERY 91, Dean Street W 1
5 30 P M Mr K I Nissen Orthopædic Surgery for Neurological Conditions

Wednesday, 20th

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields W C 2
4 P M Sir James Learmonth A Surgeon's Outlook (Joseph Clover lecture)

ROYAL SOCIETY OF MEDICINE 1, Wimpole Street, W 1
10 A M *Endocrinology* (Joint meeting with the Society for Endocrinology) Symposium on Investigations of Subjects Relating to Obesity and Diabetes, introduced by Sir Charles Dodds, F R S
5 P M *Comparative Medicine* Mr E Cotchin Dr Geoffrey Hadfield Mr W P Greening, Prof Alexander Haddow Mammary Tumours
8 15 P M *General Practice* Dr Lindsey Batten, Mr Denis Browne Dr G B Mitchell Heggs, Mr David Matthews Common Congenital Abnormalities and Their Management in General Practice

POSTGRADUATE MEDICAL SCHOOL OF LONDON
2 P M Prof W St C Symmers Thrombotic Microangiopathy

INSTITUTE OF DERMATOLOGY
5 30 P M Dr Arthur Tickner Recent Experimental Work on Hormones

INSTITUTE OF DISEASES OF THE CHEST Brompton, S W 3
5 P M Dr F J Prime Physiological Mechanisms in Acute Asthma

ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE, 28, Portland Place, W 1
3 30 P M Dr J M Alston Leptospiral Infection as an Occupational Risk to Health Throughout the World

ROYAL MICROSCOPICAL SOCIETY, Tavistock House South Tavistock Square, W C 1
5 30 P M Mr E H Leach Structural Changes in the Eye Caused by Various Diets

BRITISH ASSOCIATION OF SPORT AND MEDICINE
5 45 P M (St Mary's Hospital Medical School, W 2) Dr D J Cussen Medical Aspect of the Olympic Games at Melbourne

Thursday, 21st

ROYAL COLLEGE OF SURGEONS OF ENGLAND
5 P M Mr Edwin Haigh Acute Abdomen in Neonates (Hunterian lecture)

ROYAL SOCIETY OF MEDICINE
4 45 P M *Dermatology* Dr J S Pegum Dermabrasion.

HYPNOTHERAPY GROUP
8 P M (Royal Society of Medicine) Dr Ainslie Meares Hypnography—a Technique in Hypno analysis

MANCHESTER MEDICAL SOCIETY
8 P M (Staff House University of Manchester) *Anæsthetics* Dr A V Jenkins Pædiatric Anæsthesia. Dr J D Lumsdon Relief of Pain in Forceps Delivery

Friday, 22nd

ROYAL SOCIETY OF MEDICINE
8 15 P M *Obstetrics and Gynæcology* Mr Percy Maln Ætiology of Fibroids Mr V B Green Armytage, Pre Habitual Abortion—the Shirodkhar Operation Mr Chassar Moir Urethral Reconstruction Mr Dav Currie Wertheim's Hysterectomy

INSTITUTE OF LARYNGOLOGY AND OTOLOGY 330 Gray's Inn Road London W C 1
3 30 P M Mr William McKenzie Modern Methods of Improving Hearing

KENT PÆDIATRIC AND CHILD HEALTH SOCIETY
3 P M (West Kent Hospital Maidstone) Dr A M Jacoby Conditions which Require no Treatment

THROMBOPHLEBITIS FOLLOWING INTRAVENOUS INFUSIONS · TRIAL OF PLASTIC AND RED RUBBER GIVING-SETS

REPORT TO THE MEDICAL RESEARCH COUNCIL BY A SUBCOMMITTEE* OF THE COUNCIL'S BLOOD TRANSFUSION RESEARCH COMMITTEE

THROMBOPHLEBITIS is a common complication of continuous intravenous infusions and, though rarely dangerous, may cause the patient much pain and discomfort Recent reports, summarised in table I, show that when infusions given through standard National Blood Transfusion Service sets are continued for more than twelve hours the incidence of thrombophlebitis is over 50%

In 1953 the frequent occurrence of thrombophlebitis after intravenous infusions was considered by the Blood Transfusion Research Committee of the Medical Research Council The work of Handfield-Jones and Lewis (1952) had shown that the incidence of thrombophlebitis varies with the type of rubber tubing used in the making of intravenous drip sets Pure latex rubber tubing was associated with the lowest incidence It was decided to carry out tests with sets made of plastic tubing as it seemed likely that this tubing would be associated with a lower incidence of thrombophlebitis As soon as a plastic set manufactured in Britain became available, a subcommittee was formed to carry out the tests, and the present report summarises the findings of this subcommittee

Methods

The Plastic Transfusion Set

The tubing of the set used in the trials was made of polyvinyl chloride with added "plasticiser" and "stabiliser" The set consisted of a nylon piercing-needle, a filter chamber with a nylon mesh filter, a drip-chamber, a length of plastic tubing (approximately 6 feet) terminating in a short length (3 in) of latex rubber tubing, and an adapter fitting into a needle or cannula

TABLE I—INCIDENCE OF THROMBOPHLEBITIS FOLLOWING INTRAVENOUS INFUSIONS LASTING MORE THAN 12 HOURS, ADMINISTERED THROUGH BLOOD TRANSFUSION SERVICE RED RUBBER GIVING SETS

Article	No of cases	No reaction	Thrombophlebitis	
			No of cases	% of total
Bolton Carter 1951a	32	11	21	66
Handfield Jones and Lewis 1952	54	17	37	68
Page et al 1952	29	10	19	65
Jones 1954	26	7	19	73
Present series 1956	189	84	105	56

The set was used in conjunction with a special rubber bung incorporating an air inlet valve

Sterility, pyrogen, and toxicity tests carried out on sample sets were all negative

Thrombophlebitis Trial

The particular object of the subcommittee was to ascertain the incidence of thrombophlebitis when the set was used for continuous intravenous infusions It was decided to make a direct comparison between plastic and red rubber giving sets as this would at once give a standard of comparison for the results and also eliminate the influence of unknown factors which might operate with different techniques in different hospitals The red rubber sets used in this trial were those being supplied in 1956 by the National Blood Transfusion Service

Seven hospitals took part in this trial Several methods were used to ensure random use of a rubber or plastic set Thus, in one hospital, the choice of set depended on the day of admission, in other hospitals it depended on whether the patient's hospital number was odd or even, and in others the type of set was alternated between consecutive cases When a patient received more than one infusion, only the results of the first were included

TABLE II—FREQUENCY DISTRIBUTION OF LENGTH OF INFUSION AT EACH CENTRE FOR THE TWO TYPES OF SET *

—	Centre	Length of infusion (hours)				
		0–11	12	13–23	24–47	48 or more
Plastic	H	1	13	36	26	4
	St T	0	2	6	13	6
	R I E	2	15	9	8	5
	S	1	0	2	14	15
	M	0	0	2	3	17
	R I M	1	3	2	2	3
	B	0	0	6	1	0
	Total	5	33	63	67	50
Rubber	H	1	8	36	22	14
	St T	0	3	7	6	9
	R I E	0	8	8	14	8
	S	1	0	2	9	20
	M	0	0	1	7	14
	R I M	0	0	2	4	1
	B	0	0	1	4	0
	Total	2	19	57	66	66

* The various centres participating in the trial are indicated by initial letters H = Hammersmith Hospital St T = St Thomas's Hospital R I E = Royal Infirmary, Edinburgh S = Southmead Hospital M = Middlesex Hospital, R I M = Royal Infirmary Manchester B = Birmingham Accident Hospital

Workers in the "thrombophlebitis trial" also reported on the performance of the set, and further reports were obtained from 13 other civil and many service hospitals These reports, totalling over 700, have been used in working out a revised design Plans for the manufacture of this modified set are going forward, but the set is not yet in production

Recording of Results

Infusions were set up in the ordinary way by housemen and registrars In each centre one, or at most two, individuals undertook to make all observations and these were recorded on a special card The details noted were the times at which the infusion was begun and discontinued, the type of needle or cannula used, the site and method of insertion into the vein, and the nature and amount of fluid or fluids given Detailed information was sought on the local reaction to the infusion This was assessed by measuring the length of vein thrombosed

TABLE III—FREQUENCY DISTRIBUTION OF REACTION WITH THE TWO TYPES OF SET, FOR INFUSIONS LASTING MORE THAN 12 HOURS

Reaction	Plastic		Rubber	
	No	%	No	%
N	9	5	25	13
S	23	13	39	21
M	25	14	41	22
O	123	68	84	44
Total	180	100	189	100

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* The members of the subcommittee on trials of plastic transfusion equipment were Dr P L Mollison (chairman), Brigadier G T L Archer, M.R C P I, Mr P Armitage, PH D Dr J M Barnes, Mr J F Bolton Carter, F R C S, Prof A M Boyd, F R C S, Dr J P Bull, Dr R J Drummond, Mr H. Dudley, F.R C S, Surgeon Commander P W Edmondson, M.R C S, Dr R M Gordon, Prof J B Kinmonth, F R C S, Dr H B M Lewis, Dr W d'A Maycock, Dr J P Payne, Group Captain W P Stamm, F R.C P, Dr G Tovey, and Mr P T Jones F R C S (secretary) The present report was prepared for the subcommittee by Dr Armitage and Mr Jones

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or inflamed The presence of any perivenous œdema and the degree of tenderness were also recorded This method of recording has allowed the results to be divided into four categories, as follows

"O"—No reaction, or painless thrombosis without inflammation

"M"—Mild reaction, with less than 3 in of vein inflamed.

"S"—Severe thrombophlebitis, affecting 3 to 6 in. of vein.

"S+"—Extensive thrombophlebitis, affecting more than 6 in of vein

Results

428 cards were suitable for analysis A further 24 record cards were found to be unsuitable either because the infusion had been given into a great vein, or because insufficient details were supplied, or because the patient had died before the results of infusion could be assessed

The durations of the infusions in the 428 cases suitable for analysis are set out in table II In 52 cases the infusion lasted for exactly twelve hours, and in 7 for less than twelve hours Since thrombophlebitis did not occur among these 59, they are not considered further in this paper Table II shows that approximately the same number of infusions lasting from thirteen to forty-seven hours were given through plastic and rubber sets, but that rubber sets were used a little more commonly for infusions lasting forty-eight hours or more this is presumably due to chance A review of the record cards shows that blood, normal saline, and either 4 3% dextrose with 0 18% saline or 5% dextrose were given to almost all patients There was no significant difference in the nature or amount of fluid given to the patients in the two series Very few patients received blood only, so it is not possible to compare the incidence of thrombophlebitis in patients receiving blood-transfusions with that in patients receiving only crystalloid solutions

The distribution of reactions for each type of transfusion equipment, in infusions lasting more than twelve hours, is shown in table III The proportions of positive reactions (adding together the categories S+, S, and M) are 57 out of 180 (32%) for the plastic sets and 105 out of 189 (56%) for the rubber sets The difference (24%) between these two percentages has a standard error of 5% and is thus highly significant The probability of exceeding this difference by chance is less than 10^{-5} The proportions of very severe and severe reactions (S+ and S) are 32 out of 180 (18%) for the plastic sets, and 64 out of 189 (34%) for the rubber sets The difference between the two percentages is 16% with a standard error of 5%, a value significant at a probability of less than 10^{-3}

Thus there can be no doubt that in the centres taking part in this trial, and for the types of infusion performed, use of the plastic sets on the average considerably reduced the incidence of thrombophlebitis

It is of some interest to examine the results separately for each centre and for various lengths of infusion

TABLE IV—FREQUENCY DISTRIBUTION OF REACTIONS WITH THE TWO TYPES OF SET, AT DIFFERENT CENTRES, FOR INFUSIONS LASTING MORE THAN 12 HOURS*

—	Reaction	Centre							Total
		H	St T	R I E	S	M	R I V	B	
Plastic	S+	0	5	0	3	1	0	0	9
	S	1	2	4	9	7	0	0	23
	M	5	10	2	4	4	0	0	25
	O	60	8	16	15	10	7	7	123
	Total	66	25	22	31	22	7	7	180
Rubber	S+	9	4	2	3	7	0	0	25
	S	14	6	5	5	8	1	0	39
	M	8	8	5	10	6	4	0	41
	O	41	4	18	13	1	2	5	84
	Total	72	22	30	31	22	7	5	189

* See footnote to Table II

TABLE V—FREQUENCY DISTRIBUTION OF REACTIONS WITH THE TWO TYPES OF SET FOR VARIOUS LENGTHS OF INFUSION

—	Reaction	Length of infusion (hours)						Total
		13–23		24–47		48 or more		
		No	%	No	%	No	%	
Plastic	S+	0	0	3	4	6	12	9
	S	2	3	9	13	12	24	23
	M	6	10	13	19	6	12	25
	O	55	87	42	63	26	52	123
	Total	63	100	67	99	50	100	180
Rubber	S+	2	4	9	14	14	21	25
	S	9	16	9	14	21	32	39
	M	4	7	18	27	19	29	41
	O	42	74	30	45	12	18	84
	Total	57	101	66	100	66	100	189

Tables IV and V show the distributions of reactions subdivided by centre and length of infusion respectively Table IV shows that the incidence and severity of thrombophlebitis, with either set, varied considerably from one centre to another, and also that evidence for the superiority of the plastic set is very strong in some centres but lacking in others In a further analysis, the incidence of thrombophlebitis for the two sets at each centre was compared, allowance being made for possible differences in the lengths of infusions with the two sets (In this calculation the Manchester and Birmingham centres were pooled because of the small numbers involved) The plastic set gave a significantly lower incidence of thrombophlebitis than the rubber (at the 5% level of significance) at Hammersmith and the Middlesex Hospitals, and in the pooled results from Manchester and Birmingham In no centre was the rubber set significantly better

Similarly, table V shows that the incidence and severity of thrombophlebitis increased appreciably with the length of infusion, for each set, and that the superiority of the plastic set is apparent in each of the three length-of-infusion groups A further analysis, allowing for the different incidence at each centre, confirms that the contrast between the two sets reaches the 5% level of significance for each length of infusion

Discussion

This trial again shows the high incidence of thrombophlebitis when prolonged intravenous infusions are given through red rubber sets It also provides clear evidence that the incidence of thrombophlebitis is much lower when plastic tubing is used The fact that the incidence of major thrombophlebitis (categories S and S+) was nevertheless as high as 18% when plastic tubing was used calls for some comment Most of the patients in this trial received autoclaved glucose solutions which are known to be acid (Todd 1951), many patients also received injections of drugs into the tubing of the sets It may well be that both these factors cause some injury to the veins It would thus be unwise to conclude that the cases of major thrombophlebitis following infusions through plastic tubing were necessarily due to harmful substances contained in the tubing

The work of Bolton Carter (1951b) firmly established the importance of the period of infusion in influencing the incidence of thrombophlebitis The present observations confirm this finding and show that in infusions lasting twelve hours or less the incidence of thrombophlebitis is negligible

Summary

The incidence of thrombophlebitis following long continued intravenous infusions has been assessed in two series of recipients In one series the infusions were given through red rubber sets, as supplied by the National

Blood Transfusion Service, in the second series the infusions were given through sets made of plastic In other respects the two series were closely comparable In the series in which plastic tubing was used, the incidence of thrombophlebitis was approximately half of that in which red rubber tubing was used

The subcommittee wishes to express its thanks to all those physicians and surgeons who readily gave permission for this trial to be conducted in their wards The plastic set used in this trial was developed and manufactured by Messrs Capon Heaton & Co, of Birmingham Their representative, Mr A Boot, gave the members of the subcommittee great assistance in the design of the set and they record their appreciation of his ready help

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FRACTURES OF THE FEMORAL NECK

REVIEW OF MANAGEMENT AND RESULTS

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This is a review of the 204 recent fractures of the femoral neck admitted to the general surgical unit of the Southern General Hospital, Glasgow, in 1948–55

There was no selection of cases, many being directed to the hospital by the local admission bureau Patients were admitted from their own homes, from local lodging-houses, from a geriatric home, from a local mental hospital, or, when the accident happened out-of-doors, direct by ambulance When the accident was in the patient's home, there was often delay in seeking medical attention, particularly if the patient had been living alone 20 patients came from the West of Scotland and the Western Isles They were transferred to Glasgow either by road or by air, sometimes several days after their accident When admission to hospital was delayed for any reason, patients were often in a very poor general condition—medically, nutritionally, and mentally In some, early bedsores and hypostatic pneumonia were already apparent

General Condition of Patients

Medical assessment revealed that about 90% of patients over the age of 65 had emphysema, generalised arteriosclerosis, and hypertension, more than 60% had chronic bronchitis, and 16% had bronchiectasis Many suffered from malnutrition and most showed some anæmia in more than 20% to a marked degree Degenerative myocarditis was diagnosed in 60% of the cases and 12% had recent or old myocardial infarction In 44% electrocardiography showed left ventricular strain and/or coronary insufficiency Urinary infection was present in 30% of cases

The patient was assessed by the surgeon and the anæsthetist, between whom lay the decision to offer or withhold operation

The age of patients ranged from 7 to 95 (average 71) 20 patients were under the age of 50 and 12 of these had been involved in either an industrial or a road accident Of the 7 mental patients only 1 was over the age of 60 their average age being 55 There were 125 females and 79 males

Ætiology

Two fractures occurred indoors for every one out-of-doors, and of those which occurred out-of-doors half were caused by street accidents or by industrial accidents 44 patients reported a feeling of dizziness before falling

The hospital records were not always explicit as to the actual cause or the mode of production of the fracture The most frequent indoor causes were (*a*) falling out of bed (18 cases), (*b*) falling on a stairway (11 cases), (*c*) tripping over a carpet (7 cases), and (*d*) falling off a chair or a box (6 cases) The most frequent outdoor causes were (*a*) road accidents involving a vehicle (11 cases), (*b*) jumping off a tram or bus (8 cases, including 5 patients over 80 and 1 over 90), (*c*) direct trauma at work (7 cases), (*d*) falling from a height (5 cases), (*e*) tripping on an uneven road (4 cases), (*f*) falling on an icy road (4 cases), and (*g*) slipping on a wet street (3 cases)

The peak periods of the year were May and October–December

Bone changes seen on X-ray examination were osteoporosis, osteitis deformans, osteitis fibrosa cystica, and metastasis in bone Arthritis of the hip-joint was often present The part played by lack of mobility at the hip-joint must not be underestimated

Site of Fracture

For simplicity, the fractures have been classified as transcervical (intracapsular) and trochanteric (extracapsular) There were 91 transcervical fractures (average age 70) and 113 trochanteric fractures (average age 72) Fracture of the right femoral neck was as common as fracture of the left femoral neck 3 patients had their two femoral necks fractured on different occasions, the level of fracture was the same each time, being transcervical in 2 cases and trochanteric in 1

Treatment

Table I shows the number of recent fractures of the femoral neck admitted during the years under review together with the method of treatment Of the 204 cases 139 were treated by operative fixation and 65 conservatively

TABLE I—TREATMENT OF FRACTURE OF FEMORAL NECK

Year	Operation	Conservative	Total
1948	3	9	12
1949	4	11	15
1950	4	3	7
1951	10	11	21
1952	19	9	28
1953	28	9	37
1954	35	4	39
1955	36	9	45
Total	139	65	204

Conservative Treatment

In the elderly patient the conservative treatment of choice was Hamilton-Russell traction, in the young patient extension in a Thomas splint was used Occasionally, when impaction appeared secure and hip movements were painless, freedom without weight-bearing was allowed In 1948–51 61% of all the cases were treated conservatively, but in 1952–55 only 20%

Unfit for operative treatment (32 cases, 28 deaths)—Of all the cases admitted in 1948–51 17 (30 8%) were in this group, and in 1951–55 15 (10%) The difference (20%) between the two periods probably reflects a change in the standard accepted for operation in the more recent period 4 patients, aged 80, 83, 87, and 87, were moribund on admission, they were poorly nourished and personally neglected, had chronic medical conditions, and were hypotensive and shocked, they did not respond to resuscitation, including blood-transfusion, and died within twenty-four hours of admission.

Treated conservatively although fit for operation (33 cases, 3 deaths).—Conservative treatment was the method of choice in 31 of these cases. It was enforced in the 2 remaining cases where, because of inability to pass a guide wire through a dense femoral neck and because of failure to get an acceptable reduction, operation was abandoned. Of all the cases admitted in 1948–51 17 (31·5%) were in this group, and in 1952–55 16 (10·7%). In the former period trochanteric fractures were usually treated conservatively, as were patients with impacted transcervical fractures if in an acceptable position. In the latter period a small minority were treated conservatively for the following reasons: (1) impaction of transcervical fracture, (2) gross comminution of trochanteric fracture, (3) greenstick fracture, and (4) because nailing was abandoned.

Operative Treatment

Of the 139 cases treated by operation a Smith-Petersen nail was inserted into 63 transcervical fractures and 2 trochanteric fractures, and a McLaughlin nail and plate was applied to 74 trochanteric fractures. These 139 cases may be divided according to whether operation was the primary or the secondary choice.

Primary choice (129 cases, 26 deaths).—The average period of delay after fracture was four days. Normally the operation was done at one of two regular operating sessions during the week, usually from two to seven days after admission of the patient to hospital. Associated with the medical survey, treatment was initiated when necessary, a transfusion given when required, and the skin of the operation site prepared.

Secondary choice (10 cases, 10 deaths).—The average period of delay was eighteen days. Initially turned down as completely unfit for operation these patients showed no improvement up to the seventh day or thereafter. When, for various reasons, nailing was eventually done, 2 died the day after operation, 1 on the third day, 3 after a fortnight, 1 at three weeks, 2 in the second month, and 1 after four months.

The approach was always through an adequate lateral incision, and nailing was controlled by radiography. The operating-time—i.e., from induction when general anæsthesia was used—was usually between sixty and ninety minutes but was occasionally prolonged by technical difficulties.

Premedication

Several combinations of drugs were used:

(a) Morphine sulphate and atropine sulphate.
(b) Pethidine hydrochloride and atropine sulphate.
(c) The hydrochlorides of chlorpromazine, promethazine, and pethidine.

Although each combination produced the desired sedative effect, respiratory depression and hypotension subsequent to the administration of morphine sulphate, usually gr $^1/_6$, made morphine and atropine less acceptable than pethidine and atropine, particularly when general anæsthesia followed. The "lytic cocktail" (chlorpromazine, promethazine, and pethidine) was exhibited because of its reputed ability to protect from stress, particularly from hæmorrhage and trauma, but it often caused a preoperative fall in blood pressure.

To prevent preoperative hypotension and to maintain the blood-pressure during operation two vasopressor drugs were used: methylamphetamine hydrochloride ('Methedrine') and mephentermine sulphate ('Mephine' sulphate). The latter, besides being a stronger vasopressor than methylamphetamine hydrochloride, had a longer action.

Analgesia

During operation it is very important to avoid anoxia. To this end careful attention was paid to providing enough oxygen, to replacing blood-loss, and to supporting the blood-pressure with drugs. In this respect mephentermine sulphate again proved most useful.

Analgesia was provided by:

(1) General anæsthesia: thiopentone sodium, nitrous oxide, oxygen, and pethidine hydrochloride.

(2) General anæsthesia and local analgesia: as above together with the local injection of 1% lignocaine hydrochloride.

(3) Local and general analgesia: 1% lignocaine hydrochloride and pethidine hydrochloride.

Although the operation can mostly be done under light general anæsthesia, difficulty may arise in manipulation of the fracture. To facilitate the manipulation deeper anæsthesia may be required for a short time, or a short-acting muscle relaxant may be used. This is a stage, however, during which the patient may become hypotensive. Recovery of the blood-pressure may then be slow, and it may be difficult to sustain it at the preoperative level.

In this series the least general postoperative upset in the elderly patient was associated with the use of local plus general analgesia produced by local infiltration with 1% lignocaine hydrochloride 100 ml. and intravenous pethidine hydrochloride 25–100 mg. Oxygen inhalations were only given when thought necessary. With patience, difficulty in reducing most fractures can be overcome without resorting to general anæsthesia or to muscle relaxants. The technique has the virtue of simplicity in application and permits the anæsthetist to concentrate on looking after the patient's general condition.

Postoperative Care

During the last two years under review, preference for postoperative sedation has been for paraldehyde and pethidine hydrochloride, the latter being administered only when there was a complaint of pain. In the more recent cases, if signs of cerebral upset were present chlorpromazine hydrochloride was given. Chlorpromazine hydrochloride was not used as an occasional sedative in any of the cases, but, used specifically in association with mental disturbance, it gave a favourable impression.

After operation, medical treatment was continued where necessary. Special emphasis was placed on an adequate diet and an adequate intake of fluids. Patients were usually sitting in a chair within forty-eight hours, and they had daily hip and knee exercises. When they were considered fit enough they were encouraged to move about the ward on crutches. Those who became proficient were allowed home and returned to the outpatient department for regular review. Non-weight-bearing was usually continued for twelve weeks, and few patients, unless ambulant on crutches, got home before this time. If radiography did not definitely confirm union weight-bearing was further postponed.

RESULTS

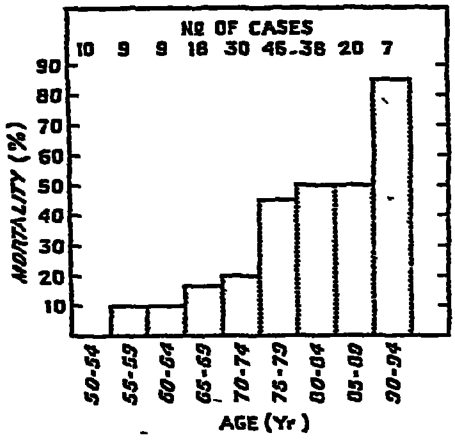
Mortality

Of the 204 patients 67 (29 males and 38 females) died in hospital—an overall mortality of 33%.

Of those operated on (139) the operative mortality, covering the arbitrary period of twenty-eight days after

TABLE II—MORTALITY IN RELATION TO TREATMENT OF FRACTURE OF FEMORAL NECK

Type of fracture	Treatment			
	Operation		Conservative	
	Cases	Deaths	Cases	Deaths
Transcervical	63	15	28	10
Trochanteric	76	21	37	21
Total	139	36	65	31



Mortality-rates in age-groups of patients with fractures of femoral neck.

operation, was 19 (14%) and covering the whole period in hospital, 36 (26%) Of the 65 patients treated conservatively 31 died (48%) in hospital (table II) but, as choice of treatment was not by random selection, the mortality-rates following operation and conservative treatment cannot be compared

The average age of those who died was 82 The accompanying figure shows the percentage mortality in each five-year period from the age of 50 onwards There was a sudden rise in the percentage mortality after the 75th year.

The causes of death are recorded in table III

The appearance of disorientation and incontinence was always ominous, but especially after operation when it was usually the prelude to general medical deterioration

Table IV shows the period after operation at which death took place In the case of those treated conservatively, the table shows the interval between the accident and death

TABLE III—CAUSES OF DEATH

Cause of death	Treatment	
	Operation	Conservative
Cardiac failure	–	6
Coronary thrombosis	1	0
Hypostatic pneumonia	7	6
Cerebral thrombosis or hæmorrhage	3	9
Uræmia	3	0
Perforation	1	0
Paralytic ileus	0	1
On operating table	2	
Unknown	19	9
Total	36	31

Follow up

An attempt was made to contact the 137 patients who had survived Where possible they returned for assessment of the functional result and bone union 27 were not seen in hospital but the functional result was ascertained in 17 of these from good follow-up records and from up-to-date reports from general practitioners.

TABLE IV—DEATHS IN HOSPITAL

Time of death	Treatment	
	Operation	Conservative
On operating table	2	
In first month	18*	24†
In second month	11	4
In third month	1	1
After third month	4	2
Total	36	31

* Including 4 deaths in first week

† Including 6 (including 4 in first 48 hr)

Table V shows these 127 patients classified according to the capabilities without reference to their previous condition and based on the following requirements

Group A: return to full mobility, requiring no support, although a slight limp might be present. In the case of the younger patients return to full employment

Group B. Mobile and able to do their own shopping but feeling they required a stick for support

Group C Mobile but requiring the support of one or two sticks and leading an indoor existence

Group D: Unable to walk, spending most of their time in bed

All cases of non-union are found in groups C or D except 5 transcervical fractures classified in group B, 1 was a fracture in an amputation stump, and in 4 there was fibrous union in good position

There were 19 cases of non-union (table VI) 16 transcervical and 3 trochanteric fractures In the absence of radiography or precise radiological reports the outcome was doubtful in 20 cases

TABLE V—CLINICAL ASSESSMENT

Type of fracture	Treatment	A	B	C	D	?
Transcervical	Operation	24	13	7	1	2
	Conservative	6	4	4	2	2
Trochanteric	Operation	32	14	5	1	4
	Conservative	8	4	0	2	2
Total		70	35	16	6	10

Discussion

It is doubtful whether the mortality-rate deserves the importance usually accorded it when the results of treatment of fracture of the femoral neck are being discussed. Indeed, perusal of the literature suggests that comparison of the results obtained in different series is of only limited value The variation in age and possibly also in the physical condition of patients contributes to this, whilst lack of uniformity in the duration of the follow-up tends to be misleading when results are interpreted Here we take the view that the general and mental condition of patients who do survive is worthy of greater consideration sharing equal importance with the recovery of function of the injured limb

The problems associated with fractures of the upper end of the femur in the elderly fall into two categories—orthopædic and geriatric Besides the patient's medical condition, other factors must strongly influence the decision to offer or withhold operation The transcervical fracture with displacement requires manipulation and internal fixation to maintain position and attain union The trochanteric fracture, however allows greater latitude in treatment Equally good results are reported from operation (Evans 1951) and from conservative treatment (Murray and Frew 1949) The remaining factors which influence the decision in favour of operation are (1) greater comfort and mobility for the patient, (2) greater facility for nursing and (3) bed economy The third factor, for reasons given below, we consider to be not in the patient's best interest

TABLE VI—ASSESSMENT OF UNION

Treatment	Transcervical fracture			Trochanteric fracture		
	Union	Non-union	?	Union	Non-union	?
Operation	30	9	9	49	2	4
Conservative	7	7	4	12	1	3
Total	37	16	13	61	3	7

The management of each case requires adjustment to obtain the greatest benefit for the patient, especially the poor risk patient. Prominent among the questions thus raised is the urgency of operation. Evans (1953) respond to resuscitation, including blood-transfusion, and died within twenty-four hours of admission

Treated conservatively although fit for operation (33 cases, 3 deaths) —Conservative treatment was the method of choice in 31 of these cases It was enforced in the 2 remaining cases where, because of inability to pass a guide wire through a dense femoral neck and because of failure to get an acceptable reduction, operation was abandoned Of all the cases admitted in 1948–51 17 (31 5%) were in this group, and in 1952–55 16 (10 7 %) In the former period trochanteric fractures were usually treated conservatively, as were patients with impacted transcervical fractures if in an acceptable position In the latter period a small minority were treated conservatively for the following reasons (1) impaction of transcervical fracture, (2) gross comminution of trochanteric fracture, (3) greenstick fracture, and (4) because nailing was abandoned

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Of the 139 cases treated by operation a Smith-Petersen nail was inserted into 63 transcervical fractures and 2 trochanteric fractures, and a McLaughlin nail and plate was applied to 74 trochanteric fractures These 139 cases may be divided according to whether operation was the primary or the secondary choice

Primary choice (129 cases, 26 deaths) —The average period of delay after fracture was four days Normally the operation was done at one of two regular operating sessions during the week, usually from two to seven days after admission of the patient to hospital Associated with the medical survey, treatment was initiated when necessary, a transfusion given when required, and the skin of the operation site prepared

Secondary choice (10 cases, 10 deaths) —The average period of delay was eighteen days Initially turned down as completely unfit for operation these patients showed no improvement up to the seventh day or thereafter When, for various reasons, nailing was eventually done, 2 died the day after operation, 1 on the third day, 3 after a fortnight, 1 at three weeks, 2 in the second month, and 1 after four months

The approach was always through an adequate lateral incision, and nailing was controlled by radiography The operating-time—i e , from induction when general anæsthesia was used—was usually between sixty and ninety minutes but was occasionally prolonged by technical difficulties

Premedication

Several combinations of drugs were used

(*a*) Morphine sulphate and atropine sulphate
(*b*) Pethidine hydrochloride and atropine sulphate
(*c*) The hydrochlorides of chlorpromazine, promethazine, and pethidine

Although each combination produced the desired sedative effect, respiratory depression and hypotension subsequent to the administration of morphine sulphate, usually gr $^1/_6$, made morphine and atropine less acceptable than pethidine and atropine, particularly when general anæsthesia followed The "lytic cocktail" (chlorpromazine, promethazine, and pethidine) was exhibited because of its reputed ability to protect from stress, particularly from hæmorrhage and trauma, but it often caused a preoperative fall in blood-pressure

To prevent preoperative hypotension and to maintain the blood-pressure during operation two vasopressor drugs were used methylamphetamine hydrochloride ('Methedrine') and mephentermine sulphate ('Mephine' sulphate) The latter, besides being a stronger vasopressor than methylamphetamine hydrochloride, had a longer action

Analgesia

During operation it is very important to avoid anoxia To this end careful attention was paid to providing enough oxygen, to replacing blood-loss, and to supporting the blood-pressure with drugs In this respect mephentermine sulphate again proved most useful

Analgesia was provided by

(1) General anæsthesia thiopentone sodium, nitrous oxide, oxygen, and pethidine hydrochloride

(2) General anæsthesia and local analgesia as above together with the local injection of 1% lignocaine hydrochloride

(3) Local and general analgesia 1% lignocaine hydrochloride and pethidine hydrochloride

Although the operation can mostly be done under light general anæsthesia, difficulty may arise in manipulation of the fracture To facilitate the manipulation deeper anæsthesia may be required for a short time, or a short acting muscle relaxant may be used *This is a* stage, however, during which the patient may become hypotensive Recovery of the blood-pressure may then be slow, and it may be difficult to sustain it at the *preoperative level*

In this series the least general postoperative upset in the elderly patient was associated with the use of local plus general analgesia produced by local infiltration with 1% lignocaine hydrochloride 100 ml and intravenous pethidine hydrochloride 25–100 *mg* Oxygen inhalations were only given when thought necessary With patience, difficulty in reducing most fractures can be overcome without resorting to general anæsthesia or to muscle relaxants The technique has the virtue of simplicity in application and permits the anæsthetist to concentrate on looking after the patient's *general* condition

Postoperative Care

During the last two years under review, preference for postoperative sedation has been for paraldehyde and pethidine hydrochloride, the latter being administered only when there was a complaint of pain In the more recent cases, if signs of cerebral upset were present chlorpromazine hydrochloride was given Chlorpromazine hydrochloride was not used as an occasional sedative in any of the cases, but, used *specifically in* association with mental disturbance, it gave a *favourable* impression

After operation, medical treatment was *continued* where necessary Special emphasis was placed on an adequate diet and an adequate intake of fluids Patients were usually sitting in a chair within forty eight hours, and they had daily hip and knee exercises When they were considered fit enough they were encouraged to move about the ward on crutches Those who became *proficient* were allowed home and returned to the outpatient department for regular review Non-weight bearing was usually continued for twelve weeks, and few patients unless ambulant on crutches, got home before this time If radiography did not *definitely confirm union*, weight-bearing was further postponed

Results

Mortality

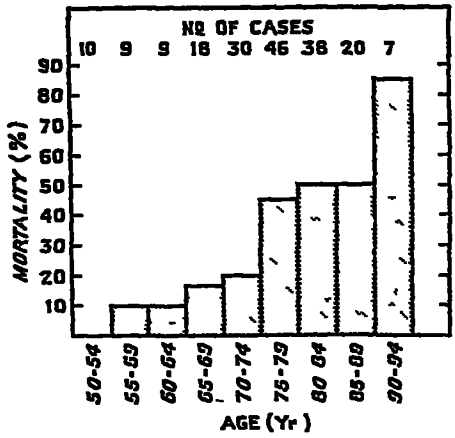
Of the 204 patients 67 (29 males and 38 females) died in hospital—an overall mortality of 33%

Of those operated on (139) the operative mortality, covering the arbitrary period of twenty eight days after

TABLE II—MORTALITY IN RELATION TO TREATMENT OF FRACTURE OF FEMORAL NECK

Type of fracture	Treatment			
	Operation		Conservative	
	Cases	Deaths	Cases	Deaths
Transcervical	63	15	28	10
Trochanteric	76	21	37	21
Total	139	36	65	31

operation, was 19 (14%) and, covering the whole period in hospital, 36 (26%) Of the 65 patients treated conservatively 31 died (48%) in hospital (table II); but, as choice of treatment was not by random selection, the mortality-rates following operation and conservative treatment cannot be compared



Mortality rates in age-groups of patients with fractures of femoral neck.

The average age of those who died was 82 The accompanying figure shows the percentage mortality in each five-year period from the age of 50 onwards There was a sudden rise in the percentage mortality after the 75th year.

The causes of death are recorded in table III

The appearance of disorientation and incontinence was always ominous, but especially after operation when it was usually the prelude to general medical deterioration

Table IV shows the period after operation at which death took place In the case of those treated conservatively, the table shows the interval between the accident and death

TABLE III—CAUSES OF DEATH

Cause of death	Treatment	
	Operation	Conservative
Cardiac failure	7	6
Coronary thrombosis	1	0
Hypostatic pneumonia	7	6
Cerebral thrombosis or hæmorrhage	3	9
Uræmia	3	0
Perforation	1	0
Paralytic ileus	0	1
On operating table	2	
Unknown	12	9
Total	36	31

Follow up

An attempt was made to contact the 137 patients who had survived Where possible they returned for assessment of the functional result and bone union 27 were not seen in hospital, but the functional result was ascertained in 17 of these from good follow-up records and from up-to date reports from general practitioners

TABLE IV—DEATHS IN HOSPITAL

Time of death	Treatment	
	Operation	Conservative
On operating table	2	
In first month	18*	24†
In second month	11	4
In third month	1	1
After third month	4	2
Total	36	31

* Including 4 deaths in first week
† Including 6 (including 4 in first 48 hr)

Table V shows these 127 patients classified according to the capabilities without reference to their previous condition and based on the following requirements

Group A return to full mobility, requiring no support, although a slight limp might be present In the case of the younger patients return to full employment

Group B Mobile and able to do their own shopping but feeling they required a stick for support

Group C Mobile but requiring the support of one or two sticks and leading an indoor existence

Group D Unable to walk, spending most of their time in bed

All cases of non-union are found in groups C or D except 5 transcervical fractures classified in group B, 1 was a fracture in an amputation stump, and in 4 there was fibrous union in good position

There were 19 cases of non-union (table VI) 16 transcervical and 3 trochanteric fractures In the absence of radiography or precise radiological reports the outcome was doubtful in 20 cases

TABLE V—CLINICAL ASSESSMENT

Type of fracture	Treatment	A	B	C	D	?
Transcervical	Operation	24	13	7	1	2
	Conservative	6	4	4	2	2
Trochanteric	Operation	32	14	5	1	4
	Conservative	8	4	0	2	2
Total		70	35	16	6	10

Discussion

It is doubtful whether the mortality-rate deserves the importance usually accorded it when the results of treatment of fracture of the femoral neck are being discussed Indeed, perusal of the literature suggests that comparison of the results obtained in different series is of only limited value The variation in age and possibly also in the physical condition of patients contributes to this, whilst lack of uniformity in the duration of the follow-up tends to be misleading when results are interpreted Here we take the view that the general and mental condition of patients who do survive is worthy of greater consideration, sharing equal importance with the recovery of function of the injured limb

The problems associated with fractures of the upper end of the femur in the elderly fall into two categories—orthopædic and geriatric Besides the patient's medical condition, other factors must strongly influence the decision to offer or withhold operation The transcervical fracture with displacement requires manipulation and internal fixation to maintain position and attain union The trochanteric fracture, however, allows greater latitude in treatment Equally good results are reported from operation (Evans 1951) and from conservative treatment (Murray and Frew 1949) The remaining factors which influence the decision in favour of operation are (1) greater comfort and mobility for the patient, (2) greater facility for nursing, and (3) bed economy The third factor, for reasons given below, we consider to be not in the patient's best interest

TABLE VI—ASSESSMENT OF UNION

Treatment	Transcervical fracture			Trochanteric fracture		
	Union	Non union	?	Union	Non-union	?
Operation	30	9	9	49	2	4
Conservative	7	7	4	12	1	3
Total	37	16	13	61	3	7

The management of each case requires adjustment to obtain the greatest benefit for the patient, especially the poor-risk patient Prominent among the questions thus raised is the urgency of operation. Evans (1953) points out that patients over the age of 70 do not tolerate pain and enforced immobility well and are quick to become irrational and incontinent. He therefore advocates emergency operation in trochanteric fractures. Having thus relieved pain and restored mobility, he proceeds with any medical treatment that may be considered necessary. On the other hand, McElvenny (1949) says "It must be definitely and emphatically stated that an intracapsular fracture of a femoral neck in an elderly patient is no surgical emergency, but may well be a *medical* emergency," and advocates a complete survey of the vital functions and systems.

In view of the average age and usual medical condition of the patients with transcervical and trochanteric fractures in this series, the latter approach to the problem has seemed to us the more logical, because each case is thus considered individually, from the time of admission, not only from the orthopædic but also from the medical standpoint. Relief from pain is important (Evans 1953) and can be achieved by operation, but patients do get relief from pain under extension and also benefit from rest before operation. Preliminary treatment by extension allows the medical survey and treatment to be instituted and adequate skin preparation of the operation site can be carried out.

In the last two years under review it was usual for forty-eight hours to elapse before operation, even in patients in whom there were no medical or surgical reasons for delaying operation. This was prolonged up to seven days if benefit could be expected from medical treatment, with special reference to ketosis, dehydration, secondary anæmia, reduced blood volume, threatened cardiac failure, and urinary infection. Delay longer than seven days, however, was not thought advisable when operation was the primary choice. When operation was the secondary choice and was performed after this period, the mortality was high.

With reference to the preoperative medical survey we agree with Gavey (1953), that "too much medical investigation in these old people may lead to unwarranted delay in getting on with the job." On the other hand, we regard adequate preparation for operation as a prerequisite in the prophylaxis of mental disturbance and in maintaining the general condition. Allison (1952) states that the recognised causes of cerebral upset are dehydration, alkalosis, and anoxia. These conditions are often present in these aged patients and may also be associated with trauma and operation under general anæsthesia. Preoperative treatment directed to correct such deficiencies will contribute to the avoidance of circulatory failure, thus helping to guard against a general effect (shock) and the direct effect on cerebral metabolism which contributes to mental confusion. Even when the operation is performed under local analgesia, therefore, attention to these points is important.

The onset of mental confusion after operation has so far not been seen when local plus general analgesia has been used. It was, on the other hand, fairly common after general anæsthesia. Mental upset when it occurred was of ominous significance, especially if associated with incontinence. As regards the avoidance of postoperative mental disturbance the sustaining effect of the vasopressor drugs, notably mephentermine sulphate, appears to be of value. It is, of course, axiomatic that, no matter what method of producing analgesia is used, meticulous attention should be paid to transfusion, as regards both replacing blood loss and avoiding overloading of the cardiovascular system.

After operation strict supervision of sedation was directed to the avoidance of mental confusion. Bedford (1955) notes that, when postoperative confusion appears in old people, the vicious circle of hypnotics, confusion, and more hypnotics must be avoided. The retention of full mental acuity and morale in these patients into the postoperative period ensures cooperation as regards nourishment, exercises, and ambulation. Without this cooperation great difficulty is experienced in attaining good function.

As reported above, patients treated by operation were usually up in a chair within forty-eight hours and had supervised exercises for their knees and hips from the morning after operation. Those in good physical condition and unimpaired mentally responded well to such treatment and quickly mastered the use of crutches. Such patients, when sufficiently adept and allowed home, could usually be trusted to remain mobile. The functional result with weight-bearing was usually good. The remainder, most of the patients in this series, required supervision in hospital. Too weak physically, they required continued medical treatment, or, lacking moral strength, they required to be coaxed at every stage and even beyond the stage of starting weight-bearing. In these cases continued leg exercises during the non-ambulant phase and instruction in walking when weight-bearing begins are important. Once fully ambulant and self-reliant, patients usually wish to remain so. To allow many of these patients home before this stage is reached would be to disregard the human factor and the fact that they often require the incentive of the hospital routine to maintain progress; otherwise the patient may lose interest or decide to rely wholly on relatives. Bed economy would be attained at the price of poor function.

Stewart (1955) notes that "some aged patients progressed less well after return home, for no other apparent reason than that discharge from hospital removed the only remaining incentive to the will to live." This was borne out in this series in the few who were discharged without crutches in the preambulant stage, in contrast to those who were sufficiently ambulant to be self-reliant before discharge. We therefore believe that hospital treatment should be continued in most cases until the patient is ambulant and has regained self-reliance.

Conclusions

If a patient with a fracture of the femoral neck is to derive maximum benefit from operation, as much attention must be paid to maintaining the general and mental condition as to factors influencing the functional result. To this end each patient should receive individual consideration from the time of admission.

An emergency operation does not appear to be indicated. Where an operation is the primary choice, however, the best time for it probably lies between forty-eight hours and seven days after the fracture was sustained.

Local and general analgesia are more satisfactory than general anæsthesia, so far as maintaining the patient's condition is concerned; adequate reduction can be achieved under local and general analgesia.

Hospital treatment of the aged patient with a fracture of the femoral neck should be continued until the patient is ambulant and self-reliant. The incentive of the hospital routine is often necessary to achieve good functional results.

Summary

All recent fractures of the femoral neck admitted to the Southern General Hospital, Glasgow, in 1948–55 are reviewed.

The management of these patients from the time of admission until they are ambulant and self-reliant is discussed.

The importance of the hospital routine in attaining a good functional result is emphasised.

We are indebted to Mr. R. B. Wright, senior surgeon, Southern General Hospital, for encouragement and constructive criticism. We also wish to thank Miss A. MacLean for secretarial help.

References at foot of next column

MYDRIATIC ACTION OF PENTHIENATE BROMIDE

A POSSIBLE SUBSTITUTE FOR ATROPINE

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AN increasing number of synthetic antispasmodic agents are being produced, mainly for use in spastic disorders of the gastro intestinal tract These agents have many of the actions of atropine and as such may be of value as mydriatics or cycloplegics Eight such substances, varying considerably in toxicity and chemical structure, were investigated experimentally in the rabbit to assess their suitability for clinical use as drops or as subconjunctival injections One of these substances, oxyphenonium bromide in 5% solution, has been discussed by Fraser (1956)

Experimental Data

Of the eight agents investigated in the rabbit (table I) the tolerated systemic dose in man was not known for the two experimental substances no 4075 and no 2515 Both these could, however, be excluded from further trial because, with the greatest possible concentration for the one and the greatest tolerated concentration for the other, no adequate mydriasis was obtained The six remaining agents fell into two distinct groups (1) local tolerance was the limiting factor in the case of adiphenine hydrochloride, propantheline bromide, and tricyclamol chloride, and (2) in the remaining three—scopolamine butylbromide, oxyphenonium bromide, and penthienate bromide—the limiting factor was a low systemic dose limiting the maximal concentration explored, for the full systemic dose was contained in four drops (two drops each eye)

Table I shows that, in the largest permissible dosages, adiphenine hydrochloride and propantheline bromide were the least, and penthienate bromide the most, promising as mydriatics Four substances were therefore carried forward for clinical trial.

Clinical Observations

Tolerance and Efficacy of Penthienate Bromide

Table II shows that penthienate bromide was the most effective of the four agents selected for clinical trial In efficacy and persistence penthienate bromide 2% drops gave results similar to those obtained with atropine sulphate 1% drops both for mydriasis and for cycloplegia

The same dilatation of the pupil as is seen with atropine was obtained in all of the fifteen cases tried Mydriasis set in within $^1/_2$–$1^1/_2$ hours, and the effect persisted for 4–6 days

In four patients with refractive errors between −1 0 D and +4 0 D retinoscopy was done 2 hours after instillation of penthienate bromide This tallied with the retinoscopy findings obtained in two cases after the use of cyclopentolate hydrochloride ('Cyclogyl') and in the two others after hyoscine hydrochloride $^1/_{20}$% Since the full cycloplegia seen with atropine is also seen with hyoscine (Sorsby et al 1955) and probably also with cyclopentolate hydrochloride, penthienate bromide is adequate as a cycloplegic Further support for this finding is given by the changes observed in the curvature of the anterior surface of the lens in one case Whereas hyoscine hydrochloride $^1/_{20}$% gave full cycloplegia at 1 hour and had worn off by 28 hours, the effect of penthienate bromide, though coming on as quickly, showed no tendency to decline till after 50 hours

Penthienate bromide in a concentration of less than 2% was unsatisfactory, used as 1% drops it proved inadequate in seven of eight patients (two children and six adults), the pupil showed only partial dilatation and that after 3–6 hours

Penthienate bromide as a subconjunctival injection used in 12 patients showed efficacy of the same order as atropine used subconjunctivally in the form of 'Mydricaine' (5 minims of water containing atropine sulphate gr $^1/_{60}$ or $^1/_{40}$ and cocaine hydrochloride gr $^1/_{10}$ or $^1/_8$ to which is added 3 minims of adrenaline 1 1000) Full and persistent dilatation of the pupil was obtained with 2 mg in 0 5 ml of water and 3 minims of adrenaline 1 1000

Penthienate Bromide as Substitute for Atropine in Treatment

Penthienate bromide as 2% drops was used in patients requiring atropine for treatment

Iritis—Eleven patients with iritis, including three with hypopyon iritis, were treated with 2% penthienate bromide Three of these had originally had a subcon-

TABLE I—EFFICACY OF SOME SYNTHETIC ANTISPASMODIC AGENTS USED AS MYDRIATICS IN RABBITS

Drug *	Dose			Mydriatic effect			Remarks
	Oral (mg)	Maximal concentration permissible (%)	Maximal concentration tolerated as drops (%)	Degree	Reached within (hr)	Persistent for	
4075			1	$^3/_4$	1	48 hr	Used at maximal solubility
2515			2	$^3/_4$–full	$2^1/_2$–3	48 hr	Delayed transient conjunctival injection and corneal clouding
Adiphenine hydrochloride ('Trasentine 6 H')	75	30	$^1/_2$	Slight	1	6 hr	
Propantheline bromide ('Pro banthine')	15	6	3	$^1/_2$	1	48 hr	
Tricyclamol chloride ('Lergine')	50	20	4	$^3/_4$	1	72 hr	
Scopolamine butylbromide ('Buscopan')	20	8	8 †	$^3/_4$	1	48 hr	
Oxyphenonium bromide ('Antrenyl')	5	2	2 †	$^3/_4$	2	48 hr	Slight conjunctival injection
Penthienate bromide ('Monodral')	5	2	2 †	$^3/_4$–full	$^1/_2$–1	7 days	

* The chemical structures of these agents are as follows
4075 phenyl cyclohexyl oxyacetic acid diethylamino-ethyl-ester hydrochloride
2515 benzilic acid diethylaminoethylester hydrochloride
Trasentine 6 H, hexa hydrodiphenylacetyldiethylamino-ethanolester hydrochloride
Probanthine β diisopropylaminoethyl xanthene 9 carboxylate methylbromide
Lergine, *dl*-1-(3-cyclohexyl-3-hydroxy 3-phenylpropyl)-1-methylpyrrolidinium chloride
Buscopan scopolamine N bromobutylate
Oxyphenonium diethyl (2 hydroxyethyl) methylammonium bromide α phenyl-cyclohexaneglycolate
Penthienate bromide, 2 diethylaminoethyl 2-cyclopentyl 2 (2-thienyl) hydroxyacetate methylbromide

† On the assumption that four drops (two drops into each eye) contain the maximal systemic dose, higher concentrations were not considered

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DR MURRAY, DR YOUNG REFERENCES

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TABLE II—CLINICAL ASSESSMENT OF RELATIVE MERITS OF FOUR SYNTHETIC ANTISPASMODIC AGENTS USED AS MYDRIATICS

Agent	Mode of application	No of patients	Time taken to produce mydriatic effect (hr)	Degree of mydriasis	Effect on accommodation	Persistence (days)
Oxyphenonium bromide	Drops 2 %	6	1–2	1/2–3/4	Partial	2–3
Scopolamine butylbromide	Drops 8 %	4	1–2	1/2–3/4	Partial	1–2
Tricyclamol chloride	Drops 4 %	4	1–3	About 1/2	Partial	1–3
Penthienate bromide	Drops 2 % Subconjunctival injection 2 mg in 0 5 ml of water and 3 minims of adrenaline 1 1000	15 12*	1/2–1 1/4–1/2	3/4–full Full	Complete Complete	1–6 6–10
	Drops 1 %	8	3–6	1/2–3/4	Partial	1–3

* One other patient had a subconjunctival injection without adrenaline added There was no congestion or other reaction, and the cycloplegic effect was satisfactory

junctival injection of mydricaine, and the treatment was continued with penthienate bromide drops Four patients had penthienate bromide 2 mg subconjunctivally followed by penthienate drops Four patients were treated with penthienate bromide drops exclusively All these cases were severe, and the best results were obtained by the combined treatment of subconjunctival injection and drops

After treatment in corneal grafting—Four patients known to be sensitive to atropine were treated postoperatively with penthienate bromide drops, which were well tolerated

Other postoperative treatment—Penthienate bromide was used as the routine mydriatic in the postoperative treatment of cataract extraction in six patients known to be sensitive to atropine Recovery was uneventful

Inflammation other than iritis—Penthienate bromide was used successfully in eight cases of keratitis or uveitis

Sensitivity to atropine—In addition to these twenty nine patients, of whom ten were treated with penthienate bromide because of their known sensitivity to atropine, eight other patients with chronic uveitis or keratitis and sensitivity to atropine were treated with penthienate bromide All eighteen patients tolerated penthienate bromide well, several of them for some months, and one for 7 months now

Side effects

Dryness of the mouth after subconjunctival injection was the only untoward symptom observed

Discussion

The value of atropine as a mydriatic is attested by the fact that it has been in use for about a hundred and fifty years Its one serious defect is its tendency to produce local irritation When this happens, it is likely that any other alkaloid will also produce irritation Lachesine ('E 3') has been used widely in recent years but it proved a poor mydriatic and is in any case no longer readily obtainable More recently cyclopentolate has been used successfully, but it is also not readily obtainable, moreover its action is rapidly transient A mydriatic with properties and persistence not unlike those of atropine would therefore be of considerable importance, especially if it were safe and free from irritative effects Such an agent is apparently available in penthienate bromide

Penthienate bromide is a quaternary ammonium compound and is chemically related to the tropine alkaloids It is used clinically in the management of peptic ulcer, gastro intestinal spasm, and allied conditions, for which the dose is 5 mg by mouth three or four times a day, or the same dose by intramuscular injection in severe cases It is reputed to have minimal side effects and apparently does not produce disturbances in accommodation when given by mouth For ophthalmic use the instillation of drops or ointment and subconjunctival injection would therefore be safe if they did not exceed the stated dose of 5 mg Two drops of 2% solution instilled into each eye contain about 5 mg , such doses are consistently free from local irritative effects and can safely be repeated 4 hourly

These doses for local use can probably be safely exceeded, for much of the agent in drops is washed out from the conjunctival sac This is suggested by the experience with atropine in daily clinical use The highest systemic dose of atropine is gr 1/60, the *amount of atropine instilled into the* conjunctival sac when two drops of 1% atropine solution are used in each eye is gr 1/25 It is perhaps for this reason that atropine ointment in the same concentration is more likely to produce toxic effects, for less of the ointment is washed out from the conjunctival sac (and possibly more atropine is instilled to begin with) Similar observations apply to almost all the drops of alkaloids used in ophthalmology

It also seems that, even when administered subconjunctivally, the systemic dose is often exceeded, because one strength of mydricaine contains gr 1/40 of atropine—a concentration higher than the systemic dose

For the present, drops of penthienate bromide should not exceed a concentration of 2%, and subconjunctival injections should contain not more than 2 mg per injection to allow for the cases in which injections in both eyes are required Where only one eye requires a subconjunctival injection 4 mg would be permissible and possibly advantageous Likewise the safe dose would not be exceeded with oxyphenonium bromide in 5% solution as recommended by Fraser (1956) if the drops were used in one eye only

Penthienate bromide, possessing in safe doses the efficacy and persistence of atropine as a mydriatic, is therefore an adequate substitute for atropine in the treatment of iritis and other inflammations of the eye Whether it will prove to be entirely devoid of irritative effects is not yet known

Summary

Eight synthetic compounds with an atropine like effect were studied experimentally to establish whether they could be used as substitutes *for atropine in ophthalmology*

In greatest possible or greatest tolerated doses four agents—adiphenine hydrochloride, propantheline bromide, and experimental substances no 4075 and no 2515—proved poor mydriatics in experiments on rabbits

Of the remaining four agents which gave promising results experimentally—tricyclamol, scopolamine butyl bromide, oxyphenonium bromide, and penthienate bromide—the dosage used was limited by the toxicity of the drug in all but tricyclamol, which itself was limited by poor local tolerance

In clinical trials on 50 patients the only agent which gave adequate and persistent mydriasis was penthienate bromide

In 18 cases of sensitivity to atropine and *19 cases* of different inflammations of the eye penthienate bromide, as drops or as subconjunctival injections, was as effective as atropine and mydricaine As drops it was used in a concentration of 2%—the greatest permissible *on* systemic dosage As subconjunctival injections it was given in doses of 2 mg in 0 5 ml of water with 3 minims of adrenaline 1 1000 added

It seems likely that penthienate bromide is as adequate as atropine as a mydriatic and is probably devoid of any tendency to produce irritation

We are obliged to Dr A K Pittman, of Messrs Ciba Ltd *for so readily* supplying some of the agents used, Messrs

Bayer Ltd for supplies of penthienate bromide ('Monodral') and Messrs Burroughs Wellcome & Co and Messrs Pfizer Ltd for other substances, and Mr L J Yarrell, chief pharmacist, and Mr G J Stephens and Mr R Harding, of the laboratory, of the Royal Eye Hospital

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LESIONS OF THE KIDNEY IN ACUTE RENAL FAILURE FOLLOWING SHOCK*

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The histological findings in "shock-kidney" have been described in great detail by Bywaters and Dible (1942), Lucké (1946), and Mallory (1947) The results obtained by the microdissection technique of Oliver et al (1951) added important facts to our knowledge of the renal lesions in acute renal failure Biopsy studies have been made by Brun (1954) and Gormsen et al (1955)

In the present investigation we tried to assess the relative frequency and significance of the different structural lesions and to determine at what stage in the course of the renal failure it was possible to recognise the various histological abnormalities

Material

We investigated 33 patients with acute renal failure following shock from different causes (table I) All had severe renal insufficiency Twenty biopsies were done on 17 patients between the second and sixty sixth days after the onset of anuria In the remaining 16 cases histological preparations were made from necropsy material In 3 cases both biopsy and necropsy specimens were examined

TABLE I—CLINICAL ÆTIOLOGY OF SHOCK

—	No of patients	Survived	Died
Acute barbiturate poisoning	9	4	5
Acute peritonitis	4	0	4
Crush injury	3	0	3
Surgical complications	3	0	3
Sepsis	3	1	2
Acute pancreatitis	2	1	1
Abortion	2	1	1
Transfusion accident	1	0	1
Obstetrical complication	1	0	1
Burns	1	0	1
Traumatic cerebral œdema	1	0	1
Concealed hæmorrhage and dehydration	1	1	0
Acute gastro enteritis	1	1	0
Intoxication with carbon monoxide	1	0	1
Total	33	9	24

Methods

The kidney biopsies were done by the technique described by Iversen and Brun (1951) modified according to Kark and Muehrcke (1954) The tissue was immediately fixed in 93% alcohol Some biopsy specimens were fixed both in alcohol and in formalin, no difference in the quality of the preparations was found

The necropsy material was fixed shortly after death by injecting about 400 ml of a 4% formaldehyde solution near one of the kidneys to prevent autolysis and thus retain the histological structure of the renal tissue

In the present report we make no distinction between renal tissue obtained by biopsy and that from early fixed necropsy specimens

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* Aided by a grant from the King Christian X Fund

TABLE II—KIDNEY LESIONS IN 33 CASES OF ACUTE RENAL FAILURE FOLLOWING SHOCK

Case no	Source of tissue (B biopsy, N necropsy)	Days after onset of anuria	Serum urea (mg per 100 ml)	Duration of renal insufficiency (days)	Infusion	Proximal tubules: Hydropic changes	Proximal tubules: Dilated	Proximal tubules: Flattened	Distal tubules: Casts	Distal tubules: Dilated	Distal tubules: Flattened	Distal tubules: Possible tubular necrosis	Casts in Henle's loop and/or collecting tubules	Interstitial tissue: Cellular infiltration	Interstitial tissue: Œdema
1	N	2	244	> 2	Dextran	–	+	++	–	++	–	–	+	–	–
2	B	3	199	20		–	–	+	+++	+++	+++	–	+	–	–
	B	9	388	20		–	–	+	+++	+++	+++	–	–	+	+
3	N	3	344	> 3	Dextran	– – –	–	–	+	–	–	–	–	–	–
4	N	3	268	> 3	Dextran	++	–	–	+	–	+	–	–	–	–
5	B	3	178	5		–	–	–	+	–	–	–	–	–	–
	B	12	155	5		–	–	–	–	–	–	–	–	–	–
6	N	4	402	> 4		–	–	+	+	++	+	–	–	–	–
7	B	5	354	> 5	Sucrose	+++	–	–	+	+	+	+	–	–	–
8	N	5	307	> 5		–	–	–	+	+	+	–	–	–	–
9	N	6	440	> 6	Dextran	+++	–	–	+	++	+	–	–	–	–
10	B	6	325	>10	Dextran	++	–	+	–	+	+	–	+	–	–
	N	10	246*	>10		++	–	+	+	+	+	–	–	–	–
11	B	6	431	12	Dextran	+	–	+	–	+	–	–	+	–	–
	B	19	97	12		+	–	+	+	–	–	–	+	–	–
12	N	7	532	> 7	Dextran	+++	–	+	+	++	+	–	–	–	–
13	N	7	350	> 7	Dextran	++	–	–	–	+	+	–	–	+	–
14	B	7	359*	34		–	–	–	+++	–	–	–	?	–	–
	N	40	274*	34		–	+	++	+++	++	++	+	+++	–	+
15	B	7	449	>15	Dextran	+	+	+	+	+	+	–	+	–	–
	N	15	246*	>15		+	+	+	+	++	+	–	+	–	–
16	B	8	500	>10	Dextran Sulphate	++	–	–	+	++	++	–	?	–	–
17	B	8	395	15		++	–	+	+	+	+	–	?	+++	+
18	B	8	394	16		++	–	–	+	++	++	–	?	–	–
19	B	9	483	20		–	–	+	–	+	++	–	?	+	+
20	N	9	456	> 9		+	–	–	–	+	–	–	+	++	–
21	B	10	462	12	Dextran	++	–	–	+	+	++	–	+	–	–
22	N	10	395	6		–	–	–	+	++	++	–	–	–	–
23	N	11	237*	>11		+	–	–	+	–	+	–	+	+	–
24	B	12	400	>15	Dextran	+	–	+	–	+	–	+	?	–	+
25	N	12	641	>12	Dextran	++	–	–	–	+++	+++	–	–	–	–
26	N	12	354	>12	Dextran	+	++	++	+	+++	+	–	+++	–	–
27	B	14	213*	>14	Dextran	++	–	–	+	+	+	–	+	–	–
28	N	15	404*	10	Dextran	–	–	+	+	++	++	–	–	–	–
29	B	17	214*	11	Dextran	++	–	+	++	+	++	–	+	+	+
30	N	18	319*	>18	Dextran	–	–	+	–	++	–	–	+	+	+
31	N	18	597	>18	Dextran	+++	–	–	+	++	–	–	–	–	–
32	B	22	153*	12	Dextran	+	+	++	+	–	+	–	–	+	+
33	B	66	30	7		–	–	+	–	–	–	–	+	–	–

The patients are listed according to the day of histological examination Dil, dilatation of tubular lumen Flat flattening of tubular epithelium +++ lesion found throughout specimen ++ common finding +, occasional finding –, not found ?, too little tissue
* treated by hæmodialysis

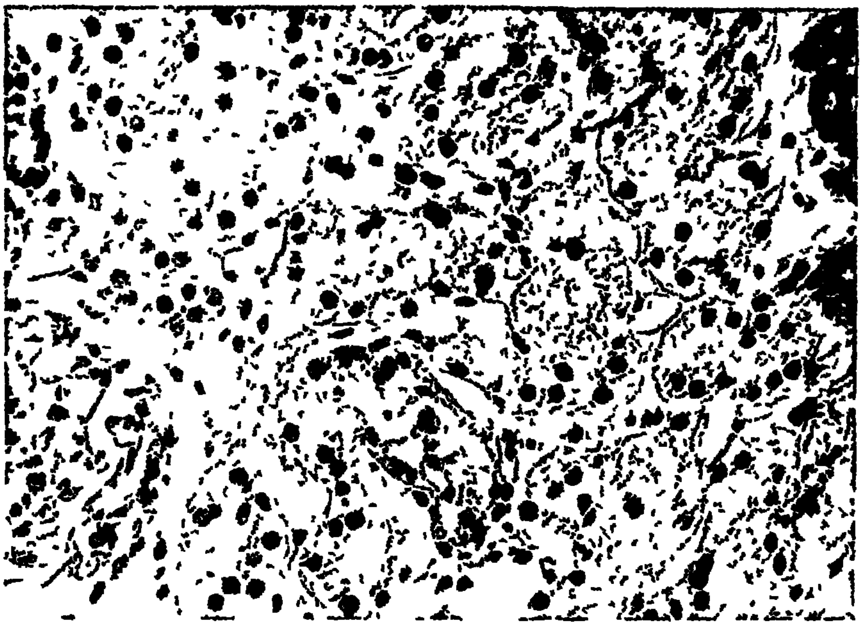

Fig 1—Case 14 kidney biopsy on seventh day of anuria from patient with severe shock and intravascular hæmolysis, showing normal proximal tubules and part of normal glomerulus, in a distal lumen a granular hæm cast and slight flattening of the epithelium, no dilatation (×280)

The duration of renal insufficiency has been taken as the number of days in which the twenty-four-hour endogenous creatinine clearance was less than 5 ml a minute

Results

The results are given in detail in table II The most striking feature was the moderate structural changes contrasting sharply with the complete functional breakdown In many patients only very slight histological abnormalities were found—e g, in case 14 the only pathological finding was a few granular hæm casts in the distal tubules (fig 1)

No acute changes were ever found in the glomerular tufts In the capsular spaces amorphous masses were discovered in many specimens, a finding which can hardly be considered of any great importance

The predominant histological changes, in order of importance were as follows

(1) *Dilatation and Flattening of Epithelium of Distal Convoluted Tubules*—The dilatation was in 3 cases very pronounced, transforming the tissue into a network (fig 2) In 12 cases the dilatation was pronounced but to a somewhat slighter degree Absence of dilatation was noted in only 6 cases In 2 of these a previous or a subsequent examination disclosed dilatation. In another of the 6 cases the examination was made after the restoration of renal function The 3 remaining cases were all examined on the third day of anuria In one of these another biopsy was done on the twelfth day with same result Thus dilatation of the distal tubules was present in nearly all the cases throughout the course of the disease, because it was observed as early as the second day and as late as the fortieth day after the onset of anuria The distal tubular dilatation was accompanied by a corresponding flat

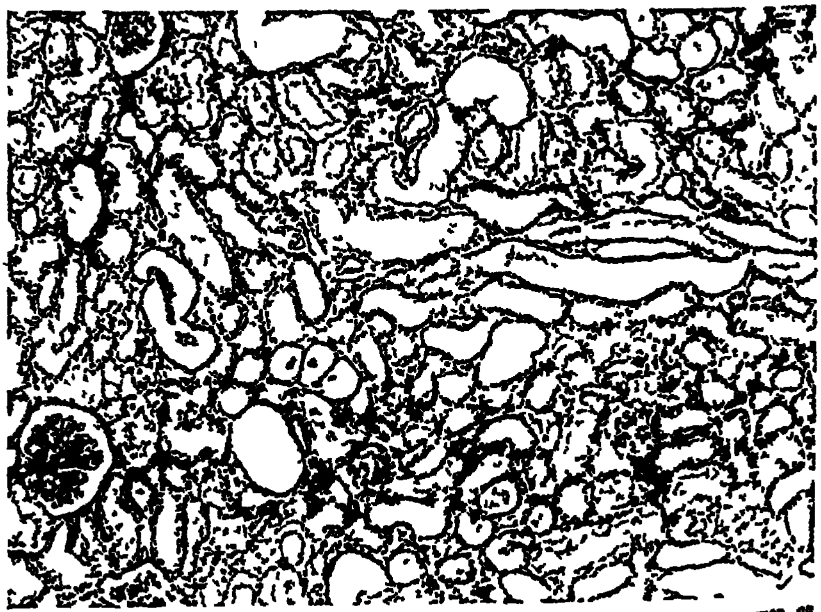

Fig 2—Case 25 necropsy specimen on twelfth day of anuria following operation for perforated gastric ulcer, showing pronounced dilatation of distal tubules with flattening of epithelium and casts in some distal lumina and well marked *hydropic* transformation of proximal tubules (×70)

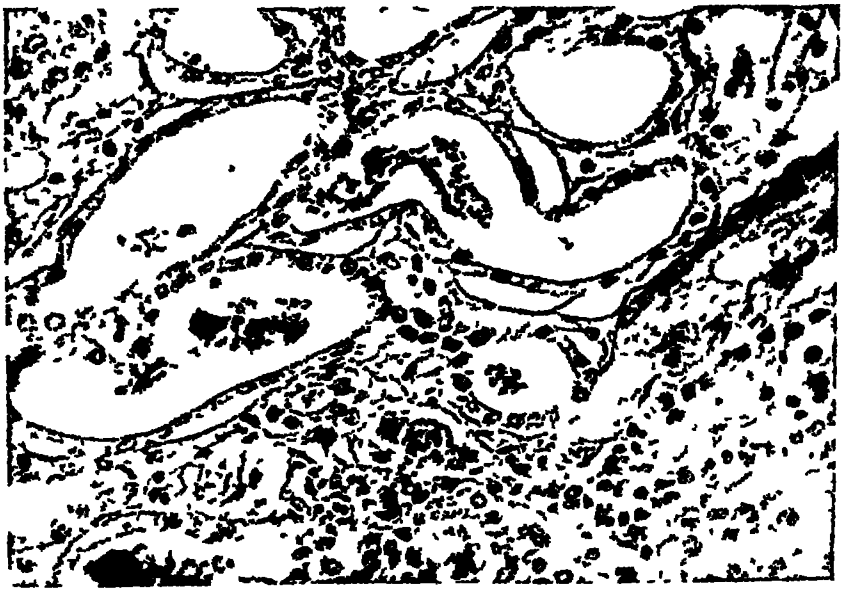

Fig 3—Case 14 necropsy specimen on fortieth day of anuria, showing dilatation of distal tubules with flattening of protoplasm and nuclei of epithelium several granular hæm casts and interstitial inflammation and œdema (×280)

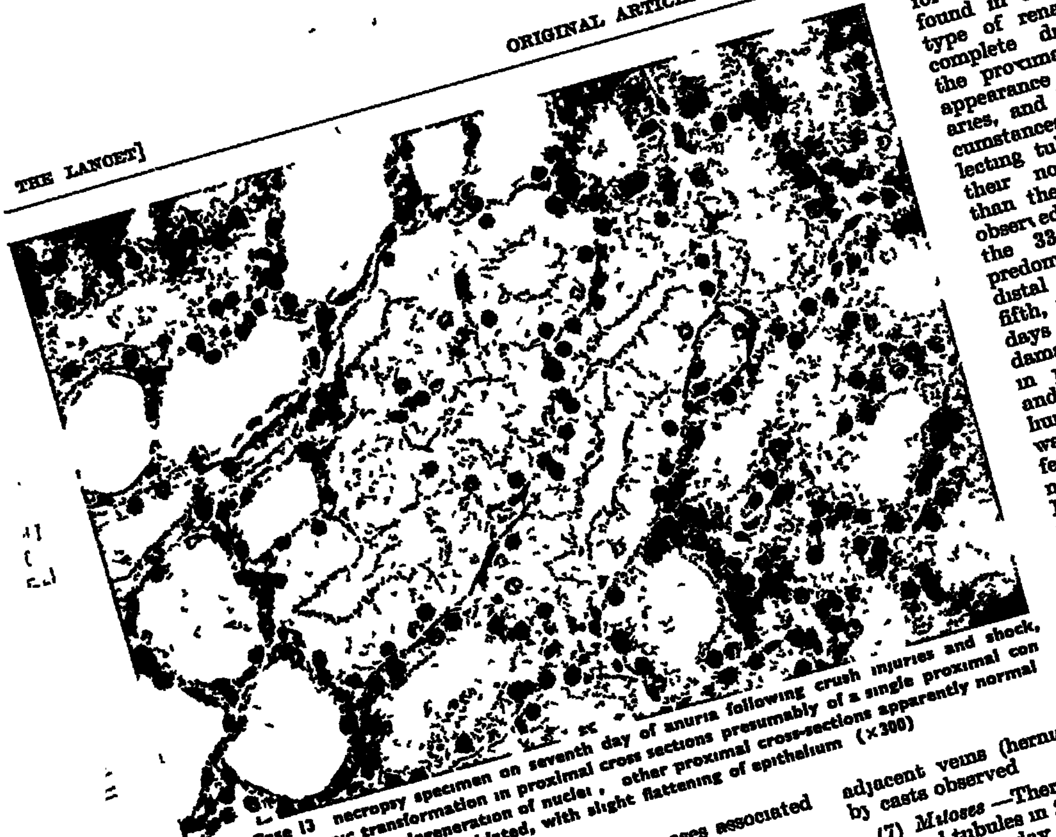

Fig 4—Case 13 necropsy specimen on seventh day of anuria following crush injuries and shock, showing hydropic transformation in proximal cross sections presumably of a single proximal convolution no obvious degeneration of nuclei, other proximal cross-sections apparently normal and distal tubules somewhat dilated, with slight flattening of epithelium (×300)

tening of the epithelium This was in most cases associated with a similar flattening of the nuclei (fig 3)

(2) *Casts* were found in all the kidneys but one In nearly all the cases the casts consisted of a granular and brownish or reddish material located in the lower nephron In some kidneys casts consisting of uniform, weakly eosinophil, hyaline material were seen, together with the type already described

(3) *Dilatation and Flattening of Epithelium in Proximal Convoluted Tubules*—In a few cases there was some dilatation of the proximal tubules, but to a much smaller extent than in the distal tubules Some flattening of the epithelium was present in about half the cases, but this change was unquestionable in only 4 patients The assessment of these slight abnormalities is rendered difficult by the fact that even normally functioning proximal tubules vary somewhat in diameter and height of epithelium

(4) *Hydropic Changes of Epithelial Cells of Proximal Tubules*—This abnormality was found in the proximal tubules, being present in about two thirds of the cases In the hydropically transformed cells the protoplasm appeared light and swollen, as if the protoplasm were œdematous The nuclei of these cells appeared normal (fig 4) Only a few nuclei were present in some cross sections, but this is not surprising when the swollen appearance of the cells is taken into account In 3 cases the hydropic changes were present in all the cross sections of the proximal tubules, in the remaining cases there were groups of affected cross sections throughout the specimen

(5) *Infiltration and Œdema of Interstitial Tissue*—Small scattered foci consisting of lymphocytes histiocytes plasma cells and occasional leucocytes were found in 12 cases in 8 of which moderate interstitial œdema was present

(6) *Tubular Necrosis*—Special attention was paid to tubular necrosis, which is generally accepted as the typical structural change in this disease Nothing like the frank necrosis seen in cases of renal cortical necrosis or the change observed in the kidney after the renal artery has been clamped for two or more hours, was found in our material In this type of renal damage there is complete disintegration of all the proximal tubules, with disappearance of nuclei, cell boundaries, and lumen In these circumstances the distal and collecting tubules seem to conserve their normal structure better than the proximal (fig 5) We observed tubular necrosis in 5 of the 33 patients The lesion, predominantly situated in the distal tubule was found on the fifth, ninth, twelfth, and fortieth days of the disease The tubular damage, when present, consisted in poor staining of the nuclei and desquamation of the epithelium When this type of damage was found it was only in very few cross sections, located between normal looking tubules (fig 6) In some preparations focal inflammation was found close to the tubules in cross sections, but, owing to the dense cellular infiltration it was impossible to decide whether or not disruptive tubular lesions were present (fig 7) Unquestionable tubular rupture was not observed In no case was bulging of tubules into adjacent veins (herniation) or penetration of venous walls by casts observed

(7) *Mitoses*—There were mitoses in the epithelium of the proximal tubules in 2 cases and in that of the distal tubules in 5 cases The day of examination in these patients varied from the third to the twenty second after the onset of anuria

Table II shows that the histological changes occurred with very nearly the same frequency in both the early days of the disease and the later stages There was a noteworthy change in only 1 of the 6 cases where the examination was repeated In case 14 the pronounced dilatation of the distal convoluted tubules present on the seventh day was absent on the fortieth day

The lesions in most cases were characteristically focal

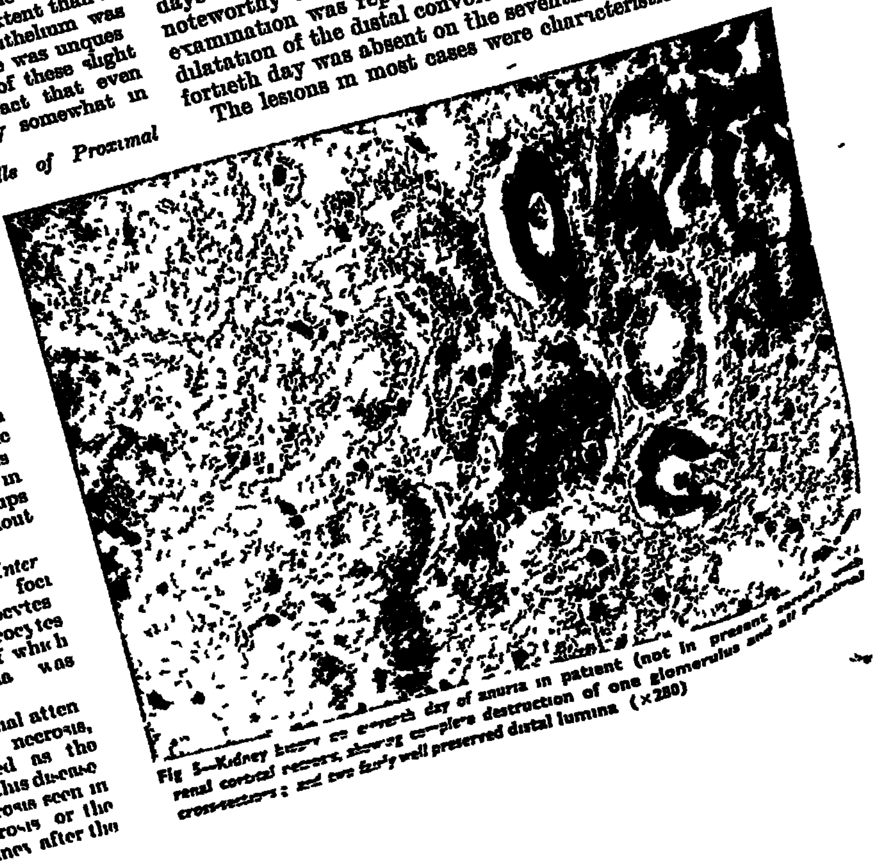

Fig 5—Kidney biopsy on seventh day of anuria in patient (not in present series) with renal cortical necrosis, showing complete destruction of one glomerulus and all proximal cross-sections; and two fairly well preserved distal lumina (×280)

in distribution, small affected areas being found here and there In a few preparations all, or nearly all, the cross sections were involved No correlation was observed between the severity of the disease and the grade of histological abnormality

Discussion

The structural changes hardly differed from those described by other workers The most characteristic alteration was dilatation and flattening of the epithelium in the distal convoluted tubules, being present in nearly all the cases This is in close accordance with the description given by Lucke (1946)

The presence of pigmented casts in the lower portion of the nephron was another characteristic feature The casts varied from brownish granular conglomerates to reddish corpuscles which were hardly distinguishable from erythrocytes, a finding which correlates well with the almost constant presence of hæmaturia It is remarkable that no casts were found in the proximal tubules

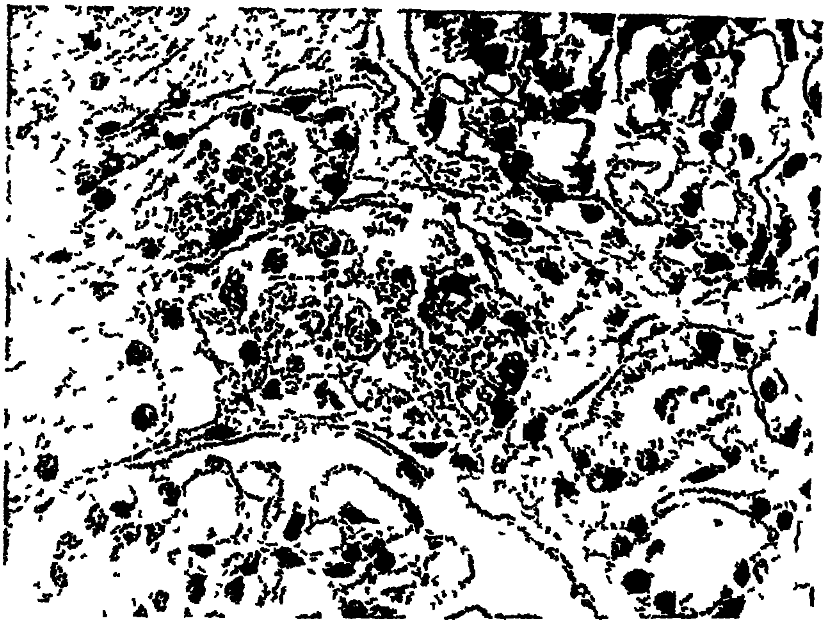

Fig 6—Case 7 biopsy on fifth day of anuria following traumatic cerebral œdema with shock, showing normal glomeruli and hydropic transformation in proximal cross-sections, two distal convoluted tubules with poorly stained nuclei desquamation of epithelium and two adjoining distal cross sections fairly well preserved (×500)

Necrosis of tubular epithelium was uncommon, when it was present, only a very few isolated cross sections were involved Admittedly the traditional two dimensional histological technique is a poor tool in the search for the tubulorrhexic lesion described by Dunn et al (1941) and Oliver et al (1951), but, even using the microdissection technique, Oliver et al reported that "in severely damaged kidneys, not all nephrons are affected, and in the moderate example only occasional ones"

Necrosis of tubular epithelium cannot be distinguished from the post mortem autolytic changes which are universally present if fixation or necropsy is not done immediately after death

Hydropic transformation of the protoplasm of the epithelium in the proximal tubules was common and striking in a large proportion of cases Many different substances can produce these hydropic changes—e g, hypertonic solutions of sucrose, glucose, lactose, and sodium sulphate (Lamy et al 1906) Helmholz (1933) and Allen (1951) observed similar changes after the injection of other substances—e g, urea, xylose, inulin, acacia, and creatinine Dextran and similar plasma substitutes can also produce this lesion in laboratory animals (Goldenberg et al 1947, Bing et al 1951) and in patients with or without acute renal failure (Johnston et al 1953, Vickery 1956) Using a specific staining method Vickery (1956) showed that the hydropic changes were correlated with intracellular dextran in the histochemical preparations

Milne (1955) and Relman and Schwartz (1956) suggest that the hydropic changes can be produced by severe potassium deficiency, but the responsibility of dextran and of inulin could not be excluded in their patients

In the present material from patients with acute renal failure there was a high correlation between the presence of hydropic changes and the infusion of the above mentioned substances, 21 of the 24 patients with hydropic changes having received infusions of dextran, sucrose, or sulphate Similar infusions had been given in only 1 of the 10 patients in whom no hydropic changes were found There was no correlation between the serum potassium level and the existence of hydropic changes

Although we cannot explain why no hydropic changes were found in 1 patient who had received dextran our results suggest that hydropic changes in the proximal tubules are not typical for acute renal failure as such but are the result of therapeutic measures

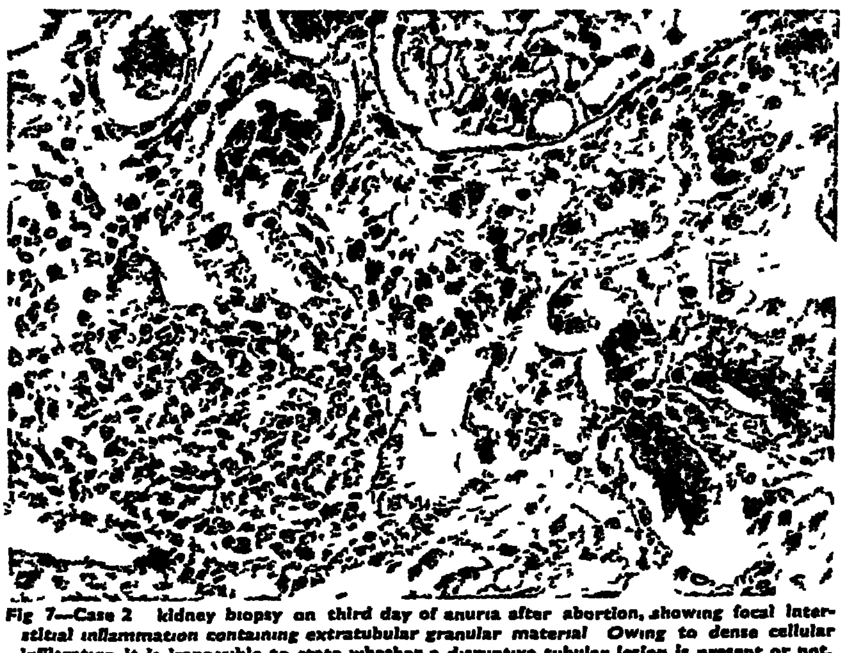

Fig 7—Case 2 kidney biopsy on third day of anuria after abortion, showing focal interstitial inflammation containing extratubular granular material Owing to dense cellular infiltration it is impossible to state whether a disruptive tubular lesion is present or not. Distal cross-sections containing hæm casts or cellular debris are seen Proximal convolutions and glomeruli normal (×280)

Summary and Conclusion

In kidneys from 33 severe cases of acute renal failure following shock the most important histological changes were (1) dilatation of the distal convoluted tubules with attendant flattening of the epithelium, (2) pigmented casts in the distal convoluted tubules, Henle's loops, and collecting tubules, and (3) interstitial changes consisting of small foci of cellular infiltrations and œdema

In many cases there were some dilatation of the proximal tubules and moderate flattening of the epithelium but rarely more than can be seen in normally functioning tubules

Hydropic changes in the epithelium of the proximal tubules were a common finding, but it is highly probable that this change was due to infusions of dextran, sucrose, or sulphate, and not to the kidney disease as such

Tubular necrosis and mitoses in the tubular epithelium were found in a few specimens No unquestionable tubular disruptive lesions were seen, but the ordinary histological technique is insufficient to show this

The various histological changes occurred nearly with the same frequency in both the early days of the disease and the later stages

The most impressive general observation was the contrast between the moderate structural changes and the complete functional breakdown

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INSULIN TREATMENT OF SCHIZOPHRENIA

A CONTROLLED STUDY

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INSULIN coma therapy of schizophrenia was introduced by Sakel over twenty years ago (Sakel 1935), and a vast literature on the results of this treatment has since accumulated And yet, despite these numerous studies, despite the claims of enthusiastic supporters, and despite the vigorous protestations of Sakel himself (Sakel 1950), the evidence for the value of insulin remains far from convincing In recent years papers critical of the evidence for the value of insulin have been published (Bourne 1953, David 1954 Gottlieb and Huston 1951, Lifschutz 1954), and there is now a growing tendency to try the effect of the new "tranquillisers" before resorting to insulin therapy Boardman et al (1956) claim similar results for treatment with chlorpromazine, and even previously enthusiastic exponents of insulin therapy have reported that they have almost given up the treatment (J N P Moore, personal communication)

If insulin coma is effective, the growing tendency to abandon it must be reversed If it is not, patients are being exposed to risks, and the hospital service is incurring expense to no good purpose If it is true that insulin coma has a specific influence on schizophrenia more research should be concentrated on the physiological mechanisms involved If there is no such specific influence, further inquiry along these lines is a waste of time and money

Clearly a reassessment of the results of insulin therapy is urgently needed, and the present work is an attempt to supply this need by means of a study designed to avoid some of the fallacies present in previous work Since the need for a further assessment arises from these fallacies, they will now be considered in some detail

Fallacies in Previous Studies

Selection of Patients

To compare the reported results of treatment by different workers, it must be possible to assess how comparable are the various schizophrenic populations, yet the age distribution and the proportion of schizophrenic subtypes composing the group studied are often not given Some workers have included atypical or schizo affective cases but have not indicated their proportion in the total group, although they are well known to have a more favourable outcome (Harris and Lubin 1952, Harris and Norris 1955)

The duration of illness is now accepted as one of the most important prognostic factors in schizophrenia, yet many studies have been rendered inconclusive by the failure to separate the recent from the chronic cases and to specify results in relation to the duration of the psychosis

Reports on large groups of schizophrenics from different hospitals involve differences in the type of patient admitted, dissimilar diagnostic practices, variability in intensity of treatment, and lack of consistency in assessing outcome

There is evidence that, in recent years, mental-hospital admissions have contained a higher proportion of less severely ill patients with a more favourable prognosis (Harris and Norris 1954) As a result the outcome of even the illnesses of recent onset treated with insulin cannot validly be compared with those of the pre-insulin era The finding by Malzberg (1943) that, in New York State, both the admission rate and the discharge-rate of schizophrenics had risen since the institution of insulin therapy suggests that belief in the efficacy of the treatment, given as early as possible in the illness, and fear of depriving the patient of its benefits had led to an increased admission of early or doubtful cases

An adequate assessment of the results of insulin coma therapy necessitates the comparison of the outcome of treated cases with those who have not received insulin but in all other respects can be considered to be alike Many workers have not reported control series at all, or have referred to those of workers from other hospitals, but all the large control series reported are derived from the pre insulin era Though details are commonly given for the composition of the insulin-treated groups, less attention is often paid to the controls, and criteria of selection are often not indicated

Even if properly matched untreated cases from another hospital or from the same hospital but derived from an earlier era, cannot properly be regarded as comparable Apart from the factor of changing patterns of admission mentioned above, the influence of modifications in the hospital environment, changes of doctors and nurses, and altered attitudes towards hospital care cannot be ignored A remission in the absence of specific treatment does not necessarily indicate that it is "spontaneous" and that no other favourable influences have played a part In the past the untreated cases were often a neglected group, but in recent years the increasing emphasis on resocialisation and individual and group approaches has so altered the pattern of hospital care that many factors unrelated to the physical treatment are brought to bear on schizophrenics in a manner that rarely existed previously The belief in the greater possibility of recovery, the atmosphere of therapeutic enthusiasm, and the increased medical and nursing attention must all be powerful forces promoting recovery

This view is supported by the recent work of Hoenig et al (1956), who compared the outcome of a group of early schizophrenics in the Maudsley Hospital in 1934–35 with a comparable group in the same hospital in 1948–50 They found that the results in the later group were much better than those in the earlier group, who had received no physical treatment However, the results in those cases of the later group who had received no physical treatment were also much better than those of the earlier group, and it was concluded that factors other than physical treatment must be concerned in the difference in outcome between the two groups

A few workers have tried to compare an insulin-treated group of patients with a parallel control group cared for under similar conditions at the same time, but none of the studies is satisfactory

Notkin et al (1939) compared a group of insulin treated schizophrenics with a control group of patients in the same ward receiving saline injections, and they claimed no difference in outcome between the two groups However, no criteria of selection for the two groups were given, and the patients appeared to be largely a chronic group not matched for duration of symptoms The method of clinical assessment and follow up procedure was also unsatisfactory

Lipschutz et al (1939) compared groups of chronic schizophrenics treated with (1) insulin coma and resocialisation, (2) insulin coma without resocialisation, and (3) physiological saline solution and resocialisation They claimed superiority of results in that order However, the groups were small, and no criteria of selection were stated The insulin and resocialisation group which had the best outcome was a larger group than the others and appeared to contain more cases of shorter duration

Libertson (1941) compared an insulin treated group with an equal number of patients not receiving insulin and claimed no difference in outcome between the groups for the early cases However, the controls were cases unsuitable for insulin because they were either chronic or already recovering Thus, although the average duration of symptoms of the controls was much larger than that of the schizophrenics, the short duration cases in the control group appeared to consist largely of specially selected cases

Gottlieb and Huston (1951) treated three groups of schizophrenics with insulin, brief psychotherapy, and electroconvulsions and claimed that the outcome was not significantly different in the three groups However, no criteria of selection of cases were given, the duration of symptoms for each group was not stated, and the group appeared to differ in their composition of subtypes Furthermore, their technique of insulin coma therapy is open to criticism

Lifschutz (1954) compared an Army group of insulin treated and non treated schizophrenics and claimed no difference in outcome between the two groups However, no criteria for selection were given, and, although these groups were named acute, chronic, and unknown, there was no indication that they were strictly matched for duration of symptoms Electroconvulsions were apparently given to both groups, but to what extent was not stated

Nowhere does there appear to have been reported a control group properly matched for age, sex, subtypes, and duration of symptoms, selected by randomisation, and treated at the same time and under general conditions similar to an insulin treated group

Technique of Insulin coma Therapy

A lack of consistency in insulin-coma technique often makes comparison of results reported by various workers difficult Often no details of the technique are reported at all, and in some investigations reported there may be variability between different workers in their criteria of sopor and coma, in the duration of coma permitted, and in the number of coma treatments given

Another serious difficulty arises from the almost general practice of administering electroconvulsions (or leptazol in previous years) in a variable manner during the course of insulin administration Clearly any control group which has not also received electroconvulsions cannot be regarded as valid for the assessment of the effect of insulin complicated in this way

Weinberg and Goldstein (1942) treated 100 schizophrenics with insulin coma three months after their failure to respond to metrazol therapy, and they claimed a high remission rate However, since a comparable group of insulin failures subsequently treated with leptazol was not reported, the factor of increased duration of hospital treatment could not have been taken into account

Rees (1949) compared the results of treatment with insulin electroconvulsions, and electronarcosis in 160 schizophrenics and claimed definite superiority for insulin treatment However, although the three groups were well matched, there is no indication whether the 160 patients were consecutive admissions or drawn from a large population, and how the selection was made which determined the treatment

Mode of Assessment of Outcome

In any controlled clinical trial the potential bias of the observer must be excluded by his having no prior knowledge of the treatment given to the groups being assessed Unfortunately this condition has never been achieved in the reported studies on insulin treatment Not only have the results always been assessed with a full knowledge of which were the controls and which were the insulin treated patients but also commonly the assessment was made by those responsible for the therapy and therefore not disinterested observers

The variable and often ill defined criteria of outcome of treatment used by many workers has created difficulties in the assessment of results

Sometimes only immediate outcome of treatment has been considered, and often results have been expressed solely in terms of percentage of patients discharged or allowed out on parole

The length of time following treatment at which the patient leaves hospital is often not stated, and in these circumstances the success cannot necessarily be ascribed to the treatment

Assessment in terms of reduced hospitalisation time also cannot be accepted by itself as a valid criterion, for increasing pressure on beds in overcrowded hospitals, and the tendency for the enthusiastic therapist to discharge his treated patients earlier than was the custom, will both tend to affect discharge policy in the direction of reduced stay in hospital

Furthermore, the ability of a patient to leave hospital and to remain in the community must clearly depend in part on social factors, such as the home conditions and the capacity of relations to tolerate and adjust to psychotic symptoms and behaviour abnormalities

In reporting results the categories "recovered" and "much improved" are often grouped together in different ways by various workers

Some workers believe that no case of schizophrenia severe enough to be institutionalised recovers without some personality deterioration (Lewis and Blanchard 1931)

Ross and Malzberg (1939) report high recovery and much improved rates, claiming "recovery" to mean symptom free with insight, and "much improved" to mean symptom free without insight

Most other workers have placed less emphasis on the presence of insight and have been prepared to accept as "recovered" all symptom free cases while including under "much improved" or "social recoveries" those patients still showing mild symptoms or personality defects who are able to return to an independent existence in the community

The frequent grouping together of these two categories allows of much variability in the range of outcome but nevertheless is to be preferred to the use by some workers of the category "remission" often without any attempt at all to define terms.

Follow-up Studies

Many follow-up studies have not indicated the methods used to assess the clinical status of the patient:

Contacts with the patient or with a relation by post, or by interview with the doctor or a psychiatric social worker, have all been used, but in what proportions in any one study it is often difficult to determine.

Sometimes the follow-up periods are fixed from the time of discharge of the patient from hospital instead of from the time of termination of treatment; consequently recoveries which have occurred in hospital long after the termination of treatment are ascribed to the treatment.

The same source of possible error occurs in the common practice of reporting the clinical status at each follow-up period in terms of percentages of the original group instead of in terms of the previous follow-up group. By this procedure recoveries occurring many years after the termination of treatment are ascribed to the treatment.

Sometimes no fixed follow-up periods are stated, and results are given for a group within which the follow-up duration varies from a few months to a few years.

Sometimes relapse rates are really readmission rates, and no account is taken of the relapsed cases remaining in the community.

In reporting follow-up results little account may be taken of untraced cases or the results stated in terms of the percentage of cases actually followed up.

Design of Controlled Study

The design of a controlled study of the therapy of schizophrenia is evidently difficult because of the ill-defined diagnostic criteria, the heterogeneous nature of the disease, its variable and only partially predictable spontaneous course, and the lack of clear-cut standards of improvement or of recovery. To assess effectively the results of insulin coma therapy many criteria must be satisfied, and among them the following appear important:

The patients selected should all have undoubted schizophrenia and be such that all experienced psychiatrists would regard them as good subjects for the treatment. The patients should thus all have a clearly defined onset of symptoms of under one year's duration and should not have had an insidious onset or a marked abnormal personality.

The age range should be such as to exclude the menopausal and adolescent psychoses, which may have a different prognosis.

To avoid including those with a tendency to rapid remission, patients should not be accepted until a few weeks after their admission.

Those undertaking the insulin therapy should not be responsible for the selection, diagnosis, and subsequent assessment of the patients.

The schizophrenic group so selected should be divided into diagnostic subtypes because these are usually believed to differ in their outcome, and the subtypes should be separately randomised into treatment and control groups. Both these groups should be treated contemporaneously under the care of the same doctors and nurses. They should be treated in the same ward; and, except for the actual administration of insulin, the controls should receive treatment which in all other respects is comparable to that given to the insulin group.

Those originally responsible for selecting the patients should assess results without any knowledge of the treatment received by the patients. This assessment should be made in accordance with previously agreed and defined criteria, and it should be made at suitable intervals after the end of treatment.

Present Investigation

Ackner (1951) suggested a project fulfilling the above criteria in which it was proposed that the controls should receive barbiturates instead of insulin to induce loss of consciousness. The implementation of this proposal took time but was finally achieved in a coöperative study initially on patients in Cane Hill Hospital and later including also patients in the Maudsley and Bethlem Royal Hospitals.

One of us undertook the insulin treatment of the Cane Hill Hospital patients, while another was responsible for the treatment of the Maudsley and Bethlem patients. The patients treated had been originally admitted under either our own care or the care of other physicians at the hospitals who had previously agreed to their patients being included in the project.

Patients with a presumptive diagnosis of schizophrenia, aged 18–40, with no history of previous psychotic symptoms, and with an apparent history of less than a year's duration were seen after they had already been fully investigated for some weeks in hospital. They were diagnosed and selected by the two of us not responsible for the treatment at the hospital in question, and no patient was accepted unless there was complete agreement on the diagnosis and duration of symptoms. No atypical cases or those already showing signs of recovery were accepted. So strict were the criteria of selection that, of all early schizophrenics offered as being suitable, nearly 50% were rejected on the grounds of doubt about diagnosis or duration of symptoms. After a patient had been accepted and the diagnostic subtype (hebephrenic, paranoid, catatonic, schizo-affective) agreed, the randomisation into the insulin or narcosis group was made by the physician responsible for the treatment and without the knowledge of the other two concerned.

METHOD OF TREATMENT

Insulin and Control Groups

The randomisation into insulin and narcosis groups was made for each sex separately for the Bethlem-Maudsley patients and for the Cane Hill patients. The procedure was as follows:

Paranoid or hebephrenic schizophrenia.—The grouping of the 1st paranoid or hebephrenic patient of either sex was decided by the toss of a coin; the 2nd patient of the same sex and diagnostic category was allocated to the opposite group; the 3rd patient according to the toss of a coin, and so on. If a patient did not complete treatment for such reasons as discharge against advice and technical difficulties in the insulin series, he was removed from the group, and his place was taken by the next patient with the appropriate sex and subcategory.

Schizo-affective psychosis and catatonic schizophrenia.—Patients with schizo-affective psychosis and catatonic states often respond well to electroconvulsions; so, to avoid the confusion of results caused by combined treatment, these patients were first given a course of ten electroconvulsions at the frequency of 2–3 treatments a week. If they were considered then by the assessors to have recovered, no further treatment was given; but, if they were considered still to be actively schizophrenic, each patient was randomised as above into the insulin or narcosis group.

Therapeutic Environment

Every matched pair of patients having insulin or narcosis treatment was treated, so far as practicable, in the same therapeutic environment in all other respects. The fact that two separate insulin units, at Bethlem and at Cane Hill, were used, and that the sexes were segregated for treatment, did not impair this aim, because all male and female patients accepted into the series were matched separately at the two hospitals.

At Bethlem Royal Hospital the insulin unit is shared by males and females, who are segregated only for treatment, toilet, and sleeping. The unit is self-contained and only includes patients under treatment.

At Cane Hill Hospital separate insulin units for male and female patients are situated in two wards which are also occupied by patients not under insulin treatment. In both hospitals all patients having insulin treatment, whether in our series or not, spent their non-treatment hours as a group, engaging in the usual programmes of occupational and recreational therapy. All the patients in our series were told they were having coma treatment and were in no way distinguished from the patients in the unit who were not in our series The purpose of the project was explained to the nurses, who were carefully trained to treat every patient alike All the patients received the same number of injections and doses of medicine in the course of the day, whether they were having insulin or narcosis treatment

Drugs Used

The problem of a suitable narcotic agent was investigated at Cane Hill Hospital, where, after a short trial, it was decided that equal parts of sodium amylobarbitone and sodium quinalbarbitone produced within an hour a state of deep sleep which tended to lighten considerably after a further thirty minutes Subsequently the introduction of dexamphetamine solution into the stomach would awaken the patients after a further period of about fifteen minutes The following agents were then used

(1) Soluble insulin (2) Sterile water		for intramuscular injection
(3) *Narcosis control mixture*		
Infusion of gentian	$^1/_2$ drachm	to be taken by mouth
Brandy	$^1/_2$ drachm	
Azorubrum	4–5 min	
Aqua ad	$^1/_2$ fl oz	
(4) *Narcosis mixture*		
Sodium amylobarbitone	gr 3	to be taken by mouth
Sodium quinalbarbitone	gr 3	
Brandy	$^1/_2$ drachm	
Aqua ad	$^1/_2$ fl oz	

Brandy was needed to suppress the taste of the barbiturates which were difficult to match, azorubrum was needed to match the red colouring given off by the sodium quinalbarbitone tablet

Therapeutic Technique

Treatment was given daily except on Saturdays and Sundays and started at 7 A M after a fast from 7 P M on the preceding day Patients in the insulin group received the appropriate intramuscular injection of soluble insulin, and those in the narcosis group were given a similar injection of sterile water At about 8 45 A M each patient in the narcosis group was given a drink of narcosis mixture, and every insulin-group patient a similar drink of narcosis control mixture

For the insulin group the definitions of coma and sopor were those used by Sargant and Slater (1954)—i e, coma is a state of unconsciousness in which the patient does not react purposefully to painful stimuli, and sopor is a state from which the patient cannot be fully aroused although able to react purposefully to painful stimuli

For the narcosis group dosages of the narcosis mixture were gradually increased until deep sleep came on at about 9 30 A M, many of the patients later reaching a state of unconsciousness equivalent to coma

After thirty minutes' coma the insulin-group patients were given a nasal feed of one pint of 33% glucose solution, while the narcosis group patients received a nasal dose of one pint of dexamphetamine solution made by dissolving in water a dose of dexamphetamine in milligrammes equal to twice that of the combined barbiturates in grains

Any insulin group complications were treated in the standard manner It was intended that, if a barbiturate coma became "irreversible," methamphetamine should be given intravenously, but the occasion never arose

35–40 insulin comas (or the narcosis equivalent) were administered in all the cases This sometimes involved a slightly longer period of treatment for the insulin group owing to the longer time needed to obtain coma dosages of soluble insulin

ASSESSMENT OF RESULTS AND FOLLOW-UP PROCEDURE

On completion of treatment every patient was seen by the two physicians who had not been responsible for the treatment, and the mental state was assessed without any knowledge of the treatment received Six months, a year, and thereafter yearly after the end of treatment the patient was again seen by the same assessors (who were still ignorant of the treatment given) and classified on two 3-point scales, one referring to his clinical state judged at interview and the other to his present social status These scales were as follows

Clinical state

(1) Symptom free and apparently fully recovered
(2) Residual defect
(3) Psychotic symptoms still present

Social status

(1) Independent
(2) Socially dependent
(3) Hospital inmate

Patients were judged to be fully recovered when no psychotic symptoms or impairment of personality could be detected and when they had apparently returned to their prepsychotic state If any psychotic symptoms at all were detected they were so categorised If no psychotic symptoms were detected but the patient exhibited personality changes—e g, flattening of affect, loss of drive, and poor concentration—he was categorised as "residual defect" Patients were judged to be "independent" if they were working and earning a living or performing their duties as housewives normally If dependent on relations or social agencies for their keep or if inefficient as housewives, they were categorised as "socially dependent"

No attempt was made to rate patients on the much used but unsatisfactory category of "much improved" Our patients were either clearly recovered or still ill in various respects

RESULTS

The clinical state at the end of treatment had often not settled fully enough to categorise adequately, but the picture six months after treatment had ended was clear enough to enable a reliable rating to be made

Up to date some patients have been followed up for more than two years, but others have not yet completed their six-month follow-up period This report present the results of the first 25 matched pairs who have completed the first six-month follow up period Of the 50 patients 48 were personally seen by the assessors, and in many cases relations were interviewed by them at length The 2 patients not seen were both in other mental hospitals, and comprehensive reports concerning their condition were received

Of the 25 pairs 12 were female and 13 male There were 18 pairs of paranoid schizophrenics, 6 pairs of hebephrenics, and 1 pair of schizo-affective psychotics

The results are shown in the accompanying table A brief note on the schizo affective and catatonic patients accepted for the series during the period under review is needed

The 11 schizo affectives were all in a state of consistent depression but showed in addition such schizophrenic features as delusions of persecution and influence of an

RESULTS

Classification	Insulin			Controls		
	Cane Hill	Bethlem Maudsley	Total	Cane Hill	Bethlem Maudsley	Total
Clinical state						
Recovered	6	3	9	5	5	10
Residual defect	2	2	4	3	1	4
Still psychotic	6	5	11	6	5	11
Social status						
Independent	7	6	13	6	6	12
Out of hospital but dependent	2	3	5	2	1	3
In hospital	5	1	6	6	4	10
Dead	0	1*	1	0	0	0
Total	14	11	25	14	11	25

* Killed while cycling after discharge from hospital

odd bizarre nature, passivity feelings, or thought disorder of schizophrenic type 6 recovered completely after electroconvulsions, 2 discharged themselves against advice, and 3 went on to the insulin/narcosis series Of the 3 catatonics, 1 recovered completely after electroconvulsions, and 2 went on to the insulin/narcosis series but being of opposite sexes did not form a matched pair

Discussion

It will be readily seen from the table that the results for the insulin and narcosis groups are so similar that no statistical treatment of significance is necessary The only possible exception relates to the number of patients remaining in hospital, where the figures show an apparent tendency in favour of the insulin group However, the difference between the 10 in the narcosis group and the 6 in the insulin group remaining in hospital is statistically not significant whether considered separately for each hospital or for the total of the two together

It will be seen that the similarity in outcome for the two groups applies not only to the overall figures but also to the two hospitals considered separately This is very striking in view of the fact that the hospital environments and personnel are different and that Bethlem and the Maudsley hospitals only admit voluntary patients Furthermore the results of treatment are not only remarkably similar but are also good Six months after treatment 40% of the patients remain fully recovered (excluding any who might be considered much improved,) and this figure has not been bettered in any reported series

The results presented are based so far on a small number of patients However, many other reported series have not contained as many as 50 early schizophrenics, and our series would have been larger by now if so many cases had not been rejected at the time of selection The small size of the series is, however, probably compensated for by the careful selection and randomisation of the groups At no time have the assessors ever had any knowledge of the group to which a particular patient might belong, and they still remain in ignorance As a result no bias in assessment was possible, and rating was often severe On a few occasions a relation insisted that a patient was fully recovered and completely back to his former self, but this was not accepted and a rating of "residual defect" was made

The results so far show that there is no significant difference in the outcome of treatment whether unconsciousness has been induced by insulin or by barbiturates They do not demonstrate that the coma regime has no therapeutic effect During insulin therapy patients are subjected to powerful group influence and receive increased medical and nursing care in a special setting Daily they are exposed as a group to the threat of being rendered unconscious Daily they are brought back to consciousness by doctors and nurses on whom they become dependent The new relationships so built up cannot be ignored, for it could be that the coma régime is helping to establish that lost capacity for relationship with others But the results suggest that insulin is not the specific therapeutic agent of the coma régime as has so often been claimed We intend to follow up these and other patients for a longer period and present further results at a later date

Summary

Schizophrenics, aged 18–40, with a history of psychosis for less than a year, were randomised separately, according to sex and diagnostic subtype, into an insulin and a barbiturate group

The insulin group received the standard insulin coma therapy, and the barbiturate group was treated in the same ward, under similar conditions, the only difference in treatment being that unconsciousness was produced by oral barbiturate

The initial diagnosis and subsequent assessment of outcome were made without any knowledge of the treatment given

The results of treatment for the first 50 patients followed up at the end of six months reveal no significant differences between the two groups

No conclusion can be drawn about the therapeutic value of the coma régime, but the results suggest that insulin is not the specific therapeutic agent

We are indebted to Dr A Walk, physician superintendent, Cane Hill Hospital, for willing collaboration, Dr D L Davies, Dr J Dewsbery, Dr W Linford Rees, and Dr F Post for referring patients to us, Mr A E Maxwell, of the Institute of Psychiatry, for statistical advice, Mr J Tremowden, chief pharmacist, Cane Hill Hospital, for his help, and the nurses and junior doctors of Bethlem Royal and Cane Hill Hospitals for their conscientious supervision of the treatment

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THE EFFECT OF AN AEROSOL DETERGENT IN CHRONIC BRONCHITIS

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IN chronic bronchitis the bronchial secretion is more copious, adhesive, and viscid than normal During an acute infection it is opaque, yellow, and less viscous During recovery and in the chronic phase it becomes clear, gelatinous, and more viscous (Elmes and White 1954) When the sputum is purulent its viscosity can be reduced by streptodornase as an aerosol (Armstrong and White 1950), but when the sputum is mucoid its viscosity cannot be reduced by any specific enzyme

Since the purulent phase lasts only a few days when suitable antibiotics are used, and since patients expectorating mucoid sputum do not benefit from chemotherapy whatever organism is present (May 1953), the great problem is to reduce the viscosity and thereby to aid the expectoration of the viscid mucoid sputum during the chronic phase of bronchitis

American workers have reported that the proteolytic enzyme trypsin given as an aerosol is of value for this purpose (Unger and Unger 1953) This substance is irritant, however, and the coughing it produces is probably the most important factor in the removal of the sputum Moreover, since trypsin is a foreign protein there is a risk of sensitisation, and pre malignant changes in the bronchial mucosa have been reported after its use (Farber et al 1954)

Aerosol detergents have been developed to reduce the viscosity of the mucoid bronchial secretion and to aid expectoration (*British Medical Journal* 1954) The effect of such a preparation, 'Alevaire,' in chronic bronchitis is reported here Alevaire is produced by Bayer Products It contains 0 125% of a detergent superinone ('Triton

WR 1339 ') in a sterile aqueous solution containing 2% sodium bicarbonate and 5% glycerin The glycerin is added to stabilise the aerosol droplets Alevaire is administered in a nebuliser which delivers a fine " dry " mist with a particle size of 0 5–3 0 µ The nebuliser is attached to a suitable air compressor or oxygen supply The two atomisers which we have used for this purpose and found very suitable are the 'Collinson' and the 'Oxygenaire' Alevaire is unsuitable for use by steam inhalation

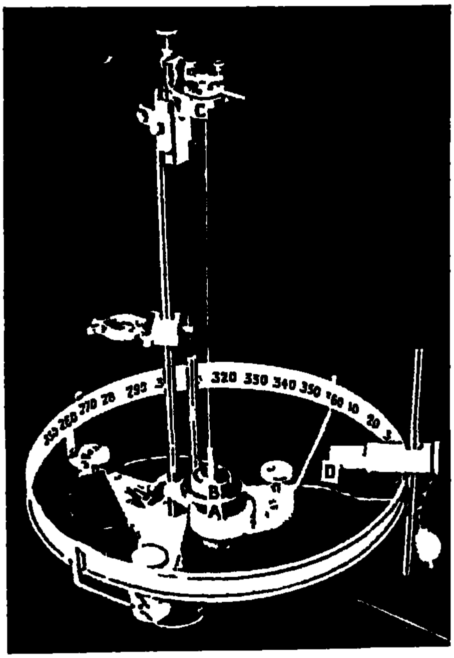
Method

Twenty-five patients with chronic bronchitis were studied They had been in hospital for several weeks, were expectorating mucoid sputum, and were not having any drugs, hence they were all considered to be in a stable phase Throughout the period of observation they were ambulant in a well heated and well-ventilated ward, and an adequate intake of fluids was ensured

The trial period extended over three consecutive weeks (1) a week with no treatment, (2) a week of daily inhalations of alevaire, and (3) a week of daily inhalations of a control solution The order of (2) and (3) was decided by random selection The nature of the substances given was unknown to the patient, the nurses, and the persons making the clinical assessment and measuring the viscosity The control solution was the same as alevaire except that it did not contain the detergent—i e, it consisted of water, 2% sodium bicarbonate, and 5% glycerin The solutions were given for an hour t d s, the solution being nebulised in the Collinson or oxygenaire apparatus by oxygen at a rate of 8 litres a minute, which is equivalent to about 15 ml of the solution an hour Assessment of the patients consisted of two parts clinical assessment and measurement of viscosity of the sputum

Clinical Assessment

The patients were examined daily Inquiry was made about cough, dyspnœa, wheeze, and any difficulty in coughing up the sputum Physical signs in the chest were noted, special attention being paid to râles and rhonchi The amount of sputum for the 24 hour period was measured At the end of each weekly period an assessment of improvement was made (1) subjective improvement (i e, whether the patient felt better and could expectorate more easily after the inhalations), and (2) objective improvement (i e, changes in râles and rhonchi and a significant reduction in the amount of sputum produced daily)



Cone-and plate viscometer A, plate rotated by constant-speed electric motor B, cone suspended on phosphor-bronze wire C mounting of suspension wire D, light beam reflected from top of cone to circular scale

Viscosity of Sputum

Viscosity was measured in a cone and-plate viscometer specially designed and constructed for this purpose (see figure) It consists of a plate (A) rotated by a constant speed electric motor, a cone (B) suspended on a phosphor bronze wire, a mounting (C) of the suspension wire designed to ensure that the distance between the cone and the plate remains constant for each measurement, and a light beam (D) reflected by a small mirror on top of the cone to a circular scale The viscometer has a low rate of shear which is constant It has a wide range and is easily cleaned after each measurement The coefficient of variation was 2% with glycerin and 10% with sputum

TABLE I—25 PATIENTS WITH CHRONIC BRONCHITIS TREATED WITH AEROSOL THERAPY

—	Improvement		Viscosity of sputum decreased
	Objective	Subjective	
Period I			
No treatment	2	2	1
Period II			
Alevaire by aerosol	4	17	3
Period III			
Control solution by aerosol	6	18	[illegible]

To measure viscosity the gap between the cone and the plate is exactly filled with 2 ml of sputum from a syringe When the motor is turned on, the plate rotates at 1 r p m, and the cone follows the movement of the plate until the torque developed in the suspension wire is sufficient to overcome the viscous forces of the sputum After a few minutes to allow for stabilisation the deflection produced is read off the scale This gives the viscosity of the sputum, the deflection increasing with greater viscosity Since the method was developed to measure changes in viscosity instead of absolute values, the scale is marked in degrees

TABLE II—EFFECT OF VARIOUS AEROSOLS ON VISCOSITY OF SPUTUM

Aerosol	Viscosity of sputum (degrees of deflection)					
	Case 1			Case 2		
	Before aerosol	After aerosol	Reduction in viscosity (%)	Before aerosol	After aerosol	Reduction in viscosity (%)
Alevaire	137°	92°	32 9	210°	170°	19 1
Control solution	135°	81°	40 0	256°	195°	23 9
Saline solution	155°	100°	35 5	228°	188°	17 6
Water	132°	85°	35 6	230°	175°	23 9

Morning specimens of sputum were used because the viscosity of the sputum was greatest then The sputum was expectorated into a dry glass container and examined as soon as possible afterwards Spontaneous daily variations in viscosity were common, therefore the means of the viscosity measurements for each week were compared When the means differed by 20° or more, the viscosity of the sputum during that week was considered to have changed

Results

The results (table I) show that aerosols of alevaire and of the control solution are equally effective in bringing about considerable symptomatic improvement in patients with chronic bronchitis, the main effect being that the patients can expectorate more easily A few patients show objective improvement and changes in the viscosity of the sputum with either aerosol No significant change in the volume of sputum produced daily was found except in the few patients who showed objective improvement during the trial, and in these the sputum either diminished considerably or disappeared (Those patients who showed objective improvement clinically were not always those that showed changes in viscosity of sputum)

Medical Societies

MANCHESTER MEDICAL SOCIETY

Surgery in Portal Hypertension

AT a meeting of the section of surgery on Feb 12 Mr A G RIDDELL said that portal hypertension may be conveniently defined as a pressure in the portal system of more than 30 cm of saline In more than 70% of cases the cause is an intrahepatic block, while in the remainder it is thrombosis in the portal vein The mechanism of portal hypertension is obscure, but it occurs in about 30% of patients with cirrhosis, there is no very clear correlation between the portal pressure and the histological appearance of the liver. Neither portal hypertension nor œsophageal varices follow ligation of the portal vein in man, for in most patients an adequate collateral circulation develops Varices occur only when there is portal hypertension Splenomegaly results from portal hypertension leading to hypersplenism Hæmorrhage almost inevitably follows the appearance of varices, and in the presence of cirrhosis severe hæmorrhage leads to fatal hepatic coma This coma is said to be due to bacterial action on the ingested blood in the alimentary tract leading to ammonia intoxication Blood-transfusions are necessary to replace the *blood-loss* and to arrest the bleeding

The two problems in the surgical treatment of portal hypertension are control of the hæmorrhage and prevention of hypersplenism After an acute hæmorrhage, blood-transfusions should be started immediately and hæmorrhage controlled by an œsophageal tam eight hours is probably the limit for th treatment, and if hæmorrhage is still unco œsophageal varices should be ligated In th of further hæmorrhages portacaval and anastomoses are now established, and t mortality and the incidence of recurrent are low Percutaneous trans splenic p of great value in determining the type of After a successful shunt operation the and may completely disappear, while hypers may sometimes regress after a portacava Since the bleeding after splenectomy is the most problem in the surgery of portal hypertension tomy alone should never be performed in the of portal hypertension, if splenectomy is then it should be followed immediately by a s anastomosis

Prof A M BOYD referred to a series of 7 of the patients were alive and had not operation Mr H A HAXTON described who had had shunt operations, including later from liver failure and 8 who underwent anastomosis, including 3 who were now well

Dr M C G ISRAËLS reported a series observed by him and Dr J F Wilkinson, in w tomy had been done for splenic anæmia patients were still alive including 6 wh further bleeding, 3 had had one hæm had had two hæmorrhages and 2 *had* bleeding

Reviews of Books

The Physiology of Gastric Digestion

A H JAMES, D M Oxfd M D Toronto, M R C P senior lecturer in medicine Welsh National School of Medicine, and deputy director of the medical unit, Cardiff Royal Infirmary London Edward Arnold. 1957 Pp 192 28s

ONE of the fascinations of the study of gastric function is that advances can still be made with simple apparatus but those who begin in this way need a primer to orient them and to warn them of mistakes of experimental design and interpretation The practising clinician on the other hand needs a more general account of what is known about gastric function Both groups will be well satisfied with this book.

Dr James selects and interprets the literature of gastric function in such a way as to relieve us of the tedium of reading the original papers with unprepared minds and he assesses the opinions of different authors in a thoroughly constructive way A few hours with this book will provide a background of up to-date information and a stimulus to thought about its clinical application This transition should not be difficult because more than half of the figures refer to observations on man

This book will be valued by physiologists and clinicians alike

Sex in Christianity and Psychoanalysis

WILLIAM GRAHAM COLE London George Allen & Unwin 1956 Pp 329 21s

THIS is an admirable book. With learning and good sense the author examines a problem which is of manifest urgency in our Western society but which is commonly discussed in partisan style or with moralising superficiality Though theology is sometimes arid reading Professor Cole presents his material in vivid well-chosen language which holds the reader's attention He has one major theme he insists that the belief that the body is sordid a tomb for the soul did not derive from Pauline Christianity as many suppose, but from Hellenistic influences, at first Pythagorean and later Stoic and Epicurean at whatever point a study of Hellenistic culture begins dualism is encountered It was the presupposition of all thought and it was the soil in which the pale flowers grew Sex was regarded as low and degradi

He expounds this contention with much fo reviews in turn the writings of Augustine, Tho Luther, and Calvin, so far as they bear on se He next states the contemporary Catholic view, in the famous encyclical of Pius XI, *Casti Connu* large book by Father Messenger, *Two in* follows this with a necessarily less unifi contemporary Protestant views, for wh representative writers Leslie Weatherhea Princeton) Emil Brunner and Reinhold a Protestant theologian, Dr Cole is not Catholic doctrine in these matters, but to offer a fair statement of it

The psycho-analytic views about part 2 of the book are not limited Dr Cole reviews also the later devel Horney, Alexander, and Rado ha In a thoughtful and bold final chapt reconstruction of Christian interp applied to the conditions of modern issues of medical as well as religious

Educating Spastic Children

The Education and Guidance of F ELEANOR SCHONELL, M A PH fellow, department of pædiatric University of Birmingham Edin 1956 Pp 242 21s

THIS book gives the benefit of th experience with spastics in Aust Canada, the U S A, and, Carlson House School, Birmingha future Dr Schonell makes a plea integration between vocational tr in the case of the educable spasti in the case of spastics with su particularly those who are traina problem of the cerebral palsied ad into psychological and intelle spastics' and particularly the educational methods The book field and particularly to educat interesting and useful material

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ancet, 1955 ii, 639

[illegible] ntral excretion [illegible] devised tubes for [illegible] se have not yet [illegible]

These me[illegible] mation on which present ideas [illegible] nia and iron-deficiency anæ[illegible] cious anæmia the evidence sho[illegible] ce of events is gastric atrop[illegible] production of intrinsic factor [illegible] to absorb vitamin B_{12} (extr[illegible] tine The serum-vitamin-B_{12} [illegible] eventually the clinical signs of [illegible] ear This sequence is known [illegible] There are, however at least tw[illegible] aloblastic anæmia In one the [illegible] *bothrium latum*) absorbs most of [illegible] ning the intestine and so deprive[illegible] itamin—a condition which has bee[illegible] Finland The other type is asso[illegible] orrhœa in which there is failure to ab[illegible] and sometimes failure to absorb vita[illegible] Witts points out that the anæmia [illegible] intestinal stenosis, or fistulas that leave [illegible] represents a combination of these two types [illegible] diversion of B_{12} and folic acid from the ho[illegible] the action of possibly abnormal bacteria, together with failure of absorption in the jejunum and the ileum In idiopathic steatorrhœa the anæmia is the result of impaired function of the small intestine (chronic jejunitis has been noted in the few recorded biopsy examinations[10]) And Girdwood's results[11] with folic acid excretion tests show that there is always failure of absorption of folic acid in this disease But some patients have diminished absorption of vitamin B_{12} as well, in contrast with pernicious anæmia, the administration of a source of intrinsic factor does *not* improve the absorption of vitamin B_{12} The few instances of neurological lesions in steatorrhœa, like those sometimes accompanying pernicious anæmia, must be due to this failure of intestinal absorption of vitamin B_{12}, there is no evidence that the stomach is involved

Witts remarks that "a generation after the discovery of the liver therapy of pernicious anæmia and the simultaneous revival of interest in iron deficiency there is still no shortage of problems for research" The clarification of our views of the ætiology of these anæmias and its relation to lesions of the alimentary tract has, however, already led to more efficient treatment

P.U.O.

The origins of fever are divided, like English social classes, into U and non-U The U in P U O stands for "unknown" in popular usage, but Har[illegible][12] maintains that the more hopeful and dignified meaning of "undetermined" was intended by the Army, who devised the term A third interpretation is "uncertain", and that is the word used in the official history of the 1914–18 war

Unexplained fever, whether it is of unknown or merely of uncertain origin, is a subject that needs reviewing every few years because it changes continually Not only do the diseases that [illegible] change their incidence, but the likelihood of [illegible] recognition alters too As soon as a condit[illegible] known as a cause of fever, it is less likely [illegible] as an explanation of obscure fever When a [illegible] condition is prominent in the list of causes of [illegible] obscure fever, the reason may be, not a high [illegible] but a high ignorance of the condition, so th[illegible] not being diagnosed as early as it might be [illegible] ledge of P U O is acquired by following cases [illegible] long as possible until a large proportion are di[illegible] and also by reviewing the case records wh[illegible] solution has been reached and asking "sho[illegible] and could this have been diagnosed earlier?"

There is no agreement on the time a fever [illegible] remain undiagnosed before qualifying as [illegible] over, patients cared for at home are less likely [illegible] diagnosed early than those who are admi[illegible] hospital soon after their fever begins As [illegible] expected, the picture of P U O in hospital [illegible] according to the time for which the conditio[illegible] remained obscure Of patients admitted with [illegible] nosed fever, over three quarters are diagnosed, [illegible] of those with fever still undiagnosed on dischar[illegible] three-quarters remain unsolved[13] It is from [illegible] that are finally if belatedly solved that clinicia[illegible] what to suspect in later cases (and half the [illegible] diagnosis is to develop the right kind of su[illegible]

Informative studies have been made by Bott[illegible] from the medical department of Karolinska Sjukh[illegible] in Stockholm, and Reid[14] at the Radcliffe Inf[illegible] Oxford Bottiger scrutinised the records of p[illegible] admitted with fever of unknown origin or [illegible] diagnoses, which comprised 2% of admiss[illegible] 1940 to 1949, and compared them with a[illegible] under the same diagnosis in 1954 to 1955 [illegible] 1 4%) The fall in the proportion of P U O cases [illegible] be significant, since the procedure relating to [illegible] diagnoses had been changed The most [illegible] diagnoses were non-specific infections (inclu[illegible] piratory and urinary infections, endocard[illegible] septicæmia) 31%, tuberculosis 11%, malign[illegible] ours 10%, and "collagenoses" 4%—of whi[illegible] three remained longer undiagnosed than the [illegible] 7 of the tuberculous patients had fever for a[illegible] of fifteen months before the diagnosis was [illegible] the malignant group (including Hodgkin's d[illegible] leukæmia) stomach, colon, bronchus, and ki[illegible] the common sites Renal cancer (hypern[illegible] of special importance, since there may be [illegible] pyelogram and no renal symptoms whatev[illegible] collagen group, Bottiger correctly emph[illegible] importance of electrophoretic examinatio[illegible] serum, which often reveals a suggestive [illegible] the gamma globulin fractions (estimati[illegible] sedimentation-rate is nearly as informative

Approaching the subject from a diff[illegible] Bottiger[16] analysed 4 solved cases of P [illegible] had remained a long time undiagnosed an[illegible] chose as representing four common [illegible] for P U O.

The first, to illustrate tuberculosis, was a [illegible] with pleurisy, fever, and hip pain for thre[illegible]

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8 See leading article *Ibid*, 1956 ii, 713
9 [illegible] *Ibid* 1956 i 17 65
10 Paulley J W *Brit med J* 1951 ii 1118
11 [illegible] R H *Lancet* 1951 ii 53 *Quart J Med* 1956 25 87
12 [illegible] *Brit med J* 1956, ii, 150
13 Bottiger L E *Acta med scand* 1957 15[illegible]
14 Reid, J V O *Brit med J* 1956, ii, [illegible]
15 Bottiger, L E *Acta med scand* 1957, 15[illegible]
16 Bottiger, L E *Ibid*, 1956, 154, 215

a story of a pleural effusion two years previously Normal radiographs, negative examinations for tubercle bacilli, and absence of response to a short course of antituberculous drugs seemed reasonable grounds for excluding tuberculosis, and antibiotics and cortisone were given till necropsy revealed the diagnosis four months later

The next 2 cases one of staphylococcal infection and the other of collagen disease, were more happily diagnosed —not by necropsy but by treatment A patient with staphylococcal endocarditis at length responded to erythromycin, and a sparse positive culture and a rising antibody titre were discovered And a patient with dermatomyositis responded dramatically to cortisone after red swollen areas over peripheral muscles and a positive skin biopsy had revealed the diagnosis

Bottiger's fourth patient was a 34-year-old woman with prolonged hectic fever and nothing helpful in the findings except a large liver and a leucocytosis of 35,000 She was naturally regarded as suffering from some form of infection until complete unresponsiveness to antibiotics suggested the diagnosis of Hodgkin's disease, which necropsy confirmed

These retrospective studies revealed no serious omission in diagnostic procedure, but they serve to show how uncertain investigations are as a means of excluding illnesses and how common illnesses like tuberculosis, blood-poisoning and cancer may lurk unobserved behind the spiked ramparts of obscure fever

Reid's findings,[14] based on 113 patients admitted to hospital with obscure fever, were very similar to those of **Bottiger** He found that among patients whose fevers remained unexplained for more than a month tuberculosis, tumours (including reticulosis) and infective endocarditis were the most likely answers **Reid** gave special consideration to his 6 patients with subacute infective endocarditis, none of whom when admitted, had murmurs, enlarged spleens, or anæmia He also examined the records of 50 other proven consecutive cases at the Radcliffe, and he found little evidence that splenomegaly cardiac murmurs, or anæmia were at all common Today subacute infective endocarditis is quite often seen among old people and the fever, weight-loss, and cachexia may be mistaken for evidence of malignancy and so not treated[17] The longest delay in diagnosis in **Reid**'s series was fourteen months and was accounted for by a hypernephroma This case, and others encountered in this country, show that **Bottiger** s accent on fever in carcinoma of the kidney is much needed Neither textbooks nor clinicians give it much place among causes of obscure fever, yet it is by no means rare It is interesting, too, that fever is not a sign of metastases, and removal of the tumour usually brings the fever sharply down

Other well known causes of obscure fever, such as brucellosis or simulation by thermometer juggling, were not very common in either the **Bottiger** or **Reid** series because these conditions are relatively familiar and are detected more or less quickly The importance of these investigations is that they bring to mind some of the less often suspected causes of fever and so make their early recognition more likely If tuberculosis septicæmia, collagen disease, and cancer (especially renal cancer) are carefully considered in all cases of obscure fever, many examples will be diagnosed earlier and others, though diagnosed late, will at least have been suspected early

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[17] Anderson H. J Stafurth J S *Lancet* 1955, ii, 1055

Ammonia Metabolism and Hepatic Coma

Recent attempts to define the significance of high blood-ammonia levels in hepatic coma are important because of their influence on treatment The reproduction of the clinical syndrome in some patients with liver disease by the oral administration of complex nitrogenous substances from which ammonia can be derived suggests that ammonia intoxication is the cause of hepatic coma, especially since ammonium salts have the same action when given by mouth or intravenously Moreover, catheterisation of the hepatic vein has shown[1] that ammonia from the intestines may reach the systemic circulation by passing through a diseased liver or by way of portal collateral vessels, and this observation accords with clinical experience, which relates the onset of hepatic coma to inadequacy of liver function, the extent of the portal collateral circulation, or both[2] On the other hand, blood-ammonia levels often correlate poorly with the clinical condition in hepatic coma, and other toxic nitrogenous substances originating in the intestines may be responsible Blood-ammonia levels may therefore signify no more than the amount of ammonia that is permitted to accumulate in peripheral blood because of shunting " through portal collateral vessels and impaired ammonia metabolism in the liver and elsewhere

Ammonia in peripheral blood is derived largely from nitrogenous constituents of the diet by both bacterial and non-bacterial enzyme activity,[3] and urea synthesis in the liver is the most important way in which it is removed Smaller amounts of ammonia may originate in the lungs,[4] kidneys,[1] and brain[5] under certain circumstances, and the peripheral tissues and the brain can extract ammonia from the blood The poor correlation between ammonia levels in peripheral veins and the neurological state in hepatic coma has been attributed[6] to the arteriovenous ammonia difference due to peripheral uptake of ammonia In the experience of **Bessman** and **Bessman**[6] arterial ammonia levels are closely related to the state of consciousness, and they suggested that ammonia uptake in the brain in hepatic coma causes a defect in intermediary metabolism because the ammonia withdraws α-ketoglutarate from the tricarboxylic acid cycle in the brain Later work by **Summerskill** et al[7] suggested that arterial ammonia levels often reflect the amount of nitrogenous material *in the intestines rather than* the neuropsychiatric state They confirmed that ammonia is used by brain and peripheral tissues but showed that the uptake of ammonia by the brain and tissues is impaired in liver disease particularly in hepatic coma They concluded that hepatic coma results from a direct toxic action of ammonia on the brain secondary to *failure* of cerebral ammonia ' uptake " Furthermore a defect in intermediary metabolism due to ammonia was demonstrated by the production of high blood-pyruvate and α-ketoglutarate

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1 White L P, Phear E A Summerskill W H J Sherlock, S *J clin Invest* 1955 34 158
2 Sherlock S Summerskill W H J White L P Phear E A *Lancet* 1954 ii 453
3 Webster L T Davidson C S *J clin Invest* 1956 35 742
4 Faloon W W Auchincloss J H Eich R Gilbert I *Ibid* p 701
5 Webster L T *Amer J Med* 1956 21 130
6 Bessman S P Bessman A N *J clin Invest* 1955 34 622
7 Summerskill W H J Wolfe S J Davidson C S *Ibid* 1957 36 349

levels in patients with liver disease who were given intravenous ammonium chloride—a finding which could explain the raised levels of these keto-acids in spontaneous hepatic coma

Treatment of hepatic coma is first directed towards correcting factors which may have precipitated coma—such as gastro intestinal hæmorrhage, intercurrent infection, high-protein feeding, and drugs, including methionine and ammonium salts Acetazolamide ('Diamox') has also been shown to cause hepatic coma, and raised blood-ammonia levels,[8] because it impairs ammonia uptake by peripheral tissues[9] This finding emphasises the importance of ammonia metabolism at other sites when the liver is failing in this way, and supports the view that toxic effects spring from interference with ammonia uptake rather than ammonia utilisation A reliable method of treatment recommended by SHERLOCK et al[2] includes elimination of nitrogenous material from the diet, oral broad-spectrum antibiotics (of which neomycin is the most effective),[10] and enemas This routine proved superior to other measures in a large series of patients[11] and, while reducing blood-ammonia levels,[7] it also has the merit of eliminating from the intestines other nitrogenous substances of possible toxicity Glutamic acid,[12] which can combine with ammonia to form glutamine, has been given in the hope of removing ammonia already in the body, but the results have been disappointing[13] MCDERMOTT et al[14] found glutamic acid of benefit when liver function was adequate, but such patients have a relatively good prognosis anyway In more severe liver disease the effect of glutamic acid on blood-ammonia and clinical state is transient A trial of aspartic acid yielded similar results[11] Lately, NAJARIAN and HARPER[15] have shown that arginine lowers peripheral-vein ammonia levels in man and that it may be of value in hepatic coma[16] Most of their patients went into coma because of hæmorrhage or intolerance of nitrogenous substances, and they therefore had a relatively good prognosis, but the recovery of 2 patients from coma due to serum hepatitis is very significant Since the action of arginine depends on its function as a precursor of ornithine in the Krebs urea cycle in the liver, its success in hepatic failure is hard to understand, and the possibility remains that coincident treatment, such as protein withdrawal or antibiotic therapy, may have been responsible This consideration applies to the appraisal of any treatment in hepatic coma and, combined with unpredictable fluctuations in clinical progress, it partly explains the disagreement about what a particular treatment can do

Thus, on both therapeutic and biochemical grounds, ammonia intoxication has not been conclusively incriminated as a cause of hepatic coma Nevertheless, now it is known that the syndrome includes various clinical sequences, it is reasonable to attribute to ammonia intoxication those components which can be reproduced by giving ammonium salts to patients with liver disease Apart from rare successes with lipoic acid[17] (which facilitates the oxidation of α-keto-acids in the citric acid cycle) and cortisone treatment of the neurological disorder is ineffective when hepatic coma results from progressive liver failure alone In such circumstances the prognosis is grave, since severe hepatic disease permits widespread metabolic disturbance, and measures directed solely at the neurological disorder will not improve liver function, upon which survival depends In contrast, coma due to intolerance of nitrogenous substances responds dramatically to protein withdrawal and antibiotics[18] Most patients fall between these extremes, and results may well be improved by the addition of specific drugs, of which the latest is arginine, to a basic regimen of careful clinical management, protein withdrawal, and neomycin

Cytological Detection of Uterine Cancer

THE method of detecting malignant disease of the uterus by the recognition of cancer cells in a vaginal or cervical smear has been in use in many centres for some fifteen years, and many different techniques for collecting the cells have been described[19] Rather surprisingly there is no very general agreement about the value of the method Views differ partly because of the different ways in which results have been reported, and partly because accounts of false positives and false negatives have caused confusion, but the main reason perhaps is that many of the reports do not make it clear how often cytology has really helped to make the diagnosis Carcinoma of the cervix can all too often be diagnosed clinically without any reasonable doubt the first time the patient is seen by the gynæcologist Less often, a confident diagnosis is impossible, though there are definite grounds for suspicion In both cases biopsy is imperative, but when the clinical diagnosis is uncertain the cancer may involve only a tiny part of the cervix, and the tissue removed may not include a sample of the malignant area unless multiple specimens are taken or the whole of the squamo-columnar junction is removed, which is by no means always done Under these circumstances, the examination of smears is a great help, and both GRAHAM and MEIGS[20] and DARO et al[21] found the smear diagnosis more accurate than punch biopsy in early carcinoma of the cervix

But it has been repeatedly shown in recent years that early invasive carcinoma, and particularly in situ carcinoma of the cervix, can be present without symptoms or signs in any way suspicious of malignancy, and even if the patient is examined by her doctor, biopsy will seldom be advised Without the aid of cytology this type of cancer will be diagnosed either by chance or not until later in the disease We do not know how common this form of malignancy is, so it is hard to assess the true value of cytology cytological methods have often been given credit for the diagnosis without any clear indication of the quality of the clinical screening of the cases. McLaren et al[22] have lately described their experiences with vaginal cytology in Birmingham, where great care was taken to establish clearly whether there were grounds for suspecting cancer or not. Of 2250 women attending the outpatient department there were 10 in whom the diagnosis of carcinoma or carcinoma-in-situ was made without any previous clinical suspicion of the disease. Anderson et al[23] reported a higher incidence (1.1%) of unsuspected cervical carcinoma, but it was not certain that their patients had always been subjected to as searching a clinical inquiry as those of McLaren et al. These figures suggest that, if cytological methods of diagnosis are to be applied to groups of women in whom there is no reason to suspect uterine cancer, early carcinoma (chiefly non-invasive) might be found as often as once in 100–250 women. Unsuspected carcinoma of the body of the uterus would probably be discovered much less often than cervical cancer, for most patients with carcinoma of the body have suspicious symptoms which prompt complete investigation. But if unsuspected cancer is, in fact, as common as this, there is much to be said for Osborn's[24] view that this kind of cytology is more rewarding than many other investigations regarded as essential in a general pathology laboratory. Further careful studies are needed, both to confirm the incidence of truly unsuspected cancer, and to extend our knowledge of the behaviour of in situ carcinoma so that its correct treatment can be established. As McLaren et al point out, cytology can uncover a disease at a stage when we have no exact knowledge of its natural history and, therefore, of its implications for the individual patient.

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[8] Webster L T Davidson C S Proc Soc exp Biol N Y 1956 91 27

[9] Dawson A M De Groote J, Rosenthal W S Sherlock S *Clin Sci* (in the press)

[10] Fisher C J, Faloon W W *Clin Res Proc* 1956 4 147

[11] Summerskill W H J Wolfe S J Davidson C S Claverhill lecture McGill University 1956, *Amer J Med* 1957 (in the press)

[12] Walshe, J M *Lancet* 1953 i 1075

[13] Schwartz I R Lehman J Hammond J Seibel J M Goldson F *Gastroenterology* 1956, 30 869

[14] McDermott W V Wareham J Riddell A G *New Engl J Med* 1955 253 1093

[15] Najarian J S Harper H A *Proc Soc exp Biol N Y* 1956 92 560

[16] Najarian J S Harper H A *Amer J Med* 1956 21 832

[17] Thompson M Gambescia J M, Lisan, P Fuchs M *Ibid* p 132

[18] Summerskill W H J Davidson E A, Sherlock, S, Steiner, R E *Quart J Med* 1956, 25 245

[19] See leading article *Lancet* 1953 i 779

[20] Graham R M Meigs, J V *Amer J Obstet Gynec* 1949, 58 843

[21] Daro A F, Rubenstein M W Gollin H *Ibid*, 1953 65 [illegible]

But if vaginal cytology is to be extended as a screening procedure, which women should be examined? It is clearly impracticable, even if it were desirable, to screen all women at regular intervals, and one view is that if we cannot examine all, we should examine none. Moreover, when a patient who has attended a cancer-detection clinic is asked to return because of a doubtful smear, fears may be sown in her mind that are hard to allay, and more harm than good may result. There is no such objection to the use of vaginal smears in women already attending a gynæcological clinic, who would normally be asked to return for a follow-up visit in a few weeks' time. If it were used in this way, and combined with carefully gathered clinical data, much more would be learned about the value of this investigation. Until there are more trained cytologists, the method might perhaps be restricted to patients awaiting a major gynæcological operation, a few of whom might thus avoid the inadequate operation of simple total (or even subtotal) hysterectomy, or amputation of the cervix, when early carcinoma of the uterus was, in fact, present unknown to the surgeon. Wachtel and Plester[25] described 2 cases in which cytological examination modified the proposed operation; and Speert[26] recorded 14 examples of unsuspected cervical carcinoma in surgical material removed for other reasons.

Nevertheless, however valuable cytology may be in detecting cancer when it is not suspected, it must not be allowed to become a substitute for clinical investigation; for there are other diseases than cancer and other organs than the uterus are subject to cancer. The diagnostic error of cytology is by no means negligible, nor is it likely to become so; Osborn considers that vaginal cytology alone is certain to miss about 10% of cases of cancer of the uterus. Whenever clinical suspicion of cancer arises, therefore, other investigations, particularly biopsy and curettage, are necessary in addition to a cytological examination, if the chances of missing the diagnosis are to be reduced to a minimum.

Annotations

REMUNERATION

Instead of arranging an increase through the Whitley Council, as they had proposed, the Government last week announced that the salaries of junior hospital doctors and dentists are to rise by 10% from April 1. This is the second increase for junior hospital doctors since 1948, and according to an analysis in the *Financial Times*[27] it gives the house-physician or house surgeon nearly (though not quite) the same purchasing-power as he had when the service started. But though the houseman will have a gross salary 33.5% higher than in 1948, to compensate him for a rise in prices estimated at 36%, the senior registrar will still have to manage on a salary only 21% higher than he had eight years ago. The *Financial Times* correspondent points out that, on the new scale of salaries offered to university staffs (without any direct pay claim) in order to maintain recruitment, non medical professors will have their salaries increased by about 50% since 1949 and clinical professors by 9%, against a price rise estimated at 34%.

The claim for a 24% increase on existing remuneration, put forward last year on behalf of all doctors in the National Health Service, was based on evidence that prices generally were 24% higher in April, 1956, than in April, 1951. Though, until the Royal Commission reports, there can be no hope of any settlement based on principle or on detailed consideration of the facts, we trust that the further "interim adjustment" of which the Prime Minister has promised to speak "in due course" will be one that reasonable people will think reasonable—at any rate in the present difficult circumstances of the nation.

THROMBOSIS OF THE PULMONARY ARTERIES

Pulmonary heart disease resulting from thrombotic occlusion of the small pulmonary arteries by repeated embolism has been recognised for some years; but massive thrombosis of the larger pulmonary arteries is a less familiar cause. For this reason, the findings of Ball et al[28] who have added 23 new cases to the 200 already on record, are particularly welcome.

In all but 4 of their patients the thrombosis was associated with some other disease (mitral stenosis, chronic bronchitis, and carcinoma of the lung, stomach, or pancreas were predominant). At necropsy the pulmonary thrombosis was usually found to be secondary to pulmonary embolism, but in a few cases it was primary. The criteria for this distinction between primary and secondary pulmonary thrombosis are not entirely satisfactory, but primary thrombosis is suggested by local disease of the artery wall, by the fact that the thrombus forms a perfect cast of the pulmonary artery, often showing laminations parallel to the vessel wall, and by the absence of any source for an embolus. Thrombosis secondary to embolism is likely when there is no disease in the artery wall, and when there is a source for the embolus, which is often coiled, not forming a perfect cast of the pulmonary artery but bearing the impress of the vessel from which it arose. Pulmonary infarction beyond the occlusion was a variable finding and did not help to distinguish the two conditions.

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[22] McLaren, H. C., Taylor, C. W., Attwood, M. E. *J. Obstet. Gynæc., Brit. Emp.* 1956, 63, 801.

[23] Anderson, A. F., Grant, M. P. S., McBride, R. M., Cockburn, M. K. *Ibid*, 1953, 60, 315.

[24] Osborn, G. R. *Proc. R. Soc. Med.* 1956, 49, 246.

[25] Wachtel, E., Plester, J. A. *J. Obstet. Gynæc., Brit. Emp.* 1952, 59, 323.

[26] Speert, H. *Amer. J. Obstet. Gynec.* 1949, 57, 947.

[27] *Financial Times*, March 14, 1957.

[28] Ball, K. P., Goodwin, J. F., Harrison, C. V. *Circulation*, 1956, 14, 776.

The clinical features were commonly those of right-sided heart-failure with low cardiac output. The onset was often insidious. Dyspnœa was prominent, and was commonly accompanied by pleural pain and hæmoptysis, suggesting pulmonary infarction. Some patients were liable to faint, especially on exertion, and several died in coma. The principal signs were those of right ventricular hypertrophy, but in some patients this was due to concomitant mitral stenosis. A pulmonary systolic murmur, a normal or soft second heart sound, a small pulse, and cyanosis were also noted. Radiologically, an enlarged right ventricle and dilated pulmonary arteries, often with diminished pulsation, were the main findings. The lung fields were sometimes oligæmic or contained shadows caused by pulmonary infarction. The electrocardiogram usually reflected the pattern of right ventricular hypertrophy.

The rare diagnosis of pulmonary-artery thrombosis must therefore be considered whenever a patient has unexplained congestive failure, breathlessness, fainting, or repeated attacks of chest pain and pulmonary infarction. If the clinical picture includes evidence of peripheral venous thrombosis, a systolic murmur in the pulmonary area, and a normal or soft second sound, then the diagnosis becomes more probable. If in addition there is radiological evidence of an enlarged right ventricle, dilated pulmonary arteries without significant pulsation and clear lung fields (or shadows of pulmonary infarction), and if the electrocardiogram indicates right ventricular hypertrophy, the diagnosis becomes almost certain.

When the diagnosis is made, a long period of anticoagulant treatment offers the only hope of preventing the thrombus from extending. If emboli are repeatedly arising from the leg veins and cannot be controlled by anticoagulants, ligature of the inferior vena cava may have to be considered.

A MATTER OF COMPLICATION

THE significance of complications following an operation or an acute illness has been much reduced by greater control of infection and by the precautions taken to prevent cross-infection in hospitals, particularly in childrens' and infants' wards, where infection may strike with disastrous speed. Similar, but less elaborate, precautions are taken in acute geriatric units, for infection can be equally hazardous at the other extreme of life. Rang[1] has lately examined the incidence of complications among patients in the geriatric unit of University College Hospital, London, during a 12-week period. These complications may be considered to be immediate, as opposed to remote. Rang found that one complication occurred in each geriatric bed every 79 days, compared with a complication interval of 298 days in an acute medical ward and 282 days in a halfway house. Moreover 68% of patients in the geriatric unit had complications compared with 9% among general medical admissions. The average age of the general medical admissions was 58, and in Rang's over-65 group age did not seem to affect the incidence of complications; why then was there this disturbing difference?

Much depends on what may reasonably be accepted as a complication. The *Shorter Oxford English Dictionary* attributes to John Arbuthnot (1667–1735) the original medical interpretation of "disease complicating other diseases." *Webster* and *Chambers* agree on a succinct non-medical meaning, "intricate blending or entanglement," and *Chambers* defines complications in the medical sense as "a number of diseases present at the same time." In Rang's survey, only conditions arising after admission and not clearly related to the patient's original illness were counted as complications. But "a number of diseases present at the same time" is the lot of many old people, and most of those who are admitted to hospital are probably "complicated" from the outset.

In whatever way an illness in an old person may arise, it is always hard to be sure that a set-back under treatment does not come within the natural history of the initial acute episode or that it is not due to aggravation of some latent condition. For example, if an old man is admitted stuporose after a cerebrovascular disturbance, severely dehydrated from any cause, or in congestive failure, the rapid onset of chest infection is an immediate probability and hardly a complication; but if a pneumonia develops after recovery from the acute phase, then it must be regarded as a complication, provided the patient's lungs were normal for his age before the vascular accident. On the other hand, if he had chronic bronchitis, quiescent at the time of the acute illness, then a sudden flare-up at any stage is a hazard of bronchitis and cannot be regarded as a complication of the cerebrovascular disease. Again, an elderly obese diabetic, who long since stopped visiting the clinic because of blindness and osteo-arthritis, is admitted with skin sepsis, a urinary infection, and heavy glycosuria. The day before she is due to be discharged, she has a cerebral thrombosis. Is this to be regarded as a complication of her diabetes or as a dissociated manifestation of cerebral arterial disease, the association with diabetes being fortuitous? Is it logical ever to regard a coronary thrombosis in the elderly as a complication, except as a calculated risk when using certain drugs? All this may seem to be a splitting of hairs, but it is nevertheless true that the presenting illness often takes the form of a complication of pre-existing disease. Senile osteoporosis often has no symptoms until a vertebra collapses; a subsequent bedsore would be a further complication, a hæmatemesis from an unsuspected gastric ulcer would not. For these reasons, the picture given by Rang's figures may be too gloomy.

Rang classes together falls and confusion because he considers they are partly due to the same thing. Certainly, a confused elderly person may easily fall if not carefully supervised, but falls in hospital are not uncommon in the mentally composed. In many hospitals the floors are uneven and worn, ready to trip, or polished to ice-rink slipperiness. Along these floors shuffle the old folk, shuffling because of slippers which do not fit, because of a nightdress which has to be twisted and held, or because of a trailing dressing-gown. Since every old lady in hospital rightly insists on carrying her hand-bag, her knitting, and perhaps a library book, morning paper, and spare blanket on her way to the day-room, it is surprising that many of them stay on their feet for as long as they do. No form of mental disturbance other than confusion is included in Rang's analysis, so presumably the term covers all mental disturbance which can be handled in an acute geriatric ward. Thus, patients who become confused shortly after admission may be delirious because of the increasing severity of their illness—a complication common to any age. It must be distinguished, among other things, from a confusional state due to cerebral arteriosclerosis, which may be precipitated by acute illness or by unfamiliar surroundings, but whose underlying cause has been present for years it seems wrong to regard the first clinical manifestations of such a condition as the complication of a dissociated illness.

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[1] Rang, M. *Lancet*, Feb. 23, 1957, p. 401.

For the 26 old people in the halfway house attached to University College Hospital the average stay is measured in years. Their complication interval of 282 days will not surprise a geriatrician who looks after a halfway house or a long-stay ward for the infirm elderly, or who maintains close association with welfare homes. In these sheltered surroundings, the old people live contentedly on for years and then one day quietly depart. Before they enter a halfway house or long-stay ward many of these patients have been in an acute geriatric unit, in all probability with an illness punctuated by setbacks—or complications. When everything that can be done has failed to restore them to independence, they must enter a new phase of life, in which it is often happily rare for episodes of acute illness to disturb the downward path.

Unless we regard most elderly patients as "complicated" because of processes involved in tissue degeneration it may be simpler to accept some setbacks as inevitable in their management, rather than class them all as complications. Whatever the accepted interpretation of his findings Rang's inquiry provides a valuable stimulus and emphasises the great care called for in the management of acute illness in the aged.

TUBING FOR INTRAVENOUS INFUSIONS

TRANSFUSION of blood and infusion of solutions containing electrolytes glucose, and other substances into a patient's veins have become commonplace, but it need hardly be said that they are not without their complications. A blood-transfusion sometimes causes a reaction and a rigor when there is no question of mismatching of blood-groups and no unusual antibodies. Even the infusion of a simple saline solution has been known to cause similar reactions. Another and more serious sequel of intravenous infusions is thrombophlebitis, which may lead to permanent occlusion of a vein—no light matter for a patient needing multiple transfusions. Even though everything has been done to ensure that the fluids infused are properly prepared, thrombophlebitis may still ensue. Suspicion has fallen on the tubing used to connect various parts of the apparatus—particularly the red rubber tubing used, and re used, in the standard giving-sets issued by the National Blood Transfusion Service. The Medical Research Council's blood-transfusion research committee have been investigating this matter and their report appears on p 595.

They begin by noting that according to recent reports, the incidence of thrombophlebitis using N B T S sets is over 50%, *when the infusion is continued for more than twelve hours*. Handfield-Jones and Lewis[1] had shown that the incidence of thrombophlebitis was much less when a pure latex rubber tubing was substituted for the red rubber tubing. The committee therefore arranged for a number of centres to carry out a comparative trial between N B T S sets and a plastic infusion set of "disposable" type. The set used 6 feet of plastic tubing, ending in a short length of latex rubber tubing fitting on to the intravenous needle, the drip chamber and filter chamber were plastic and the filter itself of nylon mesh. A special rubber bung with an air inlet valve was provided for fitting into the standard 540 ml blood-bank bottles.

In the opinion of the committee the trial showed conclusively the superiority of the plastic set over the standard red rubber and glass set. Reactions were still seen with infusions lasting over twelve hours, but in only 32% of patients when plastic sets were used compared with 56% with the red rubber sets. There were severe and very severe reactions in 18% of patients when plastic sets were used, and in 34% with rubber sets. The results also confirm once again that the longer the infusion continues, the greater the risk of thrombophlebitis, and that infusions lasting less than twelve hours carry a negligible risk. This does suggest that the properties of the tubing are not the sole factor in the production of thrombophlebitis.

Thus there now seems to be good evidence for abandoning the use of red rubber tubing for giving-sets. But to replace the thousands of N B T S giving sets by disposable plastic sets would be very costly. These disposable plastic sets are popular in the U S A, and they are used with a plastic bag holding the blood or infusion fluid, or with glass bottles fitted with a special bung into which the plastic piercing-needle can be inserted. The British sets have a special bung and metal cap to fit the N B T S bottles, and to throw these away each time seems unnecessarily wasteful. The alternative is to replace the red rubber tubing in the present N B T S sets by a safer form of tubing. For this purpose, two types of tubing are available—the pure latex rubber tubing advocated by Handfield-Jones and Lewis, and the silicone-rubber tubing whose properties have been investigated by Wilkinson et al.[2] The silicone rubber was found to be particularly suitable for intravenous infusion work. Wilkinson et al.'s results cannot be compared with those of the M R C committee, because Wilkinson et al were working with blood-transfusions and consequently the tubing was not in use for periods of over twelve hours. Nevertheless it is interesting to note that in 296 transfusions given through silicone tubing, there were only 3 reactions. Silicone tubing has the considerable advantage that it can be used over and over again, specimens of silicone tubing were washed and autoclaved over forty times before showing signs of deterioration.

If silicone tubing proves as safe as plastic tubing for more protracted infusions, the choice may well turn on cost. Latex tubing costs two to three times as much as red rubber tubing, silicone tubing will probably be two or three times the price of latex tubing but the silicone tubing can be used forty times compared with about six times for latex tubing. The disposable plastic sets probably cost as much as a length of silicone tubing for a single transfusion set. We hope it will soon be possible to take an official decision in this matter. Departments anxious to keep transfusion reactions to a minimum abandoned red rubber tubing some time ago, and the M R C committee's report will encourage more people to do so.

CYTOMEGALIC INCLUSION DISEASE

INTRANUCLEAR inclusions in very large cells were first described in the kidneys of a stillborn infant more than fifty years ago.[3] Similarly affected large cells are often found in the salivary glands of young children at routine necropsies, the incidence varying in different series from 10 to 32%.[4]

In 1920 Jackson[5] described abnormalities in the ducts of guineapigs' salivary glands which she attributed to a protozoon. But soon afterwards it was shown[6] that these lesions, which resembled those found in the salivary glands of children[4] were caused by a virus resistant to 50% glycerol and capable of passing through a Berkefeld N filter. Similar agents, all species specific and all causing the same morphological abnormality, have been recognised in rats, mice, moles, hamsters, monkeys, and chimpanzees By analogy it was inferred that the human lesions were caused by a virus and the group of agents came to be known as salivary-gland viruses In 1954 Smith[7] reported that she had propagated the mouse virus in culture of mouse embryo fibroblasts, in which the characteristic lesions could be seen Her culture fluids caused the salivary gland lesions to appear in mice *of a strain not naturally carrying the virus, and they also* infected new cultures Last year[8] she described the successful infection of cultures of human uterine wall with virus from the salivary gland of a seven-month infant and from the kidney of a one-month infant The cultured cells showed the characteristic lesions and could be protected by human immune sera The infective materials which caused these lesions in human cells could pass bacteria-retaining filters and had no effect on suckling mice or cultures of mouse embryonic tissue

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It is thus well established that the presence of abnormally large cells with intranuclear inclusions in the salivary glands and other organs of infants is due to infection with a species specific virus Why this abnormality occasionally becomes a generalised fatal disease is not known Smith and Vellios[4] found the generalised disease in 1% of 1400 necropsies, and they concluded that this was a primary fatal disease in infants under two months of age The clinical picture was usually the result of damage to the liver and hæmopoietic system In older infants generalised cytomegalic inclusions were more commonly associated with some other primary illness Cappell and McFarlane,[9] in a beautifully illustrated account of the pathological changes, emphasise the importance of thinking of this infection in hæmolytic disease when isoagglutinins cannot be found The generalised disease has been described in adults[10], but Hamperl,[11] examining material from such a patient, thought to have died of inclusion pneumonitis, was able to demonstrate the presence of *Pneumocystis carinii*, and he thought that cytomegalic virus alone could not cause pneumonitis in adults

As the kidneys of infants were involved in the generalised disease and the characteristic large cells could be seen in the lumen of the tubules, Wyatt et al[12] suggested that it might be possible to diagnose the disease during life by finding such cells in the urine, and in this way Fetterman[13] later made the first confirmed antemortem diagnosis of the disease Margileth[14] described the care and treatment (which included cortisone) of a patient who survived an established generalised infection Birdsong et al[15] have lately recorded 2 cases, 1 of them fatal, in which prednisolone and later corticotrophin were given They think that in future exchange transfusion should be considered In the child who survived, examination of urinary sediment had confirmed the diagnosis

Birdsong et al suggest that the mother of an infected infant must have an initial subclinical infection during her pregnancy—a view which is supported, they think, by the fact that the mothers are often primigravidæ from isolated rural homes. But Smith and Vellios[4] mention an example in a fourth child, and Wyatt et al[12] say that no inclusions are found in the placenta Like Wyatt et al and Bacala and Burke,[16] Birdsong et al say that symptoms and signs in the generalised disease depend on the tissues principally involved and may include jaundice, hepatomegaly, purpura, splenomegaly, thrombocytopenia, hæmolytic anæmia, and, less commonly, evidence of intracranial calcification or cerebral hæmorrhage

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SALMONELLÆ IN REPTILES

IT has been known for several years that some lizards snakes, and tortoises harbour members of the genus salmonella, but knowledge has advanced slowly because reptiles, as a tribe, are hard to find or hard to catch In the course of an inquiry into the distribution of salmonellæ in Ibadan, Collard and Montefiore[1] got over the second difficulty by employing schoolboys with catapults to collect specimens of *Agama agama*, the lizard which basks on every sunny wall in Nigeria Their enthusiastic Nimrods made a bag of 160 of which 11% were found to carry some species of salmonella in their bowels All but two of these species had been isolated previously from the human inhabitants of the town That no salmonellæ were found in 100 gekkoes (*Hemidactylus boothii*) taken at the same time may be an equally important observation Collard and Montefiore suggest that the lizards acquire infection by snapping up flies as they leave the trench latrines, while the gekkoes (which also eat flies) prefer the dark insides of buildings This implies that flies soon lose their burden of excrement or that flies from latrines do not enter houses It may be that the two reptiles have not the same taste in edible flies It is curious too that Mackey[2] in East Africa quite often found salmonellæ in a related gekko

The distribution of these organisms in reptiles is in fact, puzzling Many of the recorded isolations from snakes are from single animals, either found dead or sick or else in zoological gardens where there is often a risk of infection from some other captive Negative findings are more common than the published records suggest Since all snakes are carnivorous, they are liable to infection from their victims and this might explain the simultaneous infection of gopher snakes and turkey poults recorded in Arizona[3]

Testudo græca, the tortoise kept as a pet, is a complex of about seven sub species all native to the Mediterranean basin It is vegetarian but, whether wild or in captivity, over 90% of the specimens examined have yielded one or more species of salmonella Other species of testudo in Asia, Africa, and South America have produced very few, but the species of salmonella found have been the same as those found in *T græca* All other tortoises and terrapins examined have so far given negative results, and as far as is known no other reptile shows a carriage rate approaching that of *T græca* At the same time anyone who has examined reptilian fæces must have noticed the abundance of unnamed bacteria which seem related to salmonellæ either in biochemical behaviour or serological affinities

It is customary to speak of reptiles which harbour salmonellæ as "reservoirs of infection" Apart from the fact that man and reptiles seldom have intimate relations, the phrase may indicate a too anthropocentric view If Collard and Montefiore are right in their surmise on the source of infection in lizards, it would be more accurate to describe man as a reservoir of infection for reptiles Mackey may be right in suggesting that human food is contaminated by dust containing the fæces of infected lizards, but in many old houses man lives in more or less contented symbiosis with mice without being infected by these notorious carriers Who infects or who is infected by the solitary tortoise sunning himself in the maquis? The epidemiology of salmonella infection has been confused by a great number of attractive analogies and hypotheses, few of which have been and some of which cannot be proved

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DR FREDERICK PRICE, long editor of the well known textbook on medicine, died in London on March 10

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Special Articles

CLEAN BEDS

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INFECTION of wounds and burns in hospital depends on many factors One of these is the accumulation and distribution of pathogenic organisms by bedding materials Blankets and sheets on the bed of an infected patient, when examined by a suitable method such as the sweep plate technique, can be shown to harbour large numbers of the responsible pathogen (Blowers, Mason Wallace, and Walton 1955) Other methods can be used to show that these organisms are scattered far and wide whenever the bedding is disturbed Normal laundering does not sterilise blankets, and, after washing, some of them are more heavily contaminated than before This is not surprising since woollen materials are washed at a low temperature (about 37°C) to prevent shrinking and "felting" An ordinary laundry rotary machine does little more than redistribute bacteria between the individual blankets Cotton articles, such as sheets are usually boiled and steam-pressed in the laundry and these processes destroy most pyogenic micro-organisms

In any serious attempt to prevent cross infection of wounds hospital blankets must therefore be sterilised regularly This can be done by exposing them to steam, but after a few such treatments even at low pressure they have shrunk to some two-thirds of their original length and lost all their fluffiness The result is a small, hard, and uncomfortable article Repeated laundering even without sterilisation eventually gives the same result Shrinking due to ordinary washing can be reduced if the blankets are specially treated when new, but this does not protect them against high temperature sterilisation The cost of a 5 lb (2 3 kg) hospital blanket 96 × 72 in (244 × 183 cm) is £2 10*s* , or £2 15*s* if anti-shrink treatment is applied, so that replacement costs are high if sterilisation and washing are done as a routine In many hospitals, therefore, blankets remain not only unsterilised but unwashed for long periods

To overcome some of these difficulties various methods have been suggested van den Ende, Lush, and Edward (1940) devised a process for treating blankets with oil so that bacteria stick to the fibres instead of being scattered during bed-making Formalin disinfection is used, especially in infectious diseases hospitals, but there has always been some uncertainty about its efficacy Also it needs expensive equipment and each article has to be handled separately which increases labour costs Disinfection of blankets with quaternary ammonium compounds has been suggested (Rountree 1946, Barnard 1952, Blowers and Wallace 1955) This is highly efficacious against the pyogenic cocci, but its action against *Pseudomonas pyocyanea* is poor and against tubercle bacilli doubtful It causes less shrinking and felting than does steam sterilisation and blankets can be treated some thirty times before they have to be discarded We have found it the most satisfactory method for disinfecting woollen blankets and will continue to recommend it so long as they are used It seemed to us, however, that the right answer would be to make blankets of a material that could be boiled without serious damage Most laundries have facilities for high-temperature washing, and, if blankets could be treated in this way, all non-sporing bacteria, including tubercle bacilli and pseudomonas, would be destroyed and separate sterilisation would not be needed We therefore made preliminary trials of several materials Those showing enough promise to warrant longer trials were

1 Turkish towelling
2 Loomstate cotton weave
3 Synthetic polyester fibre ('Terylene')

New Materials

The first two materials were tried in a plastic-surgery and burns unit where unsterilised woollen blankets had previously been used Because wound infection was already a problem in the unit, it was decided to make a complete change to sterilised blankets As it was not possible to have wards fully equipped with each of the new types of blanket, it was arranged that wool, towelling, and loomstate would be used successively, each for a week This made it easy for patients and nurses to compare the three materials At the end of each week, when the change over was made, the dirty blankets were sent to the laundry and washed Woollen blankets were washed at 37°C and then treated with a quaternary ammonium compound , towelling and loomstate were washed at 100°C but without chemical treatment

The terylene blankets were tried in a surgical ward of a tuberculosis hospital Only 6 were available, so they were used and treated as part of the normal blanket stock except that they were washed at 100°C

Turkish Towelling †

This is a heavy material of the type used for bathing-wraps It is white and has a clean and pleasing appearance Each blanket measures 100 × 80 in (254 × 203 cm), weighs 5 lb (2 3 kg), and costs £3 6*s*

The patients were satisfied with the warmth and comfort of the towelling and found it equal in all respects to the usual woollen blanket The nurses found it easy to handle , visitors and administrative nursing staff commented on the neat and clean appearance of the beds made up with the new blankets

After several months' use 6 blankets were examined bacteriologically by the sweep-plate method before and after laundering The results are shown in the table together with those of 6 chemically treated woollen blankets We also include, for comparison, results from woollen blankets in another ward , these were washed in the ordinary way without sterilisation

After twelve months and twenty launderings the Turkish towelling blankets were 98 × 78 in (250 × 198 cm), an area-loss of 4% due to shrinkage The woollen blankets, originally 96 × 72 in (244 × 183 *cm*) had shrunk to 78 × 58 in (198 × 147 cm) The area-loss was thus 35% But the most striking difference between the two materials was that whereas the towelling retained its original texture almost unimpaired, the woollen blankets had become felted and hard and were nearing the end of their useful life A few towelling blankets have been used on ward and theatre trolleys for a longer period and have been washed over fifty times These, too, are still in excellent condition.

Loomstate Cotton Weave ‡

This is similar in appearance to the cellular woollen material that is already on the market It has a cream colour and is made into blankets 96 × 76 in (244 × 193 cm) weighing 3 lb (1 4 kg) and costing £1 0*s* 10*d* each These were a little less warm than the woollen and towelling blankets and some patients needed four of them instead of the usual three Bacteriological tests

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* With a grant from the Newcastle Regional Hospital Board

† Bleached Terry sheets "C" quality Two sheets 100 × 40 in , joined up the centre Made by William Cunningham & Co Ltd P O Box 24 Dunfermline

‡ Loomstate cotton blankets 96 × 76 in made by John Kershaw & Co Derby Street Mills Bolton Lancs

GENERAL BACTERIAL COLONY-COUNTS ON SWEEP-PLATES FROM SIX BLANKETS OF EACH MATERIAL BEFORE AND AFTER WASHING

Wool (37°C wash)		Wool (37°C wash + quaternary ammonium rinse)		Towelling (100°C wash)		Loomstate (100°C wash)		Terylene (100°C wash)	
Before washing	After washing	Before washing	After washing	Before washing	After washing	Before washing	After washing	Before washing	After washing
Over 2000	Over 2000	960	4	570	2	751	1	500	[illegible]
Over 2000	776	523	2	500	10	301	3	478	3
Over 2000	740	311	0	500	5	280	1	227	3
972	860	199	2	220	2	223	8	157	0
622	1028	101	4	85	2	138	1	77	1
279	752	88	1	67	2	119	2	63	0

were satisfactory (see table), and after twelve months' use and twenty washings the blankets measured 94 × 74 in (238 × 188 cm), having lost only 5 % of their original area Texture was unaltered

Terylene §

This now well-known and versatile material § is made into a staple fibre and woven to make blankets almost indistinguishable from a high-grade wool Each is 89 × 74 in (226 × 188 cm), weighs 3½ lb (1 6 kg), and costs £3 18*s* In warmth and appearance these blankets are equal to new woollen ones After eighteen months' use and thirty washings the measurements were 84 × 72 in (214 × 183 cm) with an area loss of 8 % The material is now rather less fluffy than when new, but is in vastly better condition than a woollen blanket after the same use The effect of boiling on the bacterial flora of terylene blankets is shown in the table

Discussion

We believe that patients in hospital are entitled to bedding that has been washed and sterilised since it was last used Moreover, it seems wrong that after a wound has been covered with sterile materials in the operating-theatre, the patient should be returned to a bed of heavily infected blankets We regard the bedclothes as part of the patient's wound dressing and think that they should be free from pathogenic organisms In surgical and infectious diseases wards, at any rate, all bedding should be changed and sterilised weekly to reduce dissemination of organisms during bed making All this can easily be done with the new materials that we have tried because they can be washed and sterilised in one operation

The table clearly shows the bacteriological superiority of boiling over ordinary low temperature washing The advantage of boiling over chemical sterilisation—that heat is known to be effective against tubercle bacilli and pseudomonas—is not shown in the table, and we have done no experiments to confirm that this is so under laundry conditions

The greater inflammability of cotton compared with wool must be seriously considered Blankets on a bed are not often exposed to a flame, but a lighted match or cigarette may be accidentally dropped on them This causes no more than local scorching to woollen blankets In the same circumstances the two cotton materials smoulder and sometimes burn, but the spread of the flame is irregular and slow It is difficult to say whether this is a serious objection to their use in hospital, but we are inclined to think it is not Terylene, in these circumstances, is not inflammable The cotton materials can be flame proofed and the treatment would add about 7*s* 6*d* to the cost of each blanket

The generation of static electricity by fabrics sometimes causes explosions, and when new materials are introduced into hospitals this should be borne in mind though it is not generally known that even wool is able to cause sparking Cotton is much less liable to do this but terylene builds up high charges and sparking easily occurs Blankets of this material should not be brought near anæsthetic or other explosive gases

The choice between the available materials for hospital blankets is not easy There are large stocks of woollen blankets and there can be no question of discarding the[illegible] While they remain in use they can be washed regularly by a low-temperature process and should be disinfected by a quaternary ammonium rinse It is our opinion however, that as these stocks are exhausted they should be replaced by boilable materials because the disinfecting process for these is simpler and destroys a wider range of organisms The high cost of terylene and towelling compared with wool is offset by their longer life if regularly washed and sterilised, but it seems unlikely that terylene will be accepted in most hospitals until its liability to cause sparking can be reduced or eliminated Loomstate cotton weave is cheap, durable, and free from static sparking, and seems to be the best choice at present All three materials will have to be used for several years before their costs can be properly compared with each other and with wool , but we thought it would be useful to publish these preliminary results without delay, so that others who wish to do so can make the comparison for themselves

We did not set out to investigate the effect of sterilised blankets on the frequency of wound infection nor even on the bacterial population of the ward We accepted the fact that blankets should be sterilised, and we conducted these trials with the sole object of finding an inexpensive material which could be sterilised easily and effectively Nevertheless, it was natural that we should take more than a casual interest in the incidence of wound infection during the trials Many of the patients with burns were admitted to the wards ten or more days after the accident and infection with *Staphylococcus aureus* and *Streptococcus pyogenes* was often well established by this time It was not possible to separate these patients from others with clean wounds Before our investigations began, infection often spread between patients in adjacent beds and then to those in other parts of the ward, despite the fact that all dressings were done in a room outside the ward We therefore concluded that organisms from contaminated blankets were passing through the patients' dressings and were also infecting the air of the ward During the trial wound infection became less frequent We do not attribute this entirely to the sterilisation of blankets because other methods of dust control and general measures against cross infection had been begun about the same time We think, however, that it may have played a part

Summary

Hospital blankets are reservoirs of pathogenic organisms, unless they are frequently sterilised Ordinary washing does not sterilise them

Woollen blankets deteriorate rapidly if washed and sterilised often

Blankets made from cotton or 'Terylene' can be simultaneously washed and sterilised by boiling without serious damage

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§ Supplied by Imperial Chemical Industries Ltd Terylene Council, Hookstone Road Harrogate

Blankets of these materials have been tried in regular hospital use, and have been found satisfactory in all respects, except that cotton is rather more inflammable than wool (although not dangerously so) and terylene more easily causes static electrical sparking

We wish to thank the Cotton Board for valuable advice, Imperial Chemical Industries Ltd, William Cunningham & Co Ltd, and John Kershaw & Co Ltd for providing the materials with which these trials were made, and the nursing staffs at Hemlington and Poole Hospitals for their coöperation.

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CIGARETTE SMOKING AT SCHOOL

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THOUGH many schoolmasters can make a shrewd estimate of the prevalence of cigarette smoking in their classes, more definite information is scanty This article records the smoking habits of the pupils at a secondary modern school for boys Nearly all were 11–15 years of age, but a few were 16 Each was questioned in the presence of his fellows and of his class teacher The interviews took place on two consecutive days and all the 307 pupils in attendance were seen

FINDINGS

The boys were asked whether they had ever smoked a cigarette, and (if so) when they first did so Over two-thirds of the 32 11-year olds had already tried smoking, and 38% of all the boys said that they had smoked before entering the school at 11+ One claimed that he had first smoked at 6 years, and several at 7

TABLE I—PROPORTION OF BOYS STATING THAT THEY WERE REGULAR SMOKERS

—	Age						Total
	11	12	13	14	15	16	
No of boys	32	68	75	93	34	5	307
Yes	1	19	19	41	16	1	97
% yes	3	28	25	44	47	20	32

The next question was are you smoking cigarettes regularly now? Of the boys aged 11, only 1 considered himself a regular smoker, but the numbers rose dramatically at 12 and again at 14 (table I) By their own account, no fewer than 32% of the boys in the school were regular smokers

Finally the smokers were asked how many cigarettes they smoked each week. The replies were surprising (table II) One 13-year-old regularly smoked over thirty a week, and two 14 year-olds smoked over forty (A few words with their form-masters confirmed their claims) Few in the younger age-groups smoked more than five cigarettes a week, but the consumption tended to increase with age Certain tobacconists in the town sell cigarettes singly and it was from these sources that many obtained their supplies

TABLE II—NUMBER OF CIGARETTES SMOKED WEEKLY

Amount smoked	Age					
	11	12	13	14	15	16
Under 5	1	16	13	15	8	1
5–9		2	5	13	4	
Over 10		1	1	13	4	
Total	1	19	19	41	16	1

COMMENTS

These replies cannot be verified and the boys may have exaggerated their smoking habits through pride, but an opposite bias may well have been operative in this survey, for smoking is prohibited both during school hours and whilst the pupils are journeying to and from school. The enquiry was conducted on the school premises and the investigator was known to the pupils as a result of his duties with the School Health Service A few boys may, therefore, have repressed details of their smoking habits for fear of authoritarian repercussions

The results of this survey cannot be applied unreservedly to other secondary modern schools, neither can the smoking habits of the survey pupils be regarded as typical for all boys of their age This Secondary Modern School serves a predominantly working-class area, where many of the senior pupils work outside school hours Consequently, there can be no denying that the results of this survey may be abnormally high

At present, no action is being taken to inform the public repeatedly about the possible dangers of cigarette smoking The decision is based, apparently, on the fact that scientific proof of the causation of lung cancer is lacking[1] This may be contested on the grounds that in the past, preventive action has not waited upon complete proof of causation The first public-health measures in this country were instigated on the strength of a demonstrated association between insanitary living conditions and certain infectious diseases The result was that many infectious diseases such as cholera and typhus, had been virtually eliminated before the causal organisms were identified.

Surely, a programme of school lectures on the possible dangers of cigarette-smoking would be sound, and the law forbidding the sale of cigarettes to juveniles (Section 7, Children and Young Persons Act, 1933) should be more strictly enforced It is reputed that the Battle of Waterloo was won on the playing fields of Eton unhappily, the lung cancer statistics of a future Registrar-General are being determined on the playing fields of the modern generation

I am grateful to Dr T O P D Lawson, medical officer of health for Cheltenham, and to the headmaster of the school for their encouragement and advice

UNIVERSITY DEVELOPMENTS

BETWEEN the Exchequer and the universities, finance is measured by quinquennia, and last week the Chancellor announced in Parliament (see p 642), the Treasury grants for 1957–62 These will rise from £30½ million in 1957–58 to £39½ million in 1961–62 The grant for 1952–53 was £20 million, and the increase recognises the difficulties which the universities have faced and are still facing Even so, as Mr Thorneycroft pointed out, the grants take no account of the latest increases in academic salaries[2]

In deciding how much these grants should be, he had before him the interim report[3] of the University Grants Committee for 1952–56 The committee considers that the way in which the universities have met the economic strains of the past years "should strengthen public confidence in their administration" They have had to meet rising costs by curtailing development; but, even so, in 1955–56 their aggregate expenditure exceeded their aggregate income by £326,000

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[1] *Brit med J* 1956 ii 1246
[2] See *Lancet* March 16 1957, p 583
[3] University Development Cmd 79 H.M. Stationery Office 1957 Pp 26 1s. 3d

At present, parliamentary grants provide 72 7% of the universities' income (compared with 66 5% in 1951–52) The universities disinclination to become entirely dependent on the State, either for maintenance or capital expenditure, fosters their habit of self-help and economy, and is one of the reasons for their decision—reluctant and tardy—to raise their fees to students The increases which start in 1957–58 will bring in additional revenue of £500,000–£600,000 a year

In 1955–56 the universities received £7½ million in "non-recurrent" grants for building and adapting accommodation, and in the last nine years £31¼ million has been spent on university building But their needs have by no means been met This is partly because of rising costs and partly because of the rising number of students On their visits to the universities members of the committee saw at first hand overcrowding in libraries, lecture-rooms, and student refectories They report that "in some universities laboratories are still housed in huts erected for emergency purposes in the 1914–18 war and scientific research is still carried out in ill-lit basements and cupboards"

The number of students enrolled in the universities of Great Britain in 1956 was 88,701—more than ever before The growing number of pupils remaining at school till the age of 17 (twice as many as in 1939) and the increase in university awards from public funds has more than made up for the absence of the ex Service students of the immediate post war years In view of these numbers the improvement in the staff-student ratio—1 7 in 1955–56 compared with 1 8 in 1951–52—is satisfactory, but the committee adds a warning that where additional appointments are due to the needs of research and increased specialisation the "effect on undergraduate teaching is less than might appear"

The distribution of students among the faculties is shifting, science and technology are gaining at the expense of arts and medicine 2441 students began their medical course in October, 1956 (compared with 2700 in 1955, 2674 in 1954, 2614 in 1953), while the total number of medical students was 13,035 (14 7% of all students compared with 23 8% in 1938–39) The committee considers that one of the reasons for the reduced demand for entry to the medical schools is "the continued increase in the numbers on the Medical Register"

Public Health

CONTROL OF AN OUTBREAK OF STAPHYLOCOCCAL INFECTION IN A HOSPITAL

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PATHOLOGIST

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UNITED BRISTOL HOSPITALS

STAPHYLOCOCCAL infections in hospitals are often caused by several prevalent strains of the organism Sometimes, however, a series of infections is caused by a single epidemic strain which seems to be exceptionally virulent We describe here such an outbreak and the measures taken to stop it

All the staphylococci referred to here were coagulase positive They were phage-typed by the method of Williams and Rippon (1952), using the basic set of Colindale phages (Anderson and Williams 1956)

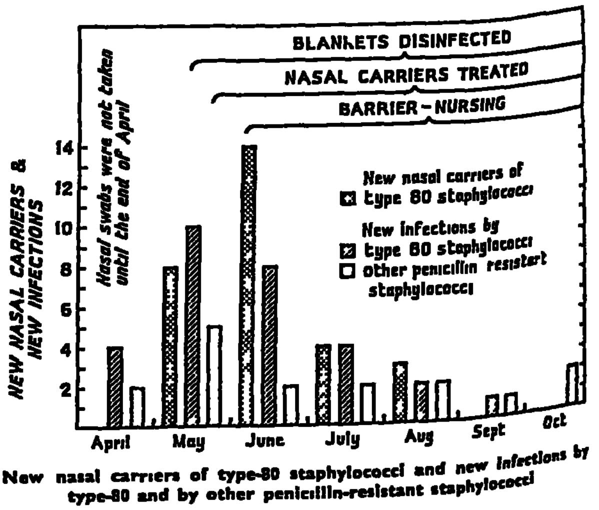
The Infections

In March, 1956, 2 babies were admitted to the Bristol Children's Hospital for treatment of staphylococcal pneumonia and empyema contracted in another hospital, where there had recently been several cases of severe staphylococcal sepsis One of the babies died after three days The other recovered and was discharged seven weeks later Pus from the chest of each yielded *Staphylococcus aureus*, resistant to penicillin, streptomycin, and oxytetracycline, and sensitive to chloramphenicol and erythromycin Both strains had the same phage type, with the basic set of phages at their routine test dilution (R T D) they were lysed by phage 80 only They produced opacity in egg yolk broth (Gillespie and Alder 1952) Similar staphylococci were isolated from the throat and conjunctiva of 1 of the patients Shortly afterwards a nurse developed a large boil on her face, from which a similar staphylococcus was isolated on April 5 She was found to be carrying the same strain in her nose She had worked for three nights in the ward where the 2 babies were

From April 1 until Sept 30 type-80 staphylococci caused twenty nine suppurative lesions in 14 patients and 4 nurses A few of the staphylococci were weakly lysed by the phage 73 at R T D as well as being strongly lysed by phage 80 The staphylococci were otherwise identical with those isolated from the two babies referred to above and probably belonged to the same strain The strain may have been introduced by the 2 babies, but this is uncertain because few staphylococci previously isolated in the hospital had been phage typed A tendency to cause repeated infections in the same person was a feature of the organism, 5 patients had two or more lesions During the same period all the other penicillin resistant staphylococci in the hospital caused only 15 infections, and no person had more than one lesion Most of the type-80 infections took place before the end of June, by which time measures to stop the outbreak were well under way (see figure)

The exceptional virulence of the type 80 strain was shown by its ability to cause most of the infections while being *greatly outnumbered* by other penicillin resistant staphylococci in the noses of nurses and patients, only 38 type 80 cultures were identified among the 174 penicillin-resistant staphylococci isolated from all the nasal swabs taken between April 26 and July 10 (Some nasal carriers were swabbed *more* than once) The virulence of the strain was also shown by its greater tendency to cause furunculosis and subcutaneous abscesses, often with unusually severe inflammation of the surrounding tissue (table I) The strain caused pneumonia and empyema in 2 patients in addition to the 2 admitted with the infection

The type 80 strain appeared to invade noses readily It was isolated from the nasal swabs of 12 of the 23



New nasal carriers of type-80 staphylococci and new infections by type-80 and by other penicillin-resistant staphylococci

TABLE I—INFECTIONS CAUSED BY HOSPITAL STAPHYLOCOCCI BETWEEN APRIL 1 AND SEPT 30

Organism	Primary sepsis of skin and subcutaneous abscesses	Pneumonia and empyema	Infections of wounds and burns
Type 80 strain	19	2	8
All other penicillin resistant staphylococci	4	0	11

For the comparison between the first and third columns χ^2 (corrected for continuity) = 5 75, $P<0\ 02$

patients who in May and early June were found to be carrying penicillin resistant staphylococci Most of these patients had been admitted after April 1 We were unable to determine the importance of nasal spread compared with other routes of spread To have tried to do so would have delayed the measures taken to stop the outbreak Nevertheless it seemed important to treat the nasal carriers of the type 80 strain and to prevent others from becoming carriers

Preventive Measures

Three steps were taken Most of the patients whose lesions or noses contained the type-80 strain were barrier-nursed, nasal carriers were treated, and bed-clothes were disinfected

At first the patients were nursed in their own wards, but after June 6 most of them were kept in one of two wards so that barrier-nursing could be more thoroughly practised The precautions taken in these wards included the use of 'Hibitane' (I C I) hand cream by the nurses who attended to the infected patients, and the application of 'Graneodin' ointment (Squibb) once or twice a day to the nostrils of all patients and nurses who were not carriers Carriers were treated more intensively, as described below

Treatment of Nasal Carriers

A search for nasal carriers was started on April 26 Swabs moistened with saline solution were taken from patients and nurses a ward at a time until the eight wards (114 beds) had been covered This programme was then repeated several times, but swabbing was done more often in the wards which contained carriers or open type 80 staphylococcal lesions than in other wards The resident medical and domestic staff were swabbed twice, but none of them were found to be carriers of the type 80 strain By Sept 26 the wards had been swabbed from five to nine times 1401 nasal swabs had been taken, and 29 carriers, including 7 nurses, had been identified

At first the swabs were plated on nutrient agar Later the medium was made selective for organisms with the antibiotic resistance of the type 80 staphylococci by adding to it streptomycin 5 µg per ml and oxytetracycline 10 µg per ml Six swabs were inoculated, without spreading, on segments of each selective plate This modification greatly simplified the work The positive egg yolk reaction of the type-80 strain was also useful in selecting cultures for phage typing, since most other staphylococci with the same antibiotic resistance-pattern were egg-yolk negative

TABLE II—RESULTS OF TREATMENT OF NASAL CARRIERS OF TYPE 80 STAPHYLOCOCCI WITH GRANEODIN

—	Number treated	Relapsed during treatment	Relapsed within 6 weeks of stopping treatment
Nurses	7	0	2
Patients	15	4*	At least 3 total not known

* 2 patients had septic lesions from which their noses may have been reinfected

Starting at the beginning of April with the nurses and six weeks later with the patients we treated the noses of the type-80 carriers four times a day with graneodin ointment, which contains gramicidin and neomycin The ointment was gently smeared inside the patients' nostrils usually with glass rods The nurses usually applied it to their own noses with their fingers It was intended to treat the patient carriers for at least a week after their swabs became negative, but several left hospital before completing their treatment The swabbing was not repeated often enough to determine how quickly the staphylococci disappeared, but in several cases a negative swab was obtained within a week of starting treatment The type-80 strain persisted or reappeared in the noses of 4 of the 15 patients while graneodin was still being used but disappeared with further treatment, 2 of these patients had septic lesions from which they may have reinfected their noses At least 3 patients relapsed after stopping treatment, but others may have relapsed after leaving hospital

The 7 nurses who were nasal carriers of the type 80 strain gave negative swabs within a week of starting treatment, but most of them continued to use the ointment for two to four weeks more The strain reappeared in the swabs of 2 nurses who had stopped treatment after shorter periods in 1 of them the carrier state was brought to an end by further treatment, the other left the hospital before further treatment could be given

The results of graneodin treatment are summarised in table II The treatment did not irritate the nostrils

Disinfection of Bedding

During the last fortnight of May all patients' garments and bedding were disinfected a ward at a time Subsequently the bedding from contaminated wards was disinfected as the patients left hospital Non-woollen articles were disinfected by laundering at a temperature high enough to kill staphylococci Blankets and other woollen goods were treated with moist formaldehyde vapour in an autoclave chamber A flexible copper tube ($^1/_{16}$ inch bore) was fitted through a gland in the door of a horizontal cylindrical dressings autoclave of capacity 22 c ft The blankets were placed loosely in a wire cage inside the chamber, 18 at a time The jacket was heated by admitting steam to a pressure of 25 lb and then turning it off Steam was not admitted to the chamber A 20 inch vacuum was then created in the chamber by means of the ejector, and 75 ml of formalin (40% formaldehyde), with an additional 400 ml of water, was allowed to flow in slowly through the copper tube, the inner end of which had been placed so that the fluid would fall on the hot jacket lining and not on the blankets After an hour the vapour was removed by creating a vacuum, admitting air, and then creating another vacuum

The formalin treatment did not shrink nor otherwise damage the blankets "Sweep-plate" cultures (Williams, cited by Blowers and Wallace 1955) showed that more than 95% of the bacteria in the blankets were killed Most of the survivors were aerobic sporing bacilli The only disadvantage of the method was the smallness of the load which could be disinfected at a time In subsequent work with an autoclave of 53 c ft capacity loads of 36 blankets have been disinfected satisfactorily

Results

The numbers of type-80 staphylococcal infections and of new nasal carriers fell sharply after June (see figure) 3 of the 7 infections which occurred during the next three months were in patients who had had similar infections previously The single type 80 staphylococcal infection in September was in a nurse who developed a pustule of the skin and a subcutaneous abscess some weeks after leaving the hospital She was known to be a carrier of the type 80 strain

Discussion

Anderson and Williams (1956) emphasise the importance of determining whether a series of staphylococcal infections in a hospital is caused by a single epidemic strain or by several strains If one strain is responsible, its recognition in lesions and in carrier sites is an important step in control For this purpose phage-typing is of first importance, but the antibiotic resistance pattern and other properties of the strain may help to distinguish it from other staphylococci and thus facilitate the selection of cultures for typing The antibiotic resistance may also permit the use of a selective medium for the isolation of the organism, as in the present work

In the control of an epidemic caused by one strain steps should be taken to reduce cross infection in general as well as to eliminate the epidemic strain The disinfection of bed-clothes is an important general measure and may be done by laundering with a quaternary ammonium compound (Blowers and Wallace 1955) or by means of warm formaldehyde vapour in the presence of saturated water vapour With formaldehyde care must be taken to ensure adequate penetration by placing the blankets loosely in the chamber Our method was a hasty improvisation and probably could be improved by using an apparatus such as that supplied by Messrs Manlove Alliott for attachment to hospital autoclaves

Both the barrier-nursing of patients with open sepsis and the treatment of nasal carriers were probably important causes of the elimination of the epidemic strain There can be little doubt of the importance of nasal carriers Hare and Thomas (1956) have shown that nasal carriers can heavily contaminate the environment with staphylococci Gillespie et al (1957) have described an outbreak of neonatal pemphigus caused by a single nasal carrier of an epidemic strain of *Staph aureus* Rountree et al (1956) reported a reduction in the incidence of neonatal infections after staphylococcal carriers among nurses had been treated with 'Neotracin,' an ointment containing bacitracin and neomycin Graneodin has proved to be reasonably effective in treating nasal carriers Like neotracin, it has the advantages that neither of its constituents is often used parenterally and that the presence of two antibiotics reduces the risk that staphylococci will become resistant to either Subsequent experience with children and adults has shown us that persistence of the staphylococcus in a nasal swab taken after a few days' treatment with graneodin usually shows that the ointment is not being correctly used The principal fault is failure to smear it over the skin inside the anterior nares Sometimes, however, it may be difficult to eradicate a staphylococcus from the nose of an infirm or elderly patient, especially if the nostrils contain many hairs Relapse after graneodin treatment, with reappearance of the same strain, does not often happen, provided that the treatment is continued for at least a week after the swab becomes negative The relapse-rate has been lower with nurses than with patients, probably because the nurses usually persisted with the treatment longer than did many of the patients E S Duthie (personal communication) has also had satisfactory results with graneodin

Unusually severe staphylococcal infections caused by phage-type 80 strains were first described in Australia (Rountree and Freeman 1955) and subsequently in this country (Anderson and Williams 1956, E S Duthie, personal communication) Probably, however, exceptional virulence is not a property of all type-80 staphylococci For more than a year we have encountered strains with the same phage pattern but differing in antibiotic sensitivity from our epidemic strain in adult surgical wards and in a maternity hospital, they have not been more virulent than the other staphylococci in the wards

Summary

An outbreak of staphylococcal infections in a children's hospital was caused by an exceptionally virulent strain of *Staph aureus* which had the phage-pattern 80

The antibiotic resistance of the strain permitted the use of a selective medium for its isolation and facilitated its speedy recognition

The outbreak was brought to an end by barrier nursing patients with open sepsis, treating nasal carriers with graneodin ointment, and disinfecting blankets with formaldehyde.

We wish to thank Mr F L Mason and Dr H. M Darlow for advice on the use of formaldehyde, and the matron and nurses of the Bristol Children's Hospital for their efficient cooperation

ADDENDUM

Since this paper was written, we have had two further opportunities of evaluating the treatment of nasal carriers with graneodin The type-80 strain was reintroduced into the Children's Hospital by a child who had been an inpatient during the earlier epidemic It spread to the noses of several patients, but was removed from each, within a few days, by the use of graneodin On the other hand, graneodin failed to remove the staphylococci from about a third of the carriers of several prevalent strains in two male surgical wards, where most of the patients were middle aged or elderly Failure was common with patients whose wounds were already infected

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Tetanus after Operation

Inquiries are continuing into the outbreak of tetanus at the North Staffordshire Royal Infirmary, Stoke-on Trent, to which we referred in our annotation last week *5 patients operated on at the infirmary* between Feb 21 and 25 were infected and 2 have died Symptoms appeared in the first case on Feb 26, the incubation periods ranged from five to eight days In 3 cases it was necessary to resort to tracheotomy, curarisation, and positive-pressure respiration The other 2 patients were treated with deep sedation and postural drainage

The theatre suite in which the patients were operated on was closed from Feb 28 and, in a written parliamentary answer, the Minister of Health stated that it will not be brought into use again until any necessary measures have been taken to prevent any risk of further infection All patients operated on between Feb 21 and 26 who were still in hospital were given tetanus antitoxin on March 1 and 2 6 patients had been discharged and their family doctors were advised to give them antitoxin

Psittacosis

In 1954 the director of the public health laboratory in Luton, Dr J H O Walker, arranged with the chest physician, Dr Brian Shaw, for blood to be taken from patients with pneumonia and investigated serologically for influenza, psittacosis, Q fever, &c Dr Shaw has continued the inquiry in association with Dr H D Holt, the present director *During 1955 there were* 11 Luton patients out of 191 (about 1 in 17) whose sera was positive for psittacosis—i e, whose antibody titre was 1/125 or over, or who showed a fourfold rise or greater During 1956 there were 40 patients out of 279 with sera positive to psittacosis—about 1 in 7 Of control sera from 300 patients, mainly from antenatal clinics, 3 were positive to psittacosis (1 in 100) We understand that the proportion of people with budgerigars or other household pets in their homes was not significantly greater in the positive group The full significance of these results is as yet uncertain, and attempts to isolate the virus might be one way of *clarifying the serological findings*

In England Now

A Running Commentary by Peripatetic Correspondents

TYRANNY can flourish in a country that prides itself on its anti-autocratic ways This thought is prompted by my experience of the after-dinner speech—an institution which, I hope, is nowhere more firmly established than in democratic Britain What happened the other evening is a fair example

The dinner began quietly, and then under the influence of *Bombe Tutti Frutti*, my neighbour revealed himself as the elder brother of Smith mi of my school days at Harlborough Smith mi ? Yes, now I remembered ! In the summer of '08 we had a famous adventure—climbing through the dormitory window and going for a midnight bathe It was a long story, and it was hardly launched when the toast master's gavel fell By then the ice had thawed everywhere, and he had to knock thrice to win attention After the loyal toast I viewed my companion through the smoke and started again, but hardly were Smith mi and I through the dormitory window when the gavel fell once more Half an hour later, at the next gap, I reminded my companion of who I was and began yet again—but this time in more subdued tones Indeed I noticed that at every table the diners, formerly relaxed and jocose, were taut and watchful, as if at a funeral where the body might appear at any moment from they knew not where When, soon after 11 30, the last speaker sat down, no buzz of eager talk broke loose I gazed at my companion and remembered that it was Robinson ma who had gone with me Smith mi had been the little stinker who had not blenched at drawing authority's attention to the outing Murmuring something about last trains, I made for the door

On the way home I fell to thinking that we have broken free from the tyranny of the usual bird at these dinners—some now offer a cut off the joint, and the very best a bit of steak followed by cheese Why can't we show the same zest for reform with the speeches, so that the diners can talk together at the time when they most want to ? For speeches five minutes should be the invariable limit Then I remembered that next week I'm going to reply for the guests at the Little Porchester Society's annual dinner My hosts might be hurt if I didn t spin out my remarks for twenty minutes—or perhaps twenty-five But that of course is an exceptional occasion

* * *

" If you call in and see me next Saturday I will have the result of your blood test "

" Well, doctor, there is some doubt whether I can make it, as I am appearing before the quarter sessions this week If I don't perhaps you could send the report on to me They give you good treatment in those places, so I am told Mind you, I have a fifty fifty chance of getting off I have a good lawyer "

On asking what the charge was I was told it was housebreaking Murmuring " Good luck ! " I left to cross to the female side of the clinic When I returned he had gone The technician who had taken his blood announced that after I had left the patient had said, " That's a nice doctor Where does he live ? " The technician added maliciously that he had drawn a map

* * *

The Lancet has always been generous in giving space to the problems of examinations as they affect the young—medical students and nurses—but I don't remember any discussion on similar troubles among the over-fifties Last month on the penultimate day of a ski-ing holiday the instructor took our names carefully, which I assumed was something to do with the ski-school office, and told us to meet behind the church next morning instead of at the nursery-slopes When we got there a group were erecting a banner over a finishing-line and we were told to climb to a distant point where our class was to assemble for the start Here, then, was I, in advanced middle-age faced once again with a trial of skill The more experienced classes came first, rushing down from higher up the mountain I discussed tranquillisers in German with an attractive young matron, comparing ' Slivovitz ' with ' Oblivon,' until I realised that she was Dutch, spoke better English than my German, and had a husband who was a pharmacuetical chemist Numbers on our chests, we waited our turn The starter appeared with a red flag, my number was called and I was off

It was a straight-forward course as these things go Something like a side of a house to start with, then a right turn, a bit of straight for recovery, a left turn and down the lower slopes to the finish where the local press photographer risked his life and camera as we flung ourselves over the line and tried to keep upright That evening at the large hotel they distributed the prizes To my great astonishment I was second of the men in my class and received an impressive certificate I was stupidly almost as thrilled as when I passed my membership—thirty years before The family think, in view of my sympathetic interest in child psychiatry, that I ought to put Dip Ski after my name but I doubt if the G M C would register it

* * *

Let not your Scot be too troubled or afraid about those twelve medically qualified Sassenachs to be found, at a cost of 7 guineas, in the Registrar General's *Occupation Tables 1951* If he will look at the corresponding Scottish volume—a mere £6 or so—he will find one doctor aged 15, one aged 16, one aged 17, and three more also under 20 Considering the disparity of population, that's pretty good going for Scotland

* * *

The steps at the entrance to the Wallace Collection are a little high, so I arrived with Janet, aged 18 months, sitting on my hip I was greeted with " I am afraid you can't bring the baby in here, Sir ! " We retired in confusion and outside the door discussed how else we could spend a cold Sunday afternoon when we had come so far Janet was now standing independently and this sight must have softened the door-keeper, who poked his head out and asked, " Can the little girl walk ? If she can walk in by herself that lets me out all right " He was assured that she could walk, and so I led her to the turnstile where she was so fascinated by the polished brass gate that she insisted on pushing it around twice before she could be persuaded to enter the realms of art There she showed a real but highly selective appreciation of all that was offered A pointing finger and barely breathed " Pretty ! " indicated her fullest approval So far we had progressed hand in hand, but I carried her (fortunately unobserved) up the main staircase to where Venice lies There we lingered rather and the small legs wearied, but I no sooner had them straddling my hip again than I was warned by a gruff, " The little girl must walk or she must go " " But she is just tired, can't I carry her for a rest ? " " If she doesn't walk she can't stay " So out we had to walk, Janet casting reproachful looks at this human who had not given her the accustomed great welcome We went on to the Tate where, to play safe, we walked Janet (with assistance) up all those steps and put her in her own quadrant of the great circular door She immediately discovered the joys of walking along the lines in the marble floor and then scrambling along the seats in the galleries But all here was friendly The attendants played peep-bo around the seats and waved bye-bye down the galleries, so that in no time I was bold enough to carry her and no-one objected All this was most circumspectly done and I hope that no trustee of the Tate who may read this will fear that our progress was a riot and resolve to ban babies from tasting art in comfort and with transport according to their needs, for there is no doubt of the delight they gather from their chosen works

* * *

Our statesmen's faith in the eternal wisdom of industrialists is once more evident in the constitution of the Royal Commission on medical remuneration Would it not be a happy reciprocal gesture to appoint a Royal Commission of doctors to investigate any current disturbance in industry ?

Letters to the Editor

GOVERNMENT AND PROFESSION

SIR,—Your leader of March 2 on the remuneration claim sets forth first of all those facts that must excite a deep disquiet in all who care for the future of the profession and then appears summarily to condemn the only means of effective action

I do believe, however, that there are compelling arguments against using the threat of mass withdrawal from the service as a weapon of coercion against the Government Firstly, those who express support for such a course include an uncertain number who hope that words and posturings may be enough and that action may never be called for, to negotiate from this position is to negotiate from weakness In the second place, not only are these tactics the least likely to be effective—and I have no doubt that the Prime Minister has the advantage of an expert assessment of the strength of such opposition from sources within the Cabinet—to attempt them is to presume that it would be sufficient if the aims of the threat were achieved But the lesson of the past ten years is that no Government guarantee is so explicit and so binding as to be able to withstand considerations of expediency, and even if the claim were now to be conceded in full the future would be packed with uncertainties, the one sure thing, indeed, is that in one or two or three years the report of a Royal Commission, whose composition and terms of reference must arouse only foreboding, will open up the sores once more

In such circumstances, all who have the long-term interests of the profession—and of their patients—at heart can hardly be satisfied until it is delivered from any service financed and administered by Government It follows that, whatever the Government may now concede, all who wish to do so must be given the chance to withdraw from the service

You would surely agree that those who may desire to do this are entitled to send in their resignations in an organised manner not in order to coerce, but in order to ensure that none may be denied this opportunity for fear of acting alone, and to afford themselves mutual help and support in the difficult times that may lie ahead for some

Rugeley Staffs P M HIGGINS

SIR,—Mr T B Layton's letter last week is most timely when the medical profession, in its more or less recent union with Government, is beginning to feel the effects of this uneasy marriage How far it should follow the examples set by others in similar circumstances is a matter for no hasty decisions

Mr Layton writes that trade unionism has become the accepted means—presumably for discussion—for those who work with their hands While I am not very clear about his distinctions between working with hands or mind, I do hope with him that the medical profession will set an example and maintain its dignity in their grievance, if this is real, rather than follow some of the worst traits of trade unionism This, I feel sure, is the immediate aim and that full work will be continued if under different conditions, while adjustments are sought, for, or so it seems, a primary principle is at stake—the freedom to work as well as to strike

If this principle is not always upheld in full then an authority may emerge in this country besides which medieval feudalism will lapse into a pale or near invisible shadow

London W 1 F D SAYER

SIR,—Instead of concentrating exclusively on direct financial issues in the present dispute with the Government, would it not be more fitting that the medical profession should take advantage of the relative fluidity of the situation to attempt instead to achieve two fundamental reforms in the health service

(1) The granting of the right to National Health Service prescriptions to patients who consult their doctor outside the service

(2) The limitation of registrar appointments to a small number of specially selected hospitals, and their replacement in the others by consultants

The first step would free general practice from the bonds of being almost exclusively a Government monopoly, and by encouraging smaller lists improve its quality as well as provide openings for the large number of young doctors seeking such openings While the latter would immediately and permanently solve the registrar problem, a problem which unless soon solved threatens the foundations of the quality of the hospital services

London, W 1 DAVID H PATEY

SIR,—An extra payment at least to general practitioners, *without prejudicing their claim and readjustment*, could be made in April simply by releasing now the payment for expenses due in January, 1958 It would be a gesture of goodwill instead of the harsh and cynical attitude of disregard Already the impression is gaining ground that the Government is always ready to give the aspirations, advice, and interests of the managers and executives of the industrial, financial and trade organisations every consideration, while the scientists, the professional men, and the workers have been allotted the rôle of dumb, faithful, and obedient servants

Epping H KORTE

URINARY STEROID PATTERNS IN BREAST CANCER

SIR,—In your leading article of March 9, on Hypophysectomy for Cancer, you suggest that a preoperative urinary analysis of the ratio of 11 deoxy, 17 ketosteroids to 11-oxy, 17 ketosteroids may prove of value in predicting the response to endocrine ablative surgery in patients with advanced cancer of the breast

Unpublished results obtained in this department employing delicate methods of analysis, based on the work of Dobriner,[1] and Edwards et al,[2] indicate no obvious correlation between preoperative steroid patterns and response to surgery

Case no	11 deoxy, 17 ks (mg per 24 hr)	11 oxy 17 ks (mg per 24 hr)	Ratio	Treatment	Response
1	1 35	0 92	1 4	Pituitary implantation and adrenalectomy	−
2	1 13	0 91	1 2	Pituitary implantation	−
3	1 29	1 22	1 5	Pituitary implantation	−
4	1 39	1 15	1 2	Pituitary implantation	+
5	2 63	1 01	2 6	Adrenalectomy	+
6	2 85	0 98	2 9	Pituitary implantation and adrenalectomy	−
7	5 48	1 62	3 4	Ovariectomy	−
8	1 20	1 33	0 9	Ovariectomy	

This in no way reflects upon the suggestion of Dr Merivale and his colleagues (March 9) that a considerably altered hormonal environment (i e, a greatly altered steroid ratio) is necessary for response On the contrary our work gives some support to this idea, since, in a few cases where clinical response was lacking, the steroid ratio, although initially high, was to a large extent unchanged following treatment

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[1] Dobriner, K *J clin Invest* 1953, 32 940

[2] Edwards R W H Kellie A E, Wade, A P *Mem*
Endocrinol 1953 2 53

The failure of a patient with a high initial ratio to respond to treatment may be due, in part at least, to a failure of the surgery to change it sufficiently Such a state of affairs would not be predicted on the basis of a preoperative urinary analysis alone

University of Glasgow
Department of Surgery
Western Infirmary Glasgow

R HOBKIRK
A P M FORREST

PENICILLIN IN THE TREATMENT OF LACTATIONAL BREAST ABSCESS

SIR,—Mr De Jode, in his article last week, places insufficient emphasis on the advantages of rest for this condition, and continuation of breast-feeding At the first sign of inflammation the patient should be put to bed flat, and when the infant is fed the patient should turn to one or other side still remaining flat Antibiotics will do the rest Of course, in hospital practice one may be faced with a full-blown abscess for which the knife must be used, the conservative treatment must be started early For recurrence of inflammation rest and antibiotics are again indicated

Longtown Cumberland

ROBERT RUTHERFORD

LONG-TERM EFFECT OF DRIED THYROID ON SERUM-LIPOPROTEIN AND SERUM-CHOLESTEROL LEVELS

SIR,—Strisower et al (Jan 19, p 120) report their investigation into the effect of dried thyroid on serum-lipoprotein and serum cholesterol levels This involved the administration of what you described in your leader in the same issue as a "strenuous course" of dried thyroid over 105 weeks to 60 schizophrenic patients in a Californian State mental hospital, the patients then being the subject of various physiological and chemical investigations The authors imply that the only criterion used in selecting the group was chronicity of the mental illness

This use as guineapigs of chronic psychotic patients, who are not able to give or withhold valid permission for experiments in physiological research of this type, must be as repugnant to many of your readers as it is to me It is certainly not in the tradition of the Scottish mental hospital service

Hawkhead Hospital
Glasgow, S W 3

JAMES MILNE

SIR,—I read with great interest the article by Mr Strisower and his colleagues

Though I admire the paper from a scientific point of view, I cannot agree with the methods from the medical-ethical point of view I think that the first thing to be fulfilled in medical experiments is the free-will of the individual to coöperate in the experiment, and I suppose that we cannot expect a free decision from a mentally ill person such as a schizophrenic Therefore I must object to this sort of experiment

Amsterdam

W P J VILTOR

*** These letters have been shown to Mr Strisower and Dr Gofman, who reply as follows "We have been engaged for several years, together with our psychiatric colleagues, in an evaluation of several metabolic and biochemical facets of the problem of schizophrenic and other mental diseases The interest on the part of many investigators about possible thyroidal relationships to schizophrenia is well known Indeed you commented on the reported tolerance of schizophrenics to thyroid in your recent editorial Surely Dr Milne would not be critical of biochemical and metabolic studies directed toward the understanding of the problem of schizophrenia"—ED L

THE B C G LESION IN SARCOIDOSIS

SIR,—I was interested in Dr Borrie's letter (Feb 23), referring to the excellent article (Jan 26) by Dr Forgacs and his colleagues Dr Borrie says "10% of normal individuals who are tuberculin-negative do not become tuberculin-positive after B C G vaccination, and I suggested at the time that this particular constitutional peculiarity may have some bearing on the future development of sarcoidosis"

In the Oxford Regional Hospital Board area, 99 6% of 7371 persons of all ages converted to positive after primary B C G vaccination My own figures for 1951–56 inclusive are 100% in hospital adult staff

I have seen a possible case of sarcoidosis developing in a person who had had B C G vaccination in November, 1951

He was Mantoux-positive to 100 T U two months later (14 mm induration) He had annual chest X rays as a bacteriological laboratory worker In July, 1953, the routine X ray showed bilateral enlarged hilar shadows consonant with sarcoidosis The Mantoux test with 10 and 100 T U was reported as negative Judged by X-rays the lesions had regressed considerably by September, 1953, and the X ray was normal by December, 1953 In January this year the X ray films were still normal, and he had a positive Mantoux test to 10 T U (15 mm) He had no symptoms in 1953 in spite of the X ray appearances, and no overt evidence of tuberculous infection at any time

Had I seen this man in July, 1953, I should have tried to ascertain whether his serum, when mixed with tuberculin in varying dilutions, would inhibit a positive reaction in those known to have one (as a result of either B C G vaccination or natural infection) using control sites as well Had this been done the data might have been of interest I understand from Dr K Neville Irvine that tuberculin testing of patients with sarcoidosis in Sweden has demonstrated the presence of a factor inhibiting tuberculin reactions, and that negative reactors have become positive after recovery from sarcoidosis, though they had been converted to tuberculin-positive by B C G vaccination previously

Patients with sarcoidosis, besides those of Dr Forgacs and his colleagues, remain tuberculin-positive in the apparently active phase of the disease, thus the inhibitory factor is by no means universal It could be that those with apparent sarcoidosis who have a negative tuberculin reaction, and fail to convert after B C G vaccination, have a disease with a different ætiology from that in the more usual cases, but at present this view can only be speculative

Case 9 of Dr Forgacs and his colleagues is damaging to this speculation, since there were skin lesions and the axillary nodes were enlarged, together with the inaccessible intrathoracic charges indicative of sarcoidosis This woman was positive to 0 1 mg (10 T U) initially, and negative to 1 mg six weeks after B C G vaccination

In short, Mantoux reactions in apparent cases of sarcoidosis can be contradictory and confusing

Royal Berkshire Hospital
Reading

GEORGE A JACKSON

SIR,—In his letter Dr Borrie says that "About 10% of normal individuals who are tuberculin negative do not become tuberculin-positive after B C G vaccination " In Lewis, among 3000 vaccinated by the intradermal route there were only 3 who failed to convert these 3000 were done between 1949 and 1953 (spring) Since 1953 another 2000 have had B C G by multiple puncture technique, and here conversion was the rule, although in the early attempts the reactions were not all one would have wished This partial failure was due to the fact that vaccine of suitable B C G content could not be obtained Now, I may say that with Glaxo freeze dried B C G, of 25 mg per ml concentration for percutaneous use, the results are exceptionally good and consistent This vaccine is issued only for experimental purposes

Stornoway,
Lewis

R STEVENSON DOIG
Deputy Medical Officer of Health

TRUSS-FITTERS

SIR,—We should like to draw attention to the scheme *for the training and certification of abdominal hernia appliance fitters*

This scheme is sponsored by the Institute of British Surgical Technicians The chairman of the board of examiners is a surgeon The object is to ensure that doctors shall have their patients correctly fitted, thereby avoiding the discomfort and inconvenience often caused by ill fitting appliances A number of courses of training has already been held, and others will be arranged at centres throughout the United Kingdom as the scheme increases in scope There are at present 230 certificated abdominal hernia appliance fitters, the names of whom will be supplied to any doctor who is interested

HENRY SOUTTAR
President

Institute of British Surgical
Technicians 6, Holborn
Viaduct, London, E C 1

H GUY RADCLIFFE DREW
Chairman of the council

FUNCTIONAL SIGNIFICANCE OF PITUITARY BASOPHILISM

SIR,—Lately several workers have sought to connect the cytomorphological changes, due to various influences, of the adenohypophysis with the production of the trophic hormones Thornton [1] has stated that cortisone treatment is followed by increase in the basophil cells of the adenohypophysis *At first sight it might seem* reasonable to ascribe this change *to inhibition of corti*cotrophin (A C T H) secretion by cortisone Purves [2] and Crooke,[3] however, expressed the opinion that the increase of basophil cells under such circumstances is connected, not with the decreased secretion of corticotrophin, but with the increased production of follicle stimulating hormone (F S H)

Our own studies,[4–6] published in 1954 and 1955, fully accord with this view We demonstrated that the changes in numbers of the basophil cells of the adenohypophysis are due, not to the intensity of corticotrophin secretion, but to the quantity of corticosteroids present in the tissues Increase of basophil cells can be seen in non-specific stresses or after cortisone intake (i e, with an augmented peripheral level of corticosteroids), whereas after adrenalectomy (when corticosteroids are practically absent in the tissues, and the production of corticotrophin on the other hand is intensive) basophil cells decrease

The numbers of basophil cells in any experimental intervention (stress, adrenalectomy, cortisone intake, &c) change in parallel with the quantity of P A S-positive cells And since only the so called glycoproteid hormones (gonadotrophin, thyrotrophin) contain groups oxidisable to aldehyde by periodic acid, it seems fairly certain that the *change in the number of basophil cells* is connected, *not with the production of corticotrophin*, but with that of glycoproteid hormones

That this hypothesis of ours is correct has been supported by parallel quantitative cytomorphological analysis of the adenohypophysis *as well as biological* titration of its gonadotrophin content We have demonstrated that where the basophil cells are increased the F S H content of the hypophyseal extracts is enhanced Further we have found that this increase caused by stress (endogenous corticoids) can be fully avoided by folliculin inhibiting the secretion of F S H; but at the same time the secretion of corticotrophin remains intensive In our current experiments we are trying to inhibit the effect of cortisone (exogenous corticoid) in enhancing the basophil cells by administering œstrogens

In summary, our studies suggest that the cytomorphological picture of the adenohypophysis can be influenced by the corticosteroids Where these are increased, from either endogenous or exogenous sources, basophil hyperplasia results This morphological change is unconnected with the extent of corticotrophin secretion but is connected with the intensity of gonadotrophic hormone production

Department of Pathology,
University of Szeged, Hungary

K KOVÁCS
M DAVID
B KORPÁSSY

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1 Thornton K R *Proc R Soc Med* 1956 49 1016
2 Purves H D *Ibid* p 1014
3 Crooke A C *Ibid* p 1019
4 Kovács K Bachrach D Jakobovits, A Horváth F Korpássy B *Endokrinologie* 1954 31 17
5 Bachrach D Kovács K David M Horváth F Korpássy B *Acta morph hung* 1954 4 429
6 Kovács K Jakobovits A Dávid M Horváth E Bachrach D Korpássy B *Endokrinologie* 1955 32 281

MUNCHAUSEN'S SYNDROME

SIR,—We wish to thank Dr Heathfield for his timely letter (March 9)

The patient he described presented at midnight last night with the same history of headaches, drowsiness, and deteriorating vision, but on this occasion she did not complain of vomiting On examination the signs were as described by Dr Heathfield On being confronted with extracts from the letter, she denied having visited any of the hospitals mentioned, and attributed her abdominal scars, at first, to a hysterectomy She eventually stated that they were, in fact the result of tuberculous peritonitis *Her alleged occupation* on this occasion was that of porteress

It must be rare for a case of Munchausen's syndrome to be so quickly identified after description in your columns Dr Heathfield's letter has saved much time and expense in pursuing profitless investigations

St. Thomas's Hospital
London, S E 1

D M ESSENHIGH
R D G PEACHEY

RHEUMATOID ARTHRITIS WITH CHRONIC LEG ULCERATION

SIR,—We were interested to read the article by Dr Allison and Dr Bettley (Feb 9) in which they presented six cases of skin ulcers, emphasising that we have overlooked the possibility of disseminated lupus erythematosus

We have reviewed our twelve published cases of skin ulceration,[1] five of them being at present under hospital care Besides these, we have found five more cases

The follow up time after the diagnosis of ulceration is now from four months to five years All these patients are still alive Except in one case, all show a classical picture of rheumatoid arthritis with typical X-ray changes According to the American Rheumatism Association's classification there were 2 cases in stage II, 9 in stage III, and 5 in stage IV In one case *mentioned above* the diagnosis has not yet been fixed, but polyarteritis nodosa has been suggested

Three of these patients have sometimes had a slight rash *in connection with gold therapy*, but have shown no other symptoms of drug intolerance No other cutaneous manifestations of disseminated lupus erythematosus have been observed in these cases One patient had pleural adhesions Slight tachycardia was present in one case In two cases both systolic and diastolic murmurs were observed Systolic blood pressure was slightly increased in three cases (190–175 mm. Hg) Proteinuria was present in one case (amyloidosis) and a trace of protein was present in the urine in another case These patients had occasional cylindruria L E cells were sought in only five cases, *the results being negative* The anti streptolysin titre was elevated in two cases Slight anæmia was present in all cases The erythrocyte sedimentation rate was increased in each case (values from 11 to 134 mm, Westergren) In *no* case was there hyperpyrexia

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1 *Acta rheum. scand* 1955, 1 113

In no case was leucopenia found, the lowest value, occasionally found in one case, was 4300 per c mm The highest value was 12,800 per c mm In two cases transitory eosinophilia was found (11 and 27%)

Biopsy of skin and muscle, performed in nine cases, did not reveal definite changes of disseminated lupus erythematosus

Thus, except in one case of possible polyarteritis nodosa, these patients with skin ulceration show a typical picture of rheumatoid arthritis, with no evidence of disseminated lupus erythematosus Further, it is interesting that Allison and Bettley's cases 4 and 5 did not show evidence of disseminated lupus erythematosus, and that in other cases this diagnosis seems to have been based only on the positive L E cell phenomenon and drug eruptions The specificity of the L E cell phenomenon is disputed Nevertheless we have seen in our clinic two patients with definite disseminated lupus erythematosus and multiple ulcers

Rheumatism Foundation Hospital
Heinola, Finland.

V A I LAINE
K J VAINIO

EPIDERMOID CHOLESTEATOMA AND CHOLESTEROL GRANULOMA OF THE EAR

SIR,—In your interesting leading article on Keratinous Cysts in the C N S (Feb 16) you refer briefly to the pathogenesis of the so called cholesteatoma of the ear

There appears to be no general agreement on the pathogenesis of this structure often complicating chronic otitis media In particular the origin, character, and rôle of its epithelial lining and the rôle of cholesterol in the formation of cholesteatoma have mystified many workers and led to some confusion

There are, in my opinion, two pathological entities to be considered, exhibiting distinct histopathological features the epidermoid cholesteatoma, an epithelial product, and the cholesterol granuloma, the result of the deposition of cholesterol crystals in the infected tissues of the middle ear

Epidermoid Cholesteatoma

The true epidermoid cholesteatoma is a cyst whose wall is lined by keratinising stratified squamous epithelium with its keratinised layers, the surface layers of the epidermis innermost (fig 1) The keratinised layers are being shed in ever increasing numbers into the cavity of the cyst and, usually, with a generous admixture of pus form its contents

It cannot be emphasised too strongly that the cholesteatoma is an epithelial structure produced by keratinising stratified epithelium It is the origin of this epithelium that has remained obscure, and several hypotheses have been advanced The most important are

(1) *Direct extension of epidermis from the external auditory canal as a result of chronic otitis media with perforation of the tympanic membrane*

Experimental evidence[1] has shown how stratified keratinising squamous epithelium may extend from the external auditory meatus or from the tympanic membrane into the experimentally infected middle ear, forming a continuous lining of the bulla of the guineapig In sections of material removed at operations on the human mastoid process, similar findings have been made in many cases of cholesteatoma[2] Moreover, the ingrowing stratified squamous epithelium could be clearly seen undermining the mucosa of the human middle ear, leaving its normal epithelial lining apparently intact

(2) *Metaplasia of existing normal epithelium to a stratified squamous epithelium, also the result of chronic infection*

True squamous metaplasia—that is, the *replacement* of cuboidal or columnar epithelium by stratified squamous epithelium—cannot be entirely ruled out, but is probably uncommon

(3) *Activated cell rests, as is the case with primary intracranial cholesteatoma*

This mode of origin cannot be doubted, but it is a rare cause of aural cholesteatoma

Both human and experimental evidence favours Haberman's original hypothesis that the matrix of a true epidermoid cholesteatoma is formed through the extension of stratified (keratinising) squamous epithelium into the middle ear from the external auditory meatus or from the tympanic membrane

Whether a good or a bad one, the ambiguous term cholesteatoma cannot be easily replaced, but it should be amended by the addition of the attribute "epidermoid"

Cholesterol Granuloma

The cholesterol granuloma differs fundamentally from the epidermoid cholesteatoma It is a granulomatous structure formed by large numbers of cholesterol crystals (clear cleft like spaces in sections) surrounded by foreign-body giant cells and embedded in fibrous granulation tissue (fig 2)

Cholesterol crystals are often present in sections of aural polypi, bone chips, and granulations removed from the infected mastoid process, deposited at the site of hæmorrhage or suppuration

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1 Friedmann I *J Laryng* 1955 69 588
2 Friedmann I *J clin Path* 1956 9 229

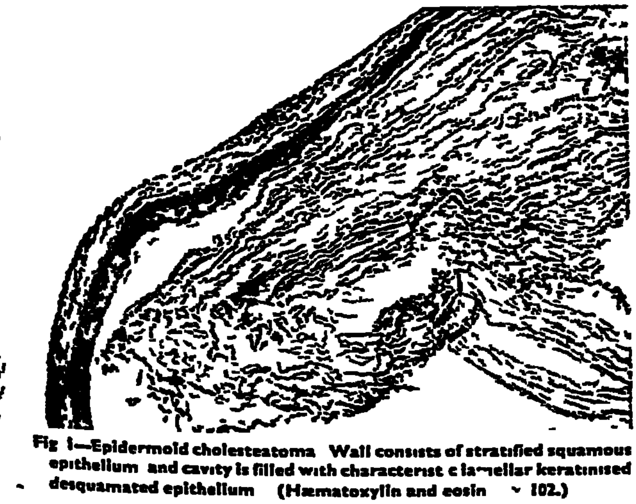

Fig 1—Epidermoid cholesteatoma Wall consists of stratified squamous epithelium and cavity is filled with characteristic lamellar keratinised desquamated epithelium (Hæmatoxylin and eosin × 102.)

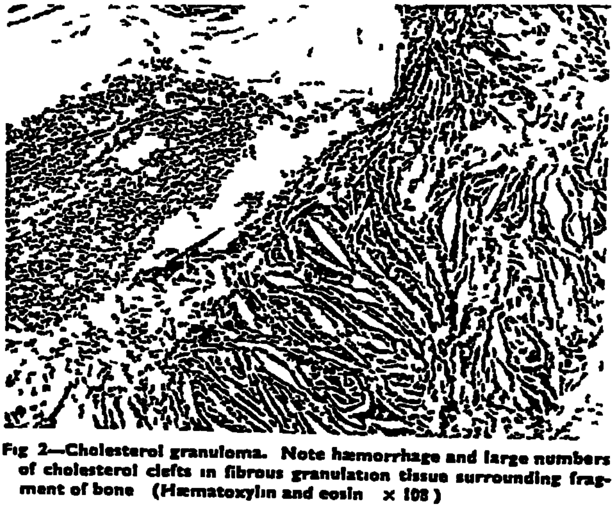

Fig 2—Cholesterol granuloma. Note hæmorrhage and large numbers of cholesterol clefts in fibrous granulation tissue surrounding fragment of bone (Hæmatoxylin and eosin × 108)

no ill effect has been observed, and the hair is left in good condition, with no sign or stigma of treatment. The use of an attractive shampoo overcomes the reluctance of the adolescent and the mother. A first-class shampoo is necessary so that all members of the family will not only tolerate the remedy, but like it and want it.

There is great need for industrial areas, irrespective of local-government boundaries, to attack the problem of infestation together and at the same time. I have tried many insecticides during the past twenty years, and the new lorexane no. 3 appears to be the best remedy.

Acknowledgment is warmly made to those who did all the work: the Salford public-health nursing service (superintendent health visitor, Miss B. M. Langton), and I.C.I. Pharmaceuticals Division for supplies of 'Lorexane' no. 3 shampoo.

Public Health Department,
Salford

J. L. BURN

DYSENTERY DURING ADMINISTRATION OF ANTIBIOTICS

SIR,—The use of antibiotics is usually followed by the appearance of a new microbial flora in the intestine, and when the host is debilitated the new micro-organisms may give rise to a secondary disease—e.g., candidiasis or staphylococcal enterocolitis. Recently we have seen a case of dysentery apparently caused by *Proteus morgani* which arose during administration of tetracycline and penicillin after an operation on the intestine.

A man, aged 30, had for several years had pain in his right lower abdomen. A diagnosis of mobile cæcum was made. At operation, severe chronic inflammation of the cæcum and ascending colon were found. The ileocæcal region, cæcum, and ascending colon were resected and an ileocolostomy was created. Since abdominal distension and high fever continued after the operation, food and water were not given orally for a week; blood and Ringer's solution were infused and vitamins injected; tetracycline 500 mg. daily was administered intravenously with 500 ml. of 5% glucose solution, and penicillin 300,000 units daily was given intramuscularly.

On the 7th day after operation, the patient had severe dysenteric symptoms. From the fæces bacteria of the proteus group were isolated in almost pure culture; they were identified as *Proteus morgani* biologically and serologically. Among the biological properties of the organism was a marked activity of histidine decarboxylase, but the significance of the active production of histamine in this case was not known. The organism was highly resistant to penicillin, erythromycin, tetracycline, chlortetracycline, oxytetracycline, and streptomycin, and only moderately sensitive to chloramphenicol. After oral administration of chloramphenicol 1 g. daily for 3 days, the dysenteric symptoms abated, the fæces became normal, and the organism disappeared from the fæces.

Proteus morgani seems to be mainly commensal but potentially pathogenic.[1 2] It has been cultured from the fæces in sporadic dysentery, enteritis, and diarrhœa, but its pathogenicity is doubtful. Under suitable conditions it seems able to multiply in the intestine, but it can hardly be ranked with the organisms of the shigella group.

In our patient, active growth of *Proteus morgani* in the intestine, resulting from the depression of the normal intestinal microbial flora, may have caused dysenteric lesions—at a time when he was undernourished after the operation on the intestine. In most reported cases, staphylococcal enterocolitis has followed nutritional deficiencies or severe cachectic states. We must therefore pay much more attention to the nutritional state of patients when antimicrobial therapy is being given.

Nagoya University School
of Medicine
Nagoya, Japan.

NOBUO KATO
YOSINORI NARITA

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1. Wilson, G. S., Miles, A. A. Topley and Wilson's Principles of Bacteriology and Immunity. London, 1948.
2. Zinsser, H. Textbook of Bacteriology. New York, 1948.

UNMARRIED PARENTHOOD

SIR,—This letter is intended to be an olive-branch. Both Dr. Tuthill and Miss Steel want to see more and more happy marriages, with more and more children growing up in confidence and security because the sexual life of their parents is harmonious and free from morbid associations of guilt. It is a little hard of Miss Steel to call the notions which seem to underlie the letter from Dr. Tuthill, who after all is only out to help those couples whose sex life has gone adrift (often because they have been indoctrinated with "guilt"), "very barbaric and sub-human." To call sex an appetite does not seem to be contradicted by experience, nor indeed by the outspoken phrases of the Book of Common Prayer. Are there not perhaps some couples who are such idealists with regard to sex that they are permanently disappointed, and permanently feeling guilty? While no-one wants children to be born of illegitimate parents there are other kinds of sexual tragedies—e.g., the conscientious couple, both brought up to regard sex as strictly "sacred," who are never free from scruple and inhibition with each other. If things go seriously adrift, such couples need help from outside, and it is possible that the only person who can help them is one who can persuade them to be less solemn and idealistic, more playful and lusty, in their sexual life. We all want to help and to be helped, and I feel we must not get too hot under the collar over the unorthodox opinions and methods of some of the helpers.

Bowers Gifford Rectory,
Basildon, Essex.

EDWARD MANSFIELD

REFLECTIONS ON CIRCULATORY CONTROL

SIR,—Dr. Cecil Gray suggests (Feb. 23) that "hypotension should be reserved for those cases in which it is clearly imperative because of the nature of the surgery; this would limit it to neurosurgical and perhaps some otolaryngological and plastic operations. . . ." Yet there are probably more contra-indications to hypotension in cerebral disorders than in those elsewhere in the body.

For example, Brown[1] pointed out the danger of using hypotension and surgical retraction in the acute phase of *subarachnoid hæmorrhage*, with its concurrent arterial spasm in the vicinity of the aneurysm. He also mentioned the danger of using hypotension in the presence of stretch or distension of major vessels from tumour or other causes. Brown[2] has since pointed out the importance of preventing a fall of blood pressure in seriously ill patients with spasm of the anterior basal perforating arteries.

Access within the skull is considerably aided by good anæsthesia with *attention to* posture, venous drainage from the head and neck, adequate respiratory exchange, the substitution of barbiturate drugs for opiates in premedication, and the use of aids such as ventricular or spinal drainage of cerebrospinal fluid during operation and intravenous infusion of hypertonic salt solution if required. Certainly by these methods operating conditions can be as satisfactory as when hypotension and hypothermia are used. Mortality and morbidity rates, however, are definitely lower, and the patient recovers consciousness more rapidly.

Where major cerebral vessels are not involved by spasm or are not stretched by tumours or other causes, hypotension may be of considerable value. For example, I would regard hypotension as an invaluable aid to the surgical removal of a cerebral arteriovenous *malformation* contributing materially to the excellent surgical results in this condition.

Department of Surgical Neurology,
Royal Infirmary, Edinburgh.

ALLAN S. BROWN.

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1. Brown, A. S. *Anæsthesia*, 1954, 9, 19.
2. Brown, A. S. *Ibid*, 1955, 10, 351.

Parliament

Prison Reform

WHEN the public purse is thin it is natural to put the claims of the widow, the sick, and the aged before those of the prisoner But it may not always be wise The public purse is rarely fat, and it is never the prisoner's turn Today shortage of staff, overcrowding, and sanitary squalor are hindering our prisons in their work for the community Members on both sides of the House last week welcomed Mr R A BUTLER's first speech as Home Secretary on this subject, because it rejected what was described as this "last of the queue approach"

Under the drab headings of the Supplementary Estimate, which he was formally introducing, Mr Butler managed adroitly to review the present difficulties of the prison service and put forward his ideas for a better future Accurate knowledge was an indispensable tool of administration, and he admitted that since taking office two months ago he had been shocked to find that in the last nine years the Home Office had spent only about £12,000 on research Some useful work had of course been done, particularly on borstal and approved-school training, probation, and detention-centre treatment, but in his opinion we needed fuller and more accurate information, especially on imprisonment itself We must use the tools which science and sociology had put into our hands to supplement the knowledge gained from experience, and he therefore proposed to give research first priority

OVERCROWDING AND UNDERSTAFFING

He selected as the most urgent problems of prison administration overcrowding and understaffing The best measure of the first perhaps was the number of men who had to sleep three in a cell A year ago this was 2500, now it was little more than 2000 despite an unhappy rise in the prison population from 20,500 to 21,600 *Last year the Prison Commissioners took over another* open prison, making 13 in all He thought it unlikely that this form of relief to accommodation could be taken much further without undue risk to a valuable method We must therefore look for help from the building programme which was now under way

Early next year a prison for 300 men near Hull would be ready for use A similar prison in Lancashire had been started, and work would begin this summer on a psychiatric institution—the East Hubert Institution A small borstal for girls would open later this year, and work on a second would start early next year A site for a borstal for boys had been acquired, and planning clearance was being sought for a second When all these buildings were in use—at least in five years' time—they would provide 1500 more places

Another way of coping with overcrowding was by reducing the inflow of prisoners The Advisory Council on the Treatment of Offenders was considering suggestions for reducing the number of short sentences Though a reduction in these would be welcome the main increase in the prison population was probably due to an increase in the length of sentences passed by the higher courts This was of course a matter for the judiciary, but the Home Office should be able to offer the judges information, based on systematic research, about the results of various forms of treatment, and fuller information about offenders before sentence In his view the most important means of obtaining an expert diagnosis of a prisoner's history and personality was the remand centre Not only would these centres keep young people out of prison but they would provide a focus for research into juvenile delinquency He would like to have an entirely separate centre for adults which would use the same specialised staff

Coming to his other big problem Mr Butler said that 1000 more officers were needed before the local prisons could turn over to a shift system which would give the prisoners a full working day Even on the present shift system the staffs were still below establishment It was important to attract and retain the right kind of men and women, and he and the Secretary of State for Scotland had decided to set up a departmental committee to review pay and conditions of service Meanwhile an immediate increase of pay would shortly be raised before the arbitration tribunal

But material conditions were not the only things that made a job attractive, and he wanted every officer in the service to feel that this was a real vocation To this end consultative committees were being set up and staff refresher courses increased Good human relations between staff and prisoners were also important, and Mr Butler described a successful experiment at Norwich prison

Every man on arrival was assigned to a small group under the particular care of two officers whose duties were arranged so that one or other of them was always about The prisoners knew that there were these officers to whom they should look for help and advice The officers were encouraged to get to know their own group, both as a group and as individuals *and to be ready to make reports on them if necessary* All convicted prisoners, except in special circumstances, were allowed to be in association outside the cells from unlocking in the morning until 7 30 P M Apart from other advantages the time saved to the staff on locking and unlocking, together with some adjustments of their timetable, had made possible for the prisoners a working day of over six hours instead of five

It was hoped soon to extend these methods to some of the smaller local prisons

RESPONSIBILITY AND RESTITUTION

Turning to the question of prisoners' earnings, Mr Butler announced that these were to be raised Under the new arrangement all prisoners would start with a minimum of 1*s* 8*d* a week He readily admitted that this did not sound impressive But more important than decisions about the exact rates to be paid was, he suggested, a reconsideration of the purpose behind the whole scheme The present scheme stimulated industry, but should we not look further. What of the prisoner's self-respect? What of helping him to realise his family and social responsibilities? These were among the declared objects of the treatment and training of prisoners Might they not be furthered by a wider and more imaginative view of the possibilities of earnings as an instrument of training? It might be possible, for example, to devise a scheme which would permit a prisoner to save to help himself and his family on discharge Or, taking an even wider view, to give prisoners a rate comparable with a normal industrial wage, out of which they would pay for their keep in prison, maintain their families, meet their social insurance and other obligations, save towards discharge, and, possibly, pay compensation to their victims

Surely these ideas began to lead us away from the simple conception of punishment, which, over many centuries, had occupied too dominating a position in our penal philosophy? Might it not be that something of value was lost when the relation between the offender and his victim was thought to be one which simple punishment could satisfy, so long as it was left to the State to carry out that obligation of punishment? Was there not also some ethical value in the older conceptions, because they were the older conceptions, of restitution and compensation? "I believe," he ended, "that we might one day come to think of our prisons not as places of punishment—though that they must be since deprivation of liberty must always be a punishment—not only as places where offenders are trained to be better men and better citizens, which is what they seek, however imperfectly, to be now, but also as places where an offender could work out his own or her own personal redemption by paying his or her debt not only to the society whose order he has disturbed, but to the fellow members of that society whom he has wronged"

University Grants for 1957–62

On March 14 the CHANCELLOR OF THE EXCHEQUER, in announcing the recurrent grants which the Exchequer proposes to make to the universities during the next quinquennium, made the following statement

The amount of annual grant to be made available for allocation by the University Grants Committee among the universities towards their recurrent expenditure is normally settled for periods of five years at a time, and I propose to follow this practice The present settlement expires next

July, and I have been considering recommendations made to me by that committee for grants for the ensuing five years

During the five years which are now ending, rising prices and wages have affected every branch of university expenditure, and though additional grants were made available to finance the review of academic salaries which took place in 1954, universities have had to meet other increases in costs without any other assistance I am satisfied that some increase in grant is necessary to enable the universities to maintain the present level of activity

When it comes to development, I have had to take account of two conflicting considerations The first is the growing number of qualified applicants for admission to the universities, and the importance of their output of graduates at a time when the need for highly trained people in business, industry, administration, teaching, and research is increasing and when the country s future requires us to keep in the forefront of scientific and technological development The second is the financial and economic difficulties of the country, which call for general restraint

Taking these factors into account, the amounts which I propose to invite Parliament to vote for recurrent grant for the five university years beginning on Aug 1 next are as follows

1957–58	£30,600 000
1958–59	£32 300 000
1959–60	£34 350 000
1960–61	£36 750 000
1951–62	£39 500 000

These sums do not include provision for non recurrent grants towards capital expenditure, and they take no account of the recently announced improvements in academic salaries

QUESTION TIME

Propaganda Against Smoking

Dr Barnett Stross asked the Parliamentary Secretary to the Ministry of Education whether he would have made a film suitable for showing to school-children at an appropriate age and to all school leavers, which will advise them of the dangers of smoking to health —Sir Edward Boyle replied No, Sir Dr Stross I wonder why we have had such an answer ? Is it not apparent that the Ministry has issued instructions to school-teachers enabling them to read an article in the particular textbook to which I am referring, so that they can warn children ? If this is sincerely meant, why not a visual aid, in view of the importance of the disease which we are discussing ?—Sir Edward Boyle I understand that a film of this kind has been made in the United States, but I rather doubt if it would be acceptable as suitable for showing to school-children in this country Mr M Stewart Could not the Parliamentary Secretary take a slightly less negative attitude about this ? Even if there is something in it which makes this film unsuitable, cannot the Ministry consider positively what it can do on this question ?—Sir Edward Boyle I think that the approach to that topic in the Department's handbook on health education shows the lines on which we are thinking, but certainly I take note of what the hon Member has said

Parental Means Test and Scholarships

Mr Frank Beswick asked the Minister if he would take steps, by revising the present parental means test procedure, to ensure that grants and awards to university entrants are not reduced —Sir Edward Boyle replied The Government do not at present intend to introduce any amending legislation. Mr Emanuel Shinwell Does the Minister realise that there are many parents anxious to provide higher education at the universities for their children who are finding great difficulty because of the operation of the means test ?—Sir Edward Boyle Later this year my noble Friend will be examining the arrangements for assessing university awards, in consultation with representatives of the universities and the local authority associations But I cannot, I am afraid, say more this afternoon Mr Beswick Does the Minister appreciate that a means test cutting across an ability test is no less objectionable because it hits hardest at the so called middle classes or professional classes ? Would he bear in mind also that the reform asked for in these questions would find much wider acceptance than any proposal to give an income tax allowance in the matter of education ?—Sir Edward Boyle This is I agree an important subject, but I cannot go further this afternoon Lord Balniel Can the Minister say how much it would cost the taxpayer to abolish this means test ?—Sir Edward Boyle I am told that the cost of abolishing the test for all university awards would be about £3$^{1}/_{2}$ million this year in respect of United Kingdom students at universities in England and Wales

Earnings of Mental Patients

Mr N N Dodds asked the Minister of Health what progress he had made in his investigations into the payment by mental patients engaged in remunerative employment outside the institution who are required to make payments from their earnings towards their maintenance as inpatients, and if a decision had yet been reached as to whether or not the patients were, in future, to be given receipts for the money they were required to pay —Mr Dennis Vosper replied My inquiries have shown that in nearly all cases receipts are given to these patients in mental hospitals, but less frequently in mental deficiency hospitals, where the wages are often paid direct to the hospital authority on behalf of the patients and receipts are given to the employers I propose to ask hospital authorities to give receipts in future in all cases where money is paid over by the patient himself and the authority is satisfied that he is capable of understanding the nature of the document

Rampton State Institution

Dr Donald Johnson asked the Minister the total number of inmates of Rampton State Institution, and how many of these had had criminal convictions —Mr Vosper replied. 1092 Full information is not available as to how many have had criminal convictions, but 539 were dealt with as mental defectives either by the courts or by the Secretary of State whilst being detained in prison, approved schools, or elsewhere Dr Johnson Is the Minister aware of the anxiety of many people that inmates who have criminal convictions are mixed with many others who have no criminal convictions of any kind ? Will he give this matter his special attention when considering the forthcoming report ? Mr Vosper I will do that, of course, but all the inmates of Rampton have this in common, that they are of violent propensities, and it would be very difficult to separate the two categories which my hon Friend has in mind

Strontium Level in Bones of Children

Mrs Butler asked the Minister what was the latest available figure indicating the level of strontium in the bones of young children, and the amount by which this had increased since the figure for the level at November, 1955, was published in the Medical Research Council's report of June, 1956 —Mr Vosper replied The average level of strontium 90 found during 1956 in the bones of young children in the United Kingdom was 0 67 unit. The highest single level observed was 1 3 units, a level which does not differ significantly from the maximum of 1 2 units given in the report published by the Medical Research Council in June, 1956 Mrs Butler Is the Minister aware that when the original measurements were taken only four hydrogen bombs had been exploded ? It is believed that sixteen tests have now taken place Is it not the case that the measurements taken in the United States six months ago showed a very high and rising level of strontium 90, which has been described as the most dangerous poison in the world ? Will he assure the House that he will keep this matter under very close and constant review ? Mr Vosper The early part of the hon Lady's question goes somewhat beyond my responsibility There has been little or no change during the year in question and, of course, the matter is very much under review

Mr Somerville Hastings In giving the very careful consideration to this matter which I know he is giving it, will the right hon. Gentleman remember that when X rays were first used in this country no one realised that there was any danger, that it was not until there had been many deaths from carcinoma of the hands and other parts of the body that the damage was appreciated ? Will he watch this matter with very great care ? Dr Edith Summerskill In view of the increasing concern of reputable scientists about the hazards to life of these bomb explosions has the Minister taken any advice more recent than that of the Medical Research Council last June ? Mr Vosper *The original* question asked for the latest available figure, which I have given I have said that investigation is continuing and that the matter is being watched very closely

Transistor Hearing-aids

Field trials began *this month* on the transistor hearing-aid designed for the Medical Research Council.

Obituary

ESTHER LILLIE CARLING

M D Brux., L S A

The story of Esther Carling's life is also a great part of the story of the sanatorium movement in this country. She treated her first patient by the open-air method in a farmhouse in the late 'nineties. By the time that she retired in 1938 over 10,000 tuberculous patients had passed through her hands, and the sanatorium which she had founded had 180 beds, including a children's section, and a farm of 60 acres.

She was born in 1870, the daughter of William Colebrook, a some-time mayor of Reading who took a keen interest in the problems of sanitation. She studied medicine at the Royal Free Hospital and qualified in 1896. From the start she was attracted to the public-health side of medicine. Tuberculosis was one of its most urgent problems, and in the village practice which she started at Peppard in Berkshire she was soon at grips with it. Dr Hastings Gilford of Reading asked her if she could improvise open-air treatment for one of his patients with phthisis. Good results had been claimed for this therapy by Walther and others in Germany, and it appealed to Dr Carling as more likely to succeed than bottles of medicine. So she arranged to treat the patient at a neighbouring farmhouse. The patient made a good recovery, and two friends who had visited her and been fired by Dr Carling's enthusiasm for the new therapy sent her a cheque for £2000 to cover the cost of treating other patients. These were not slow to arrive, and temporary shelters were designed and built for them. That was the beginning of Kingwood Sanatorium, to which Maitland House was added a little later, with money also supplied (unasked) by the friends of another patient.

Every year Dr Carling's work grew, until in 1911 she had 70 patients under treatment. In that year John Burns paid her a surprise visit. He was then president of the Local Government Board, and much concerned about tuberculosis. He also foresaw that under the National Insurance Act a considerable sum of money would be available for a more vigorous campaign against the disease. After his visit he asked her if she would consider handing over the financial responsibility for the sanatorium to the Berks and Bucks county councils, and become its medical director.

During the 1914–18 war Dr Claude Lillingston joined the staff at Peppard Sanatorium, as it was now called, and enabled Dr Carling to add to her responsibilities there tuberculosis-dispensary work in the neighbouring counties. Of their effective, if improbable, partnership he writes:

> *It was arranged that we should take duty on alternate days. Every other day she was to absent herself in order to act as district tuberculosis officer. At that time the pick-and-shovel school of auto-inoculation by graduated labour still enjoyed a certain vogue. It appealed to the enterprising element in Dr Carling's character, and she encouraged work by her patients on the sanatorium garden. At the same time I was labouring under the conviction that rest in general, and immobilisation of a tuberculous lung in particular, was the best road to recovery. With these bees buzzing in our respective bonnets, we sailed into a happily lop-sided partnership which lasted three years. On her days on duty, Dr Carling would send her patients to work in the garden. Next day I would send them back to bed. Why did she never bash out my brains? Perhaps what saved them was her love for her ailing fellow beings—a love which left no room for wounded amour-propre.*

> *The determination and courage with which Dr Carling faced and overcame difficulties were somehow communicated to her patients, and the warmth of her personality drew the affection and loyalty of her staff. But she was much more than the head of a successful sanatorium. For many years she brought her common sense and her humanity to the work of a magistrates' court. She found time to raise a family and to receive many visitors, including Sir William Osler, at her home at Peppard. Perhaps the most important and enduring of her interests was the welfare of nurses. One of her characteristically pungent letters, which we published in 1930, led to the appointment of the Lancet Commission on Nursing, and in her last letter in 1952 she was still sharply protesting, this time against the exposure of nurses in their 'teens to the risk of infection.*

Dr Carling would have been the first to point out how much she and her sanatorium owed to her husband, Henry Carling, and to his talent for administration. Of their marriage a friend writes:

> *In many respects the Carlings were as unlike as husband and wife can possibly be. She was glowing, impulsive; he was cool, methodical. Her sense of injustice over an abstract problem such as women's suffrage, or her outraged sense of compassion over some underdog in trouble, would set her expressive brown eyes ablaze, her small frame aquiver. The same incident would start him on a carefully planned campaign of rescue of that same underdog. She drove through life as she drove her car—so as to get there, without any undue attention to mechanical details. Her motto was "Leave it to Henry," who rose to every emergency, whether she had rammed the buttocks of a cow with her car or got into some administrative cobble at the sanatorium.*

Her husband's death soon after the last war left her bereft, and her active mind chafed against the physical restrictions of old age. She died on March 18 in Ipswich.

Dr H C ELDER

C K McD. writes:

Dr Elder was one of those medical teachers who had a great influence on earlier generations of Edinburgh students and graduates. His was no parochial learning and his dissertations on tuberculosis showed a firm and discriminating grasp of the world literature and activities. His clinical ability was prodigious, and to attend him on ward rounds or clinics was sometimes exhausting, since one's concentration was kept continually on the stretch. But it was a rewarding and unique experience, often followed by great hilarity when some of his shafts of wit (and occasional darts of reproof) were recalled, for his breadth of culture allowed him to couch his technical utterances in distinctive terms, but always charmingly. He brought a grace and character to medicine which we will not easily forget.

Medicine and the Law

Procedure for Intrathecal Injections

As a result of the death of a patient following an injection of penicillin, a regional hospital board has issued directions with regard to the administration of intrathecal injections. Hospital management committees in the region have been informed that, when such injections are to be given, the quantities should be checked by another doctor or a State-registered nurse or a student nurse, as well as by the doctor who is to administer the injection; a book should be signed to record that this has been done and the quantity administered. The regional board add that this rule is not intended to imply that a nurse should check the doctor's prescription. Hospital management committees have also been asked to review critically in consultation with matrons and (where appropriate) with chief male nurses their arrangements for checking the giving of drugs, especially when given intravenously.

The Medical Defence Union has protested to the Ministry of Health, and is advising its members to oppose the introduction or observation of such rules on the ground that they are an interference with clinical freedom: the responsibility for taking appropriate precautions with regard to any medical or surgical operation belongs, it says, inalienably to the doctor carrying out the procedure. Dr Robert Forbes, secretary of the M.D.U., has pointed out[1] that, although the rule relates at the moment only to intrathecal injections, in a short time it might relate to many other forms of injection.

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[1] See Brit med J Feb 16 1957, suppl p 66

Notes and News

GASTRO-ENTEROLOGY AT THE CENTRAL MIDDLESEX

ONE of the chief centres of gastro-enterology in this country is the department at the Central Middlesex Hospital, London, N.W.10, of which Dr F. Avery Jones is the physician in charge. Since last week this department has had premises more in keeping with its importance and international reputation. In close association with the ward of 50 beds, there will now be four laboratories, an endoscopy theatre, facilities for radiological investigations, a library and conference room, and offices. To allow for this development the Nuffield Foundation has given £6500 for the building, and the Medical Research Council £6100 for equipment, and the North West Metropolitan Regional Hospital Board has provided the balance of £2200. All who attended the opening on March 15 must have felt that astonishingly good value has been obtained for the money spent. Indeed in relation to the cost of many other buildings today, it is hard to see how so small a sum has been made to buy such capacious premises so well finished and attractive.

Explaining why a surgeon, Sir Gordon Gordon-Taylor, had been invited to perform the opening ceremony, Mr Maurice Orbach, M.P., chairman of the management committee, said that the department had always depended on coöperation between physicians and surgeons, and the physicians wanted to show their recognition of the partnership. He also spoke of the partnership of the Central Middlesex with the Middlesex Hospital, and its wish to emulate Sir Gordon in maintaining links with the Commonwealth.

Sir Gordon Gordon-Taylor, who said it was fifty years since he performed his first gastro-enterostomy, described gastro-enterology as now far more than a province—"really an empire of its own." Dr Avery Jones's department had become a veritable mecca and he hoped that in the new premises the cause and cure of peptic ulcer would now be discovered. Alarmed by the present prospect that surgery might otherwise reduce this nation to "a cohort of gastric geldings," he pointed out that an army fights upon its stomach "and how are we to fight the next war if most of us have none to fight upon?"

Dr Avery Jones recalled how the department had been started when in 1937 Dr Horace Joules segregated 50 beds for gastro-enterology, and went on to speak of the strong team formed by his colleagues. Dr T. D. Kellock and Dr Richard Doll have now been joined by Dr E. N. Rowlands, working half time in the department for the Medical Research Council. Dr Margot Shiner is developing the technique of intestinal biopsy, and the team has invaluable help from Dr Frank Pygott in radiology and from Dr Allan Gray, Dr George Discombe and Dr R. A. B. Drury in pathology.

A PIONEER IN MICROBIOLOGY

Agostino Bassi, who died a hundred years ago, was a pioneer in microbiology. He discovered the pathogenic organism of silkworm disease and announced his findings to a group of professors at the University of Pavia in 1834. On that occasion Bassi revealed for the first time that the disease was caused by a vegetable parasite which could be destroyed by the use of certain chemical and physical agents. According to Bassi, contagion and epidemics were caused "exclusively by living microscopic beings which are extraordinarily prolific and capable of being communicated directly or indirectly to animals in general, man, insects, wind or water, sensible to climatic variations and the state of reception of the population among which they are transplanted." Having confirmed his assumptions with the discovery of the first agent of positive pathogenic nature, he organised for the first time a prophylaxis based on caution and sterilisation.

Dr Giovanni Arcieri has rightly commemorated the centenary of Bassi's death with a specially written brochure in English.[1] He claims that Bassi was the real founder of microbiology and not merely a forerunner of Pasteur. Unfortunately he has allowed his enthusiasm too much freedom. It is difficult to agree with his contention that Pasteur, Koch, Metchnikoff, Klebs, and other eminent scientists would not be known as such without Bassi's discovery, or that the discovery should have been acknowledged by the cinema industry. Nevertheless this is an interesting biography, for it includes accounts of Fracastoro, "the first to formulate the true epidemiological doctrine," Redi, "who first undermined the theory of spontaneous generation," Cestoni, "who discovered in 1687 the parasite of scabies," and Spallanzani, "the father of experimental biology."

STAFFING THE MENTAL HOSPITAL

THE difficulty that many provincial institutions have in attracting young doctors is all too well known, and it will somehow have to be overcome. Recording that at Moorhaven Hospital, South Devon, the newly established posts of senior registrar and junior hospital medical officer remained empty for many months, Dr Francis Pilkington, the physician-superintendent, points out that one remedy is to provide good accommodation at low rents.[1] Photographs of some of the houses provided for the hospital's physicians are reproduced in his report.

Contrary to what might be expected, the fact that Moorhaven Hospital is a training centre for psychiatrists makes the shortage of staff more rather than less acute. For this there are several reasons. Firstly, a mental hospital which undertakes training always has a proportion of inexperienced doctors on its staff; secondly, the staff are more changeable and there may be gaps between the appointments; thirdly, the trained must devote some of their time to teaching the untrained; and fourthly, the untrained need much time off for studying privately or attending courses. Hence, as Dr Pilkington says, medical establishments must be more liberal in training hospitals than in others.

JOINT CONTRACTING FOR HOSPITAL SUPPLIES

IN December, 1954, the Central Health Services Council appointed a committee, under the chairmanship of Sir Frederick Messer, to investigate various aspects of hospital supplies. The committee's interim report[2] is mainly concerned with joint contracting schemes, which have already been operating in a few cases.

The committee suggests that the existing evidence shows economic advantages in bulk buying, particularly of drugs. Joint contracting might lead on the one hand to increases in range and quality, or on the other hand to drab uniformity. The committee thinks that uniformity does not matter for supplies which do not affect the service to the patient. From joint contracting it expects an improvement of standards, but no tendency to over-estimate and (with proper planning) no storage difficulties; some hospitals might hold stocks for others that have not enough storage space.

The committee advises all hospital authorities to adopt joint contracting schemes, which yield the advantages of large-scale buying without damaging the autonomy of hospital groups. The Minister has asked hospital authorities to review their arrangements in the light of the report.

University of Cambridge

On March 9 the following degrees were conferred:

M.D.—T. M. D. Gimlette, K. E. Halnan, A. S. Herington, J. O. Robinson, J. R. Seale, H. B. L. Williams.

M.Chir.—*C. H. Kinder.

M.B.—*Chit Chan Gunn.

* By proxy.

University of London

On Feb. 27 the degree of M.D. was conferred on Derrick Rowley.

University of Leeds

The council has accepted a grant from the Nuffield Provincial Hospitals Trust of £8500 a year for two years to enable the university, through the department of adult education and extramural studies, to promote a pilot scheme of courses of study for hospital administrators. The scheme will be an experiment in the design and operation of residential courses for senior members of the staffs of hospitals and of regional hospital boards. The courses will probably last not less than four weeks, and will be staffed by a full-time director of studies, two other full-time senior staff members, and part-time lecturers. The director and his assistants will also undertake research on training for hospital administration.

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[1] Arcieri, G. P. Agostino Bassi in the History of Medical Thought. Florence: Leo S. Olschki. 1956. Pp. 46.

[1] The Eighth Annual Reports of the Physician Superintendent and of the Group Secretary for 1956. Moorhaven Hospital, Ivybridge, near Plymouth. 1957.

[2] Interim Report of the Committee on Hospital Supplies. H.M. Stationery Office. 19[illegible]. Pp. 16. 9d.

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THE story of Esther Carling's life is also a great part of the story of the sanatorium movement in this country She treated her first patient by the open-air method in a farmhouse in the late 'nineties By the time that she retired in 1938 over 10,000 tuberculous patients had passed through her hands, and the sanatorium which she had founded had 180 beds, including a children's section, and a farm of 50 acres

She was born in 1870, the daughter of William Colebrook, a some-time mayor of Reading who took a keen interest in the problems of sanitation She studied medicine at the Royal Free Hospital and qualified in 1896 From the start she was attracted to the public-health side of medicine Tuberculosis was one of its most urgent problems, and in the village practice which she started at Peppard in Berkshire she was soon at grips with it Dr Hastings Gilford of Reading asked her if she could improvise open-air treatment for one of his patients with phthisis Good results had been claimed for this therapy by Walther and others in Germany, and it appealed to Dr Carling as more likely to succeed than bottles of medicine So she arranged to treat the patient at a neighbouring farmhouse The patient made a good recovery, and two friends who had visited her and been fired by Dr Carling's enthusiasm for the new therapy sent her a cheque for £2000 to cover the cost of treating other patients These were not slow to arrive, and temporary shelters were designed and built for them That was the beginning of Kingwood Sanatorium, to which Maitland House was added a little later, with money also supplied (unasked) by the friends of another patient

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[1] See *Brit med J* Feb 16 1957, suppl p 66

A CONCENTRATE OF HUMAN ANTIHÆMOPHILIC FACTOR

ITS USE IN SIX CASES OF HÆMOPHILIA

R A KEKWICK
D Sc Lond
READER IN CHEMICAL BIOPHYSICS
IN THE UNIVERSITY OF LONDON

P WOLF
M B Manc
MEDICAL RESEARCH COUNCIL GRANTEE

From the Lister Institute of Preventive Medicine, London

UP to 1954, the only effectual method of treating hæmorrhage in hæmophiliacs was the transfusion of fresh blood, fresh plasma, or plasma separated from fresh blood and quickly frozen and stored at –20°C These materials still have to be used in most cases, despite the danger that, because of the low antihæmophilic potency of human blood or plasma, however recently drawn, the circulation may be overloaded before hæmostasis can be achieved

The preparation of antihæmophilic factor of very high potency from animal blood by Macfarlane et al (1954) was a substantial advance However, since such products consist of heterologous protein, they may provoke an antigenic response in the recipient—a dangerous state that precludes the repeated administration often essential in the management of hæmophiliacs

It has long been evident that a potent preparation of human antihæmophilic factor would be very valuable, but the instability and the relatively low level of the activity in human plasma are disadvantages which have been difficult to overcome In this paper we describe the preparation of a concentrate of human antihæmophilic factor, and its use in the treatment of six cases of hæmophilia, in some of which fairly radical surgery was undertaken

Attempts to separate the antihæmophilic factor from other constituents of plasma have until recently been restricted by the lack of an adequate method for the assay of antihæmophilic activity The development of the thromboplastin-generation test by Macfarlane and his colleagues (Biggs and Douglas 1953, Biggs et al 1953, 1955), in providing a reliable in-vitro assay, made purification studies possible, and protein fractions possessing a very high antihæmophilic potency were separated, by salting out techniques, from the plasmas of several domestic animals by the Oxford workers (Bidwell 1955) We have preferred to use an assay, devised by one of us (Wolf 1956), depending on the change induced in the prothrombin conversion ratio of an artificial hæmophilic substrate by the addition of substances having antihæmophilic activity This method was used to measure the activity of protein fractions separated from normal human plasma, and to study the effect of preparations of antihæmophilic factor on the activity in the plasma of hæmophilic patients undergoing treatment

The antihæmophilic activity of citrated human plasma is reported to decrease rapidly unless the plasma is expeditiously separated from the formed elements of blood and then frozen to –20°C We found that the antihæmophilic activity fell by 10–20% in sixteen hours, and by 50% after four days when trisodium citrate plasma was stored at 2–4°C Consequently speed of operation is a major consideration, at least in the early stages of fractionation, if reasonable yields of antihæmophilic factor are to be obtained

During the serial fractionation of normal human plasma proteins, using water-miscible solvents as precipitants, the first crude fraction removed contains most of the fibrinogen and some of the antihæmophilic factor (Kekwick and Mackay 1954) In the present experiments the conditions were modified to produce a maximal precipitation of the antihæmophilic factor in the fibrinogen fraction , the potency of this crude fraction was increased by simple ancillary treatment The experiments leading to the definition of these conditions will be described elsewhere

Method of Preparation

Blood taken into 100 ml of 3% (*w*/*v*) trisodium citrate up to a total volume of 540 ml is cooled as soon as possible to 2–4°C and centrifuged for an hour at 1500 r p m at 0 0 ± 0 2°C preferably within three hours of the bleeding The plasma is siphoned from the layer of red cells, centrifuged as before for thirty minutes, and poured cautiously from the slight residue of platelets and cells

To the pooled twice centrifuged plasma is added an equal volume of distilled water at 0°C The diluted plasma is cooled to –0 5°C, and 11 vol % of cold ethyl ether is added slowly with adequate stirring, the temperature of the mixture being maintained between –0 5°C and –1 0°C during this addition When all the ether has been added, the mixture is allowed to equilibrate overnight (sixteen hours) at 0°C

The clear supernatant solution is siphoned off as far as possible, and the residual precipitate and supernatant fluid are stirred to a uniform sludge, which is then centrifuged for thirty minutes at 1500 r p m at 0 0 ± 0 2°C The packed precipitate is suspended in 30% of the plasma volume of the following solution previously cooled to 0°C sodium chloride 4 25 g and trisodium citrate 1 85 g made up to 1 0 litre with distilled water and 80 ml of ethyl ether added—and centrifuged as before for thirty minutes The washed precipitate is suspended in 50% of the plasma volume of distilled water at 0 0–0 5°C and centrifuged as before for forty-five minutes

The twice washed precipitate is then dissolved in sufficient of the following solution at 25°C to give a total volume equal to 10% of the initial plasma volume sodium chloride 17 0 g and trisodium citrate 7 4 g made up to 1 0 litre with distilled water

The precipitate, when gently agitated, dissolves completely in ten to fifteen minutes, giving a colourless and slightly opalescent solution This is frozen immediately in 100 ml quantities to –20°C in the final containers for freeze drying, and the small samples required for assay are similarly treated if the assays cannot be made at once

The equipment and solutions used were all sterile, and the preparative procedures were carried out under aseptic conditions (see Kekwick and Mackay 1954), consequently it was unnecessary to sterilise the final solution by filtration before freeze-drying Nevertheless the product passed the sterility tests appropriate for substances used for parenteral injection in man

Some Characteristics of Material used for Clinical Test

On the basis of in-vitro assay, the antihæmophilic activity in the final product has consistently been not less than 85% of the starting material, and the potency in terms of activity per mg of protein has been 20–25 times that of fresh plasma

The product is dissolved in a volume such that the resulting solution has approximately ten times the activity of normal plasma , the total protein content is about 2 2 g per 100 ml and the viscosity so low as to present no problem during administration Such solutions can be held frozen at –20°C or dried from the frozen state with negligible loss in activity Freeze-dried material has been stored at room-temperature for six months with only slight loss in activity, and it redissolves completely in twenty to twenty five minutes when the appropriate volume of distilled water is added at room-temperature

Like most of the preparations of antihæmophilic factor so far prepared in quantities adequate for clinical use, this human preparation contains a large proportion of fibrinogen , about 70% of the total protein appears in the clot formed when thrombin is added to a suitably diluted solution The separation of fibrinogen from antihæmophilic factor by a procedure ensuring a good recovery of each is a problem of some complexity The preparation was therefore tested clinically in its relatively

University of Sheffield

Dr I B Sneddon has been appointed part-time lecturer in dermatology

University of Edinburgh

Sir Howard Florey, F R S, will be among those who will receive the honorary degree of LL D at a ceremony to be held on July 5

Royal College of Surgeons of England

At a meeting of the council on March 14, with Sir Harry Platt, the president, in the chair, Mr A L d'Abreu and Mr E G Muir were admitted to the court of examiners

The following Sir Arthur Sims Commonwealth travelling professors were appointed for 1958 Prof M L Rosenheim to visit Australia and New Zealand and Prof R M Janes (Toronto) to visit parts of Africa

The Hallett prize was awarded to Dr S K Nau (Agra), and the Macloghlin scholarship to F R Jackaman (Queen Elizabeth's School, Barnet)

Scottish Regional Hospital Boards

The Secretary of State for Scotland has reappointed the chairmen of the five regional hospital boards for a further three years

Biochemical Society

The annual general meeting of this society will be held in the Department of Biochemistry, University College, London, W C 1, on Thursday, March 28, at 10 A M

Christian Medical Fellowship

At a meeting of this fellowship to be held on Wednesday, March 27, at 8 15 P M, at the Royal Empire Society, Northumberland Avenue, London, W C 2, Mr Harold Dodd will speak on the Doctor as a Person

International Cancer Congress

This congress will be held in London from July 6 to 12, 1958, under the presidency of Sir Stanford Cade Further particulars may be had from the office of the congress, 45, Lincoln's Inn Fields, W C 2

Diet and Coronary Disease

Prof John Yudkin will speak on this subject after the annual general meeting of the Nutrition Panel of the Food Group of the Society of Chemical Industry, which is to be held at 14, Belgrave Square, London, S W 1, at 6 15 P M, on Wednesday, April 10

Study Course on W H O

The World Federation of United Nations Associations will hold a study course on the World Health Organisation in Geneva from May 6 to 15, simultaneously with the World Health Assembly Further information may be had from the federation, 1, avenue de la Paix, Geneva, Switzerland

Dental Implant Society

This society is holding a meeting at 1, Wimpole Street, London, W 1, on Wednesday, May 15, at 7 P M, when Prof Talmage Read will speak on subperiosteal dental implants, and Mr Boris Trainin, L D S, will show a colour film illustrating surgical and laboratory techniques for a new type of implant Non-members who wish to attend should write to the hon secretary of the society, 109, Harley Street, W 1

International Nutrition Congress

A congress is to be held, under the auspices of the International Union of Nutritional Sciences, in Paris from July 26 to Aug 1 Further information about the congress may be had from Prof E Terroine, Centre National de Coordination des Études et Recherches sur la Nutrition et l'Alimentation 71, Boulevard Pereire, Paris, 17e, and about the union from the secretary-general Mr Leslie J Harris, D SC, Dunn Nutritional Laboratory, Milton Road, Cambridge

Dr Ronald Woolmer director of the department of anæsthetics in the Royal College of Surgeons of England is visiting medical research centres and departments of anæsthetics in the United States and Canada with a grant from the Rockefeller Foundation

Births, Marriages, and Deaths

DEATHS

CAMPBELL.—On March 13 at Corbett House, Droitwich Malcolm Campbell M A, M B, F R C S I, aged 81

CANN.—On March 11 at Ashford Hospital Middlesex, Lawrence William Cann M B, D P H

Diary of the Week

MARCH 24 TO 30

Monday, 25th

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, W C 2
5 P M Prof Arnold Sorsby Cycloplegics and Mydriatics
MANCHESTER MEDICAL SOCIETY
9 P M (Medical School, University of Manchester) *General Practice* Mr Kenneth Harrison Surgical Treatment of Deafness

Tuesday, 26th

ROYAL COLLEGE OF SURGEONS OF ENGLAND
5 P M Mr Robert Cox Management of Dysphagia Due to Malignant Disease of the Thoracic and Abdominal Œsophagus (Hunterian lecture)
ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W 1
8 P M *Medicine* Dr Thomas Hunt, Mr Rodney Smith Dr Martin Bodian Diagnostic Features of Some Pancreatic Diseases
ST GEORGE'S HOSPITAL MEDICAL SCHOOL, S W 1
5 30 P M Prof J Z Young, F R S Efferent Optic Nerve Fibres and the Crossing of the Visual Pathways—Some Speculations on the Mechanism of Vision (Thomas Young lecture)
INSTITUTE OF DERMATOLOGY, Lisle Street, W C 2
5 30 P M Dr D G James Sarcoidosis
ROYAL STATISTICAL SOCIETY
5 30 P M (Westminster Medical School, Horseferry Road, S W 1) *Medical* Mr P D Oldham Arterial Blood-pressure in Population Samples
UNIVERSITY OF LIVERPOOL
5 15 P M (Medical School) Prof B Uvnäs (Stockholm) Sympathetic Vasodilator System

Wednesday, 27th

HARVEIAN SOCIETY OF LONDON, 11, Chandos Street, W 1
8 15 P M Sir Russell Brain, P R C P Some *Disorders of the* Cerebral Circulation (Harveian lecture)
INSTITUTE OF DERMATOLOGY
5 30 P M Dr Henry Haber Specific and Foreign Body Granulomas
ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE, 28, Portland Place, W 1
3 30 P M Dr E Ann Mower White Opportunities for Health Teaching in Schools
BIRMINGHAM MEDICAL SOCIETY, 154, Great Charles Street, Birmingham, 3
8 P M *Psychiatry* Dr May Pearce *Matrimonial Causes*

Thursday, 28th

ROYAL COLLEGE OF SURGEONS OF ENGLAND
5 P M Mr D Greer Walker *Facial Development* (Arris and Gale lecture)
UNIVERSITY OF LONDON
5 30 P M (St Thomas's Hospital Medical School S E 1) Professor Börje Uvnäs Mechanism of Histamine Release
INSTITUTE OF DERMATOLOGY
5 30 P M Dr Brian Russell Tuberculosis and Sarcoidosis of the Skin
CHADWICK LECTURE
5 30 P M (Royal Society of Health, 90, Buckingham Palace Road S W 1) Sir Harold Whittingham *Problems of Hygiene in Civil Aviation*
WEST OF ENGLAND CHILD HEALTH GROUP
8 30 P M (Children's Hospital, Bristol) Dr Reginald Lightwood Home Care of Sick Children
LIVERPOOL MEDICAL INSTITUTION 114, Mount Pleasant, Liverpool 3
8 P M Dr D Noble Chamberlain, Dr Charles McKendrick Dr W P O'Regan Management of Coronary Thrombosis

Friday, 29th

ROYAL SOCIETY OF MEDICINE
2 30 P M *Experimental Medicine and Therapeutics* Prof J Lederberg, Prof M Westergaard Prof B D Davis Dr R D Hotchkiss Review of the Ciba Foundation Symposium on Mechanisms of Development of Drug *Resistance in Micro-organisms*

Saturday, 30th

MEDICAL SOCIETY FOR THE STUDY OF VENEREAL DISEASES
2 15 P M (Royal Hospital Sheffield) Mr St Elmo Hall Problems of a Mixed Community

Appointments

CAIRNS J G, M B Glasg, D P H deputy M O H, Kingston upon Hull
CONN NANCY K, M D bacteriologist (S H M O) Edinburgh northern group of hospitals based on Northern General Hospital
GARLAND, ANDERSON M D Lond, M R C P D I H deputy divisional M O L C C and deputy M O H Wandsworth
HOLLIER J M H, M B Durh, D OBST, D P H deputy M O H Rotherham
[illegible] BRYAN M B Durh assistant M O H, Kingston upon Hull

Liverpool Regional Hospital Board

BAMBER G W M D Camb, F R C P consultant dermatologist Booth Hospital and Liverpool Radium Institute
BARRY A C M B Glasg D P M assistant psychiatrist [illegible] Mental Hospital
COSGROVE M J M B, D P M assistant psychiatrist, Deva Hospital
FAIRHURST RICHARD M B, B D S Lpool, F D S R C S consultant dental surgeon Birkenhead group of hospitals

fourth day circulatory failure again threatened. On the fifth day 200 ml. of concentrate (batch EF 29) was transfused (table, episode 1a). During the following two days 200 ml. of EF 29 and 1 pint of whole blood were given daily. Since there was no further evidence of bleeding, therapy was discontinued after the second day, and the patient was then making a satisfactory convalescence.

A week later, the patient having recovered, an experiment was made to compare the change in A H F level produced by the concentrate and by fresh plasma (table, episodes 1b and c). The A H F level was determined before and after administering 200 ml. of concentrate EF 29, and next day similar measurements were made before and after the transfusion of 420 ml. of fresh frozen plasma.

Plasma volume was estimated on the basis of 76 ml. of whole blood per kg. body-weight. Hæmatocrit during episode of bleeding was 25%, and during convalescence 40%. In estimating the plasma volume these values were multiplied by 0·90 to correct for trapped plasma and for non-uniform distribution of erythrocytes in the vascular system (Mollison 1956).

Episode 2

Oct. 31.—Admitted from outpatient department, which he attended for follow-up, having been found pale and with symptoms of a recent acute blood-loss. Hæmoglobin 45%, hæmatocrit 28%. Stool contained blood. Given 300 ml. concentrate EF 39 immediately, followed by 2 pints of fresh blood. There was no transfusion reaction.

Nov. 1.—Given 900 ml. of fresh frozen plasma. In the next four days given a total of 1980 ml. of fresh frozen plasma. Melæna stools disappeared, and transfusion therapy discontinued. Patient made an uninterrupted recovery.

Episode 3

Nov. 21.—Dental extraction. Hæmoglobin before operation 60%, hæmatocrit 34%. Before operation 300 ml. of concentrate LF 43 given intravenously (table, episode 3). No transfusion reaction. General anæsthetic given through intratracheal tube. Two teeth and twenty-one roots were extracted; one root had a medium-sized dental cyst at its base, which was curetted. Dried human thrombin was introduced into the cavities, which were then lightly packed with sterile alginate wool, and dental splints were then applied. No undue hæmorrhage occurred at the operation.

Nov. 22.—No hæmorrhage or oozing, but 200 ml. of concentrate LF 45 was given to maintain A H F level. Patient complained of pains in back during transfusion.

Nov. 23.—No hæmorrhage or oozing; 200 ml. of concentrate EF 45 given, and patient again had pain in back during transfusion.

Nov. 24.—No hæmorrhage or oozing. Further 200 ml. of concentrate FF 45 given. Pains in back and chest during transfusion relieved by intravenous pethidine.

Nov. 25.—No hæmorrhage or oozing during day, but oozing from one socket started in evening. During night 600 ml. of fresh frozen plasma arrested the oozing.

Nov. 26.—Given 600 ml. of fresh frozen plasma. Dental splints removed; no hæmorrhage or oozing.

Nov. 27 and 28.—No hæmorrhage or oozing but given 600 ml. of fresh frozen plasma each day.

Nov. 29.—Packed red cells from two pints of blood given. No hæmorrhage or oozing. End of transfusion therapy.

Dec. 4.—Patient discharged from hospital.

Case 2.—A man aged 41, weight 8 st. Previous history of moderately severe hæmophilia, with joints showing chronic hæmorrhagic joint disease. Family history of hæmophilia. Admitted to hospital for extraction of tooth.

Immediately before the extraction he was given a transfusion of concentrate FF 20 (180 ml.), and the tooth was extracted under gas and oxygen. After the extraction the cavity was packed with 'Oxycel' gauze and a dental splint was applied, which was removed four days later. No bleeding whatsoever took place immediately after the extraction or subsequently up to the patient's discharge seven days later.

Laboratory findings.—Total blood-volume (determined by Dr. J. H. Crookston using chromium-labelled red cells) 3650 ml. Plasma-volume 2200 ml. Hæmatocrit 42·5%. Hæmoglobin 12·5 g. per 100 ml. For other data see table.

Case 3.—A man aged 40, weight 8 st. History of severe classical hæmophilia, with multiple and severe chronic hæmorrhagic joint disease. Admitted to hospital with spontaneous hæmorrhages into both wrists, muscles of both forearms, and both knee-joints, occurring over previous three weeks. On admission there were signs of active bleeding into the knee-joints, the pain from which had prevented him from sleeping on the previous three nights.

He was given a transfusion of concentrates LF 29 and LF 31, total volume 300 ml. After an hour the pain in both knee-joints had subsided, and the same night he slept well without sedatives. His subsequent recovery was uneventful, and he was discharged from hospital after seven days.

Laboratory findings.—Blood-volume measured as in case 2 with chromium-labelled red cells. Hæmatocrit 43·5%. Plasma-volume 2250 ml. (See table.)

Case 4.—A boy, aged 6, weight 42 lb. Family history of hæmophilia. Admitted to hospital with injury to left leg; hæmorrhage into ankle and knee, calf muscle, and muscle of thigh.

After a transfusion of 100 ml. of concentrate EF 31 he had a severe rigor lasting twenty minutes. Some of the same batch of concentrate had been administered to case 3 without untoward effect. A test for pyrogen was negative. Considerable clinical improvement followed the transfusion, and there was no further hæmorrhage.

Laboratory findings.—Plasma-volume 1070 ml. estimated from weight and hæmatocrit. Hæmatocrit 28%. Hæmoglobin 61%.

Case 5.—A man, aged 28, weight 11 st. 6 lb. Previous history of mild hæmophilia, but no family history. Various episodes of bleeding from 1947 onwards. In July, 1956, while abroad, he had a purulent discharge from his rectum. An incision to drain the abscess led to a persistent discharge of pus into his rectum. He was flown to England and admitted to hospital for radical treatment.

Oct. 11, 1956.—Given 300 ml. concentrate FF 37. Under general anæsthesia external drainage of the abscess was established. A broad tract was cut to the abscess by removing about 2½ inches of buttock tissue and part of the superficial anal sphincter. There was no undue hæmorrhage during the operation (performed by Mr. G. A. Jemson). No hæmorrhage or further treatment until Oct. 15.

Oct. 15.—Given 200 ml. of concentrate EF 37. Wound then inspected by surgeon and repacked. During the night hæmorrhage occurred and hæmoglobin dropped from 77 to 45% and hæmatocrit fell from 41 to 23%.

Oct. 16 to 22.—Patient received successively 3 pints of stored blood (Oct. 16), 2 pints of fresh blood (Oct. 17), 2 pints of fresh blood (Oct. 19), 2½ pints of stored blood (Oct. 21), and 2 pints of stored blood (Oct. 22). After this no further hæmorrhage took place, and the patient made an uninterrupted recovery, being discharged on Dec. 20.

Laboratory findings.—Plasma-volume estimated from weight and hæmatocrit. Hæmatocrit before first injection on Oct. 11 was 44% (uncorrected) and before second injection on Oct. 15 41% (uncorrected).

Case 6.—A boy, aged 18, weight 10 st. Moderately severe hæmophilia. No family history of hæmophilia. He had been admitted twenty-four times for episodes of bleeding, including hæmorrhages into joints causing limited movement of right knee and left elbow.

On Oct. 25, 1956, he was admitted for extraction of the first molar in the right lower jaw, which had an underlying abscess. Local anæsthetic. 280 ml. of concentrate EF 41 was given immediately before the extraction and was followed by an urticarial rash. Difficult extraction, dental splint applied. Oozing from socket for an hour after extraction, and slight oozing during night. No further bleeding until evening of Oct. 28. On Oct. 29 100 ml. of IF 31 and 100 ml. of IF 39 were given, and dental splint was removed. Another urticarial rash developed, with pruritus. Rash was arrested with 50 mg. of promethazine. Bleeding was arrested for twenty-four hours.

After this, intermittent oozing from socket recurred and was controlled by digital pressure and the topical application of thrombin. On Nov. 8 the socket was packed. On Nov. 11 a substantial hæmorrhage took place. On Nov. 12 500 ml. of fresh whole blood followed by 500 ml. of fresh plasma was given. No further hæmorrhage. The patient was discharged on Nov. 18. The plasma-volume (estimated with Evans blue) was 2350 ml.

Discussion

A potent preparation of antihæmophilic factor would obviously be of great value, in the management of hæmophiliacs, for preventing the development of

ASSAYS OF ANTIHÆMOPHILIC FACTOR (A H F) DURING TREATMENT OF HÆMOPHILIA

Case no	Preparation and vol given (ml)		Patient's plasma vol (litre)	A H F (units per ml)		Increase in total circulating A H F (10^3 units)	Total A H F given (10^3 units)	A H F accounted for (% of A H F given)
				Before	After			
1 Episode 1a	EF 29	200	4 63	5 6	6 3	4 5	11 2	40
„ 1b	EF 29	200	3 82	2 1	4 3	9 3	11 2	83
„ 1c	Frozen plasma	420	3 82	1 6	2 9	6 1	7 3	84
„ 2	EF 39	300	4 48	5 9	9 7	20 0	47 7	[illegible]
„ 3	EF 43	300	4 15	4 4	11 0	30 7	32 7	91
2	FP 20	180	2 26	0 62	6 0	13 2	20 5	65
3	EF 29 EF 31	300	2 25	0 07 After 23 hr 0 8 „ 48 hr 0 7	2 6	6 5	25 5	25
4	EF 31	100	1 09	0 56 After 39 hr 0 0	4 9	4 8	9 3	5[illegible]
5 Episode a	EF 37	300	3 35	4 0 After 2 hr 7 9 „ 24 hr 5 0	8 8	18 7	36 9	51
„ b	EF 37	200	3 48	2 2 After 24 hr 3 9	7 9	21 4	24 3	88
6 Episode a	FF 41	280	2 35	4 1	8 4	12 5	34 2	37
b	EF 31 EF 39	100 100	2 35	5 9	12 7	18 5	27 8	67

Unless indicated otherwise samples for A H F assay were taken 10 *minutes after the injection was completed*
Mean A H F level of fresh normal citrate plasma 12 5 units (range 8–18) per ml

impure state although, with a purification factor of only 20–25 fold, it was realised that 100 ml of solution would be needed *to* produce an effect equivalent *to 1000* ml of fresh citrate plasma

Clinical Results

The preparation of human antihæmophilic factor has been used with eminently satisfactory results in treating six cases including single and multiple tooth extractions, hæmorrhages into the stomach and joints, and radical surgery of the buttock and rectum

Some details of the cases are given below The effects of transfusion on the level of antihæmophilic factor (A H F) in the patients' plasma are summarised in the accompanying table The mean amount of A H F found in fresh normal *human citrate plasma is 12 5* units per ml (range 8–18) (Wolf 1956)

In the first episode of case 1, presented to us as an emergency, a preparation of A H F having only about half the activity of later ones was infused The initial A H F level in the patient's plasma was as high as 30–40% of normal probably as a result of the massive whole-blood and fresh plasma transfusions which had been given, but despite this he was bleeding into the stomach The bleeding stopped after the infusion of A H F concentrate Of the total A H F units given initially, 40% was found in the blood ten minutes after the completion of the transfusion, a large proportion presumably having been used up in producing hæmostasis *In later tests*, when the patient was convalescent and not bleeding, 83% and 84% of the A H F units injected as concentrate and as fresh plasma respectively, were demonstrable in the blood At this time the patient's plasma-A H F had fallen to a level commonly associated with moderately severe hæmophilia (about 15–20% of normal)

In the second episode of bleeding, about four months later, nearly 60% of the A H F injected was immediately used up

The third episode, when twenty-one roots and two teeth were extracted from his mouth, occurred after experience had been accumulated with other cases described below A preoperative transfusion of 300 ml of concentrate brought the plasma-A H F to 11 0 units per ml, which is close to the mean normal level, and no undue bleeding took place during the operation Next day, after the transfusion of 200 ml of concentrate, the plasma-A H F was 8 4 units per ml Similar daily transfusions were given for two more days to maintain the plasma activity at this level Unfortunately samples taken to establish this point were spoilt by the failure of a –20°C refrigerator From the case report it can be seen *that the treatment* was highly effective The transfusion of one of the batches of A H F concentrate (E F 45) was associated with pain in the back *No* reason was found for this reaction, and subsequent recovery was complete and uneventful, the patient leaving hospital two weeks after the operation

The results in cases 2–4 *corroborate* the efficacy of the concentrate They tend also to confirm the finding that more of the injected antihæmophilic factor disappears in a patient bleeding at the time of transfusion than in a patient treated prophylactically before surgery is undertaken

Major surgery involving highly vascularised tissue was undertaken in case 5, a mild hæmophiliac The transfusions of concentrate were given to cover only the period of the operation and that immediately following subsequent treatment being with whole blood For four *days after the operation there was no* bleeding, but, about twelve hours after the dressings had been removed and the wound repacked, a *ruptured* vessel gave rise to hæmorrhage which necessitated the transfusion of whole blood, subsequent therapy was with stored whole blood to maintain the level of hæmoglobin

In case 6 the healing of the gum after the tooth was extracted was delayed by an infection of the socket, presumably arising from the original abscess Satisfactory hæmostasis was undoubtedly established in the early postoperative period The patient developed urticaria after each injection of the *concentrate*, the idiosyncrasy was confined to this patient, for the three batches concerned *had been administered* to other patients without this complication

Case-reports

Case 1 —A *man, aged 37*, weight 12 st 5 lb Mild hæmophilia, with no serious hæmorrhagic episode since adolescence and no permanent joint lesions Family history of hæmophilia

Episode 1

June, 1956 —Admitted to hospital with severe hæmatemesis Initial treatment consisted of transfusion of whole blood and 2 pints of plasma (frozen when fresh) *daily* After five days the daily 2 pint plasma transfusions were discontinued because the bleeding had stopped and circulatory failure threatened Four days later there were further signs of bleeding *melæna* stools, and a progressive fall in hæmoglobin Treatment 1–2 pints of whole blood and 2 pints of frozen plasma daily *On* the fourth day circulatory failure again threatened On the fifth day 200 ml of concentrate (batch EF 29) was transfused (table, episode 1a) During the following two days 200 ml of EF 29 and 1 pint of whole blood were given daily Since there was no further evidence of bleeding, therapy was discontinued after the second day, and the patient was then making a satisfactory convalescence

A week later, the patient having recovered, an experiment was made to compare the change in A H F level produced by the concentrate and by fresh plasma (table, episodes 1b and c) The A H F level was determined before and after administering 200 ml of concentrate EF 29, and next day similar measurements were made before and after the transfusion of 420 ml of fresh frozen plasma

Plasma volume was estimated on the basis of 76 ml of whole blood per kg body-weight Hæmatocrit during episode of bleeding was 25%, and during convalescence 40% In estimating the plasma volume these values were multiplied by 0 90 to correct for trapped plasma and for non uniform distribution of erythrocytes in the vascular system (Mollison 1956)

Episode 2

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Episode 3

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Nov 24—No hæmorrhage or oozing Further 200 ml of concentrate EF 45 given Pains in back and chest during transfusion relieved by intravenous pethidine

Nov 25—No hæmorrhage or oozing during day, but oozing from one socket started in evening During night 600 ml of fresh frozen plasma arrested the oozing

Nov 26—Given 600 ml of fresh frozen plasma Dental splints removed, no hæmorrhage or oozing

Nov 27 and 28—No hæmorrhage or oozing but given 600 ml of fresh frozen plasma each day

Nov 29—Packed red cells from two pints of blood given No hæmorrhage or oozing End of transfusion therapy

Dec 4—Patient discharged from hospital

Case 2—A man, aged 41 weight 8 st Previous history of moderately severe hæmophilia, with joints showing chronic hæmorrhagic joint disease Family history of hæmophilia Admitted to hospital for extraction of tooth

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Laboratory findings—Total blood volume (determined by Dr J H Crookston using chromium labelled red cells) 3650 ml Plasma volume 2260 ml Hæmatocrit 42 5% Hæmoglobin 12 5 g per 100 ml For other data see table

Case 3—A man aged 49 weight 8 st History of severe classical hæmophilia, with multiple and severe chronic hæmorrhagic joint disease Admitted to hospital with spontaneous hæmorrhages into both wrists, muscles of both forearms, and both knee joints, occurring over previous three weeks On admission there were signs of active bleeding into the knee-joints, the pain from which had prevented him from sleeping on the previous three nights

He was given a transfusion of concentrates EF 29 and EF 31, total volume 300 ml After an hour the pain in both knee joints had subsided, and the same night he slept well without sedatives His subsequent recovery was uneventful, and he was discharged from hospital after seven days

Laboratory findings—Blood volume measured as in case 2 with chromium-labelled red cells Hæmatocrit 43 5% Plasma volume 2250 ml (See table)

Case 4—A boy, aged 6, weight 42 lb Family history of hæmophilia Admitted to hospital with injury to left leg hæmorrhage into ankle and knee, calf muscle, and muscle of thigh

After a transfusion of 100 ml of concentrate EF 31 he had a severe rigor lasting twenty minutes Some of the same batch of concentrate had been administered to case 3 without untoward effect A test for pyrogen was negative Considerable clinical improvement followed the transfusion, and there was no further hæmorrhage

Laboratory findings—Plasma volume 1070 ml estimated from weight and hæmatocrit Hæmatocrit 28% Hæmoglobin 61%

Case 5—A man, aged 28, weight 11 st 6 lb Previous history of mild hæmophilia, but no family history Various episodes of bleeding from 1947 onwards In July, 1956, while abroad, he had a purulent discharge from his rectum An incision to drain the abscess led to a persistent discharge of pus into his rectum He was flown to England and admitted to hospital for radical treatment

Oct 11, 1956—Given 300 ml concentrate EF 37 Under general anæsthesia external drainage of the abscess was established A broad tract was cut to the abscess by removing about $2^1/_2$ inches of buttock tissue and part of the superficial anal sphincter There was no undue hæmorrhage during the operation (performed by Mr G A Jemson) No hæmorrhage or further treatment until Oct 15

Oct 15—Given 200 ml of concentrate EF 37 Wound then inspected by surgeon and repacked During the night hæmorrhage occurred and hæmoglobin dropped from 77 to 45% and hæmatocrit fell from 41 to 23%

Oct 16 to 22—Patient received successively 3 pints of stored blood (Oct 16), 2 pints of fresh blood (Oct 17), 2 pints of fresh blood (Oct 19), $2^1/_2$ pints of stored blood (Oct 21), and 2 pints of stored blood (Oct 22) After this no further hæmorrhage took place, and the patient made an uninterrupted recovery, being discharged on Dec 20

Laboratory findings—Plasma volume estimated from weight and hæmatocrit Hæmatocrit before first injection on Oct 11 was 44% (uncorrected) and before second injection on Oct 15 41% (uncorrected)

Case 6—A boy, aged 18, weight 10 st Moderately severe hæmophilia No family history of hæmophilia He had been admitted twenty-four times for episodes of bleeding including hæmorrhages into joints causing limited movement of right knee and left elbow

On Oct 25, 1956, he was admitted for extraction of the first molar in the right lower jaw, which had an underlying abscess Local anæsthetic 280 ml of concentrate FF 41 was given immediately before the extraction and was followed by an urticarial rash Difficult extraction, dental splint applied Oozing from socket for an hour after extraction, and slight oozing during night No further bleeding until evening of Oct 28 On Oct 29 100 ml of EF 31 and 100 ml of FF 39 were given and dental splint was removed Another urticarial rash developed with pruritus Rash was arrested with 50 mg of promethazine Bleeding was arrested for twenty-four hours

After this, intermittent oozing from socket recurred and was controlled by digital pressure and the topical application of thrombin On Nov 8 the socket was packed On Nov 11 a substantial hæmorrhage took place On Nov 12 500 ml of fresh whole blood followed by 500 ml of fresh plasma was given No further hæmorrhage The patient was discharged on Nov 18 The plasma volume (estimated with Evans blue) was 2350 ml

Discussion

A potent preparation of antihæmophilic factor would obviously be of great value, in the management of hæmophiliacs, for preventing the development of permanent joint lesions by the early treatment of young patients; for treatment in spontaneous hæmorrhagic episodes where its prompt administration would reduce the period of disability; and for reducing the risks of major surgery.

Our preliminary tests indicate that the concentrate of human antihæmophilic factor we have prepared may have considerable clinical value. The provision of a concentrate of which 100 ml. is equivalent in activity to 1000 ml. of fresh plasma and which can be made available in a few minutes by the reconstitution of stable freeze-dried material is a substantial advance in the treatment of hæmophilia. We hope to achieve a further 10-fold purification so that the activity of 1000 ml. of fresh plasma could be injected in a volume of 10 ml. To do this without substantial loss in the total activity of the starting material is at present difficult. Meanwhile the potency of the present preparation is high enough to obviate the dangers of circulatory overloading during extensive treatment.

The antihæmophilic activity of some animal plasmas is considerably greater than that of human plasma and consequently animal plasmas might be considered more advantageous for the production of potent antihæmophilic preparations. The purification factor for Bidwell's (1955) bovine preparations is as high as 100–400, compared with 20–25 for our human material. However, the hazard of allergic reactions following the repeated administration of heterologous proteins is a serious restriction in the use of these substances—a restriction which does not apply to material from human plasma. In the literature there are reports of hæmophiliacs becoming resistant to therapy after repeated treatment over long periods even with human plasma and products derived from it; the significance of many of these reports is difficult to assess in the light of our present knowledge of the clotting mechanism. It is worth emphasising in view of this that in case 1, in which repeated infusions of our preparation were given over a period of five months, no resistance to therapy appeared, and laboratory tests at the end of the period did not detect any evidence whatsoever of the development of even traces of a specific circulating anticoagulant.

The problems arising in the fractionation of animal plasma-proteins are simplified because the technique can be directed to the recovery of a single constituent without attempting to conserve the others. In the large-scale fractionation of so valuable a commodity as human plasma such an approach is indefensible; the isolation of any particular constituent must be fitted into an overall scheme of fractionation which ensures a reasonable yield of as many as possible of the other constituents, and the freedom of design is inevitably restricted. Moreover, in view of the relatively low concentration of antihæmophilic factor in human plasma, any fractionation stage which does not lead to a recovery of at least 90% of the initial activity is not acceptable.

The advantages which arise from the use of water-miscible solvents for the fractionation of aqueous protein mixtures are well known, but the enhanced flexibility introduced by the additional variable of solvent concentration and the ease with which an aseptic fractionation technique can be operated are worth emphasis. Even so it is necessary to proceed cautiously, for many proteins may be altered by the presence of solvents, even at low temperatures (0 to −10°C), and so lose their characteristic biological properties. The antihæmophilic factor in our experience is especially susceptible to such influences, though whether the loss in activity which can occur is due to some intrinsic instability or to a secondary modifying effect induced by the action of solvents on other plasma constituents is at present difficult to decide. However, after aseptic isolation and drying from the frozen state the human antihæmophilic preparation loses relatively little activity over several months. In this respect it has some advantage over the animal preparations, which need sterilising after separation. Thus Bidwell (1955) could not use Seitz or Berkefeld filtration for sterilising bovine preparations because of the loss in activity on the filters and had to sterilise by ultraviolet light. Variable and high losses were also encountered when bovine preparations were freeze-dried; this has not happened with our human preparations.

In order to obtain a measure of the problem involved in the management of hæmophiliacs, let it be assumed on the basis of our limited clinical experience that a single crisis in a hæmophiliac might on the average be countered by the injection of an amount of antihæmophilic factor equivalent to that in 2 litres of fresh human plasma. This in its turn represents the plasma derived from about seven blood donations. The total number of hæmophiliacs in the country is probably close to 2000; consequently to provide each with a single injection each year would require 14,000 blood donations. This figure represents about 2% of the current total annual donations. The processing of the plasma from 14,000 blood donations by the procedure found necessary to ensure a maximum recovery of antihæmophilic factor presents a formidable problem, whose solution is not yet clear. These difficulties arise mostly because of the speed with which the processing must be done. We hope that further work may reduce them, but exploratory experiments have already indicated that neither the use of non-wettable surfaces in collecting the blood nor the use of edetic acid ('Sequestrene') in anticoagulant mixtures reduces the rate at which antihæmophilic activity is lost in drawn blood or in plasma.

Summary

A preliminary clinical trial in six cases of hæmophilia indicates that the intravenous injection of a concentrate of human antihæmophilic factor arrests internal and external bleeding, and permits surgical intervention without abnormal bleeding.

The concentrate of human antihæmophilic factor, which contains not less than 85% of the initial activity, is separated aseptically from fresh citrated normal human plasma; the purification factor is 20–25-fold per gramme of protein.

Solutions of the concentrate may be dried from the frozen state without significant loss in activity, and the activity of the freeze-dried material is retained for several months with only slight loss.

The dangers of circulatory overloading during treatment are largely avoided with this preparation, since 100 ml. is equivalent in antihæmophilic activity to 1000 ml. of fresh normal citrate plasma.

Our thanks are due to Dr J. V. Dacie and Dr J. H. Crookston of the Postgraduate Medical School of London, Dr C. Holman of Lewisham Hospital, and Dr K. E. Saunders of Dulwich Hospital for their coöperation and assistance during the clinical trials.

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STAPHYLOCOCCAL BRONCHOPNEUMONIA IN DEBILITATED HOSPITAL PATIENTS

A REPORT OF FOURTEEN FATAL CASES

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IN May, 1955, a patient in a male medical ward died unexpectedly while convalescing from coronary thrombosis, and at necropsy death was found to be due to bronchopneumonia. Although a heavy growth of a coagulase-positive *Staphylococcus aureus* was obtained from the lungs of this patient, the histological appearance of the lung lesions differed greatly from those seen in the lungs of patients dying of a staphylococcal pneumonia. Instead of multiple foci of necrosis scattered throughout the lungs, progressing in places to frank abscesses, most of the affected bronchioles and alveolar ducts were intact but surrounded by extensive areas of hæmorrhagic œdema. There was, in fact, a striking resemblance between the microscopical appearance of these lesions and those found in patients with epidemic influenza dying of fulminating secondary staphylococcal bronchopneumonia.

During the following eighteen months the lungs were examined both histologically and bacteriologically in sixty cases in which a pulmonary infection was suspected at necropsy, and thirteen further examples of this type of staphylococcal bronchopneumonia were found; in only four of these thirteen patients had any kind of acute infection of the lungs been suspected during life.

Illustrative Case-reports

Case 1.—A man, aged 76, was admitted to hospital on May 1, 1955, with an attack of severe precordial pain of 24 hours' duration and was treated as a case of coronary thrombosis. Next day, although he was relieved of his pain, his temperature had risen to 102°F, and crepitations were heard at the bases of both lungs. Crystalline penicillin 500,000 I.U. was given 6-hourly together with streptomycin 1 g. 12-hourly, but he became semiconscious and, after repeated attacks of cyanosis of varying degree and duration, he died on the fifth day after admission to hospital.

Necropsy findings.—There was bilateral lower lobe bronchopneumonia with thin pus in the bronchi and bronchioles. Histological examination of the lungs showed acute bronchopneumonia of the lower lobes, with many bronchioles and alveoli full of pus cells and clumps of gram-positive cocci, the surrounding alveoli being filled with red cells and fibrin or œdema fluid. Areas of fibrosis were found in the lateral wall of the left ventricle; the coronary arteries showed severe atheroma but there was no evidence of thrombosis. A heavy growth of *Staph. aureus* was obtained from the lungs.

Case 2.—A man, aged 63, was admitted to hospital on June 9, 1955, with acute retention of urine. His bladder was decompressed, and he was given sulphadimidine 1 g. 8-hourly. 2 days later a transvesical prostatectomy was done, and his immediate postoperative progress was satisfactory. On the 2nd day after operation his temperature rose to 100°F and he was given crystalline penicillin 500,000 I.U. 8-hourly together with streptomycin 0.5 g. 12-hourly for a suspected infection of the urinary tract. A week later his temperature was still raised when he collapsed suddenly with profuse hæmaturia, his blood pressure falling from 220/150 to 100/60 mm. Hg. In spite of the transfusion of three pints of blood he remained in a state of shock and died suddenly 9 days later, immediately after an attack of hyperpnœa. The blood-urea level, 3 days before death, was 331 mg. per 100 ml.

Necropsy findings.—There were areas of recent bronchopneumonia in both lower lobes, and the bronchi contained pale brown pus. Histological examination of the lungs showed areas of bronchopneumonia in the lower lobes, almost amounting in places to abscesses, in which there were many clumps of gram-positive cocci; the alveoli adjacent to these areas were filled with red cells and fibrin. The prostatic cavity appeared to be healing satisfactorily, but the boundary zone of both kidneys was blurred, suggesting distal tubule nephrosis, which was confirmed microscopically. A heavy growth of *Staph. aureus* was obtained from the lungs.

Case 3.—A woman, aged 68, was admitted to hospital on May 14, 1955, with 7 days' history of occipital headache, giddiness, vomiting, and increasing drowsiness. A cerebral tumour or virus encephalitis was diagnosed, and a 10-day course of chloramphenicol 0.5 g. 6-hourly was begun 2 days later. On June 1 a urinary infection was suspected and treated with streptomycin 1 g. 12-hourly and erythromycin 0.2 g. 6-hourly. A non-productive cough began on June 29 and was followed 4 days later by the expectoration of copious amounts of yellow sputum and by cyanosis and coldness of the extremities; the patient died the same day. Radiography shortly before death showed a bronchial carcinoma.

Necropsy findings.—A carcinoma was found arising from a bronchus leading to the left upper lobe, and metastases were present in the hilar lymph-nodes. There was a quantity of pus in the bronchial tree, and areas of bronchopneumonia in both lower lobes contained large clumps of gram-positive cocci. The alveoli surrounding these areas of bronchopneumonia contained many red cells and much fibrin; there were recent thrombi in several pulmonary veins. A metastasis was also found in the right cerebellar hemisphere. *Staph. aureus* was isolated in pure culture from the lungs.

Case 14.—On Nov. 28, 1956, a man fell from his bicycle and was admitted to hospital semiconscious. He had a severe lacerated scalp wound, but no fracture of the skull or abnormality of the central nervous system was discovered. His blood-pressure was 120/80 mm. Hg. He was given sulphadimidine 1 g. 6-hourly, crystalline penicillin 500,000 I.U. 8-hourly, and streptomycin 1 g. 12-hourly. For the next 6 days he remained semiconscious, by the end of which time he had developed flaccid paresis of his right arm. 2 days later his temperature, pulse-rate, and respiration-rate started to rise, and diminished air entry at the base of the right lung was found. Next day he collapsed suddenly with severe cyanosis, dyspnœa, and coldness of the extremities, temperature 105°F, pulse-rate 160, respirations 40 a minute, and blood-pressure 60/? mm. Hg. He died an hour later.

Necropsy findings.—The trachea and main bronchi contained pus in which were large numbers of cocci (fig. 1), and

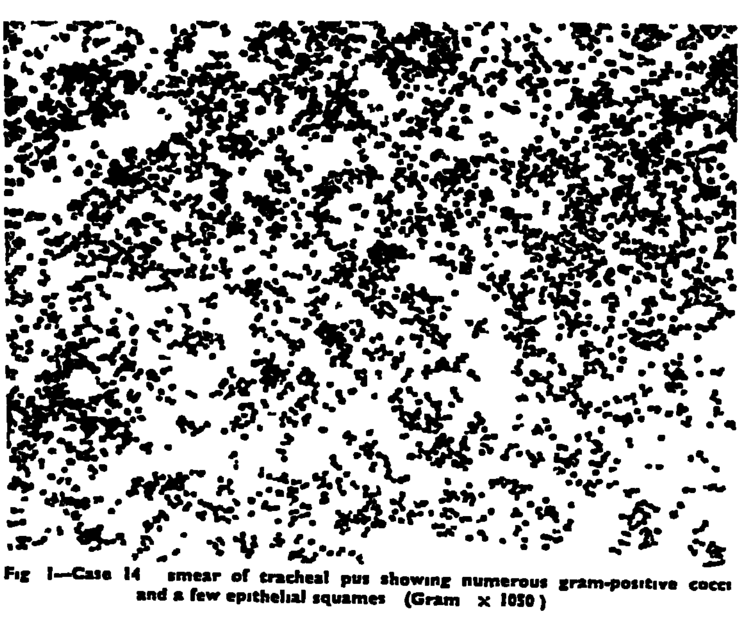

Fig. 1—Case 14: smear of tracheal pus showing numerous gram-positive cocci and a few epithelial squames. (Gram × 1050.)

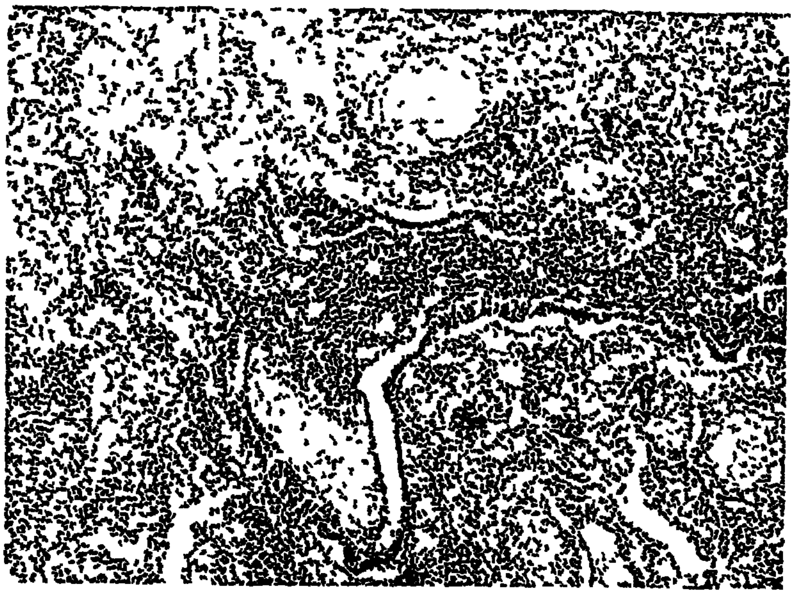

Fig 2—Case 14 section of lower lobe showing bronchiole filled with pus and surrounded by alveoli filled with red cells (Hæmatoxylin and eosin × 65)

areas of bronchopneumonia were seen in both lower lobes The bronchioles were filled with pus and clumps of gram-positive cocci Surrounding alveoli contained hæmorrhagic œdema fluid (fig 2) A heavy growth of *Staph aureus* was obtained from all lobes of the lungs

Post-mortem Findings

Histology

The microscopical appearance of the pneumonic areas in all these cases was similar There were many polymorphs and clumps of gram-positive cocci in the affected bronchioles and alveolar ducts, and the surrounding alveoli were filled with hæmorrhagic œdema fluid (fig 2) In three cases thrombi were found in some of the pulmonary vessels but never in sufficient numbers to explain the hæmorrhagic nature of the œdema fluid More advanced lesions were seen in two cases, an empyema thoracis in case 9, and numerous small abscesses just visible to the naked eye in case 13

Bacteriology

Cultures were obtained from the lungs at necropsy by the simple method of thrusting swabs blindly into the parenchyma of each lobe through small incisions made with a sterile scalpel in the overlying pleura, which had first been carefully sterilised with a branding iron The swabs were plated out on 10% horse blood digest broth-agar and "chocolate" agar, after which the swabs themselves were planted in tubes of Robertson's cooked meat medium All cultures were incubated aerobically overnight, and the amount of growth of the various organisms isolated was roughly estimated and recorded

A heavy growth of *Staph aureus* was obtained from the lungs of eleven of these patients but, in view of the large numbers of gram-positive cocci also seen in sections from the lungs of the three other patients, the poorer growth of staphylococci obtained from them was probably due to the crude method of sampling

Common intestinal organisms were also grown from the lungs of all but two patients The presence of these organisms was thought to imply the agonal inhalation of stomach contents, and they were not regarded as playing any active part in the genesis of the type of bronchopneumonia described here This view is supported by the isolation of intestinal organisms from the lungs at necropsy of forty three out of forty-seven other patients suspected of having a pulmonary infection In eighteen of these there was no histological evidence of any acute infection of the lungs, and only a very low grade bronchopneumonia with no hæmorrhagic œdema was found in the twenty five other patients

The sensitivity of the strains of *Staph aureus* isolated from the lungs of thirteen of the fourteen patients to antibiotics was determined by a simple filter paper strip

BACTERIOLOGICAL FINDINGS

Case no	Sex	Age (yr)	Primary condition	Post mortem lung cultures				Sensitivity to antibiotics of *Staph aureus* isolated from lungs					Chemotherapy in hospital
				Staph aureus	Non hæmolytic streptococci	Coliform bacilli	Proteus	Penicillin	Streptomycin	Chlortetracycline	Chloramphenicol	Erythromycin	
1	M	76	Coronary thrombosis	+ + +	+	–	–	R	R	R	R	S	Penicillin, streptomycin
2	M	63	Transvesical prostatectomy	+ + +	(+)	(+)	–	R	R	R	S	S	Sulphadimidine, penicillin, streptomycin
3	F	68	Bronchial carcinoma	+ + +	–	–	–	R	R	R	R	S	Chloramphenicol, streptomycin, erythromycin
4	M	83	? Chronic tetanus	+	+	+ + +	–	R	R	R	S	S	Penicillin streptomycin chlortetracycline
5	M	65	Bronchial carcinoma	+	–	–	+	R	R	R	S	S	Penicillin streptomycin, chlortetracycline
6	F	21	General peritonitis	+ +	+ +	–	–	R	R	R	S	S	Penicillin, streptomycin, tetracycline
7	F	63	Bacterial endocarditis	+ + +	–	–	–	R	R	R	S	S	Penicillin, tetracycline
8	M	52	Perforated gastric ulcer	+	–	–	+	Not tested					Penicillin
9	M	28	Carbon monoxide poisoning	+ +	+	–	–	R	R	R	S	S	Penicillin
10	M	66	Agranulocytosis	+ +	+	–	–	R	R	S	S	S	Penicillin streptomycin, chlortetracycline, oxytetracycline
11	F	53	Acute leukæmia	+ +	–	+ + +	–	R	R	R	S	S	Penicillin, streptomycin chlortetracycline
12	M	67	Coronary thrombosis	+ + +	–	+ + +	+	R	R	S	S	S	Penicillin streptomycin chlortetracycline
13	M	54	Mediastinal tumour	+ + +	+	+	–	R	R	S	S	S & R	Penicillin, streptomycin
14	M	52	Head injury	+ + +	(+)	(+)	–	R	R	R	S	S	Sulphadimidine, penicillin, streptomycin

+ + + heavy growth + + moderate growth + light growth (+), < 10 colonies R resistant S sensitive
S & R sensitive and resistant strains isolated

diffusion plate technique in routine use in this laboratory All strains tested were resistant to penicillin and streptomycin, and all but two to chlortetracycline (aureomycin), conversely, all but two were sensitive to chloramphenicol and all but one to erythromycin These observations are summarised in the accompanying table, which also records the antibiotics received by each patient while in hospital

Discussion

Staphylococcal pneumonia in adults usually runs a severe and protracted clinical course accompanied by much destruction of lung tissue (Chickering and Park 1919) A notable exception to this is the fulminating and often fatal staphylococcal bronchopneumonia that occurs in some cases of epidemic influenza In this type of staphylococcal infection there is little destruction of lung tissue, and death is usually regarded as being due to an overwhelming toxæmia arising from the rapid colonisation of the already infected lungs by inhaled staphylococci

Although there was no evidence that any of the present fourteen patients with staphylococcal bronchopneumonia had influenza in the first place, the histological appearance of the lung lesions was indistinguishable from that described in patients with influenza dying of a secondary staphylococcal infection of the lungs (Wollenman and Finland 1943)

This similarity between the type of staphylococcal pneumonia occurring as a fatal complication in influenza and that found at necropsy in this otherwise unrelated group of hospital inpatients could most easily be explained if there was a predisposing factor common to them all A review of the various conditions for which these patients were being treated in hospital, coupled with a consideration of the changes in the lungs in influenza, suggests that the most likely common factor was the existence of pulmonary œdema at the time of the initial infection of the lungs with staphylococci The presence of a quantity of serous fluid in the alveoli, whether inflammatory or mechanical in origin, would provide, from the outset, favourable conditions for the rapid and widespread colonisation of the lungs by staphylococci and for the subsequent production of toxæmia which are the salient features of this type of pneumonia

The pattern of resistance to penicillin, streptomycin, and chlortetracycline shown by the strains of *Staph aureus* isolated from the lungs of these patients leaves little room for doubt that they were all "hospital" staphylococci (see table) The rapidly increasing pollution of the hospital environment with antibiotic resistant organisms of all kinds (*Lancet* 1956) suggests that this type of staphylococcal pneumonia is likely to become one of the most serious of the cross infection hazards that the debilitated patient has to face in hospital

If this is the correct interpretation of the origin and significance of this condition, a careful reassessment should be made of the value and dangers of oral sprays, the passage of tubes through the nasopharynx, and the use of drugs which depress the cough reflex in the immediate postoperative period or in other conditions in which pulmonary œdema is likely to be present

Early diagnosis is also important because at present the only treatment likely to be successful is the giving of full dosage of the appropriate antibiotic before the number of staphylococci in the lungs has become large enough to produce fatal toxæmia However, in view of the fact that in only four of the present fourteen cases was any kind of acute infection of the lungs suspected during life, early diagnosis is likely to remain infrequent until the possibility of a staphylococcal bronchopneumonia is regularly considered whenever there is unexpected deterioration in the general condition of a debilitated patient

Summary

Staphylococcal bronchopneumonia, similar in type to that which occurs as a fatal complication in influenza, has been found in 14 out of 61 hospital patients suspected of bronchopneumonia at necropsy

In only 4 of these 14 patients had a lung infection been diagnosed during life, none had influenza

These cases are regarded as hospital cross infections Pulmonary œdema may be a predisposing factor

We wish to thank the consultant staff of the United Cambridge Hospitals for access to their case records, Dr. A. M. Barrett for his coöperation in the examination of the necropsy material, and Mr S T Haslam, A I M L T, for his valuable technical assistance

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SODIUM BALANCE STUDIED WITH ^{22}Na AND AN EXTERNAL COUNTER FOR MEASURING WHOLE-BODY RADIOACTIVITY

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In a previous communication (Martin and Walker 1957) we reported results obtained by measuring, with the long-life isotope ^{22}Na, day-to-day variations in exchangeable body-sodium The results were compared with those obtained by ordinary sodium-balance studies and the two methods were found to be in excellent agreement

We report here results of direct serial measurements of total body-^{22}Na with external counters and compare them with those obtained by the two other methods just mentioned The body counter used was a modification of that described by Bradley et al (1957) using four matching Geiger-Müller tubes (20th Century Electronics type G26) partly shielded with lead, mounted on a trolley, and connected in parallel to a probe unit and thence to a conventional scaler The trolley was low enough to fit under the ordinary hospital bed so that measurements could be made on bed patients

Material and Methods

Serial determinations of total body-^{22}Na, specific activity, and total exchangeable body sodium were made

TABLE I—CLINICAL DATA AND DURATION OF STUDY

Case no	Age (yr)	Sex	Diagnosis	Duration of study (days)	Clinical information
1	23	F	Adrenal virilism	20	Adrenal stimulation and suppression tests
2	47	F	Nephrotic œdema	26	Treatment of œdema with ion-exchange resin and mercurial diuretics
3	43	F	Carcinoma of breast with secondary deposits	20	Operation section of pituitary stalk (Mr F L Davis)
4	63	F	Adrenogenital syndrome	21	Adrenal stimulation and suppression tests
5	46	M	Duodenal ulcer	15	
6	63	M	Carcinoma of prostate with bone deposits	13	Operation section of pituitary stalk (Mr F L Davis)

TABLE II—TOTAL BODY RADIOACTIVITY OVER 5 HOURS FOLLOWING ADMINISTRATION OF TRACER DOSE

Time	Counting rate (per min)
10 52 A M (dose 25 µC ^{22}Na given)	
10 55 A M	10,122
11 00 A M	9787
11 07 A M	10 218
11 22 A M	10,253
11 52 A M	10,393
12 52 P M	10 497
1 52 P M	10,460
2 52 P M	10,484
3 52 P M	10,374
Mean (after 60 min) S D	10,410 ±83
Coefficient of variation	±0 8%

daily on 6 persons (2 men and 4 women), whose clinical details are summarised in table I

2 patients were on a measured intake of food and fluids The intakes of electrolytes and nitrogen were measured by analysis of duplicate diets or, in the case of patients not on a full diet, by analysis of samples of foodstuffs from the same batch as that received by the patients 1 patient was on the standard hospital low salt diet containing about 22 m eq of sodium daily The remaining 3 patients were on the ordinary ward diet

Urine was collected in twenty-four-hour periods starting at 6 A M Spot urine samples for determination of radioactivity were collected in a fasting state at the end of each twenty-four-hour-collection period Fæces were collected over several days, according to the particular study Samples of blood were taken in the fasting state at about 9 A M daily or on alternate days Patients were weighed at a fixed hour each day on a balance accurate to ±50 g

The chemical methods used for analysis of diets, fæces, and urine have been described previously (Martin and Walker 1957)

Radiosodium (^{22}Na) was given orally in doses of about 25 µC The external counter was calibrated for each patient by equating the initial counting-rate, once a constant level had been reached, with the dose given estimated in a liquid sample scintillation counter ('Ekco' type N 550) All counts were corrected for counter dead time Calibration was done in this way in each case because the calibration figure varies from person to person according to the person's size and shape The radioactivity of spot urine, twenty-four-hour urine, and plasma was measured in a liquid sample scintillation counter The radioactivity of each sample was compared with an aliquot of the administered dose, at least 10,000 counts being recorded on each sample By subtracting the amount of tracer excreted in urine and fæces in each twenty four hour period from the amount previously present in the body, the total body ^{22}Na was calculated for each day At the same time the total body ^{22}Na was measured daily with the external counter Serial determinations of total exchangeable body sodium were then obtained independently by measuring specific activity by the dilution principle (Edelman et al 1952) Since corrections for protein content of plasma and the Gibbs-Donnan effect are opposite in direction they were ignored

TABLE III—RESULTS OF VARIATION IN POSITION ON TOTAL BODY COUNTS

Observation no	Counting rate (per min)
1	10 581
2	10,552
3	10,609
4	10 587
5	10,540
6	10,610
7	10 578
8	10 496
9	10,551
10	10 586
11	10 583
12	10 684
13	10,495
14	10,628
15	10 725
Mean	10 587
Coefficient of variation	±0 56%

Results

Performance of Whole body Counter

In the 6 patients, who were of average size and body build, the dose used gave an initial counting rate of 10,000–12,000 counts a minute The background count in the ordinary hospital wards away from artificial radioactive sources was about 700 counts a minute

During the first hour repeated measurements showed minor fluctuations of ±5% Thereafter a steady state was reached (table II)

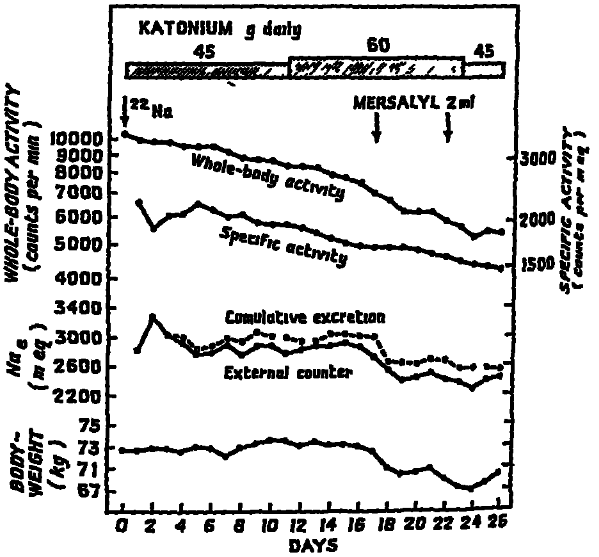

Fig 1—Case 2 (woman aged 47 with nephrotic œdema) total body counts, specific activities, exchangeable body sodium (by both cumulative-excretion and external-counter techniques), and body-weight

All measurements of whole body activity were made in duplicate or triplicate and based on at least 30,000–40,000 counts As was expected from the total counts recorded, the coefficient of variation was 0 5–0 6%

To assess the effect of variation in position of patient and counter, duplicate counts were obtained with the counter placed exactly underneath the patient with one set of counters level with his shoulders The patient was next asked to walk round the bed and lie down again in about the same position as before No attempt was made to adjust either patient or counter In 70 such observations the coefficient of variation was 0 7%, giving an overall error of 0 9% for individual measurements of total body-^{22}Na (table III)

Serial Measurements of Na$_e$

In 5 of the 6 patients the apparent calculated Na$_e$ increased with time over the first 72 hours after ingestion of the dose, and the figure obtained on the third day was accepted as the initial equilibration value The 6th patient had gross œdema due to the nephrotic syndrome, and equilibrium of distribution was not reached until the fifth day after administration of the tracer dose (fig 1) In this case specific activity over the first four days was calculated from spot urine samples Thereafter and in all subsequent cases plasma was used in preference to urine

From the known standard errors of the individual measurements involved, including flame photometer errors and counting errors, the measurement of Na_e was calculated to have a standard error of 2·4%. The accuracy of the Na_e determination based on measurements of total body-^{22}Na with the external counter are well illustrated in fig. 1. The loss of sodium in response to therapy was due to the decrease of œdema fluid accurately reflected in the change in body-weight. The daily Na_e measurements followed the alterations in body-weight so closely that the curves were almost parallel.

Comparison of Isotope Methods

Serial measurements of Na_e by the cumulative-excretion method and by the external-counter technique in the 6 patients are shown and compared in table IV and figs. 1–3. Although the agreement between the two methods is within their confidence limits, the cumulative-excretion method showed a greater gain or smaller loss than did the external-counter method in 5 of the 6 cases studied. This is further reflected in the tracer's calculated biological half-life shown in table V.

Comparison of Isotope and Metabolic-balance Data

The isotope and metabolic-balance data in 2 patients (cases 1 and 3) are compared in table IV and figs. 2 and 3. In both cases the agreement is within the confidence limit of the isotope techniques of ±50 m.eq.

Discussion

The patients formed a heterogeneous group chosen because of anticipated changes in sodium metabolism. Since we were mainly interested in comparing two methods of study under the widest range of conditions, this heterogeneity was an advantage.

The measurement of exchangeable sodium was found to have an error of 2·4%, in keeping with the degree of reproducibility shown by Veall et al. (1955) using eight instead of four Geiger-Müller tubes. These workers, however, suggested that repeated measurements made on the same subject showed a considerably wider variation —in most cases about 5% or more. Such wide variations may be explained by changes in the specific activities of urine used for calculating Na_e, because their paired measurements were made at 11 A.M. and 2 P.M., not in a fasting state, and with the midday meal intervening. The variability suggested by Veall et al. (1955) cannot therefore be accepted as being a true indication of the confidence limit of the method. To exclude errors due to fluctuations in specific activity of urine, specific activity of fasting plasma was used in the present investigation for calculating total exchangeable body-sodium except where otherwise stated.

The slow increase in Na_e over the first three to five days observed on previous occasions (Burch et al. 1952, Miller et al. 1954, Veall et al. 1955, Martin and Walker

TABLE IV—COMPARISON OF ISOTOPE AND METABOLIC-BALANCE DATA

Case no.	Duration of comparison of balances (days)	Na_e (m.eq.) Initial	Na_e (m.eq.) Final	Change in Na_e (m.eq.)	Metabolic balance change (m.eq.)	Difference (m.eq.)
1	17	1930* 1970	1950* 2160	− 20* −190	−57	37* 133
2	23	3040* 3040	2420* 2540	−620* −500		120
3	17	2020* 2020	1970* 1930	− 50* − 90	−55	5* 35
4	18	3050* 3080	3060* 3130	− 10* − 50		40
5	11	3250* 3250	3200* 3210	− 50* − 40		10
6	11	2880* 2920	3220* 3480	−340* −560 Unmeasured losses		220

* External counter data.

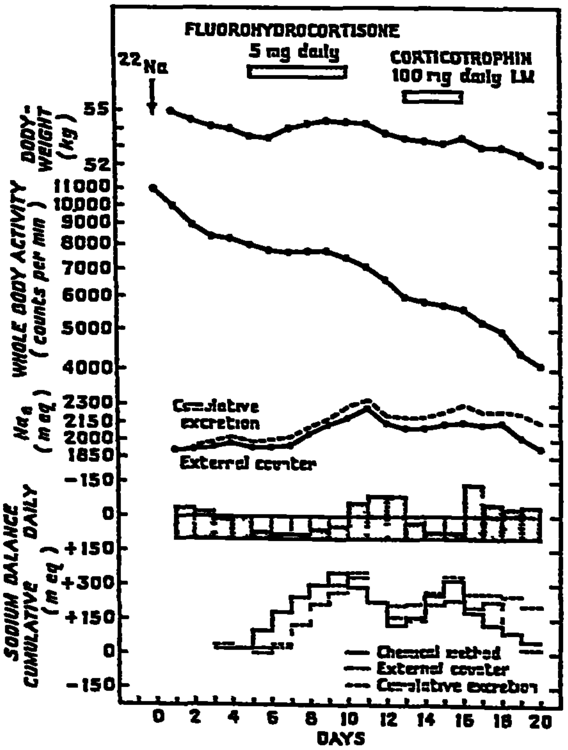

Fig. 2—Case 1 (woman aged 22 with virilism and adrenocortical hyperfunction): comparison of cumulative-excretion, external-counter, and metabolic-balance results.

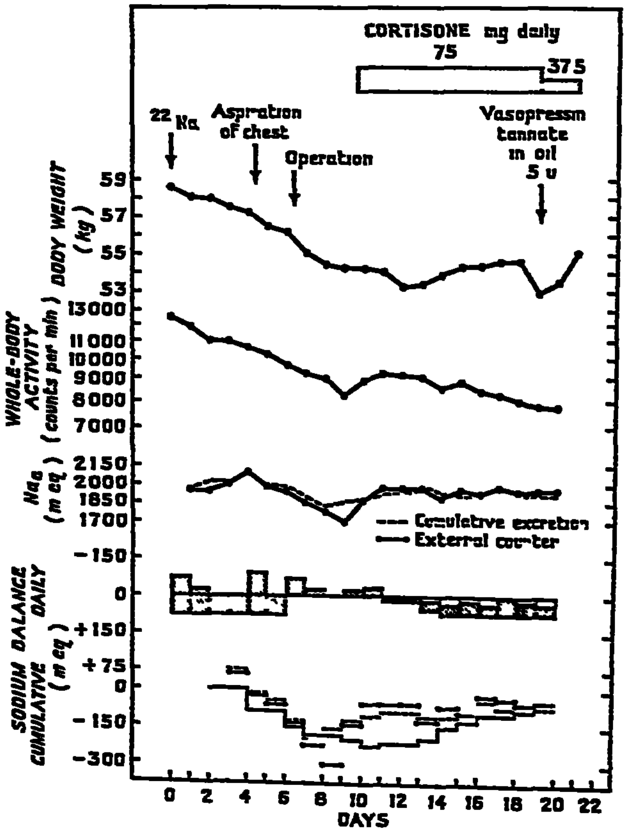

Fig. 3—Case 3 (woman aged 43 with carcinoma of breast treated by section of pituitary stalk): comparison of cumulative-excretion, external-counter, and metabolic-balance results.

TABLE V—BIOLOGICAL HALF-LIFE BASED ON URINARY AND FÆCAL SODIUM LOSS COMPARED WITH THAT OBTAINED DIRECTLY BY EXTERNAL COUNTING

Case no	Biological half-life (days)		Difference
	Cum ^{22}Na method	Ext counter	
1	18	17	1
2	30	28	2
3	25	25	0
4	35	31	4
5	25	20	5
6	34 Unmeasured losses	22	12

1957) was confirmed and is consistent with the view that some of the ^{22}Na is associated with a separate and more slowly exchanging compartment of body-sodium, which is believed to be sodium in bone (Miller et al 1954)

In considering the comparisons between the two isotope methods certain orders of variability must be borne in mind The accuracy of individual measurements of Na$_e$ is ±2 5%, hence the differences observed were still within the confidence limits of the two methods Case 6 must be excluded from the comparison because unmeasured losses rendered the cumulative excretion data invalid In 4 of the remaining 5 comparisons the cumulative-excretion balance indicated a greater gain or a smaller loss than did the external counter method In the 5th patient (case 3) the counter recorded a smaller loss, but the discrepancy was small The difference in the two methods is also expressed in the calculated biological half life, which was in 5 cases out of 6 shorter when estimated directly on total body-^{22}Na It is tempting to suggest that the differences observed indicate loss of sodium in sweat This would amount to a daily loss of 1–8 m eq of sodium in sweat Case 1, who lost the greatest amount of sodium in sweat, was allowed to leave the hospital for afternoons and may well have perspired at times in addition to insensible loss Such figures as are suggested for loss of sodium in sweat are compatible with the finding of Freyberg and Grant (1937) that people lightly clad and doing light laboratory work without visible sweating lost 2 6–9 1 m eq of sodium a day

The metabolic balance data obtained in 2 patients compare favourably with those obtained by the isotope techniques and confirm our previous findings (Martin and Walker 1957) The reproducibility and accuracy of the metabolic-balance method cannot be ascertained experimentally but are probably less than those of the isotope techniques, probably because of the variability of diet rather than unmeasured losses, although the latter may also contribute Unmeasured losses will, however, affect the cumulative excretion method, as in case 6, and are only eliminated by the external counter technique Whole-body activity after section of the pituitary stalk decreased in case 3 (fig 3) and, to a lesser extent, in case 6 out of proportion to the amount of tracer lost from the body When cortisone was given, whole-body activity increased again, the increment being outside the limits of experimental error Since neither patient had received further radioactive material, the behaviour of the external counter suggests redistribution of sodium within the body, with a lower counting-rate Sodium is known to be redistributed in acute adrenal insufficiency, and the observation made may perhaps be explained by a movement of sodium from the extracellular space into bone, an area of low sensitivity of the external counter, with self-absorption playing an additional rôle Further work is obviously required to investigate this point and to clarify the relationship of distribution of sodium reflected by the tracer and recorded by the external counter

The results obtained support the view that, with ^{22}Na, the external counter affords a method of unprecedented ease and accuracy for studying sodium metabolism Neither dietitian, diet kitchen, nor metabolic unit is required, and, once the isotope has equilibrated with the stable sodium available for exchange, results of daily gains or losses can be made known within a matter of minutes to the physician or surgeon in charge of a case The reproducibility and accuracy of the method can be assessed Cumulative errors are eliminated by directly measuring the total body content of tracer In fact the metabolism of sodium can be studied in outpatients because the complete collection of all excreta is unnecessary and the loss of sodium in sweat need not be considered

The long half life (2 6 years) of ^{22}Na may give rise to some misgivings about the radiation dose received by the patients, but the biological half life has been shown to depend on the intake of sodium as well as on the state of the sodium balance (Martin and Walker 1957), and excretion of the isotope can readily be hastened by a high intake of sodium There is no evidence of permanent retention (Veall et al 1955) The radiation hazard involved with the doses used is small, being only about half that of the permissible body burden of ^{22}Na

Summary

The total body-^{22}Na was measured directly with external Geiger Müller counters, and, by measuring specific activity, exchangeable body sodium was calculated for each day

The standard error for whole-body radioactivity was ±0 9% and for total exchangeable body sodium ±2 4%

Daily comparisons were made with the cumulative excretion method in which total body-^{22}Na was calculated by subtracting successive twenty-four hour losses, and with chemical metabolic-balance data The methods were found to be in good agreement Although the differences were small they could be explained by loss of sodium in sweat

The external counter offers a simple and accurate method for studying sodium metabolism without either collecting excreta or measuring dietary intake

We wish to thank Dr J D N Nabarro for much advice and encouragement, and permission to study cases under his care, Dr Arthur Willcox for permission to study case 5, Prof J E Roberts for facilities in the Barnato Joel Institute, and the Leverhulme Trustees for a scholarship granted to one of us (M M M)

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"Contemporary physicists have abandoned some old intuitions about the nature of the physical world They have, for instance, renounced the concept of the permanence of objects in the submicroscopic realm a particle does not exist unless it can be localized, if it cannot be located at a particular position, it loses its title as an object and must be described in other terms Now by an extremely curious coincidence it is found that a very young baby acts with regard to objects rather like a physicist The baby believes in an object as long as he can localize it, and ceases to believe in it when he can no longer do so The great difference between the baby and the physicist, of course, is that the baby's faculty of localization is less powerful"—JEAN PIAGET, *Sci Amer* March, 1957, p 46

COMPARISON OF GASTRIC EMPTYING AND SECRETION IN MEN AND WOMEN

WITH REFERENCE TO PREVALENCE OF DUODENAL ULCER IN EACH SEX

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ANY difference which there may be between the gastric emptying and secretion of men and of women might be expected to have some bearing on the prevalence of duodenal ulcer in the two sexes The present paper is intended to supplement by new methods the previous comparisons of gastric activity of men and women in the hope of throwing light on the causes of duodenal ulcer

Methods

The rate of emptying of a meal from the stomach depends in the main on two variables, the propulsive power of the stomach, and the effectiveness of the inhibitory mechanisms which normally check the emptying of the stomach The receptors whose activity slows gastric emptying lie mainly in the walls of the duodenum and upper part of the small intestine, hence they are exposed to stimulation by the material leaving the stomach For example, when the gastric effluent has a high osmotic pressure or when it contains fat, gastric emptying is slowed (Shay 1944) Once it is appreciated that the rate of emptying depends on a balance between the action of the gastric propulsive mechanism and the action of the inhibitory mechanism in the duodenum, comparisons of the gastric emptying of different individuals can be framed in terms of two questions

(1) How powerful is the gastroduodenal pump when it is not inhibited ?

(2) How effective is the inhibitory mechanism ?

Thus, for example, rapid gastric emptying might occur either with a very powerful stomach opposed by a normal duodenal brake or with a normally powerful stomach opposed by a very weak brake

Earlier experiments have shown that saline test-meals containing 100 m eq of sodium chloride per litre leave the stomach very quickly, presumably because such meals activate the duodenal brake only to a small extent (Hunt 1956) Thus the emptying-rate of a saline meal gives a tentative index of the uninhibited emptying power of the stomach On the other hand, a meal of distilled water of equal volume operates the duodenal brake and leaves the stomach at about half the rate of the saline meal Thus by comparing the emptying-rates of equal volumes of saline and water an index of the activity of the duodenal brake may be obtained

The test-meals used in this work were mainly designed to investigate gastric emptying but also allowed the assessment of the amounts of acid, chloride, and pepsin secreted in response to the meals

Technique—The subjects, who were all volunteers, were students in the medical school or in the school of physiotherapy They came fasting to the laboratory at about 8 A M To standardise the influence of the menstrual cycle on gastric emptying and secretion the women were all tested within the first seven days after the end of their menses (MacDonald 1956) After the stomach has been washed out with 250 ml of water through a tube the subjects were given a test-meal of 750 ml of water or of saline solution (100 m eq of sodium chloride per litre) at 37°C through the tube Nine minutes after the saline solution or nineteen minutes after the water meal the gastric contents were recovered through the tube Any residue was aspirated separately after a further 250 ml of tap water had been given The test meals contained phenol-red as a marker From the amount of this material recovered it is possible to calculate the volume of the gastric contents which have left the stomach From the amounts of the secretion recovered plus those calculated to have left the stomach the total amounts of acid, chloride, and pepsin secreted can be assessed The methods have been described in full (Hunt 1954)

Results

Gastric Emptying of Saline Meals and Meals of Water

The mean volumes of the gastric contents and of the original meal remaining were much the same in the twenty men and nineteen women both for the saline solution and for the water, as may be seen from the accompanying table, which also shows that the mean volume of saline meal remaining at the end of ten minutes was only slightly greater than the mean volume of the meal of water remaining after twenty minutes The data for the women were more variable than those for the men

The same data may be examined in more detail in fig 1, in which the volumes of the meal remaining after saline solution and after water have been plotted for each person Since the points fall around a straight line, it follows that those persons who emptied the saline solution rapidly also emptied the water rapidly Moreover the relationship between the two volumes is the same for the men and the women

Gastric Secretion in Response to Saline Solution and Water

The table shows that the men secreted about one and a half times as much acid as did the women in response to both saline solution and water It also shows that, both for the men and the women, the secretion of

MEAN DATA ON GASTRIC EMPTYING AND SECRETION IN MEN AND WOMEN IN RESPONSE TO MEALS OF SALINE SOLUTION AND WATER

—	Saline solution (10 min)		Water (20 min)	
	Men	Women	Men	Women
Volume of gastric contents (ml)	454 (±26)	453 (±32)	380 (±23)	398 (±31)
Volume of meal remaining (ml)	393 (±20)	393 (±30)	327 (±21)	344 (±27)
Output of acid (m eq)	2·21 (±0·37)	1·48 (±0·21)	5·22 (±0·70)	3·21 (±0·36)
Output of chloride (m eq)			8·58 (±0·72)	6·58 (±0·53)
Output of pepsin (units)	3610 (±440)	2420 (±290)	5850 (±480)	2850 (±290)
Concentration of acid in gastric contents (m eq per litre)	3·3 (±0·45)	2·3 (±0·33)	8·2 (±0·75)	5·4 (±0·67)

Figures in parentheses are standard errors of means

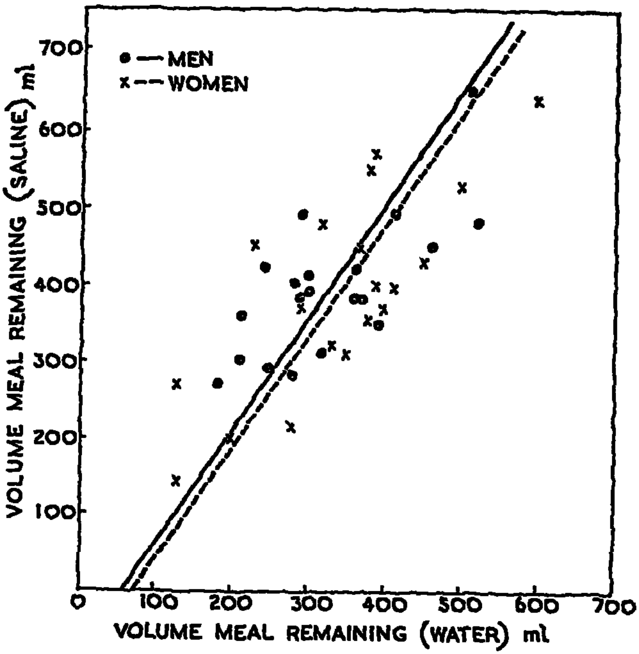

Fig 1—Volume of test-meal remaining after meals of water (20 min) and of saline solution (10 min)

acid was slightly more than twice as great for the twenty-minute test with the water as it was in the ten-minute test with the saline solution The secretion of chloride in response to water was greater in the men than in the women The secretion of chloride in response to meals of saline solution cannot be accurately determined by this method, because it is sensitive to errors in assessing the amount of chloride leaving the stomach with the gastric contents When the concentration of chloride in the meal is 100 m eq per litre, these errors dominate the small secretion of chloride which occurs in the ten-minute digestive period allotted to the saline solution

In response to both meals the men secreted more pepsin than did the women The men secreted more pepsin in the twenty-minute digestive period with water than they did in the ten minute period with the saline meal, but this difference does not appear in the data for the women

Discussion

Gastric Emptying

The present data indicate that test-meals of water and of saline solution leave the stomachs of men and women at much the same rate The meals are relatively larger for the women than they are for the men because the women are smaller than the men, but this does not seem to have any bearing on these data, for there is no correlation between body-weight and gastric emptying in either the men or the women, although the weights extend over a considerable range in both groups

Fig 1 shows that those who empty saline solution quickly also empty water quickly, which fact suggests that intersubject differences of the gastric emptying-rates for water are mainly determined by the gastric propulsive power which has been assessed from the emptying-rate of the saline solution Had the differences between subjects in the emptying-rates of water been mainly decided by the varying power of the duodenal brake, there would have been little correlation between the emptying-rates of the two meals From the present findings it can be inferred that the propulsive powers of the stomach and the effectiveness of the duodenal inhibitory mechanisms were equal in the two sexes

The data for women refer only to the second week of the menstrual cycle, for MacDonald (1956) has shown that there is a sudden small increase in the rate of emptying of test-meals at about the time of ovulation

The present experiments did not disclose any large differences between the gastric emptying of normal men and women which might explain the greater prevalence of duodenal ulcer in men Since it has proved impossible to demonstrate any difference between the gastric emptying of normal men and men with duodenal ulcers (Hunt 1957a and b), it may reasonably be assumed that women with duodenal ulcers do not empty test meals differently from normal women If a generalisation from these data is permissible, it seems likely that abnormalities of gastric propulsive power and of its regulation by osmotic factors in meals play no part in the pathogenesis of duodenal ulcer

Gastric Secretion

It is known from the work of Vanzant et al (193') that the acidity of the gastric contents after a test meal is higher in men than in women, a finding which was confirmed in the present investigation This difference is wholly explained by the higher secretory response of the men Because there was in these data no correlation between body-weight and the secretion of pepsin, acid, or chloride either in the men or women, the differences between the secretory responses of men and women to a standard meal cannot be attributed to differences in body-weight

Pathogenesis of Duodenal Ulcers

Although the greater gastric secretion in men might be held to explain the greater prevalence of duodenal ulcer in men, it might also be supposed that duodenal ulceration is the result of a defective resistance on the part of the duodenal mucosa It is therefore possible that duodenal ulcer is more prevalent in men because men more commonly have a defective duodenal mucosa If this were generally true, it would be expected that some men would develop duodenal ulcers at levels of secretion lower than those found in women with duodenal ulcer This hypothesis can be tested by the published data of Ihre (1947), which have been redrawn in fig 2 The ordinate shows the frequency in men and women with duodenal ulcer of the particular levels of gastric secretion in response to histamine marked on the abscissa It is clear that among men and women with duodenal ulcer the lower levels of gastric secretion are equally common The lower prevalence of duodenal ulcer among women can presumably be explained on the basis that fewer women than men attain to the levels of hypersecretion associated with duodenal ulcer

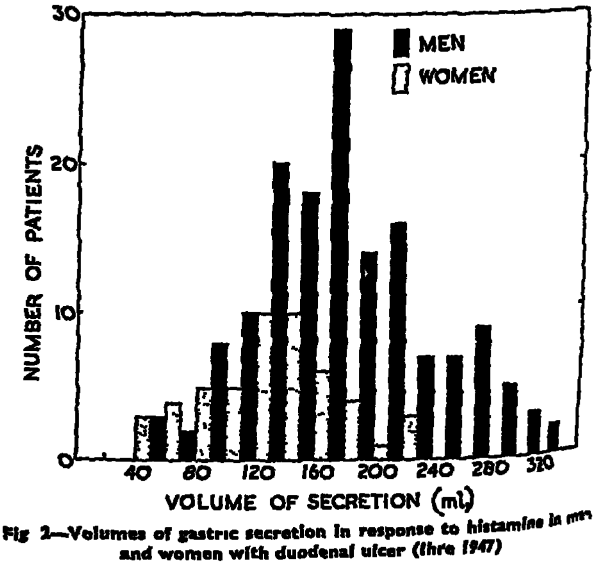

Fig 2—Volumes of gastric secretion in response to histamine in men and women with duodenal ulcer (Ihre 1947)

Conclusions

If the findings in this study are applicable generally, they may be taken to imply that the difference in prevalence of duodenal ulcer in men and women does not depend on any differences between men and women in gastric emptying, but it may depend on differences between men and women in their gastric secretion of acid and pepsin No evidence was found that among patients with duodenal ulcer defective tissue resistance is more common in men than women

Summary

Gastric emptying and secretion were compared in 20 young men and 19 young women

Test meals of saline solution were given to assess the gastric emptying power

Test-meals of water were given to assess the effectiveness of the duodenal osmoreceptors which slow gastric emptying

No difference was shown between the gastric emptying of the men and the women

The secretion of acid, chloride, and pepsin was about one and a half times greater in men than in women

It is tentatively concluded that the different prevalence of duodenal ulcer in men and women does not depend on differences in gastric emptying It might depend on differences in secretion

A consideration of Ihre's (1947) data suggests that differences in tissue resistance do not explain the different prevalence of duodenal ulcer in the two sexes

We are indebted to the volunteers for their coöperation and to the Worshipful Society of Apothecaries for the award to one of us (J N H) of the Gillson scholarship out of which part of the expenses were defrayed

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A COMBINED CINERÀDIOGRAPHIC AND MANOMETRIC STUDY OF THE GASTRO-ŒSOPHAGEAL JUNCTION*

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The nature of the closing mechanism between stomach and œsophagus is still a matter of considerable dispute Numerous methods of study have been used, amongst the latest being cineradiography (Nemours Auguste 1951) and manometry (Kramer and Ingelfinger 1951, Dornhorst et al 1954, Fyke et al 1956) In the study recorded here these methods have been combined

Methods

Investigations were carried out on 20 adult volunteers One group consisted of 11 normal medical students, average age about 21 , 3 were women and 8 men A second group, aged 24 to 57, consisted of 7 patients (6 men and 1 woman) in whom at laparotomy at least two months previously a metal clip to act as a radio-opaque marker had been firmly attached to the anterior aspect of the œsophageal hiatus of the diagram Operative examination of the gastro-œsophageal region in all 7 had shown no abnormality , 6 had had partial gastrectomy for peptic ulceration and 1 an appendicectomy In addition, a man in whom a near-total gastrectomy had been performed and a medical student who subsequently proved to have a hiatus hernia were studied

Apparatus

Pressures were measured with an electro manometer of the capacitance type (N E P Ltd) and a two channel direct writing pen recorder (Sanborn 'Twin-viso Cardiette ')

The œsophageal tubes were 'Polythene,' external diameter 2 5 mm Two types were used One had at its lower end a small balloon of thin latex, 1 cm long and 1–1 5 ml in capacity , there were radio opaque markers immediately above and below the balloon to indicate its position The second type was an open tube, with the hole either at the end or on the side and a radio opaque marker to indicate its situation

For cineradiography with image intensification and intermittent radiation, the method for cine-angiocardiography (Astley 1955, Astley and Oldham 1956) was used Each cine frame was exposed as an individual high-speed radiograph, using an exposure of 0 01 to 0 005 sec Thus movement blurring was eliminated The precise instant of each picture was indicated below the pressure-tracing on the second channel of the pen recorder Most examinations were carried out at 16 frames per second, a few at 32

Procedure

Local nasopharyngeal anæsthesia was induced with a few drops of 4% lignocaine, which the subject was instructed not to swallow A tube was passed through the nose into the stomach and the subject placed in the supine position If a balloon-ended tube was being used, it was now attached to the manometer and completely emptied and the balloon inflated the volume of air used was that required to inflate it to atmospheric pressure, as previously determined outside the body To prevent errors from possible leakage, this procedure was repeated at intervals during the examination When open tubes were used, they were attached to the manometer, filled with water, and flushed through after every recording

The subject was turned slightly into the left posterior oblique position to project the lower œsophagus just to the left of the spine and to demonstrate the level of the diaphragm clearly By fluoroscopy the marker at the end of the tube was adjusted to lie well within the stomach The subject, fully relaxed, was instructed to breathe quietly, without swallowing The tube was smoothly withdrawn at a uniform rate until the marker lay a few inches above the diaphragm , on an average, two to four seconds were taken over the withdrawal During this period simultaneous pressure and cineradiographic recordings were taken, the instant of each frame being indicated on the pressure tracing The procedure was repeated several times on each subject, keeping well within safe levels of irradiation Such gastro œsophageal withdrawal curves were also obtained during inspiration and expiration, and many of the subjects were examined by both the balloon and the water-filled open-tube systems As a routine, additional pressure tracings without cineradiographs were also obtained, using various

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* A paper read to a meeting of the Society of Thoracic Surgeons, Nov 2, 1956

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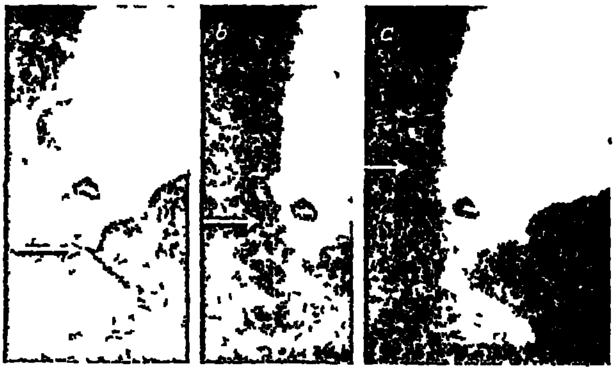
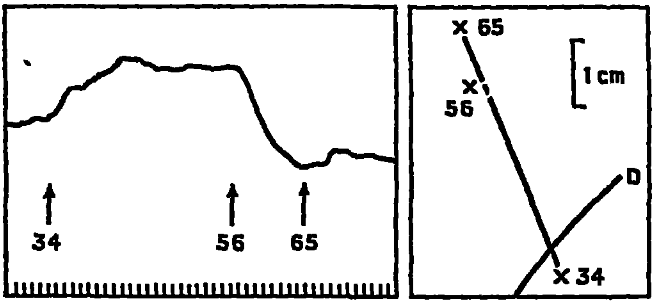


(A) Each cine frame corresponds to a known point on the gastro œsophageal withdrawal pressure curve The upper end of the radio opaque marker indicates the recording hole (arrows) and shows its position relative to the hiatal clip, the diaphragm, and barium in the fundus



(B) From each recording a composite tracing is made at a known degree of magnification, to indicate the anatomical position of salient points on the pressure curve

Fig 1—Method of analysis of recordings

recording speeds and varying rates of withdrawal At the end of the examination barium was given to localise the gastric fundus, and further combined radiographic and manometric recordings made

Tracings during which there was inadvertent swallowing were discarded, and at least ten seconds were allowed to elapse after a swallow before recording

To exclude artefacts due to a closed glottis and the action of the accessory muscles of respiration, tracings made during inspiration were recorded towards the end of the movement and not with the subject holding his breath

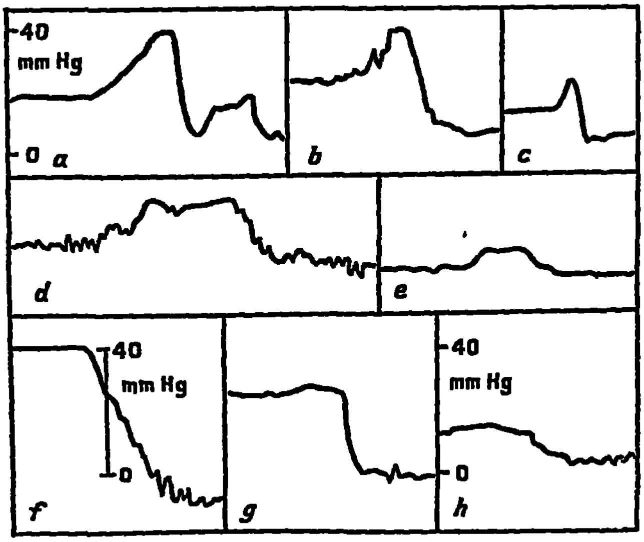
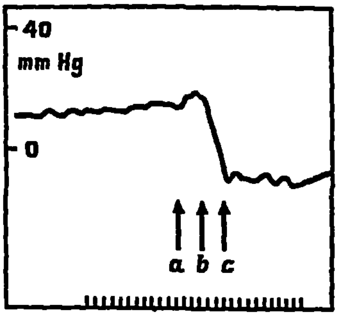


Fig 2—Types of withdrawal pressure-curve

a, b, c saw tooth type *d, e* plateau type *f, g, h* "step" type *a d* and *f* were obtained from the same subject



Analysis

The cine films were projected frame by frame through a prism on to a horizontal surface As the lengths of the radio opaque markers in the œsophageal tubes were known, it was possible to correct for varying degrees of radiographic magnification by adjusting the projector distance to obtain an image of true life size or of a known degree of magnification In actual practice twice life size proved convenient

The indication of the moment of each exposure on the recording meant that each cine frame corresponded to a given point on the pressure curve The films were projected frame by frame and composite tracings were made of each recording to show the site of salient points of the withdrawal curve relative to diaphragm, hiatal clip, and barium in the gastric fundus (fig 1)

Results

In the 18 normal subjects (i e , excluding the man with the virtual total gastrectomy and the student who proved to have a hiatus hernia), 227 gastro œsophageal withdrawal pressure-curves were obtained 133 were recorded with the open system and 94 with the small balloon There was combined cineradiographic localisation in 129

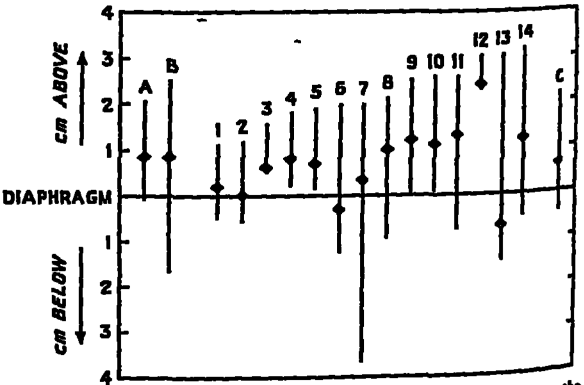


Fig 3—Average positions of the pressure-changes relative to the diaphragm (represented as in fig 4)

A is the mean of individual averages of 10 normal subjects examined with an open tube B is the mean of individual averages of the same 10 subjects examined with the small balloon 1 to 14 are the individual averages of 14 patients examined with an open tube C is the mean of 1 to 14

Types of Curve

The withdrawal curves were of three main types though these merged one with the other In a majority (64%) the pressure curve had a "saw-tooth" shape, with a rise preceding the fall to general intrathoracic level (fig 2, *a*, *b*, and *c*) Another 11% had an initial rise in pressure that assumed a plateau shape (fig 2, *d* and *e*) In the remaining 25% there was no initial rise and the withdrawal curve formed a step (fig 2, *f*, *g*, and *h*)

The type of curve depended to a certain extent on the method of recording With the small balloon a curve containing a pressure rise (either "saw tooth" or plateau) was always obtained With an open system, there was a pressure rise in 54% and a step in 46% Whether the recording hole was at the end or at the side of the tube did not influence results In a given subject there were often variations in the type of curve for which there was no obvious explanation

Site of Pressure Changes

In 10 subjects who were examined with both the small balloon and the open tube, a comparison of average results (fig 3, A and B) *shows that the descent to general* intrathoracic pressure began at the same point, whichever method of recording was used However, the gastro-œsophageal pressure changes as recorded with the small balloon took place over a longer segment, with the increase mainly in the phase of rising pressure This may be attributed to the size of the balloon, and to exclude such errors further description is confined to the results obtained with the open system

The exact situation of the pressure-changes varied from recording to recording in a given subject (fig 4)

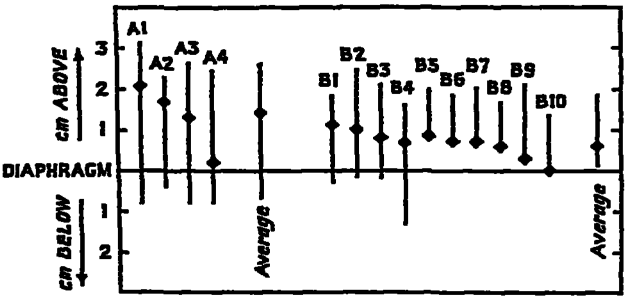


Fig 4—Situation of the gastro-œsophageal pressure changes in 2 subjects

The lowest point of each vertical line indicates the site where the pressure rise begins, the diamond shows the point at which the pressure descent begins, the upper limit is the site at which general intrathoracic pressure is reached A 1–4 are four separate open tube recordings in 1 subject, with their average, B 1–10 are separate recordings and the average in a 2nd subject

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The average results obtained in 14 normal subjects, and the mean of these averages, are shown in fig 3 In 2 the curves were always of the " step " type In the remaining 12 there was an initial rise in pressure This began above the diaphragm in 4 and below it in 8, with a mean position of 0 45 cm below In 11 of the 12 subjects the position of the gastro-œsophageal junction was shown by barium, the pressure rise commenced above this level in 6

The site at which the descent to general intrathoracic pressure began was above the diaphragm in 11 of the 14, with a mean position for the entire group of 0 65 cm above the diaphragm *The site at which general intrathoracic pressure was reached was in all cases above the diaphragm, with a mean position of 2 15 cm above* The total length of the segment over which these pressure-changes were seen varied from 0 5 to 5 65 cm, with a mean of 2 6 cm

In 6 subjects it was possible to relate the pressure-change as recorded by the open system to the level of the hiatus, which was indicated by a radio-opaque clip (fig 5) The level of the clip did not necessarily correspond to that of the diaphragm and the difference varied with the phase of respiration ; on inspiration th diaphragm descended more than the clip The averag position of the latter was above the diaphragm in subjects and below in 4, although the mean for th group showed a close correspondence of the levels of cli and diaphragm In 4 of the 6 subjects the site at whic the descent to general intrathoracic pressure began wa above the hiatus, with a mean position for the group o 0 3 cm above the clip (A similar observation was mad in a 7th normal subject who was examined only wit the small balloon)

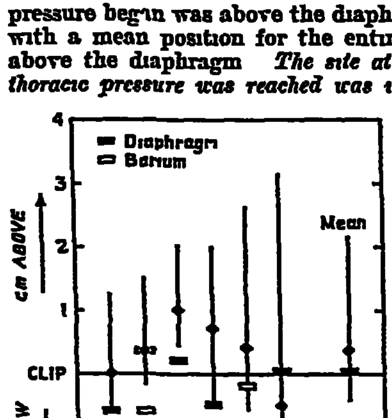

Fig 5—Average positions of the pressure-changes relative to the hiatus (represented as in fig 4)

The level of the hiatal clips is taken as the baseline Individual averages of 6 subjects, examined with an open tube, and their collective mean

Effect of Respiration

There was no obvious or constant relationship betwee the type of the withdrawal curve and the phase o respiration With full inspiration there was an increase difference between the gastric and intrathoracic pressures but the height of the rising phase (whether measure relative to the gastric pressure or as an absolute value showed no constant increase In some recordings it wa slightly higher, in others equivocal, and in a few lower

The length of the segment over which the pressur changes took place tended to be shorter during inspiration, and the point at which the descent to genera intrathoracic pressure began tended to be lower i position But this was not invariably so and the revers was sometimes seen

Miscellaneous Observations

In 1 of the normal students the recording tube was slowly pulled up and down for a few centimetres over the gastro-œsophageal junction, in other tracings the tube was lef stationary with its hole at this level and the same relativ movement obtained by breathing in and out In this subjec the recordings tended to show a three stage pressure change

One student, as already mentioned, proved to have a hiatus hernia The first suspicion of this was the obtaining of bifid tracings of an unusual type during some (but not all) withdrawals Tube movements caused slight reflux of the barium Close questioning elicited a suggestive history and a barium swallow confirmed the hernia.

In the subject who had undergone near-total gastrectomy, lack of symptoms and a barium meal examination indicated normal gastro œsophageal competence Normal types of withdrawal curve were obtained, but the point of maximum pressure rise was very low relative to the diaphragm

Discussion

Two features of the recordings are of particula interest · first, the positive pressure rise above that in the stomach found in 12 of 14 subjects and in over hal the curves obtained ; secondly, the appreciable length o the segment over which the pressure changes occurred —i.e , 0 5–5 6 cm (average 2 6 cm) This second finding is at variance with that of Dornhorst et al (1954) who concluded from manometric studies that functionally the cardia is a localised region extending over not more than 5 mm They considered the behaviour of the mechanism at the cardia to be unlike that of known muscle sphincters and favoured the existence of some form of flap or funnel valve

Our results suggest a mechanism operating in the lower segment of the œsophagus which is producing a compressing effect and therefore unlikely to be purely valvular. The fact that the recorded pressure changes varied in both degree and situation in any one individual indicates that, whatever the mechanism, this too must vary in both its compressing effect and in its exact situation relative to the diaphragm

There are two possible explanations of the compressing effect—an extrinsic one (i e , the crural " pinchcock ") or an intrinsic sphincteric mechanism The compression seems unlikely to be related to crural action since the positive deflection was not constantly increased with full inspiration—i e , when crural action would be expected to be at its maximum Moreover, in subjects who had a radio opaque clip indicating the anterior border of the hiatus, the point at which the fall to intrathoracic pressure began, which was usually also the point of *maximum* pressure, lay above the hiatus in 4 out of 6 subjects It could be argued that crural action extends above the level of the anterior border of the hiatus, but this seems unlikely since the crura slope upwards and forwards from their spinal origin

If the extrinsic factor is dismissed as unlikely to account for the pressure changes, it must be concluded that an important intrinsic sphincteric mechanism exists at the lower end of the œsophagus In the normal subject this may well be the most important component of the gastro œsophageal closure mechanism, though its existence does not exclude the possibility (indeed, *probability*, especially in the abnormal subject) that other factors play a part

Summary

Simultaneous cineradiographic recordings and gastro-œsophageal withdrawal pressure-tracings were made in 18 normal subjects Composite tracings to a known scale showed the site of salient points of the withdrawal pressure curve relative to the diaphragm, the hiatus (as indicated by a surgical clip), and the gastric fundus

The form and situation of the pressure changes varied from person to person and from time to time in a given subject They were seen over a segment averaging 2 6 cm in length In a majority there was a rise to a pressure above that of the stomach preceding the fall to intrathoracic pressure, this rise was not constantly increased during inspiration

The site at which the descent to intrathoracic pressure began was often above both diaphragm and hiatus (the levels of which were not necessarily identical) The site at which intrathoracic pressure was reached was always above the diaphragm

It is concluded that in the normal subject an important component of the closing mechanism is a sphincteric action operating at the lower end of the œsophagus

Grateful thanks are due to the subjects of our study We are indebted to Prof F A R Stammers and Prof J M Smellie for their encouragement, and to the endowment research fund of the United Birmingham Hospitals for a grant

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RADIOLOGICAL LOCALISATION OF THE DIAPHRAGMATIC HIATUS

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It has generally been accepted that the diaphragm, as seen in an anteroposterior radiograph, coincides with the level of the œsophageal hiatus The study recorded here was carried out to test the accuracy of this radiological concept by marking the hiatus with a metal clip at operation and examining it postoperatively in relation to the diaphragm

20 suitable volunteer patients of average build were examined (7 women, 13 men) The ages varied from 27 to 63 (average 43) Most of these patients had either a partial gastrectomy or a cholecystectomy Only those were selected who had benign lesions, who were in a good general condition, and who were found at laparotomy to have normal anatomy around the gastro œsophageal junction

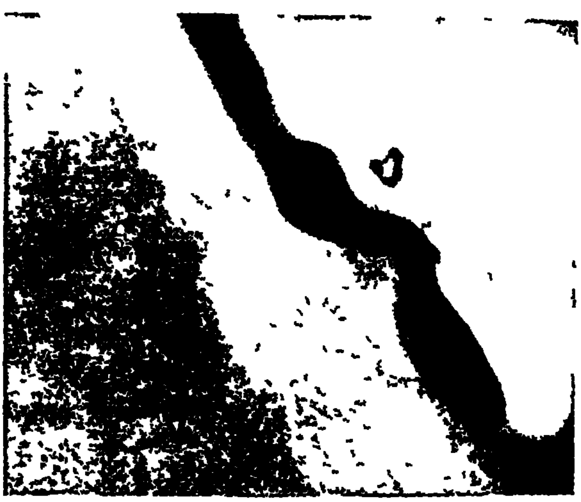

Fig 1—Right oblique, erect posture the clip lies above the line of the diaphragm but below the phrenic ampulla

Method

At laparotomy the hiatal area was carefully examined The left lobe of the liver was mobilised and reflected so that the anterior hiatal margin could be adequately visualised A metal clip was then firmly and accurately attached to the anterior edge of the diaphragmatic hiatus immediately in front of the œsophagus Each patient had a radiological examination within two and a half months of the operation Some patients had several investigations Radiographs were taken in various postures and during different phases of respiration When it was necessary to compare these pictures, the same position was ensured as far as possible by overlapping skin markers on each side of the body The relationship of the clip to the œsophagus was demonstrated by barium swallow and by a 0 8 × 18 cm balloon containing a radio opaque contrast medium that was passed down the œsophagus to the gastro œsophageal junction

Results

The comparison of radiographs is notoriously difficult, especially when taken in different postures and phases of respiration

Position of the Clip at Rest

Erect position—The clip lay at the level of the intervertebral disc of T 11–12 in 75% of patients, and its position varied from the lower border of the 10th thoracic to the upper border of the 1st lumbar vertebra It was to the left of the midline in every patient, usually at the lateral vertebral border In the lateral view the clip appeared nearer the spine than the sternum in most patients, but in 2 it lay so far forward that it was nearer the sternum Its relationship to the diaphragm varied widely In 62% it was above, in 18% at, and in 20% below the level of the diaphragm In 3 patients it was well above the diaphragm (half or more of a vertebral body), and in 2 it was well below The clip could be located above the diaphragm in oblique views, but here there was great variation, depending mainly on the degree of obliquity of the patient (fig 1)

Supine and Trendelenburg positions—The most interesting feature in most subjects was the disproportionate cephalad movement of the clip relative to the diaphragm, the diaphragm ascended higher than the clip This was slightly more accentuated in the Trendelenburg position In some patients the relative positions of clip and diaphragm remained unchanged (figs 2 and 3), but an upward movement was present in every patient, usually of from half to one vertebral body The greatest move

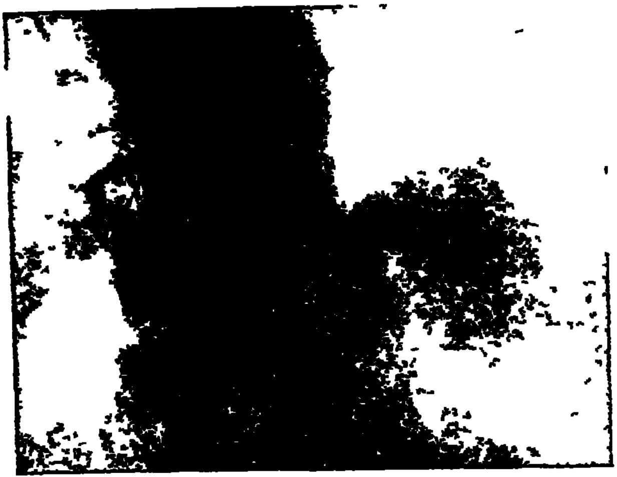

Fig 2—Supine the clip lies below the diaphragm

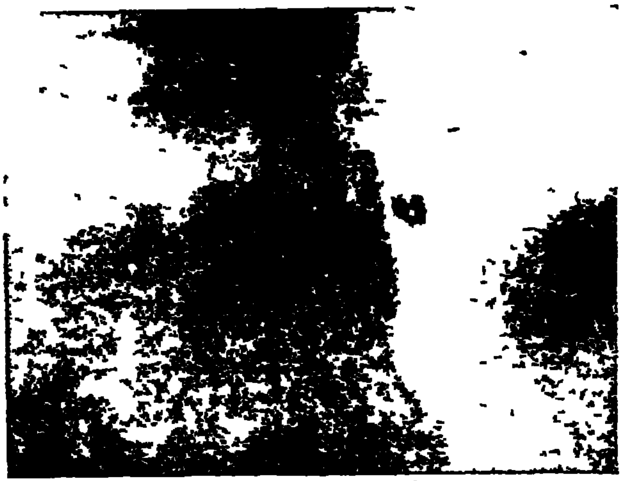

Fig 3—Supine. clip above the diaphragm

ment noticed was of two vertebral bodies (from erect, in expiration, to Trendelenburg, in expiration). A much bigger change in position took place on moving from the erect to the supine position than from the supine to the Trendelenburg. Not only did the clip move cephalad, but it tended to move to the left in most patients. In some, this shift to the left was absent. The clip was usually further from the vertebral column in the supine and Trendelenburg positions. The marker became a midline structure in the right lateral position and drew away laterally from the vertebral column in the left lateral position.

Position of Clip during Respiration

In most patients, the excursion of the clip was about one vertebral body during the respiratory cycle with the patient in the same position, but movement of two vertebral bodies was not uncommon. Though the clip moved up and down with the diaphragm, its excursion was less. During inspiration, the descent of the diaphragm was relatively greater and in most patients the clip was well above at the end of inspiration. During expiration the diaphragm ascended more than the clip did, so that in most patients it was at or below the diaphragm. The greatest excursion was observed in the supine position in a woman in whom the clip moved almost two and a half vertebral bodies.

During inspiration the clip moved medially as well as downwards. The extent of medial movement varied from patient to patient. In a few no medial movement at all was noticed. During expiration the clip moved upwards and slightly to the left in most patients. Together with the downward and medial movement on inspiration, the clip also moved posteriorly in most cases. This posterior movement was very slight and could sometimes only be seen when the lower œsophagus was displayed by means of the long balloon (fig 4). In a few patients it was absent, and in one the clip actually moved forwards during inspiration. Movement posteriorly during inspiration was much less than anterior movement during expiration.

Screening.—The radiographs were superior for accurate localisation but screening was by far the most valuable method of demonstrating the disproportionate movement of clip and diaphragm.

Discussion

In the first few patients examined, the discovery that the level of the clip was often above that of the diaphragm raised initial doubt (subsequently refuted) about the accuracy of placement of the clip on the hiatal margin. Therefore, in the succeeding operations, even greater care was taken to ensure precise anatomical fixation; moreover, correct positioning was confirmed in all the subjects by anteroposterior and lateral radiographs with the œsophagus demonstrated by barium or by the long opaque balloon.

Thus there can be little doubt that, in most people at least, the anterior margin of the hiatus is situated above the line that indicates the diaphragm radiographically. In only a minority is it at or below this level. This conclusion, which has been emphasised in a combined cineradiographic and manometric study of the gastro-œsophageal junction by Botha et al. (1957), agrees with the findings of Monges et al. (1955), who applied clips to the anterior hiatal margin and to both crura; post-operatively, X-ray examination showed that all three clips appeared above the diaphragm in that patient.

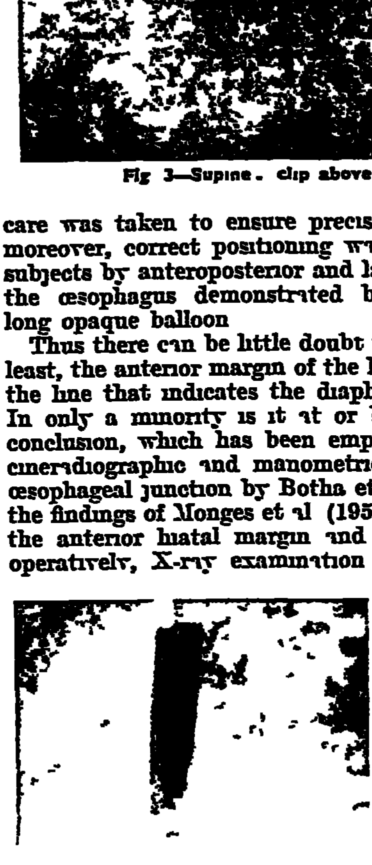

Fig 4—Left lateral, erect deep inspiration posterior movement was so slight that the balloon appears almost straight.

The relationship between the levels of the diaphragm and hiatus varies not only from person to person but also with posture and the phase of respiration. During inspiration the hiatus moves downwards, inwards and slightly backwards. Jouve-Fournier (1955) made the same observation with a radio-opaque balloon in the lower œsophagus.

The fact that the levels of the hiatus and the diaphragm do not necessarily correspond is significant for two important reasons. First, it means that various conclusions about the nature of the gastro-œsophageal closing mechanism have to be reconsidered—e.g., the manometric studies of Dornhorst et al. (1954) and the fluoroscopic observations of Poppel et al (1956), and secondly, it is important in the assessment of disease in this region, and it must be particularly remembered in the consideration of neoplasms, achalasia, diverticula, or hiatal herniæ

Poppel et al (1956) examined 500 subjects and saw "that the esophagus was indeed pinched off when the diaphragm descended in forced inspiration, however, this pinching-off did not occur at the level of the diaphragm but 0 5 to 3 cm above it It was in reality the constriction of the inferior esophageal sphincter that occurred synchronously with the descent of the diaphragm It was this action that was previously misinterpreted as a pinchcock action of the diaphragm" It is now clear that their inquiry did not reveal whether the constriction was due to hiatal action or to closure of the inferior œsophageal sphincter It is, furthermore, difficult to understand why the œsophageal sphincter should contract synchronously with the diaphragm

In considering the pinchcock action of the right crus, it is fundamental to appreciate that the crura act synchronously with the diaphragm, not independently of it Interesting diagrams in the past have convincingly demonstrated that the œsophago-gastric angle became more acute in inspiration The occluding effect of the mechanical valve at the cardia was thus accentuated, and gastro-œsophageal competence increased The present investigation, however, conclusively showed the opposite Disproportionate descent of the diaphragm and clip during inspiration opened the angle, which suggests that this factor is not so important in the closing mechanism as is commonly thought The wide variation in position and behaviour of the hiatus suggests that crural function may not be the same in every patient Too dogmatic views on crural action should therefore be regarded with suspicion

Palmer (1953) established the position of the "cardia" relative to the diaphragm after silver clips were attached to the mucosal junction at œsophagoscopy The same method was used to ascertain the degree of gastric herniation (Allison 1951, Palmer 1954) But if the hiatus is not at diaphragmatic level no conclusions can be drawn from minor upward or downward shifts of mucosal clips

Summary

The relative positions of the diaphragm and a radio-opaque marker on the œsophageal hiatus were studied in 20 patients

The position of the clip did not necessarily correspond to diaphragmatic level and there was considerable variation from patient to patient, in its position as well as in its movements The clinical, radiological, and experimental significance of these observations is outlined

I am indebted to Prof F A R Stammers, department of surgery, University of Birmingham, and the endowment research fund My thanks are due to Dr Roy Astley, radiologist to the Children's Hospital, for valuable suggestions, and to Mr T F Dee, photographer to the Queen Elizabeth Hospital, for the illustrations

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A NOTE ON HEPARIN CLEARING IN VIVO

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THE rôle of heparin in lipid metabolism has attracted the interest of many workers Since Hahn (1943) reported that intravenous heparin cleared the initial turbidity of plasma of dogs in alimentary lipæmia within a minute after injection

Kubie et al (1956a) have shown that intravenous heparin considerably depressed the polarographic protein double wave of human serum in alimentary lipæmia This depression has been attributed by Kubie et al (1956b), Marha (1955), and Reichl (1955) to the liberation of non-esterified fatty acids observed under such conditions by Grossman et al (1955)

Kubie et al (1956b) have also shown that, when precautions were taken to minimise in-vitro chemical changes in serum after the injection of heparin, the

RESULTS

Subject no	Age (yr)	Concentration of E600 in blood (M)	Turbidity of serum without added E600	Turbidity of serum with added E600	Sample*
1	30	$2\ 10^{-5}$	70	65	1
			300	310	2
			215	305	3
			210	310	4
2	21	,,	65	70	1
			253	250	2
			65	245	3
			70	200	4
3	40		75	70	1
			400	400	2
			120	430	3
			90	390	4
4	41		125	110	1
			860	860	2
			590	900	3
			520	900	4
5	41	,	120	110	1
			720	700	2
			320	695	3
			290	670	4
6	24	,,	45	50	1
			240	245	2
			55	240	3
			60	200	4
7	33	,	80	80	1
			910	915	2
			420	915	3
			180	710	4
8	45	$6\ 10^{-4}$	40	50	1
			298	290	2
			62	250	3
			45	220	4
9	22		62	65	1
			260	262	2
			60	236	3
			55	230	4
10	25	$1\ 10^{-4}$	36		1
			185	192	2
			70	125	3
			60	110	4
11	22		65	55	1
			386	401	2
			35	312	3
			40	300	4
12	27		32	30	1
			412	420	2
				320	3
			35	105	4
13	30		25	38	1
			75	90	2
			35	30	3
			20	30	4

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* 1 blood taken in fasting state
2 blood taken 3 hr after ingestion of 300 ml of cream
3, blood taken 5 min after intravenous injection of 25 mg of heparin.
4 blood taken 15 min after intravenous injection of 25 mg of heparin

depression of the polarographic protein double wave was either small or absent It was therefore of interest to know whether the changes in optical properties of the serum were merely an in-vitro effect or also the result of physiological processes in the circulation

It is known that the catalytic effects of lipoproteinase, which is activated by heparin, can be prevented by the use of suitable inhibitors in vitro Therefore we examined the effect of intravenous heparin on the turbidity of serum obtained from blood to which an inhibitor of lipoproteinase had been added immediately after withdrawal of the blood to exclude any possible in-vitro effects

Material and Method

We examined sera from 8 healthy women and 5 healthy men In each case a sample of blood was taken while the person was fasting Each person next ate a fat meal consisting of 300 ml of rich cream Three hours later a sample of venous blood was taken, and with the same needle 12 5 mg of heparin in 5% solution was injected Exactly 5 minutes and 15 minutes after heparinisation further samples of blood were collected Immediately after collection 5 0 ml of blood was mixed with 0 5 ml of a solution of diethyl-*p* nitrophenylphosphate (' E600 '), a potent inhibitor of lipoproteinase The final concentration of inhibitor in the samples of blood was $1\ 10^{-4}$–$2\ 10^{-3}\ M$ As a control a further aliquot of the same sample of blood was mixed with saline solution in similar proportions The blood was allowed to clot at 37°C, and serum was separated by centrifugation at 3000 r p m The turbidity of the sera obtained was measured with the 'Unicam' photo-electric colorimeter with the red filter

Results

The addition of E600 to cleared serum in similar proportions had no effect on its turbidity under the same conditions

The results presented in the accompanying table show that, at sufficiently high final concentrations of E600 ($2\ 10^{-3}\ M$) there was practically no optical change within 5 minutes after heparinisation In subjects 3 and 4 there was even a slight increase in turbidity 15 minutes after heparinisation there was slight clearing, but in subjects 1 and 4 the turbidity was still unchanged Decreasing the concentration of E600 increased the extent of clearing The concentrations used in such instances ($1\ 10^{-4}\ M$ and $6\ 10^{-4}\ M$) were evidently too small to inhibit clearing entirely All the control samples without added inhibitor showed the well known dramatic decrease in turbidity (clearing) within 5–15 minutes after heparinisation The in-vitro clearing was relatively smaller in cases 1 and 4 who did not show any decrease in turbidity in the presence of E600 even 15 minutes after heparinisation

Preliminary experiments with plasma maintained at 0°C without added inhibitor did not show total inhibition of in vitro clearing

Discussion

The large differences in turbidity of sera with and without inhibitor emphasise the rôle of in-vitro processes caused by heparinisation Probably the sera obtained from blood treated with inhibitor have a turbidity approaching that existing in the circulation under physiological conditions This turbidity would be the net result of formation and disappearance of chylomicra from the circulation under given conditions This may explain the changes in turbidity observed at various intervals after heparinisation It may therefore be assumed that, 5 minutes after heparinisation (under the experimental conditions stated), the rate of formation of chylomicra exceeded the rate of their disappearance, only after 15 minutes after heparinisation did the rate of disappearance of chylomicra exceed their rate of formation (except in cases 1 and 4)

The enhancement of lipolysis by intravenous heparin may be the cause of an accelerated removal of fatty acids from the blood-vessels into the tissues The evidence presented here shows that an increased lipolytic activity causes in-vitro turbidity changes which have frequently been considered to represent in-vivo changes The use of a suitable inhibitor shows that, in alimentary lipæmia in man, 5 minutes after the intravenous injection of 12 5 mg of heparin there is practically no change in turbidity

We are indebted to Dr G Kubie for his interest and advice in the preparation of this manuscript

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ADDISONIAN CRISIS DUE TO PELLAGRA

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COLLAPSE and sudden death in patients suffering from pellagra is mentioned in textbook descriptions of the disease (Cecil and Loeb 1955) The possibility of a relationship between adrenocortical function and pellagra was first considered by Finotti and Tedeschi (1902) and has recently been reviewed by Mainzer (1950) Because syncope and collapse in pellagra are usually sudden, it must rarely be possible to carry out biochemical studies in patients who collapse We have found no reports of such studies which would clearly be valuable in deciding whether addisonian crisis and acute collapse in pellagra are accompanied by similar derangements of electrolyte metabolism For this reason we present details of a patient with pellagra in whom electrolyte and steroid estimations were made during an acute phase of her illness resembling addisonian crisis

Case-report

A widowed housewife aged 60 was admitted to hospital on June 10, 1955 Her appetite had always been poor, and for about a year she had lived on a monotonous diet consisting each day of 2 pints (1200 ml) of milk, some semolina, and six slices of a proprietary brown bread with small amounts of butter Occasionally she took very small portions of chicken During this time she lost 2 stone (12 5 kg) in weight In March, 1955, she had an attack of diarrhœa lasting a week, when she passed three watery yellow stools a day Subsequently her skin became dark on the exposed surfaces Early in May, 1955, she again started to have diarrhœa and occasionally vomited small amounts of bile stained fluid, these symptoms persisted till her admission. On May 28, 1955, she sat in the bright sunlight for six hours, and as a result the surfaces exposed became more severely pigmented

She was thin and mentally dull The whole skin showed brown pigmentation which was particularly evident on the exposed surfaces She had hyperkeratotic areas on the backs of her hands and feet and some brown pigmentation of her tongue Pigment was not concentrated in the skin creases The fæces were bright yellow and loose The blood-pressure was 100/30 mm Hg and her weight 6 stone 3 lb (40 kg)

She was seen by Dr I B Sneddon, who confirmed that the skin appearances were those of severe pellagra

Investigations —A radiograph of the chest was normal The hæmoglobin was 13 g per 100 ml The fæces contained no occult blood, and the fractional test meal showed a histamine-fast achlorhydria The urine and electrocardiogram were normal The Wassermann reaction was negative The serum-sodium was 137, serum potassium 4 6, serum chloride 97, and plasma alkali reserve 26 m eq per litre, and blood-urea 26 mg per 100 ml

Progress —On the morning of June 16, 1955, six days after admission, she felt very lethargic and weak after fasting overnight for a barium meal She appeared to be shocked and very ill, her blood-pressure had fallen to 60/0 The blood sugar was 115 mg per 100 ml, but the serum-sodium had fallen to 130 m eq per litre and the serum-potassium had risen to 7 4 m eq The serum chloride was 92 m eq, but the plasma alkali reserve was only 10 m eq The blood urea had increased to 83 mg per 100 ml

Treatment and Response —She was given nicotinamide 500 mg and two ampoules of vitamin-B complex ('Becosym') intramuscularly, and sodium lactate (1/6 molar solution) 3 litres intravenously in the next twenty four hours In addition she received cortisone acetate 25 mg orally six hourly for four doses By 4 30 p m on the same day she had improved and her blood pressure had risen to 110/80 The serum sodium was 126, serum potassium 6 6, serum chloride 98, and plasma alkali reserve 10 m eq per litre, and blood-urea 36 mg per 100 ml

Next day her blood pressure was 130/80, serum sodium 127, serum potassium 4 3, serum-chloride 89, and plasma alkali reserve 24 m eq per litre, and blood urea 25 mg per 100 ml

Treatment was continued with cortisone acetate (12 5 mg by mouth twice daily) for a further seven days and one ampoule of vitamin B complex once daily intramuscularly for twenty eight days During this time she improved further, she became more alert, her appetite returned, the diarrhœa ceased, and the stools became normal The pigmentation of the skin and tongue gradually faded with desquamation of the hyperkeratotic areas The blood-pressure was maintained at 100/70

Investigations after Completion of Treatment —Serum sodium 140, serum-potassium 4 0, serum chloride 103, plasma alkali-reserve 25 m eq per litre, and blood-urea 23 mg per 100 ml The liver function tests and a liver biopsy were normal A glucose tolerance test and a barium meal examination with follow through showed no abnormality A plain radiograph of the abdomen showed no adrenal calcification

Follow up.—She was discharged on Aug 4, 1955, and has been followed since this time She required no specific therapy and maintained herself on a normal diet In November, 1956, she had gained more than 2 stone (12 5 kg) and weighed 8 stone 6$^1/_2$ lb (53 6 kg) The pigmentation had almost completely disappeared The serum sodium was 144, serum potassium 4 9, serum chloride 103, and plasma alkali reserve 21 m eq per litre, and blood urea 21 mg per 100 ml A urinary chromatogram, kindly performed by Mr D C Cusworth in Prof C E Dent's laboratory at University College Hospital, London, was unlike that seen in the pellagra like syndrome with amino aciduria described by Baron et al (1956)

Urinary Steroid Excretion —On admission five days before the crisis, the twenty four hour excretion of 17 ketosteroids was 26 6 mg and of 17 ketogenic steroids 25 6 mg —values slightly higher than those normally obtained in this hospital's laboratory On July 8, 1955, twenty two days after the crisis and fourteen days after stopping cortisone, the 17-ketosteroid excretion was 5 0 mg and the 17 ketogenic steroid excretion 7 1 mg in twenty-four hours Next day the values were 3 5 mg and 7 4 mg respectively On July 19, 1955, she was given corticotrophin 25 mg intramuscularly six hourly for four doses The twenty four hour excretion of 17-ketosteroids was 11 0 mg and of 17 ketogenic steroids 26 0 mg This is a normal response On Nov 26, 1956, the 17-ketosteroid excretion was 3 1 mg and the 17 ketogenic steroid excretion 6 7 mg

Discussion

Pigmentation of the skin and mouth are presenting features in pellagra and in Addison's disease, and asthenia, loss of weight, and hypotension are common in both diseases Mental changes, diarrhœa, dermatitis, and light sensitivity help to differentiate pellagra from Addison's disease, but the fact that so many features are common to both diseases has given rise to speculation that hypocorticism may be a feature of pellagra

Necropsy studies of the adrenal glands in cases of pellagra have shown partial or even almost complete atrophy of the zona glomerulosa as the outstanding abnormality (Aschoff 1933, Froboese 1934, Herzenberg 1935, Eger 1937, Hellwig and Forman 1942) Variable loss of lipoid (Aschoff 1933, Froboese 1934, Herzenberg 1935, Eger 1937) and sclerosis of the capsule (Froboese 1934) have also been reported, but it is striking that the zona fasciculata and zona reticularis have remained virtually unaffected A few biochemical observations have been based on indirect tests of adrenocortical function Mainzer (1949) found increased insulin sensitivity in pellagra and concluded that this afforded evidence of hypocorticism Miowski and Tadzer (1954) using Thorn's test no 1, concluded that there was some disturbance of the diencephalic-adrenal axis There was only a small fall in circulating eosinophils after giving adrenaline and this was partially corrected by corticotrophin therapy

There is little doubt that our patient had pellagra with typical skin lesions and gastro intestinal disturbances which resolved with nicotinic acid and vitamin B complex There was a gain of more than 2 stone in weight in the year after her illness The symptoms did not recur, though she had no specific therapy after the acute phase of her illness The urinary chromatogram excluded the pellagra-like disease with amino aciduria as described by Baron et al

Before the acute episode, the urinary steroid excretion was slightly higher than normal and suggested an adrenocortical stress response During the crisis the normal blood-sugar level appeared to be an indication of adequate glucocorticoid activity During and after recovery the urinary steroid excretion and the corticotrophin stimulation test were also normal On the other hand, the sudden onset of hypotension, uræmia, and high serum-potassium at a time when no appreciable diarrhœa or vomiting took place suggested a failure of mineralocorticoid secretion Such findings are identical with those found in addisonian crisis

The results in our patient therefore suggest selective damage to the zona glomerulosa which is considered to be the main secretor organ of mineralocorticoids (Landing 1955) The fact that improvement was maintained for more than a year indicated that the lesion was reversible The reported necropsy findings of selective damage to the zona glomerulosa seem to provide a pathological basis for these biochemical changes

Our patient was treated with cortisone for acute adrenocortical insufficiency, but there is no evidence that recovery might not have resulted from treatment with nicotinamide and vitamin-B complex alone

Summary

The clinical and biochemical features of a crisis in a woman with pellagra suggest an acute failure of mineralocorticoid metabolism Reports of selective damage of the zona glomerulosa of the adrenal cortex in pellagra provide a possible pathological basis for this failure

We wish to thank Dr H P Brody under whose care this patient was admitted for his help and encouragement Our thanks are also due to Mr M J Lavell for the steroid estimations and to Dr D S Munro for correcting the manuscript.

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TALC GRANULOMA OF THE UMBILICUS

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Granuloma of the umbilicus in young infants is not uncommon; but, whereas the part played by talc in the pathogenesis of granulomatous lesions within the abdomen and elsewhere has been clearly established (McCormick and Ramsey 1941, Roberts 1947), we have been unable to find any published report of a similar relationship in umbilical lesions.

In the past few months we have seen five cases in which such an association seemed to exist, as in the following one.

The infant was a healthy male delivered normally at term. The cord had separated at the seventh day, but the umbilicus did not heal, and a purulent discharge was present from the tenth day. "Something red in the navel" was seen at one month, and the discharge had continued unabated. Initially, sterile cord powder (conspers alum. et zinc oxid. pro infant. *B.P.C. 1954*) had been applied to the umbilicus, but subsequently a standard proprietary talcum baby powder was used.

On examination at six weeks the umbilicus contained a pink granulomatous mass of tissue, from which a purulent discharge exuded. Ten days later this was excised under general anæsthesia. Healing was satisfactory, and at three months the umbilicus was dry and the granuloma had not recurred.

Fig. 2—Talc crystals shown up by polarised light in umbilical granulations.

Histology

On microscopy these specimens present a gradation of features on a common background of heavy non-specific infection, which is related to the extent to which the talc crystals become incorporated into the granulation tissue. In some areas these may be wholly confined to the superficial inflammatory exudate; but, where the doubly refractile particles are situated more deeply, various degrees of giant-cell formation are found. In the actively inflamed areas this is generally slight or absent; but, where connective tissue has become organised, the talc crystals are seen in distinct aggregates, with conspicuous multinucleated giant cells. These, however, are of typical foreign-body pattern, and in no instance have we found any indication of endotheloid cell elements of follicular structure.

Discussion

In a review of disorders of the infant umbilicus Isbister (1953) considers that the umbilical granuloma, as distinct from the umbilical polyp of intestinal tissue, is usually secondary to infection. The finding of doubly refractile crystals in these granulomata must pose the question as to how often such lesions are sustained by the free use of talcum powder with which most infants are dusted from birth, particularly in view of the fact that, though such lesions are not uncommon, surgical biopsy is hardly ever resorted to.

In these cases the course of events differs from that associated with talc granuloma of the peritoneum and fallopian tubes because, in the early stages the formation of granulation tissue has not been initiated by the talc crystals, the umbilical stump healing normally by this process. There is little evidence at first of any active tissue response to their presence, as shown by the lack of foreign-body reaction, from which it seems that the crystals delay the healing largely by creating conditions favourable to the persistence of infection, and only at a later stage, when acute inflammation has subsided, does giant-cell reaction clearly develop. Possibly, after a further lapse of time, a pseudotuberculous picture might develop corresponding to those described after the traumatic introduction of silicious particles into the subcutaneous tissues (Shattock 1916, Faulds 1935) and in surgical scars (Feinberg 1937); but there are no grounds for suggesting that any long-term detrimental effects may develop in such cases.

Fig. 1—Umbilical granulations.

It seems, however, reasonable to suggest that such potentially irritant powders should not be used, at least before the umbilicus is soundly healed One might indeed go so far as to advocate that the routine use of talcum powder should be abandoned because in no circumstances can it be a substitute for proper cleansing of the skin, followed by thorough drying, but in this matter we are concerned with a ritual which is too firmly rooted in tradition to be influenced by considerations such as these

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RENAL COLIC AND PERSISTENT HYPERCALCURIA FOLLOWING SELF-ADMINISTRATION OF VITAMIN D

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Hypercalcuria has become of increasing interest to both physician and surgeon the physician sees it as an expression of endocrine disorders, biochemical disturbances, and renal pathology,[1] whereas the surgeon is more directly concerned with the increased tendency to renal calcification and lithiasis

Hypercalcuria and renal colic in the case here reported appear to have been caused by a prolonged course of vitamin D which was self-prescribed The increased urinary excretion of calcium is still present fifteen months after the vitamin has been discontinued

Case-report

A male cook, aged 55, was first seen in the casualty department at 5 A M with severe pain which had come on suddenly in his left loin and awakened him two hours previously The pain was severe and colicky and radiated into his left groin He could not lie still while the pain was present, but there was gradual relief after an injection of pethidine There was no macroscopic hæmaturia, no disturbance of micturition, and no history of previous similar episodes No other relevant past history was given at this time, and there was no significant family history

On admission the patient appeared to be otherwise fit, with no abnormal physical findings in the cardiovascular system or lung fields Blood-pressure 110/70 mm Hg His kidneys were impalpable, and tenderness in the left renal angle rapidly disappeared There were no other abnormal physical findings The first specimen of urine passed contained very numerous red cells, occasional pus cells, and no protein The urine gave a strongly positive Sulkowitch reaction for calcium and tests for cystine were negative Further inquiry of the patient elicited a history of taking "vitamin tablets" as a general tonic for the past three years These proved to be a proprietary vitamin preparation ('Ostelin,' Glaxo) containing 50,000 units (1 25 mg) of vitamin D (as calciferol) in each tablet, which also contained 105 mg of calcium and 44 mg of phosphorus

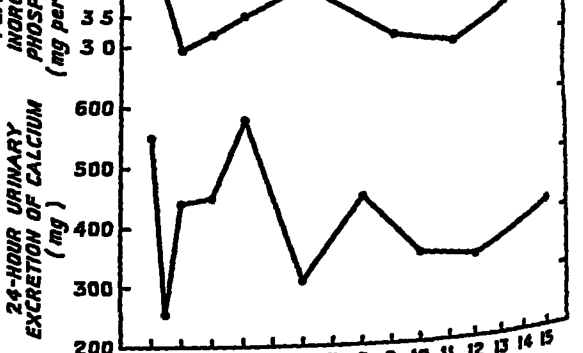
Investigations—On the day after admission the urine contained 3 red cells per $^1/_6$ field, no pus cells, no casts, and no protein, and was sterile on culture The blood urea level was 30 mg per 100 ml, and the urea clearance was 93 5% maximum and 88 5% standard The hæmoglobin was 108%, erythrocyte sedimentation rate 10 mm (modified Westergren read in 100 mm tube) in the first hour, and white cell count 9800 per c mm (differential count normal) The initial values obtained for the serum calcium level were 10 0 and 9 8 mg per 100 ml and plasma inorganic phosphorus level 4 6 and 4 6 mg per 100 ml Straight radiography of the abdomen and an intravenous pyelogram revealed no abnormality in the urinary tract, and there was good concentration of diodone Radiography of the chest showed old calcified lesions at both apices, but specimens of sputum contained no acid fast bacilli Radiography of the skeleton showed an enchondroma in the fourth proximal phalanx of the right hand but there was no evidence of generalised disease of bone The twenty four hour urinary excretion of calcium was 550 mg In view of this high value further investigations were undertaken The plasma alkaline phosphatase level was 11 0 King Armstrong units per 100 ml, the plasma electrolyte, carbon dioxide capacity, and serum protein levels were normal, and the serum flocculation tests were negative

Progress—It was considered clinically that the attack of renal colic was probably associated with his hypercalcuria and with the passage of a small stone, although this was not actually seen The vitamin D preparation was discontinued on admission, and a week later the urinary excretion of calcium was 255 mg in twenty four hours The patient was discharged, nine days after admission, on a low calcium and vitamin-D poor diet, achieved by a severe restriction of his intake of milk and dairy produce, and has been seen regularly for follow up during the past fifteen months Clinically he has remained well and has had no recurrence of renal colic or any symptoms connected with micturition Repeated estimations of the twenty-four hour urinary calcium while on a low intake have shown a persistently excessive excretion (see figure) over the accepted upper normal limit of 220 mg for this laboratory The diagnosis of renal tubular acidosis was considered unlikely in view of the normal plasma bicarbonate levels, and the failure, on two occasions, of sodium bicarbonate, in a dosage of 10 g daily for seven days, to reduce the excessive output of calcium was further evidence against this condition as a cause of the hypercalcuria The serum calcium level fell during the early months of follow up (see figure) and still remains low (8 9 mg per 100 ml) The plasma-inorganic-phosphorus level has varied during the period, and, although low values have been recorded (see figure), the most recent value was 4 0 mg per 100 ml Repeat estimations have given normal values for the plasma protein levels, the urine has remained free from protein and is normal on microscopy, and radiologically there is no evidence of calcification in the kidney or of generalised disease of bone The blood urea, plasma potassium, and plasma bicarbonate levels have remained normal, and the most recent alkaline phosphatase level is 6 9 King-Armstrong units per 100 ml

Discussion

Increased urinary excretion of calcium has long been recognised as an important association of calcification within the kidney and of an increased likelihood of calcium lithiasis

Flocks (1939, 1940) found that the excretion of calcium was raised in about two thirds of 35 unselected cases of calcium urolithiasis Furthermore, all patients with recurrent or



Changes in serum-calcium and plasma inorganic-phosphorus levels and twenty-four hour urinary excretion of calcium during follow-up period of fifteen months after end of long course of vitamin D rapidly-growing stones had a high urinary calcium Many of the patients with calcium stones had a high urinary calcium without any bone disease or evidence of hyperparathyroidism, change in blood-calcium level or blood-phosphorus level, or other demonstrable abnormality of calcium metabolism These patients responded to an acid ash diet and to vitamin D with an exaggerated increase in the urinary excretion of calcium

Albright and Reifenstein (1948), considering the metabolic disorders leading to hypercalcuria, divided them into those associated with hyperparathyroidism, osteoporosis during the stage of progression, renal acidosis, and those in whom no other abnormality was found This latter group, which they consider is probably the more common, they called idiopathic hypercalcuria, and they drew attention to a "tendency" to a low serum calcium level in this condition

Albright et al (1953) discussed further the problem of idiopathic hypercalcuria 22 patients had shown hyper calcuria with normal serum calcium and low plasma-phosphorus levels and, in most cases, evidence of past or present pyelonephritis There was also a high incidence of stone These workers suggested that infection damaged the renal tubules, thus causing hypercalcuria, a low serum-calcium level, and, possibly, by an ensuing overaction of the parathyroid glands, a low plasma inorganic phosphorus level

Pyrah and Raper (1955) examined radiologically 216 apparently healthy kidneys removed at necropsy and found small calcified foci in 10% of them. Microscopy of 206 healthy kidneys showed tiny calcified foci in 21%, and this figure might well have been higher if serial sections had been used These calcified foci were mainly found around the upper collecting tubules, but a few lay within the lumen of the tubules The origin of these foci, whether in minor pathological lesions which had healed or in temporary biochemical disturbances, was not determined

In children renal failure is sometimes associated with hypercalcæmia produced by hypervitaminosis D In the adult, renal damage following vitamin D administration is sometimes seen after long courses of calciferol given in the treatment of lupus The serum-calcium level rises, and renal-function tests show considerable impairment of function, often after many years

Dent (1954, 1956) has surveyed the influence of vitamin D on the excretion of calcium and phosphorus Among its many actions the vitamin promotes the intestinal absorption of calcium with a consequent decrease in fæcal calcium, and increases the urinary excretion of calcium even when given in doses insufficient to produce hypercalcæmia Dent has also drawn attention to the wide range of individual sensitivity to vitamin D

Care was taken in the present case to exclude the above mentioned conditions known to be associated with excessive urinary excretion of calcium The fall in the serum calcium level is of recent onset because the values were normal when the patient was first seen and declined subsequently Possibly the long-continued hyper calcuria associated with the administration of vitamin D caused persistent damage to the renal tubules and consequent continued excessive loss of calcium in the urine The gradual fall of the blood calcium level suggests that osteomalacia may appear in the future if the excessive excretion of calcium continues, and in this situation further stones and renal calcification are additional potential hazards

Vitamin D is at present added to many food preparations, in particular those used for infant feeding Since there is wide variation in individual sensitivity to the vitamin, and since severe toxic effects and persistent renal damage may follow hypercalcæmia and hypercalcuria as a result of excessive vitamin-D action, the advisability of this practice is being reviewed (British Pædiatric Association 1955) The danger is the greater for infants whose parents have been strongly encouraged to give further supplements of vitamin D in the form of cod liver oil or other concentrates The possible role of abnormal sensitivity to vitamin D in the pathogenesis of idiopathic hypercalcæmia in infants has been reviewed previously (Lowe et al 1954, Creery and Neill 1954, Bonham Carter et al 1955)

The present case has shown that not only are the known hazards present during the administration of the vitamin, but also that one complication—i e, hypercalcuria—may persist for a long time after other signs of overdosage have disappeared. It therefore seems likely that the exhibition of vitamin D, not necessarily in high dosage if combined with abnormal sensitivity, may be one of the possible causes of so-called "idiopathic hypercalcuria," perhaps presenting with its own train of complications long after the period of administration The history of such a course, if recalled by the patient, will almost certainly have been dismissed by him as irrelevant

The unrestricted sale of potent vitamin-D preparations may well need review in the light of such considerations

Summary

A patient is reported who, after prolonged self-administration of vitamin D, was admitted to hospital with renal colic presumed to be due to the passage of a small renal stone

Hypercalcuria was present without hypercalcæmia and persisted for at least fifteen months after the vitamin had been withheld This is assumed to have been induced by the vitamin D and to have been the cause of the renal symptoms

I wish to thank Dr A G Spencer, under whose care the patient was admitted, for permission to publish, Prof C E Dent for his constant help and advice, and Dr F V Flynn and the technical staff of the biochemical laboratory of University College Hospital for the estimations

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Preliminary Communication

CYTOPATHIC EFFECT ON PRIMATE AND RODENT TISSUE-CULTURES OF AGENT ISOLATED FROM MEASLES PATIENT

In 1954 Enders and Peebles[1] reported the isolation and passage, in tissue cultures of human or monkey kidney, of measles virus from the blood and throat-washings of patients Multiplication of the virus in the cultures was accompanied by characteristic changes in the cells—namely, formation of vacuolated syncytial giant cells in which the nuclear chromatin assumed a marginal position and was replaced centrally by an eosinophilic inclusion body surrounded by a clear halo In measles patients significant increases in neutralising antibody against the cytopathogenic agent developed Complement fixing antigen developed in the nutrient fluid of infected cultures, it reacted with convalescent-phase sera, but not with acute-phase sera, from measles patients

The present investigation was undertaken with two objects (1) to isolate from measles patients in London an agent producing cytopathic effects similar to those described by Enders and Peebles[1], and (2) in the event of success, to grow this agent in cultures of tissues more readily available than human and monkey kidney

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[1] Enders J F Peebles T C *Proc Soc exp Biol N Y* 1954 86 277

ISOLATION OF AGENT FROM CHILD WITH MEASLES

Nose and throat swabs were taken from a measles patient within 24 hours of the appearance of the rash The swabs were inoculated into the nutrient fluid (medium 199) of a monkey kidney tissue culture After 10 days' incubation at 36°C vacuolated syncytia were observed With continued incubation the cytopathic lesions increased in size and number The culture was stained on the 20th day after inoculation and numerous eosinophilic intranuclear inclusions were seen The nucleoli were preserved

GROWTH OF AGENT IN CULTURES OF PRIMATE AND RODENT TISSUES

Eleven passages of the agent were made in monkey-kidney tissue cultures, and cytopathic changes similar to those in the primary culture were seen at each passage level

Nutrient fluids from monkey kidney cultures showing typical cytopathic changes were used for inoculating tissue cultures of human infant kidney (excised), human amnion, human chorion, epithelial-like cells derived from human kidney by Chang,[2] HeLa cells, chick embryo lung, and the kidneys of a 5 week-old hamster, an 8 week old mouse, an embryo guineapig, a 5 day old guineapig, and an adult guineapig In all these tissue cultures, except of chick embryo lung, cytopathic changes developed which, during incubation and on staining at the 10th–20th day after inoculation, were essentially similar to those seen in the infected monkey kidney cultures Uninoculated tissue cultures of each type were incubated and observed, but no similar cytopathic changes were seen in them

Positive results were obtained in complement fixation tests using human convalescent measles sera and, as antigens, nutrient fluids from cultures showing cytopathic changes The results with nutrient fluids from uninoculated cultures were negative

COMMENT

There can be little doubt that the cytopathic changes in the inoculated tissue cultures were due to measles virus This view is supported by the fact that the primary culture had been inoculated with swabs from a patient in the exanthematous stage of measles, that antigens of the infected tissue cultures fixed complement in the presence of convalescent measles sera, and that the cytopathic changes were similar to those which Enders and Peebles[1] found in tissue cultures of human kidney or monkey kidney inoculated with measles virus Recently, other workers have reported the growth of measles virus in cultured cells of human origin (Jordan,[3] Dekking and McCarthy,[4] Black et al[5]) The results of the present investigation would seem to indicate that measles virus can be grown not only in cultures of primate tissues but also in those of rodent tissue Further work will be required to confirm and extend the investigation It will be of interest to see whether virus from measles patients can be isolated in rodent tissue cultures, and whether the virus can be serially propagated in such cultures Progress with this method would permit study of measles virus in the tissues of a small and conveniently obtainable animal, and a gain in knowledge regarding virus specificity

I thank Dr C H Andrewes for his encouragement and valuable advice, Dr T B Williamson and Dr G D W McKendrick for facilities for the work, Dr A Isaacs Dr H G Pereira, Miss D M Chapronière, and Mr L G C Maslen for their interest and help, Dr A P Goffe for monkey kidney cells, and Mrs R Villanueva for technical assistance

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[2] Chang R S M *Ibid*, 1954, 87 440

[3] Jordan W S jun *Ibid*, 1956, 92 872

[4] Dekking, F, McCarthy, K *Ibid*, 1956, 93 1

[5] Black F L Reissig, M, Melnick, J L *Ibid*, p 107

New Inventions

A DROP-TILT BED FOR THE LABOUR WARD

ABOUT two-thirds of maternal deaths associated with anæsthesia are caused by inhalation of stomach contents It is usually emphasised that such deaths are avoidable, but there is lack of agreement on the method of prevention

Gibberd[1] proposes a postural method and describes a labour-ward bed which can be tilted into a head-down position at a moment's notice by a simple movement of the anæsthetist's foot He says "The proper management of regurgitation of stomach contents . . . is to recognise it immediately, and immediately to lower the [patient's] head so that postural treatment has been adopted *before* [italics mine] the vomit can be inhaled" The essence of this method is its simplicity, but it cannot be used effectively unless the right type of bed is available Many labour-ward beds have no tilting device at all, some can be tilted by mechanisms which require manual operation and involve dangerous delay Delayed action is not enough Instantaneous action, which will save lives and prevent near fatalities, depends on a *split second* tilting device operated by the anæsthetist Gibberd rightly insists on the device being foot-operated so that the anæsthetist's hands are free for the performance of other urgent duties Head-harnesses for keeping the

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[1] Gibberd G F *Lancet*, 1955, i 901

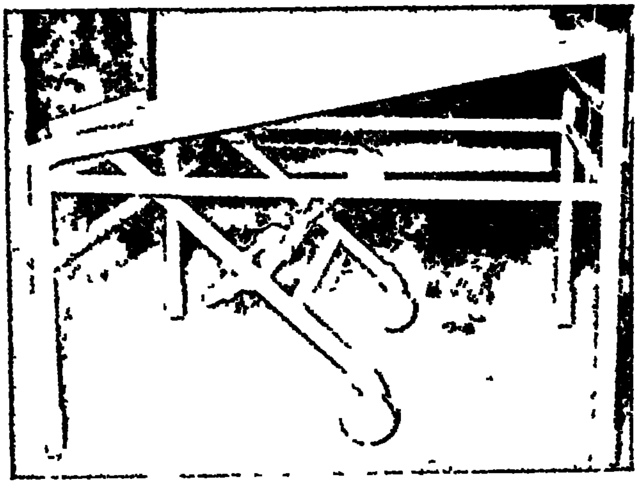

Fig 1

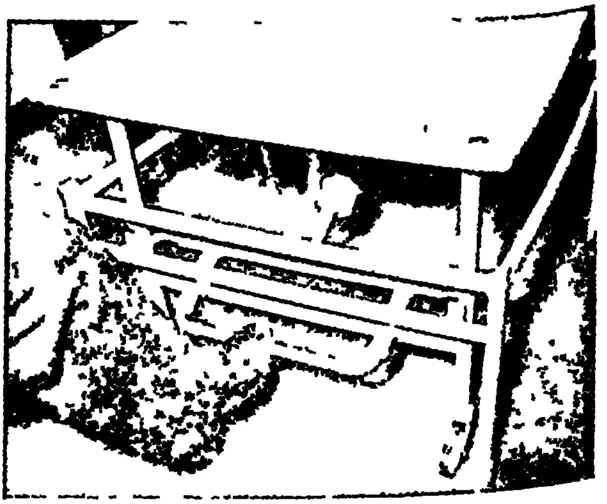

Fig 2

anæsthetic mask in position have no place in the labour-ward

I hope that the bed described here will focus attention on the postural method again and make possible a more general application of the principle of foot-operated drop-tilting

The bed is made in two sections a rigid section which supports the patient's legs, and a tilting section The rigid section (not illustrated) is on castors and can be easily disconnected from the tilting section and wheeled away. A rubber mattress covers each section

Fig 1 shows the tilting section in its head-down position. This tilt can also be obtained while the rigid section is in place, the patient's legs remaining on the rigid section while the rest of her body tilts It is therefore safe to induce anæsthesia before removing the rigid section and placing the patient in the lithotomy position The lower ends of the lithotomy poles can be seen in their holders

Fig 2 shows the locking device being released The wheel-bearing legs are prevented from running backwards by the lower of the two cross-bars which connect the short rear legs They cannot run forwards until the locking device is released This device is kept locked by the cylindrical lead weight It is released by the anæsthetist placing his foot on the kick-bar with sufficient force to counteract the effect of the lead weight The two U-shaped side-arms of the locking device are now clear of the cross-bar, against which they are normally held by the weight One simple movement of the foot unlocks the legs and starts them on their forward journey The patient, deprived of the support of these legs, drops into a head-down position Shock is absorbed by two small rubber buffers

When the tilted platform is lifted back to its normal horizontal position, the chain automatically pulls the legs back to their vertical locked position

The two holes which can be seen near the rear edge of the tilting platform are sockets for a removable head-rail

The major problem in design was to achieve stability Because the top surface tilts by pivoting round a rod which connects the upper ends of the front legs, any forward drag on the top surface will cause these legs to tilt forward Such drag occurs when traction is applied to the obstetric forceps and when the patient moves, or is moved, forwards on the bed Any forward tilt of the front legs is transmitted as an upward movement to the lower side-bars, which would lever the short rear legs off the floor This is prevented by a small metal plate on each wheel-bearing leg projecting over similar plates on the lower of the two cross-bars which connect the short rear legs Upward movement of these legs being stopped in this way, forward tilting of the front legs cannot take place The result is complete stability

This bed is now in use at the War Memorial Hospital in Nakuru, Kenya It was made locally The framework is made of British Standard Pipe, and the U-shaped pieces of the locking device are standard one-inch cross-overs

I wish to thank Mr Gustav Kramer for presenting the bed to the hospital, Mr Robert Heller and Mr Hans Gordon for the constructional work, and Mr A. G Kavlor for the photographs

St Luke's Hospital
Guildford

G C BIRD
M.B Lond

Reviews of Books

How to Live With Your Nerves

HENRY HARRIS, M D, D.P.M Pp 144 8s 6d

How to Live With Your Blood Pressure

BADEN BEATTY, M.B, D.P M Pp 142 8s 6d

How to Live With Your Duodenal Ulcer

ROBERT KEMP, M D, M.R C.P Pp 111 8s 6d

How to Live With Your Rheumatism

OSWALD SAVAGE, O.B E, M.R.C.P Pp 142 8s 6d

Family Doctor books London British Medical Association 1956

HERE are four essays in the widely practised but difficult—if not dangerous—art of expounding medicine to the layman ignorant of anatomy and physiology

One of the four is addressed solely to those with a proved duodenal ulcer, and one to sufferers from "rheumatism"—a clinical concept, if scarcely an entity But we all have a blood-pressure and nerves, we can all start looking at them and wondering about them, if encouraged, and some of us will almost certainly be healthier people and better patients if we know that we know nothing about them and are content to be ignorant than if we have the wealth of information here provided—more especially on blood-pressure

The crucial experiment of giving these books free to every appropriate reader in, say, Gloucester, while withholding them from all the citizens of Worcester, and shrewdly questioning a good big sample of patients and doctors in each city five years later, cannot be performed but it is probably fair to say that while a doctor could hand out *Duodenal Ulcer* or *Rheumatism* without hesitation he had best size up his man or woman before giving them *Nerves* or *Blood Pressure*

What can be said for certain is that all four books are well informed, up to date, and written with the single intention of helping the reader and his doctor

The Scientific Investigation of Crime

L C NICKOLLS, M SC A R C.S, F.R.I C, D.I C, director, Metropolitan Police Laboratory, New Scotland Yard London London Butterworth. 1956 Pp 398 50s

THE quality and usefulness of technical books on the scientific investigation of crime have improved remarkably in the past ten years Paul Kirk Svensson, and others have set a high standard, and any new book in this field must compete at the same level or fail Apart from the Hans Gross, which was written for routine police use, no English authority has attempted this task until now

Mr Nickolls, whose position as head of the forensic science laboratories at Scotland Yard provides him with abundant material, has made excellent use of it in this quite small and very practical handbook In the physical sciences the material, though restricted, covers the ground very well Not everyone will regret that British experience in firearms is too meagre for any forensic textbook from this country to compete with those from other parts of the world where gunplay is more familiar The section on wood, hairs, and fibres is particularly comprehensive for so small a book Those who would expect Mr Nickolls's specialty of forensic toxicology to receive lengthy treatment are put right in the introduction, where it is made quite clear that nothing more than a short review of method will be found in the toxicological section Those who want to go further into any subject have a full bibliography to help them For a start, however, this book gives them an authoritative and well-illustrated guide

The Cytology of Effusions in the Pleural, Pericardial and Peritoneal Cavities

A I. SPRIGGS, D M, M R C P London Heinemann Medical Books 1957 Pp 71 £2 2s

THIS atlas is intended for use "with the standard hæmatological atlases in order to help in the identification of the cells of pleural, pericardial and peritoneal fluid" It is surprising how old this subject is, and Dr Spriggs considers that it has been neglected because poor techniques have given poor results With proper technique much more can be made out of the cytology and, in particular, the study of the cells in these effusions may help to disclose malignant conditions

Dr Spriggs gives a clear account of his not too complicated technique, which demands nothing not already in the clinical laboratory and uses the standard May Grunwald Giemsa blood stain The results are illustrated in 5 colour plates made from paintings by Gereth M. Spriggs These plates are very good clearly printed, with well reproduced detail, and the cells are represented at a proper size so that they give a true idea of what will be seen in the microscope There are also 40 photomicrographs in monochrome, these are, on the whole, very good too though some suffer more than others from the inevitable lack of clarity of high power magnifications They certainly convey the variety of appearances encountered in the different conditions It is interesting to see that positive diagnostic results were obtained in 71% of pleural or peritoneal effusions due to malignant disease

The text is purely descriptive, and two chapters are devoted to this important matter of malignant effusions Dr Spriggs lists the criteria of malignancy but adds the warning that "none is pathognomonic and in practice conviction comes with experience and not with enumeration of criteria" We agree heartily

This, then, is a useful atlas which should encourage clinical pathologists to take more care with cytological preparations from pathological exudates, and so extract more information from them

The Child and the Family

First Relationships D W WINNICOTT, F R C P London Tavistock Publications Ltd 1957 Pp 147 12*s* 6*d*

IN this book are collected many of Dr Winnicott's radio talks about babies and young children and their parents

At his best Dr Winnicott has a poetic gift of expression, and he is at his best when talking to what he believes to be an unsophisticated audience When he speaks to the "ordinary devoted mother" or "normal parents" of the immensely important part their normal loving impulses play in the growth of the individual and society, he is to a certain extent idealising his audience The implication is that any departure from this idealised normal is the result of adverse external influences, the normal mother knows how to deal with her newborn baby unless her self confidence is shaken by those caring for her This has been at least partly true—the expert in physical care often does not appreciate how closely interwoven are the physical and psychological in babies and young children But many would not agree with Dr Winnicott's criterion of "normality," believing that it is "normal" for parents to feel irritation or anger with their offspring at times, and that the all loving, all giving parents would cause their children to feel great guilt Also it cannot be denied that many of the doubts which beset parents come from within, even if they are sometimes reinforced by the experts There must be few parents (however "normal") who have not felt that they were at least temporarily losing their way with one or another of their children

Few who try to help parents and children would not be glad of some of Dr Winnicott's perceptiveness and gift of communication This book may be most helpful to those to whom it is not directly addressed—experts on maternal and child care, general practitioners, nurses, obstetricians, and pædiatricians

Statistics of Therapeutic Trials

G HERDAN, M SC, PH D, LL D, lecturer in medical statistics, University of Bristol New York Elsevier Publishing Co London Cleaver-Hume Press 1955 Pp 367 50*s*

THIS is a disappointing book, although the author has an erudite and novel approach to teaching the application of statistical method to clinical trials

Instead of the more conventional systematic progress through the development of statistical concepts and techniques with illustrative examples on the way, he has started with a series of practical problems for which he prescribes the appropriate statistical method of analysis This is an attractive approach, but anyone who had read no other text on medical statistics might find himself at a loss when faced with a situation not covered by the series of prescriptions By cutting out the mathematics and giving the formulæ dogmatically a deceptive air of simplicity is achieved The standard deviation, for example, is dealt with in eight lines, and this may lead to a rather mechanical and unrealistic approach in practice If the rational basis of tests of significance is too briefly emphasised, the discussion of the design of clinical trials is rather long and at times obscure Those with practical experience in the conduct of clinical trials may be surprised by the author's failure to comment on the limitations of strict alternation or the importance of selection in the interpretation of the published comparison between survival times after various forms of cancer therapy

In short, although experienced workers will find some *stimulating ideas in this work, it cannot be recommended* as an introduction to the subject

The Adrenal Cortex

I CHESTER JONES, B SC, PH D, lecturer in zoology, University of Liverpool London Cambridge University Press 1957 Pp 316 37*s* 6*d*

THIS monograph, which treats the subject from the angle of comparative physiology, is particularly valuable since reports on different species are apt to appear in widely different types of specialist journals, and it is only too easy to miss relevant work

The clinician will be interested chiefly in the first and longest section of the book, which deals with the Eutheria, and in the last sections, where the embryology of the organs is considered and the author attempts to correlate structure and function In dealing with the Eutheria, after considering the gross and microscopic anatomy of the glands and the chemistry and biosynthesis of their hormones, the author discusses the control of adrenocortical secretion and devotes a long subsection to function Particularly interesting at present is the section on water and electrolyte metabolism and the possible coordination between the adrenals and the posterior lobe of the pituitary There is also a useful summary of what are called natural abnormalities of function—i e, diseases arising from hyper or hypo function of the adrenal cortex The diagrams and photographs are clear and the *price is reasonable*

This book will be much appreciated by anyone working in the field of endocrinology

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A Textbook of Psychiatry (8th ed London Oxford University Press 1956 Pp 745 35*s*)—The changes in "Henderson and Gillespie" do not appreciably alter its merits and defects Edited by Sir David Henderson with the help of Dr I R C Batchelor, it remains a well organised coherent statement of middle of the road psychiatry Contentious matters are treated with easy tolerance rather than intellectual rigour, and the citation of authorities is somewhat arbitrary With the advent of Dr Batchelor, the chapter on epilepsy has been recast and some of the discussion of ætiology amplified, the distinction between schizophrenia and paranoid states, asserted in recent editions, is now confidently treated as established, though one of the three reasons given—that patients with paranoid states "rarely exhibit the gross intellectual and emotional deterioration which is so characteristic of schizophrenia"—is questionable as fact and perhaps contains a *petitio principii*

Biographical Memoirs of Fellows of the Royal Society (Vol 2 London The Royal Society 1956 Pp 345 30*s*)—Nearly half of these twenty one masterly biographies deal with medical men or scientists who have worked in close touch with medicine Each includes an assessment of the contribution made to science, a detailed bibliography of published work sometimes of astonishing length, and a signed photograph of unusual excellence Of how many scientists could it be said that "the secret of his greatness is probably that he could recognise a problem that could be dealt with by experimental methods, that he could then reduce the experimental technique to something very simple and that in carrying out the experiment he could distinguish the essential points from the confusing details" Physiology is represented by Gleb Anrep, biochemistry by Harold King and Otto Rosenheim, experimental pathology by Charles Martin Bacteriology has lost O T Avery, Alexander Fleming, and Richard Pfeiffer Patrick Buxton made entomology his life's work, Sheldon Dudley epidemiology, and J A Sinton tropical medicine The biographies cover many subjects including advanced mathematics, philately, and nonsense verse with an unexpectedly amusing illustration It cannot be often that a publication of the Royal Society includes representatives of the two senior Services Sir Sheldon Dudley was medical director general of the Royal Navy during the 1939–45 war, and Brigadier Sinton did valuable work on malaria for the Army This series of biographies is of world wide interest and importance

A Therapeutic Index (2nd ed London Baillière Tindall, & Cox 1957 Pp 156 12*s* 6*d*)—For the new edition of this practical handbook by Dr C M Miller and Dr B K Ellenbogen some sections have been extensively revised and a few new ones added; and the antibiotic dosage tables have been modified

THE LANCET

LONDON SATURDAY MARCH 30, 1957

"Withdrawal"

THE choice may not be easy, but it is necessary. Doctors cannot have both the prestige of a profession, whose strength lies in the merits of its case, and the power of a trade union which is organised to apply pressure. In the public mind Dr Jekyll's status as the beloved physician will not survive his repeated transformation into Mr Hyde, the medical workman, who is ready to use political force in his own interest.

Granted its premises, the British Medical Association's plan[1] for constraining the Government is a good one: it does not come into action till October, and, even after it begins, its development by stages makes it at first no more than a warning of what is to come. But, though every chance is to be given to the other side to come to terms, the possibility remains that their resistance will harden and that a struggle will take place. In this, we are told, the aim would be to embarrass the Government without inconveniencing the public, yet it is hard to see how the Government would be embarrassed except in so far as the public were inconvenienced. True, no patient would be deprived of medical help, but he would normally be expected to pay for it and people might be as much upset by this as they would be if, in a railway strike, they were told that their season tickets had been cancelled but they could get to work by paying the railwaymen a special fare. The action recommended by the General Medical Services Committee is not a strike in the sense that services are to be withheld: doctors work for their patients, not for the Government, and they are going to continue this work, though under fresh arrangements of their own. But it would none the less be regarded by the public as a strike, because it is an attempt to secure better pay by threatening to make the paymaster's organisation unworkable. It is well to recognise, too, that sooner or later hostile critics would point to the advantage enjoyed by doctors in such a dispute—namely that, whereas the worker in industry risks his wages when he threatens to walk out, the doctor knows that many of his patients will not dare refuse him fees.

In giving these indications of the awkwardness of combining professional and trade-union techniques, we shall be told that the latter have often been used in the past *pro re nata*, without affecting the status of the profession, and that now (as sometimes before) they are the only means of getting the Government to pay attention to injustice. But the B.M.A.'s many unquestionable successes have not in fact been gained without cost—though, oddly enough, it is often those who believe most strongly in forceful methods that are readiest to note and deplore a less respectful attitude towards doctors nowadays, just as they are often the people who are particularly keen to keep medicine "out of politics". As for the argument that attention is paid only to negotiators who get tough, we believe, on the contrary, that nothing would be so likely to appeal to the sense of fairness of British Governments as the knowledge that they were dealing with a profession which in no circumstances would use its political weapons. For the present this moral asset has been thrown away, and doctors are urged to embark on a trial of political strength, on a purely monetary matter, in which it is far from certain that public opinion would be on their side.

The handling of medical remuneration by successive Governments has been lamentable: as we said earlier this year,[2] they have behaved not like partners in the enterprise of National Health but like intransigent and short-sighted employers. But the profession is itself to blame for losing opportunities to urge a review which might by now have provided a firmer and more durable basis than the Spens reports.[3] Moreover, the only Government that concerns us at the moment is Mr MACMILLAN's, and in his short time as Premier he can at least be said to have paid attention and taken action, even if we do not think it the right one. To the man-in-the street it may well seem that "something on account," and an inquiry intended to produce a permanent settlement, is a sensible way of dealing with an obviously complex problem, and in the present critical industrial situation his sympathies will probably be with the Government rather than with any group which seems to be asking favoured treatment. Actually the profession's case, strong though it is, does not look as overwhelming to the layman as it does to the doctor. Breach of contract? Few outsiders would accept the view that the Labour Government's acceptance of the Spens reports constitutes an automatic guarantee of doctors (and doctors alone) against suffering through inflation. Refusal of arbitration? There is less inconsistency than the B.M.A. imputes to him in the PRIME MINISTER's advocacy of arbitration in the shipyards and his denial of arbitration to doctors. For the doctors' claim is not against an industrial employer but against the Treasury, and, since the size of the claim is such as to affect the level of taxation, no Government who think it their duty to govern would willingly entrust the decision to an independent arbitrator. (How many of us, in Mr MACMILLAN's place and with his knowledge of the coming crisis in shipbuilding and engineering, and on the railways, would in fact have settled the doctors' claim first, or in full?) When the PRIME MINISTER expresses his faith in "some form" of arbitration he may feel that so far as doctors are concerned, he has provided the best possible form in the Royal Commission which is already at work. The fear that the terms of reference of this body might prevent its giving due weight to the Spens reports, and to their implications, is clearly removable; and the present Government cannot be accused of altogether rejecting negotiations if they argue that the time for attempting a lasting settlement is *after* the Royal Commission has reported. It is then—perhaps in nine months or a year—that the profession will be able to decide whether the suggested arrangements are satisfactory or whether doctors should withdraw from the National Health Service

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[1] Outlined on p 697

[2] *Lancet*, 1957, i 31

[3] *Ibid* 1954 i 1277

The words "withdrawal from the service" are being used in two different senses which need sharp distinction The kind of withdrawal which we for our part think both mistaken and professionally wrong is temporary like the industrial strike, it is an interruption of normal work lasting only till one or other side gives way, and when directed against a Government it is an attempt to impose terms on the community by extra-parliamentary means But the same objection does not, of course, arise when withdrawal is not being used politically, and there need be nothing unprofessional in doctors leaving the N H S, either individually or en masse, provided their notice is sufficient and their decision is irrevocable As to the purpose of the operation, some people are now talking as though a little "direct action" will not only make the Government pay what is claimed but also make them change the service in some beneficial (though usually unspecified) way Others, who have disliked the N H S from the start, see this as the moment when a new MOSES should invite his people to follow him out of bondage Before accepting such an invitation, however, general practitioners may well ask for detailed information on life in the wilderness, and they should consider, soberly rather than in anger, the nature of their present discontent

Apart from the dispute about money, this discontent arises chiefly from a feeling that the relationship of doctor and patient is no longer what it was, and that organisation has made medicine less enjoyable than in the days of purely private practice, also that it favours mediocrity and impedes progress We may note, however, that in so far as this is true it is not peculiar to the British system not long ago an American authority was saying that insurance schemes in the United States have altered the relationships of doctors, patients, and hospitals, which are now on a less personal basis[4], and in a lecture to students another American teacher has been speaking of "present mediocrity" and a degeneration of motive in which "achievement becomes less impelling than security" Very possibly the capitation fee is not in fact the best means of paying the family physician[2], but even so, its disadvantages cannot all be laid at the door of our Governmental oppressors, since it is the method which the profession itself has preferred to maintain[5] Given a cessation of the cold war which has been doing so much harm to the service, profession and Government should be able to consider seriously together what alterations in such arrangements can and should be made That even without such radical alterations there are big opportunities for improving general practice within the service has been proved by the enterprising minority of family doctors who have latterly done so much to raise its standards and increase their satisfaction in their work

Meanwhile, exacerbation of the cold war must damage not only the service but—even more—the profession From deep conviction, the B M A s chairman of council ominously insists that, for the sake of medicine and our children, every practitioner must agree to withdraw complete unity and loyalty are essential[6] But, from conviction as deep, many will decline to support a course which, whatever its immediate rewards, cannot but be ultimately harmful Today the general public still pays the profession the compliment of seeing something amusing, because incongruous, in the action recommended by the B M A there can hardly be a doctor in the country who has not had to suffer the greeting of some humorist "Hullo doctor! You on strike?" But if current emotion prevails over traditional wisdom, and practitioners follow the fashion of industrial disputes, such action will never seem incongruous again, and one of our most valuable if least ponderable possessions will have been lost Instead, the real need now is twofold—that the Government should restore confidence in the Government and that the profession should restore confidence in the profession Only then will they be able to work together to the same important ends

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[4] *New York Times* Feb 17 1957

[5] See *Medical World Newsletter* March 1957

[6] See *Times* March 25 1957

Phosphatases and Prostatic Carcinoma

ENZYMES which split organic phosphates and are most active around pH 5—"acid phosphatases"—are present in many human tissues, but their concentration in the adult prostate is several hundred times greater than in other organs[1] This high prostatic level is not present before puberty, and has been demonstrated only in man and monkeys, and to a lesser degree in dogs, it is not found in cats, rabbits, guineapigs, or rats[2] In human seminal fluid, acid-phosphatase levels are even higher than they are in the prostate[2] The physiological function of this enzyme is unknown, but, as we noted earlier[3] the acidity which is most favourable for its action corresponds to that of the vagina at the time of ovulation The subject of prostatic acid-phosphatase levels in serum is complicated by differences in methods of assessing activity and in the range of phosphatases measured Not all of the acid phosphatase in the serum comes from the prostate Of particular importance is the red-cell acid phosphatase, the serum level of which rises sharply if hæmolysis occurs The method of ABUL FADL and KING[4] involves inactivation of this fraction, but not of the prostatic fraction, by formaldehyde ABUL FADL and KING[5] also reported the almost specific inactivation of prostatic acid phosphatase by L-tartrate—a means of differentiation which has been found to be of value[6] but has not yet been so widely used as their formaldehyde method

In 1938, GUTMAN and GUTMAN[7] described raised serum acid-phosphatase levels in patients with prostatic carcinoma, and their work has been confirmed and extended by many others[8–13] Using the formaldehyde method, MERIVALE[12] found that 22 out of 23 patients with carcinoma of the prostate had serum levels above 3 units per 100 ml, 15 of them above

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[1] Kutscher, W Wolbergs, H *Hoppe Seyl Z* 1935 236 23

[2] Sullivan T J, Gutman, E B, Gutman, A B *J Urol* 191
48 426

[3] *Lancet* 1945 i 790

[4] Abul Fadl, M A M King, E J *J clin Path* 1948 1 80

[5] Abul Fadl M A M, King, E J *Biochem J* 1949 45, 51

[6] Ozar M B, Isaac C A, Valk W L *J Urol* 1955, 74 150

[7] Gutman A B Gutman E B *J clin Invest* 1938 17 473

[8] Huggins C, Scott W W, Hodges, C V *J Urol* 1941, 46

[9] Wray S *Lancet*, 1945 i 783

[10] Woodard, H Q *Cancer N Y* 1952, 5 236

[11] Herbert F K *Quart J Med* 1946 15 221

[12] Merivale W H H *Guy's Hosp Rep* 1951, 100, 223

[13] Wray S *J clin Path* 1956 9 341

5 units In contrast, of 101 patients with other prostatic or non-prostatic conditions, 19 had levels above 3 units per 100 ml, and only 5 of them above 5 units By the same method, WRAY[13] noted levels above 3 units per 100 ml in 43 out of 73 patients with prostatic carcinoma, but only in 1 out of 427 with other conditions Various explanations have been suggested for the normal levels often found in proved carcinoma of the prostate It is possible that "barriers exist in the normal prostate gland that prevent the escape of acid phosphatase into the circulation"[10] and that invasion or metastasis is necessary before the serum levels rise[2 8] Production of the enzyme may cease in anaplastic growths[2], and previously raised blood-levels may be temporarily much reduced during intercurrent fever[8] An acid-phosphatase inhibitor has been demonstrated in some cases[14] Whatever the reasons, normal serum-acid-phosphatase levels cannot be taken as evidence against a diagnosis of carcinoma of the prostate But levels between 3 and 5 units per 100 ml, by the formaldehyde method, should be regarded as suspicious and levels above 5 units as strong evidence for such a diagnosis Urinary retention,[13] prostatic massage,[15] liver disease, and Paget's disease of bone[4 11] may all, however, give rise to "false-positive" results The effect of œstrogen therapy on prostatic carcinoma with high initial serum-acid-phosphatase levels can be judged by following the return of these levels to normal[2 9]

A phosphatase active at an alkaline reaction is related to bone production[16] Raised serum-alkaline-phosphatase levels are found in many bone diseases, including secondary malignant disease,[17] and in obstructive jaundice[18] Workers who have studied alkaline as well as acid phosphatase in serum in relation to carcinoma of the prostate have generally found that alkaline phosphatase is sometimes increased but it is not of much clinical value[8] WRAY, however, lately recorded characteristic patterns of behaviour of plasma-alkaline-phosphatase levels after œstrogen treatment of prostatic carcinoma[13] When the plasma-alkaline-phosphatase value was initially normal, a rise started immediately after stilbœstrol therapy began After reaching a peak, the value fell to normal more slowly When the alkaline phosphatase was much raised at the start there was an initial fall coinciding with the start of stilbœstrol, but after a few days it began to rise again and reached a peak above its initial value within thirty to forty days Thereafter there was a gradual fall, as in patients with initially normal alkaline-phosphatase levels WRAY found these changes helpful in confirming the diagnosis of metastasising prostatic carcinoma, in indicating the presence of unsuspected secondary deposits, and in judging the effects of treatment In at least 1 patient, failure of the expected pattern to appear was followed by the discovery that the primary tumour was bronchial not prostatic Such findings, if confirmed, will provide a useful supplement to acid-phosphatase studies in the diagnosis and management of carcinoma of the prostate

University Apartheid

WHEN the United States Supreme Court decided in 1954 that, for white and coloured students, "separate educational facilities are inherently unequal," it was making an observation as relevant to South Africa as to the United States In the same way that the Jim Crow colleges and schools acquired an inferior status and a reputation for poor training, indifferent staff and inadequate funds, South African non-European institutions have been handicapped in comparison with those for whites, and neither schools nor colleges "for non-Europeans only" have reached anything like European levels At the "mixed" universities of Cape Town and Witwatersrand European and non-European students have been given opportunities that were as nearly equal as seemed possible For medical graduates, the rewards of qualifying may be less (African, Coloured, and European interns, for instance, working at the same hospital, are paid at different rates), but the degrees of all students are nevertheless equal These mixed universities have been a healthy feature of South African life, for they have provided one of the few social meeting-places for young men and women of different races A spirit of racial cooperation has distinguished these students from their contemporaries, white and black, of segregated universities in the country, and the main opposition to segregated university education comes from these universities and their graduates

When, in 1951,[1] the Durban medical school was established as part of the Natal University, it represented to some extent a compromise between mixed and segregated institutions Natal University had students of all races, but conducted parallel classes for Europeans and non-Europeans, thus accepting internal segregation In the hope of those who had worked for its establishment, the Durban medical school was to be "primarily non-European,' but not exclusively so The Union government, however, offered to take full financial responsibility for the school, and it made the condition (reluctantly accepted by Natal University) that only non-Europeans were to be admitted to the school, except when special permission was granted by the minister of education Moreover, to further the aim of segregation, bursary-loans were offered to medical students on the condition that bursars undertook to confine their practice to non-Europeans and to work only in areas approved by the South African government One of the government's objects in developing the Durban medical school was to enable it to remove non-European medical students from the mixed universities and offer them alternative places in Durban The minister of education specifically promised that the Durban school, though segregated, would be equal to the white institutions, and this makes developments at Durban of crucial interest to multiracial societies everywhere it provides one more experiment in segregated education

Men and women of distinction were attracted to the posts at the Durban school, partly because of its association with the university, partly by the promise of stimulating teaching and research in a non-European school All were completely determined that no inferiority in standards or status would be tolerated Natal University was closely concerned in the development of the medical curriculum, and a seven-year degree course was planned, with several interesting features The preclinical years include courses in history, sociology, psychology, and a language The department of social, preventive, and family medicine (sponsored by the Rockefeller Foundation) gives the medical student, throughout his last three years, practical and theoretical training in family practice, with all its social and psychological implications The medical school has encouraged interesting educational methods and research programmes relevant to modern medical education and to problems of health and disease in Africa The record of teaching and research in this young medical school has been outstanding But, perhaps because of the segregation policy of Natal University, the parallel classes, and the separate student representative bodies, the Durban medical school could not make the same contribution to better relations between the races as the mixed universities, though non-white students—African, Indian, and Coloured—enjoy the advantages of association in class and residence As a constituent of Natal University, and with its high academic reputation, however, the school stands out in South Africa as an institution for non-Europeans that is on a par with similar schools for white students This itself was a significant achievement

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[14] Hudson P Progress Report Department of Urology Columbia University 1954

[15] Hock F Tessler R N J *Urol* 1949 62, 488

[16] Robison R *Biochem J* 1923 17, 286

[17] King E J Delory G E *Postgrad med J* 1918 24 290

[18] Sherlock S *J Path Bact* 1946 58 523

[1] Report on the Government's intended action to remove the Faculty of Medicine from the University of Natal Durban Medical School, March 4 1957

Unhappily, it is now reported that the South African government has decided on complete segregation for South African universities[2] It has announced legislation to close Witwatersrand and Cape Town Universities to non-Europeans, and the Durban medical school is no longer to be a constituent of Natal University Instead, the University of South Africa (at present a correspondence college) is to become the examining body for the medical school, and the minister of education will control its policy, including the appointment and discipline of its staff Members of the staff, it is said, will be subject to dismissal if they "publicly comment adversely upon the administration of any department of the Government " or if they are associated with propaganda calculated "to cause or promote antagonism among any section of the population of the Union against any other section of the population " or "to impede, obstruct, or undermine the activities of any Government department" Thus, the medical school will become a State department and the independence of its teachers will be destroyed The University Apartheid Bill provides for Bantu colleges for Bantu, Coloured colleges for Coloureds How this will be achieved in Durban is still not known Strong protests have come from many quarters, medical and academic, and the government's action, taken without consultation, is regarded as a serious invasion of university autonomy University independence has been much treasured, the more so in the stress of the complex South African situation And many hold that to alter the character of the medical school in this way is to break faith with staff and students

In South Africa, medical schools have evolved and developed in the universities and they owe their vitality to this association There is no parallel in South Africa to the medical school growing up around a teaching hospital, nor is there anything comparable to the Royal Colleges in this country In Natal, the association with the university has been particularly important, firstly, because its potentialities attracted staff of high ability, in spite of the restricted student body, and secondly, because a small staff and a small group of students needed all the stimulus and assistance that other specialists could offer Thus, the psychology course, spread over two years, is the best the university could devise for the needs of medical students, though on paper there is only one part time lecturer responsible for this course The University of South Africa is not comparable to a university in this sense, and there seems no doubt that to reduce the medical school to the level of a State department is to destroy its claim to equality with the other medical schools It will lose its university status and, as the published protests have made clear, it will lose the confidence of staff, students, and the medical profession Posts at a school thus debased and restricted are unlikely to attract teachers of standing

With Witwatersrand and Cape Town reserved for Europeans and the Durban medical school under the minister of education, South Africa achieves total segregation in the training of its doctors Many fear that the standard of training of the non European doctor will be lower than that of his white colleague, and the South African Medical and Dental Council, which has not so far been prepared to admit dual educational standards for doctors, will, it is hoped, stand firm on this point The South African government is clearly determined to impress its policy of racial segregation on every corner of the Union, and nurses have lately joined those who have permitted racial divisions to be made in their organisation There can be little hope of reversing this manifestation in Durban, but the Medical and Dental Council will be widely supported, in South Africa and in many other countries, if it continues to insist on the maintenance of high teaching standards Those in positions of influence in the medical profession in South Africa will, we hope, realise how much they stand to gain in the esteem of their colleagues all over the world if they speak out boldly against this attack on the freedom of university and doctor

Research Beyond the Tweed

THE Scottish Hospitals Endowments Research Trust administer a fund of well over £2,000,000, transferred to them from the endowments of the old Scottish voluntary hospitals The income from this sum (over £90,000) is used to foster medical research, and in their first report[1] the Trust set out their powers and duties and their approach to their functions Much care is taken to avoid duplication of work and the Trust keep in close contact with bodies making similar grants They hope that universities and hospitals will continue to finance research from their own funds, the Trust favour applications made after preliminary work has been done Major apparatus bought by grants remain the property of the Trust, to ensure that it is put to good use (elsewhere if need be) when the project for which it was bought has been finished The Trust do not finance the purchase of normal basic laboratory equipment Before making any grant the Trust consult the Scottish Advisory Committee on Medical Research The seven trustees, whose chairman is Sir John Maxwell Erskine, hope that Scottish people will remember the Trust when they consider donations or bequests for research

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[2] Times March 14 1957

[1] Scottish Hospitals Endowment Research Trust First Report H M Stationery Office 1957 Pp 18 1s 3d

Annotations

HUMAN ANTIHÆMOPHILIC FACTOR FOR THERAPY

We have known for a long time that classical hæmophilia is associated with absence of a factor normally present in human plasma In 1937 Patek and Taylor,[1] working in Boston, Massachusetts, obtained from normal human plasma a globulin fraction with enhanced antihæmophilic activity Work at the same school showed eight years later that the antihæmophilic factor was associated with fibrinogen,[2] and then, in 1946, that the factor could be separated from fibrinogen [3] It seemed as if the preparation of a dried frozen human antihæmophilic factor, readily available, after simple solution, for administration to the bleeding hæmophilic patient, was in sight But unexpected technical difficulties connected with the exceptional lability of antihæmophilic globulin, and causing unpredictable inactivation of the fractions, have prevented the issue of such a preparation so far For the treatment of hæmophilia we have had to rely on transfusion of fresh blood or, more recently, of fresh plasma quickly separated from the cells and frozen at –20°C Such precautions are necessary because antihæmophilic activity falls off rapidly in blood stored in the usual way at 2–4°C, it is reduced by at least 50% after twelve hours under ordinary conditions

In an effort to overcome this difficulty preparations of antihæmophilic factor from the blood of animals have been tested, and these can have high activity Macfarlane et al [4] used a bovine antihæmophilic globulin, Fraenkel and Honey [5] recorded the successful treatment of a wounded hæmophiliac with an antihæmophilic globulin prepared from pigs' blood But these animal preparations have a strictly limited value because they are foreign proteins and repeated administration soon leads to reactions that can be dangerous Accordingly the article on p 647 of this issue by Dr R A Kekwick and Dr P Wolf, describing preparation of an effective concentrate of human antihæmophilic factor, is of great interest, representing what we hope is the penultimate step along a surprisingly long road It is not quite the end, because their preparation still contains fibrinogen

Kekwick and Wolf point out that progress in the preparation of concentrates of antihæmophilic factor was much accelerated when adequate methods of assaying antihæmophilic activity were developed The thromboplastin generation test of Biggs and Macfarlane [6] was the first in the field, but Kekwick and Wolf prefer the method, recently described by Wolf,[7] which provides a simple numerical value related to the prothrombin conversion of recalcified plasma This method uses an artificial substrate, resembling hæmophilic plasma, which is prepared from the supernatant solution left after precipitation of fibrinogen and antihæmophilic globulin from fresh normal plasma By this method the level of antihæmophilic factor in fresh normal citrated plasma is 8–18 units per ml (average 12 5 units per ml), and in classical hæmophilia the level is usually less than 3 units per ml This technique enabled them to assay quantitatively the antihæmophilic activity of the concentrates Another technical advance that has helped this work is the refrigerated centrifuge, most of the manipulations involved were carried out at temperatures near freezing-point The final products were dried from the frozen state at –20°C and stored at this temperature The product Kekwick and Wolf have used has about ten times the activity of normal plasma, the protein content is about 2 2 g per 100 ml and the viscosity of an appropriate solution in distilled water is so low that intravenous administration presents no difficulties About 70% of this protein is fibrinogen, the problem of separating antihæmophilic factor from fibrinogen, and at the same time ensuring good recovery of an active material, has not yet been satisfactorily solved

They report results in 6 patients with hæmophilia, in 3, extraction of teeth was undertaken The volumes of antihæmophilic-factor concentrate used varied from 100 to 300 ml (corresponding to 1 to 3 *litres* of fresh plasma), and these relatively small volumes helped to avoid overloading the circulation Assay of antihæmophilic-factor activity in the recipient's plasma showed mostly a satisfactory rise after administration of the concentrate Not unexpectedly it was much harder to raise the patient's plasma-antihæmophilic-factor level when actual hæmorrhage was occurring, for example, in one incident where the concentrate was given to a patient who had alimentary-tract bleeding, 60% of the administered antihæmophilic factor was immediately used up

No resistance to this form of therapy has appeared so far, one patient had repeated doses of one of their preparations over five months But Kekwick and Wolf insist that there are still many difficulties We cannot, it seems, expect just yet to replace blood-transfusion by injection of antihæmophilic-factor concentrate in the routine treatment of hæmophilia Antihæmophilic globulin is susceptible to handling even at low temperatures All the steps of the preparation must be carried out aseptically to avoid final filtration, with its inevitable losses They point out, too, that the average hæmophilic patient who is bleeding requires a dose of antihæmophilic factor equivalent to 2 litres of fresh human plasma derived from about seven blood donations There are thought to be about 2000 hæmophiliacs in this country, and a single annual treatment for each would involve processing plasma from 14,000 blood donations Such a manufacture, they say, "presents a formidable problem, whose solution is not yet clear" Perhaps the best to be expected at present is that the special centres which undertake the care and treatment of hæmophilic patients will carry a small stock of the frozen dried antihæmophilic factor for emergency use, it keeps for several months Meanwhile, other tissue sources of antihæmophilic globulin are being explored, for instance, Nour-eldin and Wilkinson [8] have prepared from brain tissue antihæmophilic globulin which was free from fibrinogen

These special preparations of antihæmophilic factor are of value only to patients with classical hæmophilia, such fractions are useless in the clinically indistinguishable Christmas disease If, therefore, a patient with "hæmophilia" is admitted as an emergency case to hospital, and it is not known whether he has hæmophilia or Christmas disease, he should be treated by transfusion of fresh blood until the diagnosis has been clarified by the thromboplastin-generation test

BERYLLIUM POISONING

Poisoning by beryllium is rare in this country, but in the United States over 500 case records have been collected and are now available for study at the Massachusetts General Hospital Hardy [9] has used this unique material to investigate one of the most interesting features of the disease, its relationship to sarcoidosis—or, as some would say, to other varieties of sarcoidosis Acute beryllium poisoning has almost been eliminated by better protection of workers and it is only the chronic form that is likely to cause diagnostic difficulties Workers may be exposed to beryllium during extraction of the metal or production of its alloys, in the manufacture of fluorescent lamps and tubes, in atomic energy development, and in certain ceramic operations Beryl ore is not harmful, but beryllium itself and certain of its oxides and acid salts, especially the fluoride and sulphate, are toxic As in other types of sarcoidosis, the granulomas have been found in the liver, spleen, kidney, myocardium, skin, lymph-nodes, pleura, and lung, but no eye lesions, such as iritis and uveitis, have been reported, nor have lesions been found in the tonsils and parotid glands There are other differences from sarcoidosis So far no case has been found in the American records in which there was radiographic evidence of enlarged hilar nodes without abnormalities in the lung fields, nor have cystic changes been found in bones The prognosis of beryllium poisoning is worse than that of sarcoidosis Although there may be spontaneous remissions, some respiratory disability and radiographic abnormality persist The history of possible exposure to beryllium and the distribution of the abnormalities may make the diagnosis highly probable, but spectrographic or chemical detection of beryllium in the lesions is the only conclusive finding

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[1] Patek A J Taylor F H L *J clin Invest* 1937 16 113
[2] Minot G R Davidson C S Lewis J H Tagnon H J, Taylor F H L *Ibid* 1945 24 704
[3] Lewis J H Tagnon H J Davidson C S Minot G R Taylor F H L *Blood* 1946 1 166
[4] Macfarlane R G Biggs R Bidwell E *Lancet* 1954 i 1316
[5] Fraenkel G J Honey G E *Ibid* 1955 ii 1117
[6] Biggs R Macfarlane R G Human Blood Coagulation Oxford 1953
[7] Wolf P *Brit J Hæmatol* 1956 2 386
[8] Nour-eldin F Wilkinson J F *Ibid* p 433
[9] Hardy, H L *Amer Rev Tuberc* 1956, 74, 885

Hardy points out that the term "berylliosis" is confusing It is an ugly word and can easily be corrupted to "berylosis," which is misleading, for it wrongly incriminates beryl as the toxic agent She suggests that "berylliosis" should disappear and that the disease should be called "beryllium poisoning"—a welcome suggestion

THE FLOPPY INFANT

A RECENT newcomer to the group of muscle disorders in infants is the congenital myopathy described by Shy and Magee[1] They describe a family in which there were five affected persons, four of them male, in three generations The abnormality was noted at birth, or within a few months, as hypotonia and weakness of the legs, and in one instance the mother said that fœtal movements had been less noticeable than during a normal pregnancy There was weakness of the proximal muscle groups, more severe in the legs than the arms, and this led to delay in walking In one patient the sternomastoids and orbicularis oculi were weak Unlike most myopathies, however, the disease was not progressive Biopsy showed aberrant fibrillary bundles in the centre of almost every muscle fibre, which Shy and Magee believe are characteristic in anatomical arrangement and histochemical reactions

This disorder must be distinguished from other causes of primary muscular hypotonia in infants, notably Werdnig Hoffmann's disease, in which muscular weakness affects particularly the proximal muscles and begins within the first year of life Though Werdnig Hoffmann's disease is also familial, it usually appears in siblings rather than in successive generations, and steady deterioration leads to death within a few years The primary lesion lies in the spinal cord affecting the anterior horn cells and ventral roots, and those who prefer pathological terms maintain that the condition should now be called "infantile spinal muscular atrophy" The other label which is attached to limp and floppy babies is amyotonia congenita No firm pathological basis has been established for this condition, and this is not surprising, for Walton,[2] who followed up 109 cases diagnosed at major hospitals as amyotonia congenita, showed that they represent a wide variety of pathological conditions He recommends that the term "amyotonia congenita" should be abandoned or used only to describe a clinical syndrome Nevertheless, 17 of his 109 cases resembled the condition described as amyotonia congenita by Oppenheim[3] There seems little reason, therefore, to abandon the original term, but the diagnosis should be made with great caution and should be followed up to make certain that an alternative diagnosis does not present itself—myopathy, polymyositis, cerebral palsy, mental defect, or skeletal or nutritional disorders To this list Chambers and MacDermot[4] have lately added polyneuritis, which they think was responsible for the picture of amyotonia congenita in 3 children they studied

None of these conditions is common Nevertheless it is important that they should be distinguished from each other, since, in some, treatment may considerably influence the outcome

GASTRO-ENTERITIS IN UGANDA

MANY doctors come from other parts of the Commonwealth to Britain for postgraduate training, and they welcome, among other things, the opportunity to meet specialists working with new techniques and to see other aspects of research As we remarked a few years ago,[5] this traffic is predominantly one way and there is much to be said for arranging matters so that more young British doctors can have the advantage of experience abroad, and more of them would be ready to go if they were sure that they would not thereby lose a chance of promotion at home and if they were helped to take their families with them They would learn much—perhaps not least to appreciate the difficulties that face some of their Commonwealth colleagues We would like to see an extension of the existing arrangements for exchanges of senior registrars with other Commonwealth hospitals, and we welcome, therefore, as a sign of the value of such exchanges, the recent paper by Luder[6] from Mulago Hospital, at Kampala in Uganda, for it springs from that hospital's association with the Hospital for Sick Children, Great Ormond Street

In an inquiry into the diarrhœa and vomiting syndrome in African children in Uganda, Luder analysed the result in 100 consecutive children admitted to Mulago Hospital Many were moribund on admission, and there was seldom a single cause They were treated by the unusual method of re establishing normal feeding as soon as the diarrhœa showed signs of diminishing, often two days after admission to hospital, and there was no intermediate stage of dilute feeding 29 patients were fed intravenously, but the mean stay in hospital in all 100 cases was still only just over five days Some children, however, were removed from hospital before they had been fully cured, and 12 died, 10 within twenty four hours of admission, which partly explains the extremely short mean stay in hospital Nevertheless, 60 of the children were well in three days

Todd and Hall[7] were the first to show, in a carefully controlled trial, the value of *chemoprophylaxis* of infantile gastro enteritis due to the specific serotypes of *Escherichia coli* More recently,[8] they found that *chemotherapy* was of little use in mild infantile gastro-enteritis, except when it was due to the specific serotypes of *Esch coli*, when it was of very definite value This finding emphasises the importance of looking for these organisms, if only to help the clinician decide which patients would probably benefit from antibiotic treatment Luder did not look for these serotypes, but it seems unlikely that they caused many of the infections he investigated the patients did not come from slums or institutions the course of the illness was shorter, and in 75% the fæces contained pus and blood, which are rare in enteritis due to *Esch coli*, but not uncommon in salmonella and shigella infections Cultures were made from only 76 specimens, and these were taken from rectal swabs, which many workers have found less satisfactory than fæces Luder does not say whether carrier medium was used to transport the specimens, or what interval elapsed between taking and culturing the rectal swabs, so it is hard to assess the importance of the information that only 9 shigella and no salmonella strains were isolated

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[1] Shy G M Magee K R *Brain* 1956, 79 610
[2] Walton J N *Lancet* 1956 i 1023
[3] Oppenheim H *Mschr Psychiat Neurol* 1900 8, 232
[4] Chambers R, MacDermot, V *Lancet*, Feb 23, 1957, p
[5] *Ibid* 1952 i 11
[6] Luder J *J trop Pediat* 1956 2 115
[7] Todd R McL Hall E G *Brit med J* 1953 i 1359
[8] Todd, R McL Hall E G *Arch Dis Childh* 1955 30 315

One aim of Luder's investigation was to determine "whether clinical observation or simple clinical pathological tests, suitable for poorly-equipped tropical hospitals, would enable cases to be subdivided into groups with possible ætiological significance", and this question was apparently answered because simple pathological tests seemed to provide inadequate evidence to help his clinical judgment Though his work has produced some interesting data, the very fact that it was limited to simple clinical pathological tests has restricted its usefulness

ROVSING'S OPERATION

FOR nearly fifty years the place of surgical decompression in the treatment of polycystic disease of the kidneys (Rovsing's operation) has remained a controversial subject Variations in the extent and behaviour of the disease and the lack of reliable information about postoperative renal function have made the results hard to assess Moreover, for patients with advanced disease, the operation carries a high mortality In a recent review of 18 cases treated surgically, however, Yates-Bell[1] drew attention to the symptomatic improvement and prolongation of life that can be achieved In 2 of his patients it was possible to compare the beneficial effect of unilateral decompression with the deterioration in the other kidney (as shown by excretion pyelography) after periods of eleven and nineteen years respectively Several other patients' symptoms were relieved, and in some there was a transient reduction of hypertension The immediate effect of the operation on renal function, however, was always adverse, though some later improvement could often be expected For this reason, in Yates-Bell's view, surgical treatment has little place in advanced polycystic disease with severe renal failure and should be reserved for early cases and those in which there is pain or recurrent hæmaturia

The immediate and often dangerous deterioration of renal function which follows exposure of the kidney and decompression of the cysts has in the past been ascribed largely to postoperative œdema and subsequent fibrosis of the residual renal tubules A preliminary report by Patton and Bricker,[2] however, indicated that many of the cystic nephrons retained some function, and their destruction at operation may well contribute to renal failure This thesis has lately been extended by a thorough study of renal function in 4 patients subjected respectively to bilateral decompression, unilateral decompression, surgical exposure only, and conservative treatment[3] After decompression clearance values fell immediately and were still low at the end of a year, but there was no notable change after simple exposure or conservative treatment Bricker and Patton conclude that decompression is not a satisfactory means of improving renal function and may even do permanent harm

The place of Rovsing's operation depends, therefore, on the respective values of these clinical and laboratory studies, and each individual case must be carefully assessed Everyone agrees that advanced cases should not be operated on, but a reasonable argument may be made out for decompression in patients with satisfactory renal function who are having symptoms On the other hand, symptoms are often transient, though recurrent, and they often respond to conservative measures With regard to prognosis it is doubtful, in the light of laboratory and genetic investigations, whether surgical treatment can, in general, influence survival Inquiries into the familial disease indicate wide variations in its natural course, often apparently related to the average prognosis of affected members in the family concerned[4] Any apparent prolongation of survival by operation must, therefore, be considered from this aspect and preferably substantiated by serial tests of renal function The position is to some extent analogous to that of bilateral "staghorn" lithiasis, though slow deterioration of renal function is the rule in this condition, operation is often best avoided unless serious symptoms demand it

SOME QUESTIONS

AMONG the flying spray of political persiflage some important questions were asked, if not answered, in the recent debates on the social services, the latest of which is reported on p 690 Freed from party undertones and emotional overtones, they reflect the real difficulties which beset the Welfare State today Can we afford to spend so much on the social services? Does the falling value of money mean that we are in fact spending less on them? Has their proportionate share of the national income fallen? How should the money be collected? Should the contributor pay more and the Exchequer less? Should all benefits be freely given to everyone? Should some be reserved for those who need them most?

It is in their attitude to this last question that the Government and the Opposition differ most sharply The Government believe that our limited resources should be concentrated where the need is greatest Let us, they say, discontinue or diminish indiscriminate benefits, such as subsidies on bread, milk, and school meals, so that we may offer more help to the widow, the sick, and the aged, to guard against extravagance, let us put charges on prescriptions, to give priority to children and expectant mothers let us make some charge for dental treatment The Opposition reply that a benefit may too easily become a charity when it is in fact available only to the less fortunate A charge, like a subsidy, they point out, falls indiscriminately and clumsily on everyone Those on whom it falls too heavily, say the Government, may reclaim their money from the National Assistance Board For many reply the Opposition, this procedure is too complex, for many humiliating

On the other hand members of both parties were prepared to accept it as reasonable that the many who are at work should contribute substantially to the social services The latest increase is earmarked for the National Health Service, and it was suggested that this arrangement might in hard times prove a valuable shelter from Treasury economies But it would be dangerous if the Exchequer contribution came to be regarded as a constant, and expansion, and indeed maintenance, of the services came to depend on rising contributions The weekly stamp is a blunt tool. So long as every man pays the same, it is inevitably tied to the amount that the lowest wage-group can afford, and several Labour members suggested that a system of graded contributions might be worth considering

Lord Hailsham, among others, has lately said that the design of our social services is distorted because it was planned to mitigate the hardships of the past rather than to meet the difficulties of the present Certainly inflation today is a more urgent threat than unemployment The cost of the Welfare State is higher than we expected and the taxpayer is hard-pressed But the nation's future depends on the education, health, and security of its citizens, and they in turn will probably depend on our finding the right answers to some of these questions

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DR SIBYL HORNER has been appointed Senior Medical Inspector of Factories in succession to Dr E R A Merewether

DR F C O VALENTINE, reader in chemotherapy in the University of London at the London Hospital, died on March 23 at the age of 59

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[1] Yates Bell, J G *Lancet* Jan 19 1957 p 126

[2] Patton, J F, Bricker N S *J Urol* 1954, 72 285

[3] Bricker N S Patton J F *New Engl J Med* 1957 256 212

[4] Ferguson, J D *Proc R Soc Med* 1949, 42 806

Special Articles

ORGANISATION IN GENERAL PRACTICE

Success of a Shift System

P M HIGGINS
M B Lond , M R C P
GENERAL PRACTITIONER, RUGELEY, STAFFS

THE cost of building and the restriction of capital make it essential, in planning a group practice or health centre, to study those designs and methods that allow more work to be handled without *proportionately increasing* the amount of space required Improvements in organisation and administration may serve this end so well as to affect considerably the planner's basic conceptions of what is needed

The traditional routine of general practice has been modified in many places and in various ways, but in most practices, for a large part of the working day—perhaps six hours or more—the surgery premises are unoccupied Where the surgery is part of the doctor's house this may be of little consequence, but in a group centre such a routine is wasteful of accommodation and staff

In 1954 our practice was faced with a sudden and unexpected increase of work As there was no prospect of enlarging our facilities correspondingly, the only solution was to improve organisation so as to make the best use of the existing premises

Our Patients and Our Surgery

In 1953 the practice consisted of four partners and an assistant One of the partners was almost wholly engaged in a small community of about 1800 people, while the others looked after about 10,500 patients in Rugeley itself and the surrounding area In that year a group centre was opened to serve this population An existing building was adapted to make a waiting room and office, and a lavatory and three consulting rooms were built on at the rear

While this work was under way a National Coal Board estate was constructed in the town Tenants began to move in during 1954, and by the end of 1955 there were 15,132 patients in the practice—an increase of just over 2800 But the increase in work was out of proportion to the numbers the new patients were 21% of the total practice, but they accounted for an average of 26% of the new calls (table I), and men from the new estate made 42% of the total male attendances (table II) Though another partner joined us, the practice and its facilities were greatly overburdened At each surgery the waiting room was full, the queue often reaching the doors An hour and a half before the evening surgery started, the waiting-room would begin to fill, and by 5 30 P M there might be 50 or more people waiting During 1955 there were 43,253 attendances at the surgery, on a Monday evening 130 or 140 patients might attend

To deal with this situation separate clinics for children and expectant mothers were held during the afternoons and an appointments system was started Similar arrangements have been successful in other practices, and they helped us too But the root of this problem was how to enable more than three doctors to work at each surgery session The simplest solution—to build one or two extra consulting rooms—had two disadvantages (1) the considerable capital cost, and (2) the administrative awkwardness of enlarging, in a linear fashion, the existing building The alternative solution—to work a shift system —would not have these disadvantages and would, moreover, spread, instead of concentrating, the work-load As we could not get permission to extend the premises, the first solution was in any case impossible, and we started a shift system on Nov 1, 1955

Surgery Hours

The final plan was that in the mornings—except on Wednesday and Thursday which were off duty days for some—two doctors would see patients from 8 30 to 10 30 A M and would then give way to two others who would work until 12 30 P M These four would see patients by appointment only, and, as it was then thought essential to make provision for casual attenders, without allowing them to destroy the appointment system, a fifth doctor was to be available from 9 to 11 A M to see such patients In actual fact, eventually all doctors saw patients by appointment, casuals were fitted in as necessary and proved much less of a problem than was feared

TABLE I—NEW CALLS, COUNTED EVERY FOUR WEEKS DURING 1955

Week ending	Total	New estate	% new estate
Jan 8	171	45	26 3
Feb 5	196	49	25 0
March 5	156	41	26 6
April 2	149	32	21 5
April 30	138	37	26 8
May 28	178	35	19 6
June 25	159	63	39 6
July 23	206	51	24 8
Aug 20	136	32	23 5
Sept 17	155	49	31 6
Oct 15	176	33	18 7
Nov 12	170	65	38 3
Dec 10	192	50	26 0

On Monday evening six doctors were accommodated in the three consulting-rooms—three from 4 30 to 6 P M and three from 6 to 8 P M , $10^1/_2$ surgery hours were thus available and 120 to 130 patients could be seen without strain On Tuesday evening five doctors worked similar shifts

The surgery premises were then in use during the following times

Monday
Surgery 8 30 A M –12 30 P M
Children's clinic 2–3 30 P M
Surgery 4 30–8 P M

Wednesday
Surgery 9–11 30 A M
Antenatal 2 30–5 P M
No evening surgery

Friday
Surgery 8 30 A M –12 30 P M
Antenatal } 2–3 30 P M
Children's clinic }
Surgery 5–7 30 P M

Tuesday
Surgery 8 30 A M –12 30 P M
Antenatal 2–4 30 P M
Surgery 5 30–8 P M

Thursday
Surgery 9–11 30 A M
Surgery 5–7 30 P M

Saturday
Surgery 8 30 A M –12 30 P M
No evening surgery

Thus on most working days the centre was being fully used from 8 30 A M to 7 30 P M or later During 1956 seven doctors, including a trainee assistant, were fitted into this scheme, using only three consulting rooms

TABLE II—SURGERY ATTENDANCES OVER THE PERIOD DEC 5-31, 1955 (COUNTED FOR 32 OUT OF A TOTAL OF 40 SESSIONS)

Total attendances	Total male attendances	New estate male attendances	% new estate
2773	1583	666	42

Staff

Under our old *régime* we employed two receptionists who had some help from the dispenser from the branch surgery Now we have an extra receptionist to work half time, but this addition has not been made solely because of extra work the dispenser has been freed *from some of her duties* in the main centre and the working hours of the staff have been organised into a more reasonable pattern The work has of course increased , in particular the number of telephone calls has gone up But the work is now better spaced , cards for most patients can be looked out before the surgery begins and the flow of patients is spread over a longer period The staff are now, however, almost wholly concerned with the reception and organisation of patients and have little time for other duties

Results

An immediate lightening of the strain and the burden of work was noticed by all the doctors, and it was at first put down to the season. Not until the end of the month were the figures produced, which showed that, in fact, in the first three weeks of November, the attendance-rate had been the highest for the whole year.

It is also worth relating the figures to the social classes in the practice population (table III). The main industry in the district is coal mining, but there are some light industries in the town mainly employing women. The practice also serves the agricultural area around the town. The occupation groups were derived from the 1951 census; the exact number of working males in the new population is unknown but it must be over 700, falling almost wholly into social classes III and IV.

To assess the success of the appointment system, a count was made of the number of appointments:

(1) By 3 P.M. for the evening surgery at 4.30 or 5 P.M.

(2) By the end of the evening surgery, for the next morning.

These criteria were fixed in order to rule out any possibility of the numbers containing any casuals turning up early to "queue", but, needless to say, these are minimum figures. By no means all the patients whose appointments were booked later than these times were casual callers who had to wait their turn. Particularly is this true of the morning surgery, because many more appointments for it would be made over the telephone before the surgery began. That few were casuals is shown by the numbers in the waiting room at the beginning of each surgery. From July to September there was an average of 62% appointments. Later weekly percentages were:

Week commencing Oct. 22—69% (total attendances 917)
„ Oct. 29—72% („ „ 855)
„ Nov. 12—73% („ „ 855)

(The figures for the last two weeks are not complete, relating to seven out of ten sessions in the week commencing Oct. 29 and eight out of ten in the week commencing Nov. 12.) Table IV gives detailed figures for the week with the largest number of surgery attendances (937)—i.e., that commencing Nov. 5.

TABLE III—SOCIAL CLASSIFICATION, RUGELEY AND STAFFORDSHIRE

—		Rugeley urban district	Administrative county (Staffordshire)
Total males (occupied and retired) aged 15 and over		3144	310 356
Social class	I	59	6040
	II	298	38 927
	III	1711	168 562
	IV	726	56 837
	V	350	39 990
Proportions per 1000 total	I	19	19
	II	95	125
	III	544	544
	IV	231	183
	V	111	129

TABLE IV—APPOINTMENTS FOR THE WEEK BEGINNING NOV. 5, 1956

—	—	Attendances	Appointments No.	Appointments %
Mon.	Morning	98	40	40
	Evening	116	111	95
Tues.	Morning	89	59	66
	Evening	92	81	88
Wed.	Morning	94	53	56
Thurs.	Morning	89	56	62
	Evening	113	105	92
Fri.	Morning	103	80	77
	Evening	52	38	73
Sat.	Morning	91	54	59

It is interesting to note that the evening surgeries appear to be much more fully booked, and over the four weeks Oct. 22 to Nov. 19 the percentage never fell below 74% and once was as high as 95%. The lower figures (ranging from 40% to 84%) for the morning surgeries may be due in part to the limiting effect of the criteria adopted; the true figure is almost certainly higher than this.

These figures show the extent to which patients made use of the system; we come now to examine its effectiveness in practice. The method chosen was to have the number of patients waiting counted every half-hour. Owing to staff changes and pressure of work these figures were collected for only fourteen sessions between Dec. 5, 1955, and Feb. 24, 1956. The maximum number waiting varied between 6 and 26, with an average of 11—except for one unusual occasion when it rose to 33 because one partner had fallen ill and another had been delayed half an hour in starting his surgery. When it is recognised that up to 140 patients were seen at one session, it will be seen how effectively the system worked. Moreover, the numbers waiting have to be broken down in three ways:

(1) They are waiting to see three doctors.
(2) Some are accompanying patients.
(3) Some are early for their appointments.

The effect of these last two factors became clear one evening when all three doctors were working to schedule, yet the waiting-room contained 12 people.

The maximum number waiting was almost always at its greatest at the time when the shifts changed, and we are now trying to diminish the effect of this by allowing a gap of 15 minutes at this time. Experience has shown the way to other improvements. The general rule is that 3 patients are booked every quarter of an hour, but allowance is now made for the individual doctor's rate of work. A profitable study could be made of the consulting-time needed by different groups; for example there is an impression that, on the whole, women patients need more

TABLE V—NUMBERS WAITING FOR WEEKS COMMENCING OCT. 22 AND NOV. 5 1956

Date	Day	Total attending A.M.	Total attending P.M.	8.30	9.0	9.30	10.0	10.30	11.0	11.30	12.0	4.30	5.0	5.30	6.0	6.30	7.0	7.30	8.0
Oct. 22	Mon.	89	125	2	10	12	8	15	5	0	0	6	7	5	9	12	9	0	0
	Tues.	90	116	1	4	13	12	14	8	1	0	8	4	9	12	15	–	0	
	Wed.	77		0	0	8	6	12	14	3	0								
	Thurs.	70	95	0	3	0	6	6	0	0	0	4	6	7	4	5	2	0	0
	Fri.	84	73	0	3	7	8		2	0	0	0	4	12	16	14	4		
	Sat.	89		3	4	6	10	7	2	0	0								
Nov. 5	Mon.	98	116	6	5	10	14	14				10	13	6	14	17	14		
	Tues.	89	92	Not counted								4	2	1	2	14	15	5	–
	Wed.	94		1	4	7	10	17	18										
	Thurs.	89	113	2	10	2	16	19	9	7		3	3	10	9	16	–	–	–
	Fri.	103	52	0	0	11	11	15	9	4		2	15	7	0	0	0		
	Sat.	91		0	3	9	7	0	0	–									

time than men and might therefore, with advantage, be given appointments towards the end of the surgery

More complete figures for the weeks commencing Oct 22 and Nov 5 are given in table v They relate to a period when, as will be mentioned, a fourth consulting room was in use, the figures of patients waiting must therefore be divided by four, and not by three

The main factor in this improvement has been the appointments system The chief effect of the shift system has been to spread the load Up to 30 patients are seen before the time when surgeries used to start (at about 9 30 A M and 5 30 P M), and this has diminished the bulge in the waiting room

The most significant evidence of improvement has been that we have now been able to reduce the size of our waiting room so that it now accommodates about 20, instead of 60, patients Not only does this make it a more attractive place, and lessen the risk of cross infection, but the space saved has been used to provide a new and more efficiently designed office The former office has been converted into a double purpose room which can be used either as a surgery or for dispensing and office procedures It has in fact been used as a fourth consulting-room with an adjustment of our shift system

No claim is made that the above represents an ideal arrangement, what has been done has been done under the pressure of events and in the face of severe limitations Further developments wait on better days and more spacious surroundings Until they come, purely administrative changes have enabled this practice to increase its facilities, to deal with an extra 2800 patients, and so to improve its organisation as to serve adequately a population of over 13,000 from a centre occupying approximately 1100 sq ft

I wish to express my thanks to the staff of the centre for their help in collecting the figures set out in this paper, to Dr Gerald Ramage, county medical officer of health, for providing the information in table III, and to Mr S Clewes, clerk to the Staffordshire executive council, for figures on the practice population

The members of the partnership are Dr B A Abbott, Dr P M James, Dr Stanley Dillon, Dr P J MacMonagle, and myself

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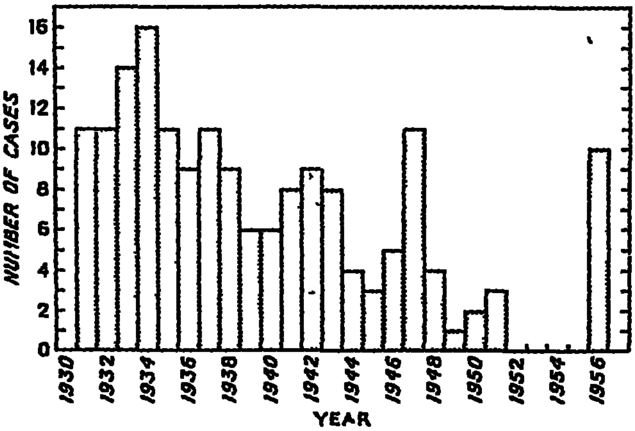
Public Health

"OPHTHALMIA NEONATORUM" AND MINOR NEONATAL INFECTION

I GORDON
M D Edin, M R C P, D P H
MEDICAL OFFICER OF HEALTH, ILFORD

IN Ilford, as the accompanying figure shows, notifications of ophthalmia neonatorum were steadily falling, until there were none in the four years 1952–55 In 1956, however, there were 10 (see figure) The disease notified is not classical opthhalmia neonatorum When the notification was received, each case was visited by a member of the public-health department, and by that time the condition had practically subsided No doubt many would have diagnosed the cases as "sticky eye", but why did the Ilford practitioners notify these 10 cases in 1956, and none in the previous four years, when undoubtedly they must have seen many cases of sticky eye? Presumably in 1956 they were stickier than usual

The 10 cases were notified by six different doctors, none notified more than 2 5 of the infants were born at home in different parts of the town, and 5 in hospital—four different hospitals, scattered over Greater London In 2 of the home confinements there was the same midwife, in the 3 others different midwives Hence there is no question of a local epidemic or individual reporting idiosyncrasies No publicity of any nature had been directed to this condition or its notification in the past few years locally



Cases of ophthalmia neonatorum notified each year in Ilford

I suspect that what is being notified is probably a mild staphylococcal infection Nearly all the extensive literature on antibiotic-resistant staphylococci refers to hospital practice, and half of these infants were delivered at home But, in resuming work in an infant welfare centre after some six years' absence, I have been impressed by the present extent of minor sepsis in the newborn—"sticky eye," mastitis (infective, not secretory), paronychia, blisters in the flexures, and discharging navels, and I get the impression that such sepsis is becoming as important as impetigo was in school children before the war

In New Zealand staphylococcal infection of the newborn and pemphigus neonatorum are now notifiable diseases,[1] presumably because New Zealanders are worried as to its prevalence May this have any relation to the system of paying practitioners according to the number of items of service they provide, which must encourage the use of antibiotics?

The national figures do not, so far, reflect any rise in the notifications of ophthalmia neonatorum It will be interesting to see whether the Ilford figures are an indication of the shape of things to come

Immunisation against Diphtheria

Observations in Heston and Isleworth have led Anderson[2] to conclude that in immunisation against diphtheria booster doses of antigen provide no significant advantage over primary immunisation only In a review of children born in 1941, 1944, and 1947, he found that of all who had undergone primary immunisation and had later received a booster dose 91 1% were Schick-negative, whereas of all who had undergone primary immunisation only 89 9% were Schick negative This difference being very small, Anderson concludes that, so long as the incidence of diphtheria remains low, reinforcing inoculations should not be undertaken

Population of England and Wales

The Registrar-General[3] reports that projections of the population of England and Wales show that, on certain stated assumptions, the total population will increase from 44,821,000 (as at mid-1956) to 45,569,000 in 1961, 47,423,000 in 1976, and 48,545,000 in 1996 In 1956 births registered exceeded deaths by 177,657 The corresponding increase for 1955 was 140,000, and the average increase for the five years 1950–54 was 107,349

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1 *Med Offr*, 1957, 97, 16
2 Anderson, A *Ibid*, March 22 1957 p 161
3 Registrar General's quarterly return no 432 H M Stationery Office Pp 32 1s 6d

In England Now

A Running Commentary by Peripatetic Correspondents

FEELING is running high among children throughout the country that so far there has been no reply to their plea that they should have an immediate rise to 1s for each extracted tooth A representative of the children said in London yesterday "There has been no increase in the agreed 6d bonus over the past thirty years During that time the price of cinema seats has doubled, bars of chocolate cost three times as much, and the advent of the new atomic weapons and Davy Crocket hats is placing enormous strains on our resources" The President of the Dental Practitioners' Union has said that dentists are unanimously opposed to a rise and that no interference from the State will be tolerated "Let us fight it out with the children," he said, "it is the only way to justice" Ministers are known to be deeply concerned that the situation should not worsen as there is clearly a risk that children will soon demand further rises in pocket-money, thus increasing the general inflationary effect on the economy "Let us arbitrate now—it will have to come to arbitration in the end," said the Minister of Paradontics last night He is confident that the Commission on Dental Awards will be able to produce a just solution for all

* * *

My dentist works at St Cecil's-in-the-South, across the way from our place, and, as we were students together in the high-and-far-off-times, my treatment is erratic to say the least When Conferences bow me down, it is too easy to mutter that old Bell won't mind, and send a message across In the same way he knows that to cancel my appointment won't lead to much heartache and waiting about Our average day seems to go something like this

I get a phone message at about 11 50 A M saying "Mr Bell rang but you were with the Professor and he says he's very sorry he won't be able to make your 12 o'clock appointment today but would you ring him back?" I ring back, and after a search they say "We're very sorry, but Mr Bell has just left and we don't know where he went Please may he ring you back?" I leave a clear account of my expected movements with both telephonists and tell them to flash my lights as well, but in the middle of the afternoon I absentmindedly settle in the one part of the outpatient department where the 3 per second flash does not penetrate "Oh *there* you are doctor, they've been ringing everywhere, there's a call for you from St Cecil's" The slightly hysterical telephonist says he couldn't wait any longer but would I ring back shortly By then Bell has been called to an unexpectedly fractured jaw, and is even now at the table I ask him to ring me back, and go home "Hallo, old chap," he says that evening over the phone "There you are at last, what was it you wanted?" "I don't want anything thanks, what did you want?" "Don't be silly," he says "You asked me to ring you back," "I know," I reply, "But you asked me to" "But you asked me to ask you to ask me to ring you back first!" he claims triumphantly "Nonsense, *you* started all this" I am emphatic on this point "Do you know, I do believe you're right now I come to think of it" he apologises "O.K, but what the hell *do* you want?" "Do you know, I'm not sure now" He is helpless with mirth "I believe it was to say I was sorry I couldn't make your appointment, yes it was Well, do *come over to* lunch tomorrow"

"Thank you," I reply "I'll ring you back"

* * *

Our hospital is a postgraduate teaching institution and it attracts a number of American nurses who pause there in their intensive global tour Our Senior Night Sister, seeing one of them on duty for the first time, remarked brightly, "Good evening, Nurse," to which the other replied "Hi," waving a hand in friendly greeting It was, accordingly, with some surprise that a recent arrival was observed to be polite and aloof to the point of coldness, adding a respectful "Sir" *to each* sentence Poor girl, we thought, she must have heard so much about the polite and formal British, and we gave her time to settle in At last my patience broke I had known her for some weeks, and one quiet evening I said "Please, Nurse, stop calling me Sir" She looked at me through those acutely angulated lenses and growled unexpectedly and quite without malice: "O K you lousy bum"

* * *

It was late and it was raining Bright shop lights added to the confusion of sodium street-lamps, zebra-crossing beacons traffic signals, keep-left signs, and all the other means of keeping the motorists' eyes off the road A little green Ford dragged itself reluctantly past the red light and shook bumpers with a big black one There this not unfriendly encounter might have ended, but for the long arm of the law

The hall of the stipendiary magistrate's court was crowded when, two months later, my solicitor looked gloomily at the notice-board and said "Yours is the last case of the day You won't get away before six Consider yourself lucky it's such a trivial affair If all goes well you might come off quite lightly Of course, you'll be fined, you know They all went up this year, so don't expect less than five guineas There will be costs on the top of that, they are often quite a tidy bit Of course, that's only for the first charge You'll probably get the same again for careless driving Let's hope they don't get you for dangerous driving—you could lose your licence for that Do you have to use your car in your work? Never mind, this should be quite a simple case Why don't you go inside and hear some of the *other* cases to take your mind off it?"

The first case was that of a young lady who had walked up and down the Strand a few times She was fined 40*s* The apologetic gentleman who next stood in the dock had failed to pay his taxes on time "Have you paid them yet?" the magistrate asked him Apparently he had "Then you must pay a fine of 10 guineas," said the magistrate The third prisoner was charged with stealing 6*d* It was not his first offence "What have you to say?" he was asked, to which he replied that he was very sorry and would take advantage of the earliest possible opportunity to repay the stolen sum "In that case, you shall be given your chance," he was told, "but you must first go to prison for five months"

I can't think why more people don't go into the legal profession Hearing cases at a magistrate's court seems to be rather like taking a G P surgery, except that you need think only half as hard, you get through the list twice as fast, and you are immune from litigation But I can hardly be said to speak entirely without bias

* * *

Last week I had to attend an important interview for a post in pædiatrics The prospect did not unduly worry me, though I was promised a gruelling hour's interview The night before the great event, however, I went through the interview in my dreams, and to my surprise it was so thorough that it included the *examination* of my *tonsils* One of them was said by the chairman of the board to be infected, and somebody else got the job

* * *

Why do doctors put strings of strange letters after their names? What use are L M S S A, M R C P, or D P M in helping a patient to find the type of doctor he wants? Why not initials to give a clue to the doctor's professional personality—e g, V S (very sympathetic), J H (jocular and hearty), or G G E (gives good examination)

* * *

The pioneers of America might be less surprised than is commonly supposed if they returned today The *spiritual descendants of Billy* the Kid, for instance, now show their killings by notches on the bumpers, are more often arrested by the sheriff, and are convicted in terms of blood-alcohol estimation and an inspection of brake-linings Methods of making tea devised at the Boston Tea Party are still in use to judge by the result Indian war-cries are still to be heard by *tuning* the radio to almost any station The standard crew cut of the American male shows only too well that the technique of scalping is not a lost art.

Letters to the Editor

FŒTAL AND NEONATAL ANOXIA

SIR,—While agreeing with almost all you say in your leader of March 16, I am unable to see the logic of your statement that the fact of infants being able to survive long periods of asphyxia without damage to the nervous system is "an encouragement to those who plead for more active resuscitation of the newborn" Presumably "more active" refers to positive-pressure oxygen We can all agree that if there is evidence of obstruction which cannot be relieved by posturing and nasopharyngeal suction, it is logical to pass a tracheal tube under direct vision and apply controlled suction But these *cases do not require artificial respiration*, the baby is capable of breathing, but breathing is obstructed The cases which are controversial are those in which intranatal factors (prolonged labour, low hæmoglobin in the mother, hæmorrhage, anæsthetics, analgesics, &c) have caused anoxic injury to the midbrain with failure of respiratory activity The baby is suffering from "white asphyxia" It is limp, pale, or cyanosed, and makes no respiratory effort In such cases it is doubtful whether the lungs can be made to expand and take up oxygen by positive pressures which do not also rupture the lung I have seen one case recently with bilateral pneumothorax following positive-pressure oxygen, this infant did not survive

No doubt this problem of the anoxic infant will become less urgent as all possible measures are taken to secure physiological parturition, but we are very far from this position at present and in the meantime it astonishes me that there is not universal acceptance of the value of intragastric oxygen Here is a method which is safe, which is available to any midwife if she is given the necessary equipment, and which secures oxygenation of the blood (enough to abolish clinical cyanosis) in perhaps 3 out of 4 such cases *It is a reasonable assumption* that this degree of oxygenation will prevent further cerebral damage and put the infant in the best position for spontaneous recovery of respiratory function Some experienced operators consider that there are times when intragastric oxygen fails to produce, or perhaps to maintain, a good colour in the baby, and when intubation will allow *bronchial* absorption of oxygen enough to save life, for this, relatively low pressures of oxygen are required This may well be the case, but laryngoscopy and intubation can be carried out only by someone medically qualified, with the necessary training and equipment More than three quarters of all deliveries are by midwives alone

Farnborough Hospital
Kent

D G LEYS

BRONCHIAL CARCINOMA

SIR,—We deplore the complacency of recent letters and wish to support Mr Vernon Thompson's plea (Feb 23) for a greater sense of urgency in the diagnosis of bronchial carcinoma and a greater awareness of its possibility in any doubtful respiratory illness Too often procrastination in actively making a diagnosis removes the chance of successful surgery Experience in Birmingham of 4103 cases recently reviewed [1] has shown that a successful excision of the growth by pneumonectomy or lobectomy offers a 21% chance of surviving five years, but only 12 2% had a resection This deplorably low figure was largely due to the fact that 63% of cases had inoperable growths or metastases when first seen at hospital Up to some point in their history, all growths must be essentially resectable Hence early recognition is vitally necessary

Most cases come to be examined on account of symptoms In 10% their first symptom has been of an inoperable nature (*neurological, metastasis*, swelling of the neck, &c) The others demand an X-ray of the chest since most (73%) are referable to the lungs That is where the "wait and see" policy, the "review in 6 weeks," the "unresolved pneumonia," and other futile reports spell death to the patient In a disease so common and with such prominence in the mind these days, it is extraordinary to us how reluctant *radiologists* and physicians are to consider the possibility of cancer There is no time to be lost—analysis of 1592 cases in 1950 [2] showed in untreated cases an average time from first symptom to diagnosis of 4 4 months and of life after diagnosis of 4 0 months Surgeons can hardly expect to cure their patients if they arrive only in the last stage of their illness

Edgbaston
Birmingham, 15

A L D'ABREU
A BRIAN TAYLOR.

HOSPITAL MEDICAL RECORDS

SIR,—I wish to refer to a problem of some urgency regarding the fate of medical records in National Health Service hospitals

Hospital medical staffs of the National Health Service have recently been, or are likely soon to be, asked by their management committees to advise them on the question of keeping or destroying medical records This advice should be given with circumspection

Medical records—i e, case papers, reports, X rays &c —are, like other hospital records, Public Records, within the meaning of the Public Records Office Act This means that their preservation or destruction is subject to legal limitations and not to local or individual caprice In 1954 the Ministry of Health issued a circular (H M 54/47) to management committees informing them that at that time no records could be destroyed until definite permissive regulations had been issued These *regulations issued by the Ministry of* Health with the Public Records Office appeared in December, 1956 (*H M 56/103*), *comprising* a circular and a schedule of a list and particulars of certain classes of document accruing in hospitals and offices of hospital authorities not considered of sufficient public value to justify their preservation in the Public Records Office This deals with all manner of medical and hospital records many not of medical character

Under the terms of this last circular and the accompanying schedule, it is now permissible for management committees to destroy medical records of patients six years after their last attendance at the hospital in question except in the case of mental hospitals In the case of patients who died, the notes may be destroyed three years after *their death Both* circulars explain that this legislation is permissive and suggest that the records should in fact be kept for the longest possible time This point deserves great emphasis

The period of six years that is employed is probably inspired by legal considerations and from the medical viewpoint seems very short This is obviously so in relation *to the life time of* a child patient, or in respect of a disease liable to recurrence—for example, rheumatic fever It is also short in respect of a disease like disseminated sclerosis, which has a long extension in time

Aside from the welfare of the individual patient however, a considerable amount of genetic, statistical, and large scale social *medical* research must involve consulting records extending over a longer time than this Moreover, it is at least a tenable proposition that patients are entitled not to have their records destroyed at all Almost certainly they have no such right at present but whether they should not have one is worth consider-tion The provision of a medical dossier for all patients might be a proper and valuable feature of the National Health Service Perhaps a National Medical Archive Office storing microfilm copies of records is not an impracticable suggestion

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[1] United Birmingham Hospitals Annual Cancer Report 1954 vol [illegible]

[2] Taylor A B Waterhouse J A H *Thorax* 1950 5,

Meanwhile, the practical problem of keeping patients' records revolves around the question of the space required for their storage The ideal way of keeping records is probably in their original and complete form Less satisfactory is to employ some selection of types of records to be conserved Microfilm records obviously save an enormous amount of space but the initial cost of the apparatus, as well as the continual employment of extra staff to operate it, represents a formidable financial burden, and such a solution might be more suitable to a Central Medical Archive Office than to smaller units such as hospital groups

In my view it is better that case-papers be kept intact and indefinitely and in their original form until some further consideration be given to this problem on a national scale It seems unsatisfactory that the fate of patients records should be decided at the level of local hospital management committees whose practice will certainly vary

Lewisham Hospital
London S.E 13

M O Skelton

INSULIN TREATMENT OF SCHIZOPHRENIA

Sir,—I should like to congratulate Dr Ackner Dr Harris, and Dr Oldham on their controlled study, a masterpiece of planning and execution, described in your last issue (p 607) Whether we like it or not, we shall have to accept their conclusion that insulin is not the therapeutic agent of the coma regime However, this need not sadden the old hands, it simply confirms that for getting there in medicine there is nothing like the prescription Sweat makes good mortar

Isleworth Middlesex.

H Pullar-Strecker

HEBERDEN SOCIETY

Sir,—Your report of March 16 (p 565) of the papers read at the meeting of the Heberden Society on Feb 22 contains a number of inaccuracies which we would be grateful if you would correct

First, with regard to the electrodiagnostic changes in polymyositis, no evidence of spontaneous lower-motor-neurone activity was found and it was the association of a high rheobase with an intensity-duration curve characteristic of denervated muscle that was of significance The characteristic electromyographic change was a predominance on volition of the short duration and polyphasic motor unit potentials typical of a myopathy with, in half the cases, the coexisting features of a neuropathic lesion—i e, long duration polyphasic motor unit potentials with occasional fibrillation potentials and positive potentials

Second, the paper on the electrophoresis of serum-proteins referred not as you report, to "glycoproteins," but to "mucoproteins" the fractions M_1 and M_2 of which form a part only of the α_1 and α_2 glycoproteins respectively Therefore, mucoprotein M_1 or M_2 should be read for α_1 or α_2 glycoproteins throughout your report While the spot shapes indicative of fraction micro heterogeneity were obtained after two dimensional electrophoresis, semi quantitative estimation of the two mucoprotein fractions were in fact based on a single electrophoretic analysis at pH 4 5

Finally, in the paper on sheep cell agglutination tests, the figures you report—e g, positive results in 48% of cases of lupus erythematosus—relate to those quoted from the world literature and were not the results obtained at this hospital upon which the paper was based More important however is the fact that not all of our lupus cases with positive agglutination with the supernatant had a positive result with the precipitate and as a method of distinguishing between rheumatoid arthritis and lupus erythematosus it was apparently reliable in the event of a positive agglutination with the supernatant Finally it was the cases of systemic lupus erythematosus without joint involvement that appeared to have a higher incidence of false positive Wassermann tests (especially the cardiolipin test) and it was in two cases, not one, of systemic lupus with positive agglutination tests that the activity lay in the β globulin zone

Department of Physical Medicine
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Royal Free Hospital
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A T Richardson
J H Jacobs
R L Markham
E V. Hess

CIGARETTE SMOKING AT SCHOOL

Sir,—I was most interested in the article by Dr Parry Jones in your issue of March 23 I notice that he thinks his results might be abnormally high

I am at present conducting an investigation into the smoking habits of school-children in this county This is being carried out by means of an anonymous questionnaire following an explanatory talk to the pupils The eventual total number involved will be in the region of 9500 children between the ages of 11 and 16 and attending all types of school. Several months will elapse before the survey has been completed and analysed, but preliminary results indicate that Dr Parry Jones s findings are not in any way abnormal, and, in fact, some of my earlier findings show that the incidence of smoking is higher than he has quoted

Health Department
Oxfordshire County Council
Oxford

P W Bothwell
Deputy County Medical Officer

RHEUMATOID ARTHRITIS WITH CHRONIC LEG ULCERATION

Sir,—It was not at all our intention, in our article of Feb 9, to suggest that varicose ulceration may not coexist with rheumatoid arthritis It would indeed be significant if two such common disorders were not often seen in the same patient We are naturally familiar with cases like the one Dr Rivlin mentions (March 9) in which, as he says, the ulcer obviously results from venous stasis

Our point is that in the cases we described we could decide that the ulcers did not so originate We need hardly detail the bed rest and ancillary treatment we gave for these ulcers except to emphasise that the methods we used were those by which we regularly heal stasis ulcers and that failure of these cases to heal was striking and at first unexpected

We agree with Dr Laine and Dr Vainio (March 23) that the L.E.-cell phenomenon is not specific, but we had more evidence than this Because of the clinical similarity of the cases, all showing skin ulceration with rheumatoid arthritis in the absence of vascular stasis we thought it right to group them together, and it then is seen that among six patients four had shown drug sensitivity, all had serum abnormalities four showed the L.E.-cell phenomenon, and there were many other features which taken together can all be covered by the diagnosis of disseminated lupus erythematosus and by no other single diagnosis

In describing these cases as "rheumatoid arthritis with chronic leg ulceration" we were careful to avoid calling them "disseminated lupus erythematosus with leg ulceration" and in our discussion we indicated the contrast between these cases and the more acute case in which the diagnosis of disseminated lupus erythematosus is more acceptable

In general the diagnostic criteria of disseminated lupus erythematosus cannot be precisely laid down If, therefore, we put these cases into the category of disseminated lupus erythematosus, it is only tentatively and with the realisation that further study may show this to be unsound Our chief purpose has been to indicate the need for further study

London, W 1

J H ALLISON
F RAY BETTLEY

A NEW CLINICAL ENTITY?

SIR,—Since the beginning of this year, I have seen more than 60 patients suffering from an infectious disease which has become epidemic It seems to fall into the category of benign myalgic encephalomyelitis, group II,[1] as seen at the Royal Free Hospital in 1955

In all cases there have been fever, generalised muscular aching, severe headache, and glandular enlargement In many these have been the only findings though the glands of the posterior triangle are most prominent, the occipital group is spared, thus distinguishing the illness from rubella and mononucleosis The Paul Bunnell test has been negative and the leucocyte count normal in those cases tested

Most patients present with respiratory-tract symptoms, unusual for this time of the year, and painful pharyngitis is common Aspiration pneumonia has occurred in a few

Serious complications are rare, but hepatitis, polyarthritis, and skin rashes have been observed

A recent development has been a recurrence of high fever during the apparent recovery stage

In all of the severe cases there is extreme weakness during the attack, sometimes with disproportionate depression It seems probable that a period of post infective debility extending over several weeks, may result in these patients

It has not been possible in a general practice to embark on laboratory investigation in all cases, but from the clinical standpoint, this is probably another outbreak of "a new clinical entity"

Brighton
South Australia

DENIS A HICKS

ÆTIOLOGY OF PRE-ECLAMPSIA

SIR,—Professor Franklin,[2] speaking on behalf of himself, Mr Sophian, and others, postulated that "toxæmia of pregnancy is, or includes, a progressively increasing tendency for the renal shunt to be brought into operation, and that fatal bilateral cortical necrosis is the maximal, irreversible result of this tendency" Mr Sophian, in his letter of March 16, has again claimed that the "primigravid uterus by resisting stretch imposes renal ischæmia, and that this change is responsible for the pre eclamptic syndrome"

Bilateral renal cortical necrosis is a very rare condition and there has only been 1 death from it in Bradford during the past ten years, during which there have been over 50,000 confinements It is almost invariably associated with toxæmic accidental hæmorrhage, and the most serious cases tend to occur at about the 30th week of pregnancy, and in multigravidæ Further, 20% of all cases of eclampsia occur in multigravidæ and 33% of cases of eclampsia occur before the 32nd week Pre eclampsia occurs frequently in multigravidæ and before the 34th week, and hydramnios in a single pregnancy is practically never associated with eclampsia These clinical facts do not support Mr Sophian's contention any more than do the findings of Dr Morris which were reported at the same meeting

The point I wish to stress, however, is that bilateral renal cortical necrosis occurs in infants and in non-pregnant women as well as in pregnant women, and does not cause the pre eclamptic syndrome[3] [4] The patient with this condition, who is doomed to die within a few days, may have a normal blood pressure and manifest no œdema She suffers initially from neither coma nor convulsions Conversely, some eclamptic patients secrete urine freely throughout the attack

At the same meeting I claimed that from 10 to 1[illegible] of all women were incapable of adjusting themselves adequately to the pregnancy lactation syndrome because of inherent defects, such as chronic nephritis, hypertension (whether revealed or latent), diabetes, and hypoplasia of the arterial tree, of the endocrine system or of the genital organs Adequate antenatal care, which involves weekly visits after the 24th week, can all but eliminate eclampsia and severe pre eclampsia, cut down the incidence of proteinuria, and delay serious symptoms until about the 36th week, when the infant is viable, but cannot decrease the incidence of hypertension

The nutritional-mechanical hypothesis thus postulates that serious disturbance of *la fixité du milieu intérieur* is prone to occur in "defective" women as a result of their efforts to adjust themselves to pregnancy, and can only be prevented by adequate nutrition, rest in bed and to a lesser extent by the use of hypotensive drugs

Bradford

G W THEOBALD

A STUDY OF WAKE

SIR,—Dr Cruden's "approach to the problems of insomnia" (March 16) calls, I feel, for much criticism Starting with an inadequate definition of sleep which he takes from an encyclopædia rather than a medical book he speaks of sleep and wake without mentioning "state of consciousness," which is the unifying concept for both phenomena A standard textbook[1] defines sleep as "a physiological depression of those parts of the brain concerned with consciousness, induced by the appropriate state of the reticulo-hypothalamic system" This definition would, clearly, do also for wake, if the word depression were replaced by "activation" Therefore Dr Cruden's calling wake "a temporary cessation of sleeping state" is rather nugatory and not exactly a "fundamental reorientation of thought"

Although I would not object to his statement that "We must be awake to study any problem, including that of sleep-wake," I cannot agree with him when he goes on to say that wake is taken for granted Much and well-known work (by Bremer, Hess, Magoun, and many others) has been done, *indicating* that the state of consciousness referred to as wake is the result of an activation directed to the cortex and produced by stimuli which are mediated chiefly by the brain stem reticular system, involving mostly the hypothalamus and the thalamus It is true, of course, that our present knowledge of the phenomena of consciousness, including sleep, is far from satisfactory, but this should not allow theories to be advanced uncritically

Next, Dr Cruden postulates that sleep is *the basic* state of life Such a postulate, if meant to be philosophical, should be dismissed as far too vague and dogmatic; seen from a strictly medical angle, on the other hand, it is quite incompatible with the accepted views on the attributes and propensities of life and its relation [illegible] with consciousness The main argument which Dr Cruden produces to prove orthodoxy wrong and support his postulate is "sleep" during the fœtal state and infancy Yet by calling the fœtal state sleep one is simply driven to unnecessary semantic confusion, because, logically, sleep should then also extend to the state of fertilised ovum!

Obviously, the application of the term *sleep* in its neurophysiological and psychological sense to the fœtus [illegible] becomes an absurdity The fœtus and the newly born are so immature neurologically and psychologically that their inert state can only be interpreted in structural developmental terms Increasing maturation that brings about cortical activity (and a differentiated state of consciousness) is followed also by inhibition Whether the latter is done by an inherent mechanism or by some chemical products of activity in general (as the earlier "hypnotoxin" theory had it) or by both has not yet been determined It seems, however, a fact that this inhibition is proportional to, and therefore a physiological requirement of, the amount of activity (not a "basic state of life," as Dr Cruden claims), while both are changing in duration as the developmental curve of human life takes us from the inertness of infancy to the full activity of adulthood and to the decline of senescence

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[1] See *Lancet* 1956 i 789
[2] Franklin K J *Proc R Soc Med* 1949 42, 380, 387
[3] Kellar R J Arnott W M *Edinb med J* 1953, 40 101
[4] Theobald G W The Pregnancy Toxæmias London 1955 chap 30

[1] Brain W R Diseases of the Nervous System London 19

Dr Cruden's other postulate of "wake maintainers" is no more fortunate, for it is only another name for stimuli—impinging on the central nervous system at a time when the reticular activating system happens to be uninhibited

I dare say that doctors are aware of the importance of stimuli (physical and mental) in relation to going off to sleep, and treat their cases of insomnia accordingly, so I fail to see how calling these stimuli "wake maintainers," and claiming that wake is a temporary cessation of sleep, could alter the prospects of the unfortunate sufferers from insomnia

Reading the conclusion of the article I wondered whether the idea that arousal stimuli are "a threat to well-being" means, according to Dr Cruden's views, that "well-being" is sleep? This would, indeed, be an interesting point for discussion

Bethlem Royal Hospital,
Beckenham Kent

G M JACOBIDES

SIR,—In Dr Cruden's fascinating essay the conclusion is drawn by philosophical argument that "Wake" is the product of a Selye's "alarm reaction"

Approaching the subject from a practical angle, this view was put forward by Dr Galley and Dr Rooms as a result of their experiences with 'Viadril'[1] They suggested that a viadril analogue, waxing under the stress of waking and waning during sleep, may explain the mechanism of the alternating rhythm occurring in the sleep-wake cycle

The more our experience enlarges with this "bio-anæsthetic" viadril, the more we feel that by its administration we are producing a true sleep state

London S W 3

L H LERMAN

UNMARRIED PARENTHOOD

SIR,—Mr Mansfield (March 23) does little to solve the problem In this day when most people are calling for "their rights," the child-to be-born has only the "vagitus uterinus"—which, were it articulate, is perhaps too late But it has been aptly stated[2] that every child has a right to be conceived in love, to be born into happiness, and to be nurtured in security This is the basic teaching which must be given to married and unmarried alike, whether from school, youth club, church, or guidance clinic

Implicit in it is a condemnation of coition out of marriage, which may lead to unhappiness and insecurity and which is lust and not love Only within marriage is coition legitimate, not as Mr Mansfield suggests, more playful and lusty, but in the beauty of holiness Marriage between man and woman is a symbol of Christ and the Church[3] and anything intensifying that symbolic relationship is a sacred privilege

Raigmore Hospital
Inverness

WILLIAM HAMILTON

SIR,—In table VI of my article (Jan 19) I inadvertently transposed the number of legitimate and of illegitimate births in the group where social class was not stated Accordingly the last column of table VI should read, from above down 4, 1614, and 99 75

The corrected table shows that in nearly two-thirds of illegitimate births no information is available about social class Where social class is stated, the proportion of illegitimate births would appear to indicate the association to which I drew attention, but little weight can be attached to this since the omission of information may be highly correlated with social class

Crichton Royal
Dumfries

CYRIL GREENLAND

ALLOXAN AS A POSSIBLE THERAPEUTIC AGENT FOR PRIMARY CARCINOMA OF THE LIVER

SIR,—Two letters have appeared since the publication of our preliminary note on this subject on Jan 12

The remarks and suggestions of Dr Loxton (Jan 26) are most stimulating and indicate that he has appreciated fully, and apparently agrees with, our own orientation to the possible mode of action of alloxan We are not sure whether alloxan exerts its experimentally demonstrated effects in animals solely by virtue of the diabetes which it induces In fact there is considerable clinical evidence of a greater incidence of cancers in diabetics than in non-diabetic human subjects[1] In addition, maintained hyperglycæmia failed to develop in all but one of our cases with proven carcinoma, although there was quite strong clinical evidence and suggestive pathological indication that the alloxan injections had had some adjuvant effects on the liver cancers It therefore seems likely that alloxan may perhaps induce its anti-carcinogenic action by exerting a widespread effect, intra cellularly, on carbohydrate metabolism in *all* cells and perhaps especially on tumour cells—the latter believed to be more dependent on glycolysis It is at present our impression that the action of alloxan is transient, hence our recourse to repeated injections at intervals of about 2–4 weeks in all cases where follow-up was possible—a real difficulty in our work with uneducated Africans We have no information yet on the production of "oxidosis" by alloxan, nor have we tested the effects of dehydroascorbic acid as suggested by Dr Loxton We understand that other workers are investigating the action of this latter substance in experimental animals

As for the remarks of Dr Goldner (March 2)—we *were* unaware of the earlier studies on this subject, with some of which he was associated We have now consulted the first two of his references, the third not being available We feel that it is important to stress that following the 12 alloxan injections hitherto administered by us (repeated injections in several cases), renal damage has occurred in only one of eight cases—all with primary liver cancers We did not induce any other untoward reactions (aside from transient flushing) by alloxan administered according to the method and dosage which we detailed previously We venture to suggest the following explanation of the results reported by Dr Goldner and others who attempted the use of alloxan on a limited number of cases suffering from various types of cancers (but none with primary hepato cellular carcinomas which may perhaps be particularly susceptible to alloxan)

1 The nausea vomiting, chilling, and cyanosis induced in some of their cases may well have been attributed to a pyrogen in their solutions and *not* to the alloxan, more especially since these reactions did not appear in *all* their or in any of our cases

2 They administered enormous doses of alloxan, much more frequently than did we—e g, 220, 400, and 950 mg per kg body weight in human cases, in one case four times weekly, as compared with our usual dosage of 100 mg and maximal 150 mg at intervals of 2–4 weeks Doses as large as those used by Goldner and his associates are well known to be severely nephrotoxic and hepatotoxic in dogs

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[1] Galley A H Rooms M *Lancet* 1956 i 990
[2] Mearns A G D P H Lectures Glasgow University
[3] *Ephesians*, ch 5 p 25

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[1] Glicksman A S Rawson R W *Cancer*, 1956, 9, 1127

3 The ineffectiveness of alloxan on the cancers in their cases, and the occurrence of renal and hepatic damage, may also have been due to the very slow rate of administration of this drug—in their cases given over an hour or more, as compared to 1 *minute* in all our cases Duration of action of alloxan on islet cells is known to be very short lived—alloxan having a half life of only about 5 minutes in respect of its diabetogenic action Perhaps its action in intracellular carbohydrate metabolism generally may also be short lived, while hepatotoxic and nephrotoxic effects may perhaps occur only after long exposure to some other action of alloxan

In the light of the above, we do not think that Dr Goldner's evidence contradicts our findings or contraindicates further testing of alloxan in the treatment of carcinoma in man—especially if our dosage and method of preparation and administering alloxan are strictly adhered to, and if urine and blood are examined for evidence of renal damage before treatment On ethical grounds, the consistently hopeless prognosis, at least in our cases justifies almost any therapeutic measure, which holds out *any* hope of improvement Moreover, Sir, further studies—both clinical and experimental—in our laboratories clearly indicate certainly the theoretical and possibly also the practical value of alloxan therapy for understanding carcinogenesis We have now treated a total of eight patients In two of these, in whom hepatic pain was so severe as to require the use of analgesics, this symptom disappeared promptly and completely in both within 24 hours of the first alloxan injection In four cases the grossly enlarged liver diminished in size—in one by three fingers' width—within a fortnight of the first injection, and without deterioration in the clinical condition during this period Finally, our preliminary experimental observations in rats indicate that the metabolism in the ciliary body of alloxanised rats is influenced by feeding butter-yellow and also that the carbohydrate content of the benign hepatomas (preceding true malignancy inducible by butter-yellow in rats) seems to be different in alloxanised as compared with control rats These experimental findings suggest that the effects of alloxan on cancer induction or tumour growth may perhaps not be attributable solely to its diabetogenic action via the pancreatic islets, but possibly to some more subtle and diffuse effect on the carbohydrate metabolism and thereby on protein synthesis in all cells to a varying degree, but especially in carcinoma cells Experimental and clinical investigations on the actions of alloxan in carcinoma are being continued in our laboratories and hospital

Schlesinger Organisation
Medical Research Unit
Department of Physiology
and King Edward VIII Hospital
Faculty of Medicine,
University of Natal Durban
South Africa

THEODORE GILLMAN
MICHAEL HATHORN
N McE LAMONT

SIR —I found the observations of Professor Gillman and his colleagues stimulating Dr Loxton's comments on alloxan and cancer of the liver were also very interesting He was referring to Warburg's discovery that, in cancer cells, respiration is decreased and glycolysis increased alloxan may be able to block the main pathway—glycolysis—from which cancer cells derive their free energy and thus retard their growth

Dr Goldner has referred to earlier trials of alloxan in cancer

I should like to report my own observations on 2 patients treated with alloxan They were selected in the course of experiments designed to increase resistance to cancer growth or to reduce its invasiveness They were given repeated injections of alloxan but in smaller doses than those of Gillman et al Alloxan failed to induce diabetes and there were no obvious clinical signs of hepatorenal damage Of interest also is the post-mortem report in one case by Dr J C Burne

"Liver subcapsular adenocarcinoma, central congestion of lobules Bronchial lymph node papillary adenocarcinoma Pelvic mass papillary adenocarcinoma in wall of large intestine Spleen nothing abnormal Pancreas *considerable postmortem autolysis*, but no obvious hydropic or other change in islets

"No obvious degenerative changes in malignant cells, but mitoses scanty compared with those seen in operation specimen"

These findings suggest that tumour growth may have been retarded, and that abnormal carbohydrate metabolism can be associated with cancer

Bexley, Kent

W GROS

CHRONIC BRONCHITIS AND SMOKING

SIR,—As one who was fortunate enough to attend the N A P T symposium on chronic bronchitis, recently mentioned in your columns (March 16, p 593), may I draw attention to one considerable omission in the otherwise excellent series of papers? There was virtually no mention of cigarette smoking—one of the major ætiological and/or exacerbating factors

A N A P T pamphlet on chronic bronchitis describes smoking as "a very pleasant social habit" Medically, such a description is misleading, to say the very least, socially, it is just not true—as anyone will agree who considers the atmospheric pollution, litter, fires, and financial hardship it produces "It all depends which end of the cigarette you are on," as one of my friends aptly put it

Leicester

J P ANDERSON

BIRTHDAYS OF SPASTICS

SIR,—Dr Bevan (Feb 16) divides his sample of 62 spastics into three groups (table I) and notes that "The largest numbers were born in the period June to August (25)" He is *statistically* correct in suggesting that "This difference hardly seems to be a matter of chance" for $\chi^2 = 11\ 38$ and $P = < 0\ 01$ However, he may be *logically* incorrect if the three group division was made *after* he examined the distribution

TABLE I—MONTH OF BIRTH OF 62 SPASTICS

Month of birth	Observed	Expected	χ^2
XII, I II III	10	20 68	5 52
VI VII VIII	25	15 51	5 81
IV, V IX, X, XI	27	25 85	0 05
—	62	62 04	11 3

TABLE II—MONTH OF BIRTH OF 209 SPASTICS

Month of birth	Observed	Expected	χ^2
I	20	17 42	0 38
II	15	17 42	0 34
III	17	17 42	0 01
IV	21	17 42	0 74
V	20	17 42	0 38
VI	19	17 42	0 14
VII	16	17 42	0 12
VIII	21	17 42	0 74
IX	20	17 42	0 38
X	13	17 42	1 12
XI	12	17 42	1 69
XII	15	17 42	0 34
—	209	200 04	6 38

In our series of 209 spastics which were taken from a larger series of 448 cerebral palsy children, the months of birth were randomly distributed throughout the year (table II) for $\chi^2 = 6\ 38$ and $P = 0\ 90$

Department of Medical Genetics
The Montreal Children's Hospital,
and Department of Genetics,
McGill University

JULIUS D METRAKOS
GILBERT I PAUL

OBSTETRIC FLYING-SQUADS

SIR,—I have read Professor Nixon's letter in your issue of March 16.

I should like to point out that the rules of the Central Midwives Board do not prohibit the administration of ergometrine with the crowning of the head by midwives in domiciliary practice.

Central Midwives Board
London S.W.1

ARNOLD WALKER
Chairman

SIR,—As one who has for seven years worked among unurbanised tribal Africans in the Belgian Congo, I may perhaps be permitted to comment on Dr Grantly Dick-Read's statement last week that postpartum hæmorrhage is almost absent in uncomplicated labour in such a population. This is definitely not the case.

Such well-recognised predisposing factors to postpartum hæmorrhage as multiparity, anæmia, and multiple pregnancy are commonly present in these people. Every year we admit to the Baptist Mission Hospital at Bolobo, Belgian Congo, a number of women who have been reduced to a severe degree of anæmia by postpartum hæmorrhage.

I would agree with Dr Dick-Read that much serious postpartum hæmorrhage is due to faulty midwifery. It is difficult to imagine conditions under which more faulty midwifery is practised than among primitive Africans. In the area where I work, bearing down in the first stage is universally encouraged by ignorant village midwives. If the placenta does not separate, indiscriminate traction on the cord is practised, and where delivery is delayed interference of the most appalling kinds is indulged in. From experience I can assure Dr Dick Read that Africa is not the obstetric Utopia he imagines it to be.

Stoke on Trent

J. T. GRAY

EFFECT OF QUINIDINE ON POTASSIUM FLUX

SIR,—In their preliminary communication (March 16) on the effect of quinidine on potassium flux Dr Kärki and his colleagues state that at 37°C "the metabolic processes which drive Na^+ out of the cell and which raise the concentration of K^+ within the cell were active."

Since quinidine is a cell poison, we would expect quinidine (and probably most cell poisons) to have an unfavourable influence on such metabolic processes and to retard the re-entry of K^+ into the cell. It seems premature, however, to conclude that "this finding makes it seem likely that the action of quinidine is due to a reduction of the permeability of the cell membrane to potassium."

Rotterdam

C. K. V. v. DOMMELEN

FRACTURES OF THE FEMORAL NECK

SIR,—The review by Dr Murray and Mr Young (March 23) of the management and results of fractures of the femoral neck is a valuable presentation of fact, and as such is of great interest to all concerned with accident services. A study of the statistics gives a clear idea of the objects of the report, but note must inevitably be made of the high mortality-rate for both conservative and surgical treatment. The mortality for the total of 204 patients is 33%, for patients treated conservatively 48%, and for those operated on 26%.

Statistical comparison is often erroneous and in this instance may be invalid owing to unrecorded local factors, but on their face value these figures compare unfavourably with those from other clinics. The average mortality for 564 patients treated surgically, collected from the literature was 16.8%.

It is surprising to find that these authors conclude by saying that "... an emergency operation does not appear to be indicated ... the best time for it probably lies between forty-eight hours and seven days after the fracture was sustained." I believe the reverse to be true—that is that the operation should always be regarded as an emergency unless the patient is hopelessly moribund. It should be performed, not immediately, but within the first twenty-four hours.

Mervyn Evans,[1] reviewing the surgical treatment for trochanteric fractures in 101 patients from the Birmingham Accident Hospital, gave a mortality-rate of 10.9%. He wrote: "The best time to nail a trochanteric fracture is on the day of accident or on the following day, and where facilities are such that operation cannot be performed early it is probably better not done as a routine."

In my experience a careful anæsthetic and well-conducted operation, within twenty-four hours of injury, kills very few. It is often life saving and almost invariably promotes a marked improvement both in mental and physical health.

London W.1

PHILIP NEWMAN

GOVERNMENT AND PROFESSION

SIR,—Many of us are sick at heart. We feel humiliated, degraded. We are letting the country down when she can *least afford it*.

In the National press we are classed with the rest of the strikers. The engineers are striking in designated areas only, presumably where they can do most harm. Are they following our suggestions or are we following them? And make no mistake about it, it is a strike we are contemplating, and *we* are striking at the old and the sick. The British Medical Association say that we may tell the patients that the fees we charge should be reimbursed by the Government, but isn't this a gamble, and if it does not come off, who loses? Not the doctor, who has already pocketed his *5s.* or *7s. 6d.* Then about medicines. The patient takes his form along to the chemist, and it is the chemist, poor man, who has to take the risk. If he supplies the medicines prescribed by doctors outside the National Health Service, and does not charge the patient, he may not get remunerated by the State, and if this happens it will not take long to ruin a small man. Again, we are not the ones who get hurt, it is either the chemist or the patient.

Strikes come. Pay goes up. There is increase in the cost of production, and the cost of living goes up. Strikes again and the circle is complete. Cannot we who do not practise medicine only for a monetary gain but perhaps, too, because we love our work, be the first to stop this vicious spiral?

Exmouth

ARMOREL NETTELL

SIR,—If it is accepted that there is a just case for a rise in remuneration, then a settlement of this claim should be pursued. However, the very worse possible outcome of the present situation would be for a general rise of 24% in all our incomes, and I, and a good number of my professional colleagues, feel that our negotiators may be at fault in merely pressing the matter of remuneration whilst neglecting to stress the urgent needs for a reform of the service as a whole.

The needs for some reassessment and re-examination of the whole structure and organisation of the service after nearly ten years is very apparent to all those who work in it, and now that a Royal Commission has been formed it would be a pity if the opportunity for some such re-examination was missed.

Dealing primarily with matters of remuneration and speaking as a general practitioner, I would like to suggest a few possible measures that might be considered in any readjustment of our remuneration and as possible steps to improve standards and save public money. Before remedies can be discussed certain faults should be accurately defined.

(*a*) *Equal Pay for Unequal Work*

Apart from the present capitation fees which produce an increase in pay with the size of the practice, there is no grading of the services that are given by the doctor, and the size of a practice is certainly no criterion of the skill of the doctor or how hard he works

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[1] Evans, L. M. *J. Bone Jt Surg.* 1951, 33B, 192.

(b) *Lack of Incentives*

There are at present no real financial incentives for improving standards It is all too easy for a doctor to do the minimum of work and get away with it

(c) *Lack of Supervision and Control of Standards*

Freedom of the individual to practise medicine according to his own views and principles must be jealously guarded and maintained, *But* at the same time since we are being paid *out of public monies to care for our patients* it seems only right that some steps be taken to ensure that the public is receiving a sufficient standard of medical care

At present, apart from very infrequent visits by the local medical officer of the Ministry and the rather ludicrous attempt at "inspection" of practices carried out last year (the results of which have never been published) by the local medical committees, there has been no activity to see that the lay public are being cared for properly

No one likes "controls" or "interference" but, on the other hand, there exist innumerable safeguards in hospital practice to see that suitable standards are being maintained and these are accepted as inevitable and reasonable interferences

If we are to receive increased remuneration then we should make it clear that we do not wish to receive it without at the same time endeavouring to remedy some of the faults of the present systems of remuneration and organisation, but the manner in which the claim is being pressed at present offers few such opportunities

Increased remuneration should be selective and in proportion to the work done Incentives must be provided for better work, and for the achievement and maintenance of high standards in general practice, and so must increased opportunities and scope for registrars in hospitals to climb the consultant ladder

Expenditure must be cut by carrying out a drastic re appraisal of the whole service and introducing some remedies to the ever-rising cost

Having noted some of the faults what of the possible solutions ?

The Royal Commission should have its terms of reference broadened to include this re examination of the N H S and its composition altered to include medical representatives

Regarding future methods of remuneration, I suggest that in general practice this should continue on the present basis of a capitation fee with the increases being obtainable by increasing opportunities and incentives, as follows

As a measure to improve standards and at the same time stressing the preventive side of general practice it is suggested that the practitioner is paid a fee of, say, 10s for regularly examining certain of his patients at certain specified periods and completing a form, as is the present case with forms for vaccination and *immunisation—at birth, in infants at* 1 and 3 years of age, in children at 5, 10, and 15, in adults around the vulnerable middle age, in the elderly at retiring age of 60–65, and in the aged at 70 and then at regular 6 or 12 monthly intervals In this way the average G P with a list of around 2500 will increase his remuneration by some £450

A much more delicate matter that is somewhat allied to "merit awards" might be the provision of some such system whereby the *practitioner who is providing a high standard* of care would have a scale of increased remuneration based on some agreed standards Thus, this scale might be based on the types of accommodation provided, on the organisation of the practice, including secretarial arrangements and record keeping, on the provisions for investigations, on group practices, and so on The manner in which this assessment is carried out would require further thought

To balance these increased opportunities for remunerative rewards there must also be some *saving* of money

With the practitioners undertaking an ever increasing proportion of routine school and infant examinations then eventually there would be no need for the present local infant welfare and school clinics This would be a considerable public saving

Prescribing costs must be reduced and methods for this purpose should be explored, beginning with an examination *of the whole principles of therapy* A good deal of unnecessary and irrational prescribing undoubtedly occurs, especially in connection with the newest and most expensive drugs and it might be well *to* consider the reimposition of some [illegible] on the excessive use of the broad spectrum antibiotics and the corticosteroids by the reintroduction of the restrictions to their use to certain specific diseases In hospitals junior residents should not be allowed to use these and other expensive drugs haphazardly without the specific permission of the consultant in charge of the case The Cohen committee might also undertake a stricter revision of the categories of drugs allowable on E C 10s

The hospital services account *for* the largest bulk of the service and it is here that large measures of economy could be considered It is surely reasonable to expect inpatients to contribute something towards their board residence Time and motion studies should be carried out by "business efficiency" experts *to* see where further cuts can be made in the administrative services, for it is quite common to hear of hospitals where the administrative staffs have increased by as much as 200% since the N H S began, without any increase in the clinical work of the hospital

I feel sure that I am expressing the opinions of many of my colleagues in *voicing* my concern over the course of the present disagreements between the profession and the Government and in deploring the stress that is being laid on remuneration and the lack of mention in official circles, of the needs for a complete reappraisal of the service

Beckenham Kent JOHN FRY

Parliament

The Government and the Social Services

IN opening this debate on March 19, Dr EDITH SUMMERSKILL criticised the Government's social policy on the grounds that it placed "an undue and increasing burden on those least able to bear it," and would, if continued, seriously weaken the country's social services As examples of this retrogressive trend she cited the reduction of the food subsidies, the increases in the price of school meals and milk, especially welfare milk and the increased prescription charges Yet though the Government had found time to introduce these economies, nothing had been done about the cost of proprietary drugs Doctors, for instance, were still receiving lavish samples of tranquillisers, a practice which she described as "not only extravagant but harmful to the whole nation" She considered that the Government's policy revealed a characteristic disregard of the needs of the poorest and a lack of coordination among its own departments

Mr DENNIS VOSPER, the Minister of Health, maintained that the Government's policy recognised that the amount which could be spent on the social services was not unlimited It was therefore important to eliminate waste and inefficiency and to make sure that the services were available to those most in need He suggested that the Opposition when they were in power had failed to establish these priorities and as a result spread their resources in social services too thinly

Turning to his own department for examples of improvements made possible by this realistic policy Mr Vosper said that the money allocated *to* hospital building would be £20 million in 1956–58 and he hoped that it would be possible to keep on allocating increased sums Waiting-lists, though still too big, had fallen from *526,000 in 1953 to 433,000 in 1956* This was due to a better use of beds, which was in turn dependent on better recruitment Every category of hospital staff had added to its members in the past few years During the past five years 2000 more general practitioners had joined the service, and, though no-one could be complacent about the shortage of dentists, the number now practising was the highest ever known The number of courses of dental treatment for 1956–57 for England *and* Wales was 11 million, 10% higher than the previous maximum before the introduction of charges

The cost of the whole health service for Great Britain for 1957–58 would be £690 million compared with £450 million in 1949–50 Much of this increase was due to rises in pay and prices but there would be an increase of 15% in real terms When the health service was started it was assumed that the Exchequer would bear 72 4% of the cost This year it was bearing 80 2% The proposed increase in the contribution would do no more than reduce the Exchequer percentage to 74 1 It would restore the contributory element by asking those who were at work to pay towards those who were not Surely this measure was fair and fell on those who could bear it The major part of the cost would still be borne by the taxpayer

Whatever the merits of the charges, Mr Vosper continued, the number of dental courses and sight tests were increasing to record levels It was too early to judge the effect of the change in the prescription charge December, 1956, compared with the previous December, showed a fall in the number of prescriptions of 25%, but January, 1957, showed a fall on the previous January of only 14% He doubted whether vast savings could be made through restrictions on proprietary preparations

He defended the increase in the prices of welfare milk on the ground that there was still a subsidy of 50% School meals, he thought, were still a good bargain at 1s , and here too it was surely good sense to reduce a general and indiscriminate subsidy to enable expansion in other directions

CONTRIBUTION OR TAX

Miss **Alice Bacon** pointed out that, though more money had been spent on the social services in the past few years, population, prices, and wages had been rising She reminded Members that the Guillebaud Committee had found that the cost of the National Health Service as a proportion of our national resources had fallen She was uneasy about the increase in the National Insurance contribution which was to be earmarked for the health service It seemed to carry an implied rejection of putting any further charge for this service on taxation Mr **Niall MacDermot** feared that if more and more people were to pay directly for the social services, and where the burden was too heavy turn to the National Assistance Board, the principle that the social services were a right and not a charity would be lost

Sir **Spencer Summers** thought that there was a danger that the ever-growing expenditure on the social services might, if uncontrolled, destroy the whole system He suggested that it would be reasonable to expect people to carry individually the normal running expenses of life, such as spectacles, but to join together to protect themselves from such hazards as old age or a serious operation Those who were receiving National Assistance, and indeed those who were just above the subsistence level, should of course be helped In the normal running expenses of life he included two children If the present family allowance for the second child in wage-earning families were discontinued, £55–£60 million would be available annually—perhaps to increase the allowances for the larger families or retirement pensions

Mr **Somerville Hastings** said that we had rightly decided that uneducated children and unhealthy people would be a national disaster and we had provided the social services to avoid this He was hopeful that when the Minister of Health could give more attention to the prevention of illness the cost of the health service might be reduced Dr **Donald Johnson** also put forward a claim for prevention, this time in the sphere of mental health, and asked for better domiciliary psychiatric services which, by keeping the patient in his home, would relieve and support our overcrowded mental hospitals

Mr **R P Hornby** pointed out that the proportion of the cost of the health service borne by public funds was greater in Britain than in any other country in Europe —90% compared with 32% in Belgium, 30% in Sweden, 30% in Denmark, and 20–25% in Norway He thought that the health service would gain if its demands were insulated to a greater extent from other demands on the Exchequer The illusion that the weekly stamp paid for the health service was dangerous It would be a gain if people realised what was involved in financing the service

Mr **William Shepherd** was willing to accept the increased charge for the weekly stamp if the prescription charge could be abolished Mr **James Griffiths** was also prepared to reconsider the insurance contribution In his view at *7s 5d* it had become a kind of regressive taxation putting the biggest burden on those least able to bear it The only person today who paid the full insurance contribution was the person who did not earn enough to pay income-tax The flat contribution had reached the stage when it was an obstacle to progress

Mr **John Boyd-Carpenter**, the Minister of Pensions and National Insurance, said that it was not the duty of any Government to preserve every detail of the existing system, but to modify it by expansion in some directions and reduction in others That was what the Government had been doing Examples of expansion were the increases in benefits for widows and their children and for disabled war-pensioners, and the improvement in the earning-limit for retirement pensioners and in family allowances In concentrating resources on the areas of greatest need the Government had taken into account that the bulk of the population had a higher standard of life than ever before

Turning to the health service he said that no Government was prepared to allow any particular service to impose an unlimited charge on the Exchequer If the cost of the health service must be limited there were three alternatives increased charges, a cut in the service, or the addition to the stamp Opinion could legitimately vary on the precise emphasis to be placed on one social service rather than another, but it was unfair and untrue to say that the Government had attacked the services as a whole The worst betrayal of the services and their beneficiaries would be to allow their foundations to be eroded by financial strain, too heavy a load of expenditure to accumulate, and the whole system to collapse

Foreign Patients and the N H S

On March 18 Mr **Gerald Nabarro** raised once more the question whether foreigners should not be charged for medical or dental treatment which they received under the National Health Service The cost of the service was now high The Government had been obliged to refuse an increase in remuneration to the doctors, to charge more for prescriptions, and to increase the weekly contributions In circumstance of this kind, he thought it scandalous that foreigners, and others who could well afford to pay, were treated free, at the expense of the British taxpayer

Mr **J K Vaughan-Morgan**, parliamentary secretary to the Ministry of Health, began his reply by pointing out that in this connection the term "foreigner" was not wide enough to cover these uninvited patients More exactly they were "non-residents," for the group included not only foreigners but also Commonwealth citizens, those from overseas Colonies, citizens of the Irish Republic, and United Kingdom citizens resident abroad but here on holiday or on leave The exact size of this group was not known One estimate was 1,200,000, and of these he understood that about 800,000 stayed less than six months and the average length of stay was only a fortnight Compared with the rest of the population that number was equivalent to about 12,000 bed-days at any given time and the total cost might be roughly estimated at £60,000 According to the London executive council's records, in any one quarter in the London area about 14,000 temporary residents were treated by general practitioners Of these fewer than a quarter were from abroad About 3000 were people from overseas Australia headed the list, followed by the United States, the Irish Republic, South Africa, and Canada On the basis of these figures the outside estimate of the cost of all non-residents using any part of the National Health Service was probably £150,000

Two kinds of treatment were involved First, there was accident or emergency He thought that everyone would prefer to continue on what has been called the Samaritan principle but he wished there was more reciprocity with other countries It was one thing to lead the world, but it was more consoling if others were following a little nearer behind But the crux of the grievance was of course the alleged use of the hospital services for expensive operations and the dental and ophthalmic services for costly work In practice steps were taken to see that these privileges were not abused and that those who came here for the express purpose of obtaining free treatment were so far as possible prevented from doing so All aliens coming into the country were interviewed, or could be interviewed, at the port of entry by immigration officers One of the purposes of the interview was to satisfy the authorities that they were not coming here to exploit the health service If there was reason to think that they were, those concerned were either not allowed entry into the country or the appropriate authorities were warned that they should be treated as private patients Last year about 1000 foreigners were dealt with in this way This procedure did not apply to Commonwealth citizens, but persuasion was used to achieve the same end, with some success If there was any exploitation of the dental or ophthalmic services we had to remember that a substantial charge was made and possible delays in securing and completing treatment really made it available only for long-term visitors But he agreed that the occasional loophole existed In short we had the informal machinery to prevent exploitation, but it was informal and incomplete To extend it would mean closer controls at the ports, imposing on doctors, dentists, and hospitals the unwelcome responsibility of discovering whether a patient was entitled to receive treatment, and bringing back the identity card at a cost of £1 million—surely a costly sledgehammer for such a small nut But the Government recognised the exacerbation which the present position caused Though the problem was not as large as had been suggested, and though the solution was not easy, it was much on their minds

Reciprocal Agreements

In a written answer the MINISTER OF HEALTH set out the following agreements under which British subjects may obtain medical treatment abroad

Multilateral Agreements

A reciprocal agreement is in force between the United Kingdom, France, Belgium, the Netherlands, and Luxembourg for giving medical treatment to indigent persons A convention extending this agreement to all members of the Council of Europe is in force between those countries which have ratified it (the United Kingdom, the Irish Republic, the Netherlands, Belgium, Norway, Denmark, the Federal Republic of Germany, and Sweden)

Bilateral Agreements

Under a reciprocal agreement with the Channel Islands visitors from the United Kingdom are provided with free inpatient and outpatient hospital treatment in Jersey and Guernsey and general practitioner services (excluding dental or ophthalmic treatment other than emergency ophthalmic treatment) in Guernsey

Agreements are in force whereby British subjects employed in France, Italy, the Netherlands, and Luxembourg who participate in the social insurance schemes of those countries can have their United Kingdom insurance taken into account in reckoning their entitlement, and that of their dependants, to medical benefit An agreement with Sweden, which is expected to be ratified shortly, entitles all British nationals in Sweden, including tourists, to use the Swedish health services A similar agreement with Norway awaits signature

Under Australian legislation free medical treatment is available to various classes of pensioners and their dependants A reciprocal agreement enables citizens coming from the United Kingdom to Australia to qualify for such pensions, and hence for free medical treatment, by virtue of their United Kingdom insurance

In general, the countries with which agreements have been made meet the major part of the cost of treatment

Homicide Bill

This Bill has been passed by both Houses without amendment It received the Royal Assent on March 21

QUESTION TIME

Remuneration

Mr MARCUS LIPTON asked the Minister of Health what consultations he was now having with the medical profession about the interim adjustment of pay for general practitioners—Mr DENNIS VOSPER replied I have nothing to add to the Prime Minister's reply on March 19 Mr LIPTON If no consultations are taking place and if arbitration is denied how [illegible] is this problem being dealt with? How long is this policy of drift and shift to continue? Will the right hon Gentleman take note of the fact that both the *Times* and the *Daily Mirror* consider that general practitioners have a legitimate grievance? Mr VOSPER My right hon Friend said he would make a statement in due course Nothing has happened since March 19 to affect that position

Bovine Tuberculosis in Scotland

The whole of Scotland is now within the area plan for the eradication of tuberculosis in cattle, and it is hoped that all the areas will be cleared by the end of 1959 At present [illegible] of the cattle of Scotland are in attested herds

Mental Nurses

On Sept 30, 1956, the mental hospitals of England and Wales had in their employment 10,709 whole time and [illegible] part time men nurses and 9649 whole time and 6740 part time women nurses The estimated shortage, in terms of whole time staff, was 2900 men and 4500 women

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Obituary

HENRY ERNEST SIGERIST

M D Zürich, Hon D Sc Lond, D Litt., LL D, F R C P

Professor Sigerist died on March 17 at his home in the Swiss village where, since 1947, he had been working on his great new history of medicine As a historian he was unusual in his interest in the present His fine intellect enabled him to be a scholar, but his intelligence and his enjoyment of the world made him much more His approach was not that of the antiquarian he was always, he said, primarily interested in the general problems of medicine, investigating the past in order to get a clearer understanding of our own time and to help in preparing the future "To me the best way to understand a complex phenomenon has always been to study its genesis" He early recognised, too, that medicine is but one aspect of the general civilisation of a country—"that it is always determined by the general cultural conditions and by an underlying philosophy"

His own 65 years were eventful enough Born in Paris the son of a Swiss business-man, he was brought up in Zurich but at the age of 20 spent some time in London at the School of Oriental Studies After graduating in medicine at Zurich in 1917 he served as a doctor in the Swiss army, worked as a pharmacologist, and held a chair in his own university Then in 1925 came his first great opportunity, when he was invited to Leipzig to succeed Karl Sudhoff as director of the institute of the history of medicine [illegible] unique His career may now have seemed settled [illegible] in 1932, during a long and active visit to the United States, which provided material for his brilliant *American Medicine*, he was asked by William H Welch to succeed him in his chair at Johns Hopkins and take charge of the first American institute of the history of medicine Already he had shifted from French to German and the American appointment would mean adopting a third language—"which to a writer is a serious matter" But this was something that Sigerist, a good philologist, could take in his stride apart from his professional studies in Arabic, Latin, and Greek, he was at home in Italian and Spanish and by 1936 he could get along in Russian

In that year he was spending the second of two summers in the U S S R to collect information for his *Socialised Medicine in the Soviet Union*, first published

In 1937 and republished in 1947 This new book he regarded as a necessary complement to what he had written about America, for he had thought for some time that "the future of medicine will largely depend on what will be done in the United States and the Soviet Union" But, like many other visitors to the Soviet Union at that time, he perhaps allowed his sympathies to be engaged too strongly, and valuable though it is as an account of Russian medical organisation, his book too often leaves the impression that everything works as well as it is supposed to work The man who believed that in America medicine "has infinitely more to give than the people actually receive," and that medicine throughout the world is still in its first stage, was something less than fully objective in his attitude to a country where he saw science worshipped and "its progress is applied to life immediately for the benefit of the people" That is not to say, however, that he was unaware of the cost

During his years at Baltimore he visited not only Russia but also South Africa and India Of the Indian expedition W D-C writes

We had gone as members of a specially selected group of health experts from various countries to give evidence before the Health Survey and Development Committee (usually known as the Bhore Committee after its chairman Sir Joseph Bhore) which was planning the future health services of India Before giving our evidence we were all sent all over India to get an idea of the background of the committee's work by seeing the conditions and meeting the people of all kinds Sigerist proved to be a delightful companion on such a journey, full of interesting information, acute in his observations, penetrating though always urbane in his inquiries, with a delightful sense of humour and tolerant of those with slower brains than his own His intimate knowledge of Russia and its language provoked many questions from certain members of the committee attracted by what they had heard of Russian achievements, and I remember well Sigerist being asked on one occasion whether it was not true that the Russians had succeeded in a certain project He paused momentarily and than answered quietly "Yes, but at the cost of five million lives"

In 1947 after some fifteen years in America, Sigerist returned to Europe, though still linked to Yale University as a research associate with professorial rank. He had produced various "interim" books, including *Civilisation and Disease*, and *The University at the Crossroads*, but he longed to get down to what was to be his final work Unfortunately the plan was not to be fulfilled, and only the first of the eight volumes has so far appeared—his *Primitive and Archaic Medicine* Though he was able to produce his Heath Clark lectures delivered at the London School of Hygiene in 1952, illness increasingly interfered with his activities

Of this final period H E L writes

I had the pleasure of visiting Professor Sigerist last summer in the little village of Pura It was obvious that he was still physically weak after a cerebral accident some months previously, but the conversation flowed easily and he insisted that I should not go, as I intended, after half an hour

He spoke about his student days in Switzerland, his appointment at Johns Hopkins University and the influence he found there of William Welch He spoke about his work during the war when he built up some understanding of Russian medicine, and then ultimately of his return to Switzerland to do his 'serious work" For me, it felt like being taken into a dim room and then suddenly seeing it in a penetrating light which left me with a vivid image and a new appreciation This he did again and again that afternoon

Most of this talk was over tea It turned out that he was a connoisseur of tea, and we were now tasting from about a dozen little sampling cups On looking back now, I am sure that I was asked to stay probably because I did not ask for milk and sugar The only demand that he ever made on his students from Asia, he told me, was that they should keep him supplied with exotic teas But he also added 'The most interesting teas I buy from the shop in Piccadilly in London"

His serious work was the great *History of Medicine* of which he had completed the early volumes Although he knew that he would not live to finish it he felt that he had at least formulated the plans and laid the foundations His untimely death has left a gap in the ranks of men who are civilising the world

THOMAS GRAINGER STEWART

M D Edin, F R C P

Dr Grainger Stewart, consulting physician to the National Hospital, Queen Square, with which he had been actively associated for over forty years, died at his country house at Wantage on March 18, at the age of 79

The son of Sir Thomas Grainger Stewart, professor of the practice of physic at Edinburgh University, he was educated at Edinburgh Academy and Edinburgh University, where he graduated M B in 1900 After holding a house-physician appointment at Edinburgh Royal Infirmary he came to London and in 1902 was appointed house-physician at the National Hospital, where later he was successively resident medical officer and assistant pathologist before being appointed assistant physician in 1908 For a short time he was on the staff of the Metropolitan Hospital, and in 1909 he joined the staff of the West London Hospital on which he remained until 1937 He was also neurologist to the Central London Ophthalmic Hospital He obtained the M R C P in 1904 For his M D thesis in 1912 he was awarded a gold medal, and the following year he was elected F.R C P

During the 1914–18 war he worked at the Ministry of Pensions hospital in Hammersmith His association with this Ministry continued until a few years ago, when he retired from Queen Mary's Hospital, Roehampton—a hospital in which he was greatly interested, and where his experience proved invaluable in assessing neurological disorders associated with Service conditions At the National Hospital he became full physician in 1924 He was due to retire in 1942, but as many of his younger colleagues were on active service he went on working there until the war ended

Dr Grainger Stewart went to Queen Square at a time when great advances were being made in clinical neurology, and he made his own contributions to these, notably in two important papers written in collaboration with Sir Gordon Holmes , Their joint paper in 1905 on the Symptomatology of Cerebellar Tumours was a landmark in the diagnosis of destructive lesions of the cerebellum and the clinical differentiation between intra- and extra-cerebellar tumours This report was followed in 1908 by their joint paper on the connection of the inferior olives with the cerebellum in man In 1906 he drew attention in this journal to the occurrence of tremor in tumours of the frontal lobes He was joint author with the late W Aldren Turner of a Textbook of Nervous Diseases (1910)

F M R W writes

To an old house physician, and later, colleague of Dr Grainger Stewart at Queen Square, the news of his death brings back many pleasant memories of a high principled and unselfish man, a considerate chief and colleague, a sound clinician of the old school, a conservative in the best sense of that abused word, and a man conscious in his later years of having lived into an age he liked less and less

Haste was unknown to him, and slow in speech as in movement, his outpatient sessions and ward rounds were no brief events, but went on, regardless of the clock, until he had discharged his sense of duty to the task in hand The weekly pattern of notional half days that forms the chessboard upon which the modern consultant makes his permitted and allotted hospital movements could not have contained him, and had one, unkindly, explained it all to him and discussed its influence upon the life and thought of the physician of today, he would have been horrified

When in 1939 so many of his young colleagues left Queen Square for activities elsewhere, he quietly took on outpatient work again and so continued until their return, when, as quietly, he disappeared almost unnoticed from the hospital

Except as a young man he wrote little An excellent textbook of neurology written together with his senior colleague, Aldren Turner, did not have the success it deserved Indeed, after Gowers' classic text became out of date, the separate neurological text did not thrive in this country for very many years

Nor was he a notably attractive clinical teacher, and it may be said that his house physicians were the only real recipients of the great store of clinical knowledge and judgment that he possessed, and in these young men he inspired a deep affection One of his most distinguished pupils, Professor Monrad Krohn of Oslo, was amongst Grainger Stewart's warmest admirers and friends, and to have inspired this feeling in a neurologist of international fame, himself a brilliant writer and teacher of neurology, is perhaps an indication for the discerning of the qualities that Grainger Stewart so unobtrusively possessed

In 1922 Dr Grainger Stewart married Lady Playfair, widow of Sir Patrick Playfair, who survives him

FREDERICK WILLIAM PRICE

M D Edin, Hon M D Belf, F R C P

Dr Price, whose death we announced last week, served for many years as physician to the Royal Northern Hospital Though his chief specialty was cardiology, he had also gained useful experience in diseases of the chest while working at the Mount Vernon Hospital and the City of London Hospital for Diseases of the Chest But he will of course best be remembered by the famous textbook which is familiarly and respectfully known as *Price*

Lafayette

He was the son of William Price of Weston-Rhyn, Shropshire, and he was educated at Ruabon Grammar School, North Wales, and the University of Edinburgh After graduating M B in 1898 he held a house-appointment at the Edinburgh Royal Infirmary before coming to London to take up the post of assistant resident medical officer at the Brompton Hospital After some years as pathologist and registrar to the City of London Hospital for Diseases of the Chest he became medical registrar at the Westminster Hospital He was also at this time physician and pathologist to the Mount Vernon Hospital for Consumption and Diseases of the Chest To this period belonged his collaboration with James Mackenzie and Arthur Cushny in the research on the efficacy of drugs in cardiac diseases He also carried out independent investigations on the action of digitalis and aconite In his opening address to the Academy of Medicine in Toronto in 1912 he described some of this work

His growing reputation as a cardiologist led to his appointment to the staff of the Royal Northern Hospital, and of the National Hospital for Diseases of the Heart He was one of the first physicians to restrict his private practice almost entirely to diseases of the heart

His book on *Diseases of the Heart* appeared in 1918 and he contributed articles on his specialty to many of the well-known systems of medicine before his own appeared in 1922 In welcoming the first edition we said that "its place was in the hands of the practising physician," and for the past thirty years that is where succeeding editions have been The task of revision, as carried out by Dr Price, was arduous, for he was a painstaking editor, scrutinising and if need be modifying every page of every manuscript submitted Despite periods of serious ill health he was himself responsible for the first eight editions, often working in his study when he was too unwell to go to hospital or see patients

G G relates how Price used to go through a manuscript with a contributor

I had a great shock the first time, for the pages were full of corrections and a schoolmaster would have given me very few marks in composition He then proceeded to go through it line by line asking me exactly what I wanted to say and suggesting alterations which I usually accepted unless I expressed a different meaning He was always anxious to vary the words so that I should not have too much repetition Every now and then he would stop and say "Is this all necessary? I don't understand it" I used to reply "Yes," and perhaps give an explanation He would usually thank me and continue reading aloud The whole process took a long time, but he impressed his own style on the book and it was certainly easy to understand I believe he treated all the contributors in the same way and some were much annoyed Although I did not always agree with his corrections, I am grateful because I learnt a great deal from his comments His book has certainly fulfilled his ambition to be a credit to British medicine

In 1943 Dr Price married Miss Hilda Brown, of B[illegible] She survives him

A memorial service is to be held at All Souls' Church, Langham Place, W 1, on Monday, April 1, at 12 30 P M

ISAAC JONES

M D Melb, F R C P

Dr Jones, chief medical officer and consultant physician to the Metropolitan Police, died on March 24 at the age of 74

An Australian by birth and education, he graduated from the University of Melbourne in 1909, and later held the appointment of clinical pathologist at Melbourne Hospital After postgraduate study in Vienna, Berlin, and Paris he served during the 1914–18 war as a [illegible] in the R A M C On demobilisation he settled in London and for a time acted as deputy director to the medical unit at St Thomas's Hospital In 1929 he succeeded Sir Maurice Cassidy as chief medical officer at Scotland Yard From that date until a day before his death he gave unstinted service to the Metropolitan Police For this work, writes C M P, he was singularly well qualified by his vigorous personality and solid physique—in some degree developed by his Australian upbringing

An uncompromisingly robust and common sense attitude to clinical problems was associated with a deep knowledge of medicine especially in gastro-enterology Though not trained in psychology, he recognised its importance in a force which is exposed to exceptional strains and was most successful in getting many men back on to a level keel by his understanding. On the administrative side he was responsible for the establishment of a most efficient dental service To the police nursing home and the convalescent home at Brighton he gave unswerving support and cooperation The introduction of the National Health Service in 1948 considerably modified the medical control of members of the police He accepted the position and by tact and management continued to maintain contact and indirect control to a remarkable degree

At St Thomas's Hospital he made many loyal friends and exerted a powerful influence on the teaching of practical medicine to many generations of students But his main interest remained the welfare of the Metropolitan Police Though by inclination a confirmed countryman, he took, in the opinion of his less energetic colleagues, absurdly short holiday breaks By his devotion he won the confidence and affection of all ranks of the force—from commissioners to constables

Dr Jones was elected F R C P. in 1939 He leaves a widow and two sons

JOHN FREDERICK NICHOLL

M B Belf, D M R

Dr Nicholl, a senior cancer clinic associate at the Allan Blair Memorial Clinic of the Saskatchewan Cancer Commission, who died on Feb 25, at the age of [illegible], was born in Belfast He graduated M B from Queen's University in 1912, and after studying therapeutic and diagnostic radiology at University College Hospital, London, he was appointed senior assistant radiotherapist at St Thomas's Hospital in 1940 He took the D M R in 19[illegible] In 1950 he went to Canada as chief of radiotherapy and associate in diagnostic radiology at Victoria General Hospital, Halifax, Nova Scotia Four years later he joined the Allan Blair Memorial Clinic at Regina, [illegible] as radiotherapist but giving most of his time to the development and expansion of the radio isotope laboratory nt of newer techniques in this field Outside his work chief interest was ornithology and he was an enthusi- ic member of the Regina Natural History Society

He is survived by his widow, a daughter, and three sons

KATE FRASER

O B E, M D, B Sc Glasg, D P.H

Dr Fraser, who was the first woman to take part in e work of the General Board of Control for Scotland, ed on March 20 at the age of 79

She was born in Paisley, where her father Dr Donald aser was a general practitioner with a special interest mental disorders She took her B SC at Glasgow niversity in 1900 with special distinction in physiology d went on to study medicine, graduating M.B in 1903 ter holding resident appointments at the Bridge of eir sanatorium, the Crichton Royal, and the Southern unties Asylum at Dumfries she spent five years in neral practice in Glasgow With this she combined ork at the Royal Hospital for Sick Children and for the ovan parish school board Her interest in the problems mentally defective children grew steadily, and by 13 she was using Binet-Simon tests in their examina- on and assessment In 1913 she took the D P H, and in e same year she was awarded the M D degree with gh commendation for her investigation on syphilis a cause of mental deficiency She also studied the lationship of this disease to epilepsy The reputation hich she had already won was recognised by her ppointment in 1913 as a deputy commissioner of the eneral Board of Control for Scotland In 1935 she was ppointed a commissioner During her 33 years with the oard she had a long record of distinguished service r Fraser was responsible for the setting up of the x-Service Psychiatric After-Care Organisation in Scot- and She successfully urged the inclusion of the mentally andicapped in the provisions of the Disabled Persons mployment Act She was appointed C B E in 1945

After she retired in 1947 her wide experience of both ospital and community care of the mentally ill and the entally defective continued to be of great value While ost of her time was given to the work of the Scottish ssociation for Mental Health, of which she was a ounder member, she also served on various committees nd on the board of management of two hospitals and as associated as psychiatric adviser with the work of everal voluntary bodies In 1952 she was made an onorary member of the Royal Medico-Psychological Association, of the Scottish division of which she had een chairman for three years

T F writes

Dr Kate Fraser never seemed to become lost in the anonymity which so often invests the senior Civil Servant Everyone knew and respected her Yet she did not at all covet publicity, she was quiet, almost shy, fired with an obviously genuine interest in the welfare of the mentally afflicted which opened every door She had no enemies and when, on retiral, she went to live in Paisley it was just in the expected nature of things that she should continue to give freely of her wisdom and administrative sense to the Scottish Association for Mental Welfare and, in particular, to the notable work long carried on in Paisley in the interests of retarded children—a work which she had helped to pioneer Dr Kate Fraser had a unique place in Scottish mental health affairs and in Scottish affection, she will be greatly missed

A former colleague writes

In Kate Fraser's earlier years as a deputy commissioner roads and transport in the more outlying parts of Scotland (parts which she particularly loved) were less adequate than they later became In visiting patients under guardianship—work which she greatly enjoyed—she walked for miles over tracks, crossing bogs barefoot to reach some isolated croft Rather than return without seeing a patient in the most northerly island of the Orkneys, when the steamer could not berth because of the gale she let herself be thrown from the deck, as the steamer swept past in the heavy sea on to a pile of sacks on the North Ronaldshay pier and was storm bound on the island for some days The indomitable spirit that would not yield to bogs or gales was unquenched in her later years Difficulties were still to her a challenge and although latterly her physical appearance became fragile she was still possessed of drive in planning and vigour in attack Her strength of character was combined with a lively sense of humour, a happy friendliness, and a generous self giving To those who knew her well she has left the impact and influence of her great qualities of mind, heart, and spirit

MALCOLM CAMPBELL

M.A, M.B Edin, F R C S E

Dr Campbell died on March 13 at Droitwich where he had practised for many years as a consultant in rheumatology He was born in Edinburgh of Highland parents in 1873, and he graduated M A from Edinburgh University in 1895 and M B in 1900 After holding a resident appointment at the Royal Infirmary he took his F R C S.E in 1902. He spent a postgraduate year in Paris where he studied obstetrics In 1905 he was appointed as lecturer in obstetrics to the University of Edinburgh, and for the next three years he was assistant to Sir Halliday Croom

In 1908 Campbell settled in general practice in Brechin, but in 1914 septicæmia, followed by pyæmic joint-infection, laid him low for months He was sent to Droitwich as a patient and remained to practise For a time he was medical officer of health for the borough, but he turned more and more to the practice of hydrology, and his reputation in this specialty grew steadily In 1933 he was the British Government's representative in Toulouse at the International Conference of Hydrology, where his fluent French proved useful During the late war he was a president of the Vigornian Society, which met at the Worcester Royal Infirmary, and whose meetings were stimulated by the enthusiasm of the many American Army doctors who were stationed in the district before D day In the county he was a president of the Worcestershire Lawn Tennis Association and a vice-president of the Worcestershire Cricket Club He was also an expert gardener, with a particular care and affection for roses, sweet peas, and orchids

J W T. P writes.

One of Campbell's chief distinctions latterly was his brilliance as an after dinner speaker His Irving-like appearance, his easy style, and his choice diction never failed to win approval, and many who never knew him personally will remember him in this capacity But he will be missed by a great many people up and down the country, for under a somewhat austere and unapproachable exterior lay a kindliness which he was loath to show and an integrity which never wavered

His only son, Dr A M G Campbell, is a physician to the United Bristol Hospitals

GERALD STANLEY HOVENDEN

M D Lond

Dr Hovenden, who was a general practitioner in Barnes for over 50 years, died in Putney Hospital on March 14 at the age of 87 He was educated at the Whitgift School and qualified from Guy's Hospital in 1894, taking the M.D Lond two years later In 1900 Dr George Rodman, a cousin by marriage, who was in practice in Barnes and East Sheen, invited Gerald Hovenden and his twin brother to join him as partners. This they did and they remained in practice together till Dr Arthur Hovenden's death in 1946 Dr Gerald Hovenden finally retired only a few years ago

A colleague writes

During the late war, when his brother's health had broken down and his junior partners were called up, he managed to hold the practice together with only part-time assistance His appearance of being unhurried, even when he was doing four men's work, is still remembered by his patients He belonged to a generation when it was still possible for a general practitioner to claim that he was up to the standard of clinical assistant in the various specialties, and he was a skilled anæsthetist with chloroform and ether, he performed many Ts and As, he was a good dental extracter, he was a particularly good pædiatrician (he had been a clinical assistant at Great Ormond Street), and he had a large midwifery practice

His own family was the centre of his life and, through his kindness and understanding of human problems, he became the friend and counsellor to several generations of families in his practice His unsparing devotion to his patients' welfare inspired complete trust, and his gentle, genial manner and obvious enjoyment of his simple pleasures were typical of a man who was contented with his life He was also intensely interested in modern developments, both in medicine and in general—he was, for instance, a pioneer motorist He loved riding and, up to the late war, was a familiar figure in Richmond Park riding with his family He was a keen walker and dinghy sailor and enjoyed holidays abroad He was an excellent bridge and chess player, and the pleasure which he enjoyed from reading—in English, and in French and German—lasted till a few days before his death

He was married twice and had one daughter and three sons Two of his sons are doctors, one carries on his father's practice and the other is a surgeon commander in the Royal Navy

DESMOND WILLIAM GEORGE FARIS

O B E, LL D Malaya, M B Lond, D P H

Dr Faris, who till last year was dean of the faculty of medicine of the University of Malaya, died at Hove on March 20

He was born in 1901 and was educated at Thetford Grammar School in Norfolk and at Epsom College He entered the London Hospital Medical College in 1919 and took the Conjoint qualification in 1924 and the M B Lond in 1925 In the same year he was appointed as a medical officer in Malaya, and he took up his duties there in 1926

He soon began to make a special study of preventive medicine, and he took the D P H in 1931 His anti-malarial work and his keen interest in health conditions on rubber plantations and tin-mines earned high praise During the Japanese occupation, he was interned in Changi camp, but he did not allow this to break his spirit and made a useful contribution to the life of the camp under harassing conditions

After the war he was appointed chief medical officer of Singapore, and later he became principal of King Edward VII Memorial College of Medicine and, in due course, dean of the faculty of medicine in the University of Malaya In this post his past experience in public health proved a valuable asset He wrote the history of King Edward VII College and last year received the honorary LL D of the University of Malaya His death, so soon after his retirement, will be regretted by his many friends of all races in the Far East

JOHN GARVIN STEBBING

M B *Lond*

Dr Stebbing died on March 23 at the age of 32 Educated at Dulwich College, he began his career at Guy's Hospital in 1942, and he soon made his mark as a leader in work and in extracurricular activities After he qualified he held house-surgeon posts at Guy's and then for a year he worked in the physiology department Thereafter he spent two years on research of fundamental value in the department of surgery As H J B A recalls, "in 1953 Stebbing decided to go into general practice in Bermondsey and from then until his death he devoted his great qualities as a doctor to the care of his patients A certain shyness and a quiet manner concealed a strong character which was revealed to its full only during the last few years when, with superb courage, he carried on quietly with his work, knowing that he was suffering from an incurable disease, even though this work was interrupted from time to time for X-ray therapy Throughout his life he adhered to the rigid standard of conduct which he inherited from his father, the late Dr G F Stebbing, who, in his generation, also served the people of South London with such devotion and skill"

In 1935 Dr Stebbing became a member of the council of the Medical Protection Society He leaves a wife and daughter

ALEXANDER ALAN GUILD

M A Camb, M D, Edin, M R C P, M R C P E

Dr Guild, consultant physician and physician sup intendent of Lambeth Hospital, died in London March 9 at the age of 40

He took his preliminary medical course from C College, Cambridge, graduating B A with first-cla honours in the natural sciences tripos in 1938 He was a college prizeman He continued his studies at Edinburgh University, where he won medals in pharmacolo therapeutics, and public health, as well as a Murchiso scholarship in clinical medicine After graduating M in 1941, he spent six months as house surgeon at Edin burgh Royal Infirmary before he joined the R A M C He served with a field-ambulance in North Africa, Sicily Italy, Palestine, and Greece, and was mentioned in despatches He was appointed A D M S, Land Forces Greece, in 1945, and was demobilised with the rank of lieut -colonel the following year

After the war he returned to Edinburgh Royal Infirm to take a postgraduate course in internal medicine, befo becoming house-physician at the Southern Gene Hospital He passed the Edinburgh M R C P, wi neurology as a special subject, in 1947, and took t M D the same year In 1948 he took the London member ship and the same year he became clinical tutor to t medical unit at the Western General Hospital, Edinburgh In 1951 he was appointed physician superintendent a Lambeth Hospital He was one of the authors of t section on neurology in Davidson's *Principles and Pra tice of Medicine*

A colleague writes

Guild had exceptional ability and a profound knowledge *medicine In addition he had many interests outside medic* including music, art, and architecture He was widely re the classics, languages, and history He was a man of h principle and integrity who put his work before any ot consideration The welfare of his patients meant everyth to him and he spared neither himself nor his staff to attain th highest standard of treatment He took a special interes the neurological work of the hospital From his father inherited a judicial outlook, and he proceeded with th utmost caution in any matter which might lead to litigati In committee he could outline his policy with extreme clear ness, for he never seemed to lack the right phrase to descr the subject under discussion

His fellow consultants found him a loyal upright an friendly colleague His junior staff held him in high estee and learnt from him how to combine a good bedside manne with a thorough examination and investigation of a patient His ward sisters regarded him with affection and respe *He was a hospitable man and many of the staff were welcomed at his home When his house officers sought his guidance* in planning their future career he wrote them long and friendly letters

In 1951 Dr Guild married Miss Marion Bell, daughte of Sir Gordon Bell of Otago University, New Zealand She survives him with two young children

Appointments

BAILY R A J M B Camb, F R C S consultant [illegible]
surgeon, Weston super Mare group of hospitals
BYERS IRIS E M B Dubl assistant maternity and child we
M O, co Durham
COONEY MARY F M B N U I, D C H, D P H assistant mat
child welfare, and school M O, Derbyshire
KNAPPE S S M D Warsaw deputy medical superint
Sandhill Park Hospital, Bishops Lydeard Somerset
MACKINNON, N A M, M B Edin, D P H part time con
dermatology, Northern Regional Hospital Board [illegible]
MARKS, HANNAH M, M B Dubl D A anæsthetist [illegible]
Cumberland group of hospitals
RANDALL D H M B Lond, F R C S part time consultant
surgeon Rotherham Hospital
TWOHIG, NORA T M B N U I D C H assistant maternity
welfare and school M O Derbyshire
VINCENT H R M R C S assistant A M O Sheffield [illegible]
Hospital Board
WILLIAMS R I M B Lond D M R D consultant radi
Aylesbury/High Wycombe area

Births, Marriages, and Deaths

DEATHS

HOVENDEN—On March 11 at Putney Hospital [illegible] Hovenden M D Lond of Glenholme, Barne [illegible]

Notes and News

PLAN FOR WITHDRAWAL FROM N.H S

A LETTER addressed last week by the General Medical ervices Committee to all practitioners in the National Health ervice says that the British Medical Guild will take steps o obtain the resignations of all of them These will be put ito effect initially in selected areas, the number of which vill be progressively increased if need be

Practitioners in the areas selected will be asked to notify xecutive councils on July 2 of their intention to withdraw rom the medical list from Oct 2 They will not be asked o withdraw from the obstetric list This means that from ct 2, with the exception of maternity medical services, eneral practice under the National Health Service will ease in these areas

During October former N H S patients will be treated rivately but no private fees will be asked of them The ublic will be informed that doctors in these areas are anxious o give the Government one last chance to honour the promises nade to family doctors when they entered the N H S in 948, and that they are doing everything possible to avoid position in which their patients suffer financially Nevertheless, if the Government still decline to agree to a satisactory settlement or to arbitration it will be necessary after Nov 1 for general practitioners in those areas to charge their patients a standard token fee which it is recommended hould be 5s a consultation and 7s 6d a visit

Patients will be given receipts for these fees, and will be dvised to take them to the nearest National Insurance office in order that the Government may have an opportunity of efunding the sums involved Doctors will, of course, have liscretion to waive or modify these fees in special cases "

If a settlement is not reached, practitioners will later be ompelled to make full economic charges for their services

Practitioners who resign will be advised to issue prescriptions on private forms for the duration of the emergency It will be for the Government to decide whether they will refuse to accept prescriptions issued in this way

No National Insurance certificates will be issued General practitioners will issue their own private certificate forms

WORLD HEALTH ORGANISATION

TWENTY international experts met in Copenhagen last August to discuss research problems connected with the effects of radiation on heredity The committee was apparently concerned with only the peaceful uses of atomic energy Its report (which will be published within a few months, together with several specialised papers) says that "all man made radiation must be regarded as harmful to man from the genetic point of view," but holds that some risk must be accepted in view of the potential contribution of nuclear energy to man's social and cultural development

The report lists 13 fields in genetics needing urgent research if the harmful effects of radiation are to be minimised The effects of radiation are probably additive and may not be felt for some generations The radiation received by the gonads of the average individual is estimated at 2–5r in 30 years from natural sources, and 1–3r from medical X ray examinations, besides smaller amounts from other sources There is special danger in the increasing use of fluoroscopy by physicians who have had no formal radiological training

An accompanying paper by Prof R M Sievert, of Sweden, points out that many foodstuffs have lately been shown to contain artificial radioactive elements with a radiation level often greater than that of the natural elements, but the dose of radiation received by tissues from this source cannot yet be estimated Among the recommendations of the report are an increase in research and teaching in human genetics, the systematic registration of hereditary diseases, and the collation of data on fertility, consanguineous marriages and parental ages The group was much impressed with the hazards from man made radiation in medicine, industry, and experimental science

AN ACCOUNT OF THE HEALTH SERVICES

THE Central Office of Information has issued a reference pamphlet[1] describing the National Health Service and the various other public health services in Britain There are also chapters on medical research and on professional training The pamphlet presents much information in handy form

Royal Society

The 25 newly elected fellows of this society include Dr Saul Adler, professor of parasitology in the Hebrew University Jerusalem, Dr E C Amoroso, professor of physiology in the University of London at the Royal Veterinary College, Dr John McMichael, professor of medicine in the University of London at the Postgraduate Medical School, Dr Bruno Mendel, professor of pharmacology in the University of Amsterdam, Dr C L Oakley, Brotherton professor of bacteriology in the University of Leeds, Miss Charlotte Auerbach, D SC, lecturer in animal genetics in the University of Edinburgh, Mr J F Danielli, D SC, professor of zoology in the University of London at King's College

University of Oxford

It is proposed to confer the honorary degree of D LITT on Prof J F Fulton

University of Leeds

At a recent examination the following degrees and diploma were conferred

M D—Mary McMillan (with distinction)

M B, *Ch B*—C D Holdsworth P H Smith, Brenda Thiede (with second-class honours) J S W Brierley, Dorothy C Campbell J H Chippendale H M Chung, J E Cox Norman Cross Alan Darnborough, Eileen M. Gillespie Philip Goodwin L L Hemsy, P H Holmes David Jarratt, D T Jones, Vera E Lawton J W Lewis, Mohsen Mahloudji J W A Moxon D T Price, B E Roberts Audrey Sarfas, Margaret Sawyer Marion Sherman J N Smith R I Swires, R J Taylor D L Thiede F E Tomlinson Barbara F Turner R W Turner, Brian Whitaker, Dorothy M Wootton

D P H—E W G Birch Carl Burns George Cust J A G Graham John Harkness, M E O'Neill John Pemberton William Turner J A G Watson, Marianne H Witt

Dr G J R Soutter has been appointed lecturer in pædiatrics and child health

University of Birmingham

Prof Rustin McIntosh, director of pædiatric services at the Babies Hospital, New York City, will deliver the Leonard Parsons lectures at 4 P M on Tuesday and Wednesday, May 7 and 8, at the medical school His subject will be growth and development

Dr E H L Harries has been appointed lecturer in physiology

University of Dublin

At a recent examination for the D G O the following were successful

Nand Kishore Allahbadia B H Marten, Santosh Madan Santosh Khosla Saroj Kumar Ghosh Parkash Jit Kaur, Simon Froman

Royal College of Surgeons of England

At the annual dinner of the Faculty of Anæsthetists, on March 20, Mr Dennis Vosper, the Minister of Health, expressed his belief in the National Health Service The service would have been a bit different if it had been introduced more slowly, but once a big step forward had been taken it was difficult to take even a small step back. His job was to make the existing service work Replying for The Faculty, Dr Frankis Evans, its dean, spoke with pride of the research department, housed on the sixth floor of the Nuffield College This lusty infant was now assured of a healthy childhood, for industry and the great foundations had come to their help The director was unfettered by undergraduate or postgraduate teaching—a unique arrangement The next major requirement was a chair of anæsthetics, and for this a capital sum of £150,000 would be needed Sir Edwin Herbert replied for The Guests to a toast proposed by Dr John Gillies, who welcomed Mrs Pandit, the High Commissioner for India, as one "whose greatness—particularly as a champion of the underprivileged—is enhanced by her modesty"

At a meeting of the faculty, Dr H J Brennan (Manchester) and Dr H H Pinkerton (Glasgow) were elected to the board of the faculty for eight years Dr H C Churchill Davidson (St Thomas's Hospital) was re elected to the board for four years

St Mary's Hospital, London

Mr Edgar Lawley has been appointed chairman of the board of governors of this hospital in succession to Mr Anthony de Rothschild

Association of Clinical Pathologists

The general meeting of this association will be held at Torquay on April 11, 12, and 13

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[1] Health Services in Britain 1957 H M Stationery Office Pp [illegible] 3s

Royal College of Obstetricians and Gynæcologists

At a meeting of council held on March 23, with Sir Charles Read, the president, in the chair, Mr J B Blaikley was appointed to visit New Zealand and Australia, and Prof T N A Jeffcoate to visit Canada and the Caribbean area, both as Sims-Black professors

Dr Claud Taylor will deliver the William Blair Bell lecture at the college, 58, Queen Anne Street, London, W 1, on Friday, May 24, at 5 P M He is to speak on mesodermal mixed tumours of the female genital tract Admission is by ticket only, obtainable from the secretary of the college

Hæmophilia Society

The annual general meeting of this society will be held on Sunday, April 7, at 3 P M at the Hospital for Sick Children, Great Ormond Street, London, W C 1, when Sir Weldon Dalrymple Champneys will deliver a presidential address

Naval Medical Compassionate Fund

A meeting of the subscribers to this fund will be held at 2 30 P M on Friday, April 12, at the Medical Department of the Navy, Queen Anne's Mansions, St James's Park, London, S W 1, to elect six directors of the fund.

Royal Institute of Public Health and Hygiene

Prof Philip Drinker, D SC, who holds the chair of industrial hygiene at the school of public health of Harvard University, will deliver the Harben lectures for 1956 at the institute, 28, Portland Place, London, W 1, on May 13, 14, and 15 at 5 P M He is to speak on air pollution and the public health

Wessex Rahere Club

A dinner of this club will be held at the Royal Clarence Hotel, Exeter, on Saturday, April 27 Membership of the club is open to all Barts men practising in the West Country Further details may be had from Mr A. Daunt Bateman, the hon secretary, 11, The Circus, Bath

National Spastics Society

Dr C P Stevens has been appointed director of this society

Dr Stevens is a former deputy senior administrative medical officer of the South West Metropolitan Regional Hospital Board, and his last appointment was as general secretary to the John Lewis Partnership

Stobhill Hospital, Glasgow

On March 19 Prof J W Howie opened a new department of bacteriology at this hospital Till now a disused Army building has served as laboratory The new laboratory has cost between £12,000 and £14,000, but in Professor Howie's view it is still not up to the standard appropriate to a hospital like Stobhill In preventing the spread of infection the public health service and the hospital both turned to the laboratory, and he suggested that it had therefore an important part to play in bringing them together

Drug Costs in New Zealand

Addressing the biennial conference of the New Zealand branch of the British Medical Association in Wellington, Mr J R Hanan, the minister of health, said the individual doctor was responsible *not only to his patient but also to the taxpayer* He was referring to the sharp increase in the social security pharmaceutical bill, which, he said, would exceed £2 a head of population this year In 1948 the total cost of pharmaceutical benefits was £1,558,000 In 1956 it was £4,039,000 "If the doctor is not going to consider the cost, with due regard to medical need first," Mr Hanan said, "then more controls will have to be established to keep the costs within the funds available"

Carlsberg-Wellcome Travelling Research Fellowships

The directors of the Carlsberg Foundation, in Copenhagen, and the Wellcome Trustees, in London, have decided to institute these fellowships, to encourage cooperation between Danish and British research workers in human and animal medicine

One fellowship will be awarded annually to a candidate from the United Kingdom for a year's work in Denmark and one to a Danish candidate for a year's work in the United Kingdom The stipend may range from £800 to £1200 per annum for whole time research Travelling and some incidental expenses will be provided in addition It is intended that the first fellowships will begin in September, 1957 Further information may be had from the scientific secretary of the Wellcome Trust 52 Queen Anne Street London W 1 Applications must be submitted before April 30

Faculty of Homœopathy

At a meeting of the faculty at the Royal London Homœopathic Hospital, Great Ormond Street, W C 1, on Thursday, April 4, at 8 P M there will be a discussion on the treatment of migraine

Association of Medical Microtomists

This association is to hold a demonstration of histological and allied techniques in the biology laboratory of Guy's Hospital Medical School, London, S E 1, on Friday, April 5, at 7 P M

Medical Inspectorate of Factories

Dr Sibyl Horner has been appointed Senior Medical Inspector of Factories in succession to Dr E R A Merewether, who will retire on Aug 31

Dr Horner, who studied medicine at the London School of Medicine for Women and St Mary's Hospital, qualified in [illegible] and took the D P H two years later She held a house appointment at Charing Cross Hospital and was an assistant medical officer in the school medical service of the London County Council before she joined the factory inspectorate During her 32 years service including 9 as a deputy senior medical inspector she has made a special study of industrial dermatitis

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Diary of the Week

MARCH 31 TO APRIL 6

Monday, 1st

MARLBOROUGH DAY HOSPITAL, 38, Marlborough Place St John's Wood, N W 8
8 15 P M Dr F K Taylor Mental Epidemics and Such Social Phenomena

Tuesday, 2nd

ROYAL COLLEGE OF PHYSICIANS OF LONDON, Pall Mall East, S W 1
5 P M Dr L C Hill Systemic Lupus Erythematosus (First of two Lumleian lectures)
ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W 1
8 30 P M *Orthopædics* Mr E Stanley Evans Changing Patterns in Skeletal and Articular Tuberculosis (Presidential address)
GUY'S HOSPITAL MEDICAL SCHOOL London Bridge, S E 1
5 P M Dr Alexander Nadas (Harvard Medical School) Complete Auriculo ventricular Block in Children

Wednesday, 3rd

ROYAL COLLEGE OF SURGEONS OF ENGLAND Lincoln's Inn Fields W C 2
5 P M Prof R M James Tumours of the Parotid Gland (Moynihan lecture)
ROYAL SOCIETY OF MEDICINE
3 P M (Charing Cross Hospital, W C 2) *Surgery* Mr N[illegible] Lake Spinal Anæsthesia, Mr Norman Tanner Gastroenterostomy, Mr A R Makey Duodenal and R[illegible] Atresia
5 P M *History of Medicine* Dr T J Rendle Short N[illegible] in History with Special Reference to Children Mr T F Layton Horace Walpole's Quinsy
ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE, 28 Portland Place, W 1
3 30 P M Dr H D Paviere Relations of Hearing to [illegible] Exposure
INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330, Gray's Inn Road, W C 1
5 30 P M Dr H A Sissons Bone Structure and Bone Path[illegible]
MANCHESTER MEDICAL SOCIETY
4 30 P M (Medical School, University of Manchester) *Medicine* Dr R E Smith Immunological Problems of [illegible] Diseases

Thursday, 4th

ROYAL COLLEGE OF PHYSICIANS OF LONDON
5 P M Dr Hill Systemic Lupus Erythematosus (Second of two Lumleian lectures)
ROYAL COLLEGE OF SURGEONS OF ENGLAND
5 30 P M Dr R D Hoare Angiography in Throat, Nose and Ear Surgery
ROYAL SOCIETY OF MEDICINE
8 P M *Neurology* Mr J McN Potter Dr E C [illegible] Dr P O Yates Mr R T Johnson Disorders of the Hind Brain Circulation
UNIVERSITY OF SHEFFIELD
5 15 P M (University Building Sheffield Royal Infirmary) Dr Bernard B Brodie (Bethesda, U S A) 5 Hydroxytryptamine, Reserpine and the Central Nervous [illegible]

Friday, 5th

ROYAL SOCIETY OF MEDICINE
5 30 P M *Anæsthetics* Dr Ole Secher (Copenhagen) Some Problems in Anæsthesia for Cardiovascular Surgery
INSTITUTE OF NEUROLOGY National Hospital, Queen Square, W C 1
5 30 P M Dr E J Moran Campbell Respiratory Muscles and the Control of Breathing
MIDLAND THORACIC SOCIETY
3 P M (Prestwood Sanatorium Stourbridge) Dr R D Cal[illegible] Corticotrophin in the Management of Pulmonary Tuberculosis Dr John Aspin Steroid treated Pleural [illegible] Dr A MacDonald Occupational Risks in Local [illegible]

SOME ASPECTS OF INFLAMMATION AND INFECTION*

A H T ROBB-SMITH
M A Oxfd, M D Lond, F R C P
NUFFIELD READER IN PATHOLOGY IN THE UNIVERSITY OF OXFORD, DIRECTOR OF PATHOLOGY, THE RADCLIFFE INFIRMARY, OXFORD

IN 1927 Professor Kettle gave four lectures for the University of London on Some Aspects of Inflammation and Infection He would, I believe, have been fascinated, as I have been, by the changed approach to the pathogenesis of disease and of infection in particular, during the past fifteen or twenty years

In Kettle's lectures he looked at inflammation and infection from the viewpoint of the histopathologist who used experimental methods to clarify problems of morphogenesis, not from that of the experimental physiologist or the bacteriologist As he put it,

> "Without belittling the importance of bacteriology, it must surely be admitted that in any infective process, the microbe is only part of the story and not the most important part either, it is the reaction of the host to the presence of the microbe which constitutes the condition we have to study, and though regarded as an exercise in the science of botany, the intensive study of the tubercle bacillus has great merit, it will never solve the problem of tuberculosis"

Kettle showed that the inflammatory reactions to non-bacterial and bacterial agents were individually characteristic and that it should be possible to recognise the *nature of the irritant or the group of organisms involved, from the type of the reaction* He concluded his lecture with these words

> "It seems highly probable that a closer study of microbic inflammation will reveal specific tissue changes which may be of significance in the attempt to combat these infections If we understand exactly why particular bacteria makes good their footing in the tissues and how the tissues respond to their presence, it might be possible for us to devise logical methods of modifying or combating infection"

The Concept of the Biochemical Lesion in Pathology

This greater understanding of the nature of tissue reactions, that Kettle anticipated, is taking place, we are coming to realise that morphological changes are the resultant of alterations in cellular or extracellular function and that such function or dysfunction can often be defined in biochemical terms and in particular in terms of enzyme action

This change in thought cannot be attributed to any specific discovery or particular school, but it is probably the result of many influences all springing from an increased awareness of spatial and functional biochemistry One might try to trace the concept back to the iatrochemical pathology of the 17th century, or the serious attempts made by Virchow to interpret pathological changes in chemical terms, but in reality the germinal idea can be found in Gowland Hopkins's concept of dynamic biochemistry, admirably expressed in 1929 by Sir Rudolph Peters in his Harben lectures on Coordinative Biochemistry of the Cell and Tissues It is interesting to recall that Peters's thinking had been profoundly influenced by the work of Sir William Hardy, who, starting as a zoologist, in 1899 abandoned histology because he believed that any progress in our understanding of the structure of tissues must await advances in the knowledge of the molecules which composed them His own contribution was the development of colloid chemistry

In 1931 Kettle was puzzling over the pathogenesis of silicosis and carried out the classic experiment in which he showed that crystalline silica rendered insoluble by a coating of ferric oxide was harmless, and therefore that the lesion in the tissues in silicosis was not due to simple mechanical irritation but must be induced by the chemical action of a solubility product of silicon on the cells (Kettle 1932) In this same year Gavrilescu and Peters published a paper entitled The Biochemical Lesion in Vitamin-B Deficiency It had been known for some time that the opisthotonus and convulsions of rice-fed pigeons could be cured in a very short while by injecting thiamine, but in this paper Peters showed that, *in vitro*, thiamine had a specific action on the lowered oxygen uptake of avitaminous brain tissue, this was the first display of the pyruvate oxidase system of the brain, but it also formed the ground work for Peters's idea of the biochemical lesion in disease, which has inspired some brilliant research and I believe has a very wide application in pathology In essence, Peters's (1951) concept is that in many disease processes the initial lesion is a biochemical—usually enzymic—change in the tissues, and that this precedes any morphological alteration that could be recognised by ordinary microscopy, furthermore, these biochemical lesions may be reversible, and so from the point of view of therapy it would be desirable to detect them before they have disorganised the tissues

There has also been a change in bacteriological thought, so that toxins have ceased to be regarded as thaumaturgical poisons, which maim or kill their host, but as specific metabolic products to be defined in their action both chemical and pathological, the concept of competitive inhibition of enzyme systems has inspired chemotherapeutic research, and, although no agents comparable with the sulphonamides have been produced, metabolite analogues have been used with much profit in fundamental biochemical studies Advances in immunochemistry and the integration of the immune mechanism with protein synthesis has in some ways clarified and in some ways obscured the defence reaction

In the past few years, the remarkable developments in molecular biology have provided the morphologist with opportunities to see structural changes almost at the level of chemical reactivity But we must remember that at present it is *almost*, there is still a gap to be filled and structures to be resolved, which are smaller than 50Å, and it is in these dimensions that the problems of life are concealed

In this lecture I cannot present a formal review of inflammation and infection I would rather offer you a series of vignettes, and in many cases as in those delightful Victorian photographs, only one view will be apparent, the rest fading into a background of uncertainty

Phases in Inflammation

We can recognise four phases in inflammation—the initial reaction to injury, the early cellular and humoral reactions of the host to the injurious agent, the noxious effects of the agent, and the delayed or granulomatous reaction Naturally, it is not as simple as that, and according to the character of the noxa one or other phase may be inconspicuous or predominate

THE REACTION TO INJURY

Connective tissue is the commonest site for an inflammatory reaction to take place, and each of its components may influence the way in which the reaction evolves In essence, connective *tissue is a network* of scleroproteins and mucosubstances in which cells are lying, surrounded by vascular and lymphatic capillaries The intercapillary distance ranges from 50 µ in muscle up to 300 µ in fascia and tendon, these are seen to be of quite considerable magnitude when we realise that if a glucose molecule were the size of a man it would have to travel 50 miles to get from a capillary to a cell in the dermis

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* From the Kettle Memorial lecture for 1956 delivered at the Wright Fleming Institute, St Mary's Hospital Medical School, London, on Nov 30

In this intercapillary space, there is an interlacing fabric of collagen bundles, of varying size, and an occasional elastic fibril, between the fibres are the connective tissue cells (fibroblasts, histiocytes, mast cells, and lymphoid cells) lying in the ground substance, which varies from a gel to a sol state and consists essentially of plasma—the extravascular plasma protein pool is about twice the mass of that in the circulation—with a considerable range of mucosubstances and collagen or collagen precursors in a globular or soluble form In the immediate vicinity of the capillaries there are numerous mast cells and mesenchymal cells, and the capillaries themselves are surrounded by a network of reticulin—a very stable form of collagen—and consist of endothelial cells separated by an intercellular cement and covered on the intravascular surface by a protein component derived from plasma, and perhaps, platelets

If we consider the basic type of inflammatory reaction—the triple response of Lewis, or a nettle sting—in Kettle's day it was delightfully simple, we had, in miniature, the classical physical signs of Galen, the alteration in capillaries and connective tissue as described by Addison, Waller, and Cohnheim; and an explanation (based on Lewis's work) that the initiating agent was a histamine-like substance

However, Kettle was not entirely content with this unitary hypothesis, and mentioned "that products of protein degradation are capable of producing vasodilation" as an illustration of the multiple factors that may be concerned in an inflammatory process

CHEMICAL MEDIATORS OF PERMEABILITY

These doubts appeared to be well substantiated when, in 1936, Menkin described a permeability factor "leukotaxine" which he had recovered from inflammatory exudates and had prepared in a pure crystalline form Although it was soon shown that Menkin's leukotaxine was neither pure nor crystalline, there is no doubt that his basic observation—that enzymic digests of fibrin induce some of the features of inflammation—which were soon confirmed, revived serious interest in the proximate mechanism of the inflammatory reaction which is still in full flood It has become clear, by the work of Spector (1951) and others, that a whole range of polypeptides of varying solubility, with physiological activities similar to those of leukotaxine, can be isolated from autolysing tissue or tryptic digests of plasma-proteins Furthermore, the inflammatory reaction to agents such as turpentine is not prevented by the use of anti-histamine drugs or histamine depletion

Lewis had shown in 1927 that the reaction to the nettle sting was indistinguishable from that produced by a local injection of histamine, but it was not until 1947 that Emmelin and Feldburg found that the nettle hair in fact contained both acetylcholine and histamine in sufficient amounts to account for the triple response and the itching and burning sensation In 1956 Collier and Cheshire reported that it also contains 5-hydroxytryptamine (5-H T, serotonin) and this may also explain the pain and itching, it is rather pleasing that Brittain and Collier (1956) have now detected a 5 H T antagonist in dock leaves So here we have the situation that the nettle sting, which thirty years ago appeared to be a perfect example of the simple reaction to injury, in fact introduces into the dermis a gamut of active amines which could fully explain the tissue changes without postulating any intrinsic tissue factors, and yet we have ample evidence of a whole range of tissue factors affecting capillary permeability

The tissue mast cells contain heparin, histamine, and 5 H T, and histamine and 5 H T are also present in the epidermis and in platelets Then there are the permeability factors in serum-globulin described by Miles and his colleagues (1955), this is a system of inactive precursors and inhibitors in plasma which is activated on dilution—that is to say, dissociation—or ageing and can increase capillary permeability in a matter of minutes, it is unaffected by anti-histamine drugs, but is antagonised by trypsin inhibitors, suggesting that it is a protease although distinct from plasmin Although Miles et al. had no definite evidence that their permeability factors played any part in the inflammatory reaction, Spector (1956) has demonstrated a very similar permeability factor and inhibitor in an experimental inflammatory exudate Macfarlane and Pilling showed, ten years ago, that the fibrinolysis system could be activated by dilution, and recently Lewis and Work (1956) have found that, in vitro, plasmin is able to release from plasma proteins substances which stimulate smooth muscle and produce vasodilatation similar to, if not identical with the polypeptide known as bradykinin which is generated from plasma by the action of trypsin or snake venom Armstrong, Keele, and their co workers (1957) have found in inflammatory exudates a pain producing substance, which they believe to be very similar to bradykinin, which is liberated on contact with a foreign surface—although there is a lag period before activity develops reminiscent of the lag in plasma-thromboplastin generation With such a plurality of vasodilatory mechanisms and agents, one is temporarily left somewhat doubtful of the wisdom of Isaac Newton's axiom *Natura enim simplex est* However, many of these findings are based on test-tube observations under conditions not strictly comparable to those in injured tissues, though they may well illuminate the biological mechanism I believe it is possible to put forward a hypothesis, based on experiments of this type and direct observations on the changes in connective tissue due to localised injury such as has been made by Zweifach (1954), Allison et al (1955), and others, and of course, like any heuristic approach to a problem, it is propounded for destruction rather than acceptance

A HYPOTHETICAL INFLAMMATORY SEQUENCE

The earliest change to be observed in the immediate vicinity of an area of microtrauma is a degranulation of mast cells and a change in the ground substance so that it becomes more fluid, so there has been a local release of histamine, heparin, 5 H T, proteolytic enzymes of the cathepsin type and tissue thromboplastin (Mast cells are extremely easily damaged and the release of these agents could well induce the physical change in the ground substance) Next alterations are observed in the adjacent capillaries—I am not attempting to describe in detail all that can be seen—a thickening of endothelium or a laying down of gelatinous material on the intravascular surface nearest to the injury To this leucocytes become adherent, and they then emerge through the wall in a random manner, consequent on their motility rather than chemotactic influence, there appear to be local defects in the capillary wall, the while there is degranulation of the pericapillary mast cells, with increasing œdema of the ground substance, which becomes more metachromatic We can interpret this as indicating that, either as a direct action of the injury on the endothelial cells or mediated through the substance released from locally damaged mast cells, there has been a cytoplasmic exudate to which platelets become adherent and thereafter rupturing to release coagulation factors and 5 H T which acts as a mediator of histamine release In this gelatinous exudate to which fibrin has now been adsorbed, there is dissociation of plasma proteins with activation of permeability factors which may perhaps act directly on the inter endothelial cement Once a stage such as this is reached it is easy to visualise, as a result of exudation of plasma and leucocytes into the ground substance, a whole series of reactions which can explain, in pharmacological terms, the morphological changes to be observed in the early inflammatory reaction

However, as we pile assumption upon experiment, we should remember Madame de Deffand's reply to Cardinal Polignac when he was trying to impress her with the miracles of St Denis, the first Bishop of Paris, and told her that the saint, after his execution, carried his severed head from the headsman's block in Montmartre to the site of the abbey which bears his name, "and thus," said the pompous prelate, "was a distance of no less than two leagues" "Ah, Monseigneur," replied the Marquise, "I believe in such circumstances it is only the first step that counts" It is the first step that matters in explaining so many pathological processes, and it is usually the most difficult phase to analyse

In regard to inflammation, we must recognise, as Kettle showed so clearly, that each injurious agent will modify the inflammatory reaction perhaps by reason of the physiological activities of the agent itself, as is the case in the stings of plants, venomous beasts, and bacteria, or by direct action on the cells or their metabolic processes

THE REACTIONS TO BACTERIAL INVASION

When we consider the reactions to bacterial invasion, there is once again the necessity of trying to determine what happens in the tissues in relation to the presence of bacteria as against the findings of innumerable in-vitro experiments

Naturally, we think first of phagocytosis, and, though it is still just as certain that the ingestion of micro-organisms by neutrophil leucocytes and macrophages is of prime importance in the initial localisation of an infection, yet it is also quite clear that it is not the straightforward teleological battle that Metchnikoff described in Odessa seventy years ago

We do not know why it is that some organisms which appear tough are readily destroyed, while others, which are delicate, such as brucella, proliferate and give rise to intracellular infections, and others such as the leprosy bacillus enjoy an intracellular parasitism The battery of enzymes present in leucocytes, although able to break down dead organisms, have no effect on living bacteria The one exception is lysozyme, in which neutrophils are very rich, but once again there are few living organisms which lysozyme can attack, although it has a wide bacteriostatic range and the high lysozyme content of inflammatory exudates may well be of importance Recently Hirsch (1956) has described a protein, phagocytin, which has bactericidal properties for gram negative organisms and is present in high concentrations in neutrophils but apparently is only to be found in the rabbit A number of other antibacterial substances, basic peptides for instance, have been obtained from necrotic tissues, but there is little evidence as yet that they play any part in natural defence

It is quite probable that the inflammatory milieu is of greater importance in the localisation and destruction of bacteria than the activity of antimicrobic substances of cellular origin

The physical characters of inflamed connective tissue, with its collagenous membranes and gelatinous ground substance and fibrin network, would tend to localise micro organisms and facilitate surface phagocytosis Then there is the marked acidity, both of the phagocytes themselves and of the extracellular environment, consequent on the release of lactic acid due to the glycolytic fermentation Pathogenic organisms are very sensitive to acidity and more particularly to the type of anions present, lactic acid is much more toxic than keto acids, and this may be one of the factors that influences the course of infections in diabetes and during cortisone therapy, for it has been shown that under these conditions leucocytes form less lactic acid

Interest in the non-specific humoral factors has recently been revived by the work of Pillemer (1955) on properdin and the related work by Rowley (1956) on bacterial lipopolysaccharide

Pillemer and his co-workers showed that there is present in the normal serum of man, and of many other species, a bactericidal system effective over a large range of micro-organisms and viruses which does not require specific immunisation for its activity Its components are properdin, a globulin of high molecular weight, the four parts of complement, and magnesium ions. Lipopolysaccharide fractions of bacterial cell walls enhance the properdin levels and it has been suggested that a specific configuration of the polysaccharide of the cell walls acts as a specific receptor site for the properdin system, thus enabling the destruction of bacteria to proceed It is possible that the infection-promoting activity of epithelial mucins and certain complex sugars, such as highly polymerised dextrans and levans, may be due to their ability to combine with properdin and neutralise it, and that in certain micro organisms the cell wall may be covered with antigenic envelopes so that the properdin receptor sites are blocked

Apart from stimulating properdin, bacterial lipopolysaccharides initiate a whole range of physiological reactions in the host—fever, leucocytosis, stimulation of the reticulo-endothelial system and adrenal cortex, Schwartzman activity, and the specific immune response

I shall not attempt to deal with the immunological reactions to micro organisms, as I have tried to restrict myself to the early stages of infection Although antibodies cannot be recognised in the blood-stream for several days after an initial infection, it is important to remember that they may be formed locally in a matter of hours, though in quantities too small for their overflow into the circulation to be detected There is some experimental work in favour of this idea, and if it could be substantiated it would explain a number of anomalous observations with regard to local resistance to bacterial infection

A Detour to Look at Snake Venom

Now I would like to depart from my main theme for a few minutes to discuss the biology of snake venoms, because it is related on the one hand to the initial inflammatory tissue reactions and on the other hand to the effects of micro organism on the tissues, which I shall be considering shortly

Snake venoms are generally regarded as one of the most lethal of biological secretions and are known to contain a whole range of enzymes in high concentration The type of reaction varies from species to species and in the same species according to its physiological state and habitat, but in essentials there are two phases—the local and systemic effects The local effects are characterised by intense pain and swelling at the site of injection which becomes hæmorrhagic and necrotic, while the systemic effects may be paralysis in the case of colubrine venoms, or shock and circulatory failure in the viperine venoms

Analysis of snake venoms has shown a remarkable spectrum of enzyme activity (hyaluronidase, lecithinase, protease, peptidase, phosphatase cholinesterase, and ophio amino acid oxidase) and it is possible to correlate quite closely the changes observed in animals exposed to the venoms with the known action of their constituent enzymes—for example the hyaluronidase, by its action on mucosubstances in the connective tissue, will facilitate the penetration of the venom, the lecithinase will act on capillary endothelium and erythrocytes, the proteinases will produce their effects on blood coagulation, the cholinesterase on nervous transmission, and so forth. Indeed, it is obvious that they form a most effective offensive weapon, but perhaps this is an unduly anthropocentric reflection and it is well to consider that matter from an evolutionary standpoint. Serpents cannot chew or tear their food to pieces, the while lubricating it with digestive enzymes, they swallow the rodents, or other small mammals which are their normal diet, whole, and yet their digestive enzymes must be able to play their part in nutrition. The most primitive snakes have a simple fang structure at the rear of the upper jaw, and the venom producing glands are related to the salivary glands, as their prey is swallowed it is injected with venom. During the course of phylogenetic development, the length of the maxilla decreases and the fangs shift towards the front of the mouth and develop into weapons of attack. Nevertheless, with the exception of hyaluronidase and ophio amino oxidase, all the enzymes found in snake venoms are present in the digestive juices of other animals, and contrariwise it is possible, for example, to detect thromboplastic activity in human saliva. Ophio amino oxidase, which appears to be peculiar to snakes, is not a toxic enzyme but is able to activate the proteases and peptidases of the prey and so facilitates their digestion, it is probably a factor in the rapid necrosis that occurs in snake bites.

I have taken this detour because it emphasises, I believe, the point that our interpretation of the effects of substance produced by living material on their hosts or prey is tacitly teleological, whereas it may be that in the normal environment these substances are but metabolic by-products or play a part in the organism's nutrition.

Micro-organisms in Relation to Disease

Now how should we approach the problem of the mechanism of disease production by micro-organisms? It is only eighteen months ago that there was a symposium on this very subject under the ægis of the Society of Microbiology, and the difficulties, both semantic and experimental, were admirably discussed by Miles (1955b). I wish to evade the problems of definition and see how far we can go in assessing which, if any, definite characters of a micro-organism can be related to the clinical and morphological features of the disease state with which it is associated.

But there are still a number of problems to be faced. There is the circuitous difficulty that, in many disease states, the morphological lesions are not of themselves so characteristic that we can say this can only be an infection due to such and such an organism—although, as Kettle rightly pointed out, the reverse is more often true as far as a group of organisms is concerned.

Then we have the far more serious difficulty that it does not follow that the metabolic character of a micro-organism grown on artificial media are those which it reveals when growing in vivo. This is well recognised, and attempts have been made to overcome it—e.g., the work of Watson and Cromartie (1952) on the streptococcus and anthrax which has been continued by Smith et al. (1955), and Lurie's (1939) studies on tuberculosis. Although the results of this sort of work are often disappointing and confusing, in contrast to the clear-cut findings that may emerge from in-vitro experiments, yet I believe they must be persisted with because they can simulate natural disease, and techniques using the hamster pouch or granuloma pouch of Selye might well prove of value. Even when we think we have all the information—the morphological characters of the lesions, the mode of action of the bacterial factors which are associated with virulence—we may still be left qu uncertain as to how to integrate the information and display the stages by which these virulent factors induce not only the local lesion of the disease but also those systemic features which are often the real characteristics of an infection. Nor will immunology always help us to determine which are the harmful factors: the strain of diphtheria which is most effective in producing antitoxin has never been known to produce the disease, and the strain of *Clostridium welchii* used for the same purpose came not from a case of gas gangrene but from an old hat!

With all these difficulties before us, is it worth while for a morbid histologist to try to offer any observations about the pathogenesis of infection? I hope it is. Even if I fail to convince my bacteriological colleagues, my jejune speculations may perhaps stimulate them to look into these problems further.

THE STAPHYLOCOCCUS

In man the staphylococcus manifests itself in three principal forms: (1) circumscribed purulent lesions which may be localised or associated with a bacteræmia transient or persistent, (2) widespread membranous lesions, such as may occur in the respiratory passages or the intestinal tract, and (3) the severe shock-like syndrome which was seen so dramatically in the Bundaberg disaster, when a number of children died after being injected with a diphtheria toxin antitoxin contaminated by a staphylococcus. The staphylococcus is known to have a whole range of toxins—hæmolysins, leucocidins, fibrinolysin, hyaluronidase, and coagulase—but there is little possibility, as yet, of discovering the relation between these factors (some of which are enzymes) and staphylococcal disease.

Menkin (1935) suggested that localisation of staphylococcal infection occurs very rapidly because of the occlusion of the adjacent lymphatics by fibrin thrombi, but Miles (1955a) was unable to detect any lymphatic blockade in the first few hours of infection, and Young (1954), using the hamster cheek pouch, came to the same conclusion.

Young's observations were of some interest, in the first two hours the changes were of the classical reaction-to-injury type and were limited to the site where the organisms were injected. After that the vascular connective tissue changes became generalised throughout the pouch, and from five to twenty-four hours staphylococci could be cultured from anywhere in the pouch, but by forty-eight hours, an abscess had developed which was always at the initial point of infection, and by this time the rest of the pouch had become sterile.

One of the many problems of the staphylococcus is the undoubted relationship of pathogenicity with coagulase production. Until recently there was little evidence that the coagulase property was itself harmful, but Smith and Johnstone (1956) have just reported that in large doses it is lethal to rabbits with widespread intravascular thrombi, and Boake (1956) has claimed that immunisation with coagulase gives some degree of protection. Smith and Dubos (1956) showed that in mice the reaction to virulent and non-virulent staphylococci, injected intravenously, is similar to that observed with many other organisms, there is initial destruction of both forms apparently equally, and then the few coagulase-positive organisms which have survived inside phagocytes begin to multiply and produce local abscesses.

This ability to survive and multiply after the initial destruction is very characteristic of virulent organisms and so far as I know there is no satisfactory explanation for it. The suggestion has been made that virulent organisms form proteolytic enzymes which destroy part of their antigenic structure and so reduce their immunising activity, Lord Stamp (1953) has shown that such a phenomenon can occur in vitro and certain protozoa have an infinite capacity for altering their antigenic pattern

The staphylococcal filtrate—presumably the α hæmolysin—has a most powerful vasoconstrictor effect and there is no doubt that its dermonecrotic property is consequent on this Thal and Egner (1956) showed that when the filtrate was given intravenously, in addition to the renal vascular changes which de Navasquez (1938) studied it caused omental sequestration and a drop in portal venous pressure which is in accord with the shock syndrome

THE STREPTOCOCCUS

Our ignorance of the mechanism of staphylococcal pathogenicity is all too apparent, and when we turn to the streptococcus our plight is even worse Again there is a galaxy of toxins—erythrogenic toxin, streptolysin, leucocidin, fibrinolysin, hyaluronidase, protease, ribonuclease, and desoxyribonuclease Most of them have been separated on immunological grounds, but this gives us little guidance to the morphogenesis of streptococcal infections Naturally, the erythrogenic toxin is associated with the rash of scarlet fever, the hyaluronidase will assist penetration of ground substance by hydrolysing mucosubstances, and there is evidence that hyaluronidase production is often more active in vivo than in vitro Perhaps the fibrinolysin plays a part in lysing or preventing the formation of fibrin coagula, thus explaining the spreading character of a streptococcal cellulitis, while the ribonuclease will depolymerise viscid exudates rich in nucleic acids But all this provides us with a not very illuminating picture of streptococcal activity However, there are one or two additional clues with regard to two conditions which are undoubtedly associated with streptococcal infections—nephritis and rheumatic heart disease

Rammelkamp (1956) has shown that there is an association between the occurrence of acute glomerulonephritis and nasopharyngeal infection with strains of streptococci belonging principally to groups 12 and 4 This is in keeping with a number of other observations on the epidemiology of streptococcus induced disease, and naturally the idea of specificity is attractive, but there have been a lot of disease specific streptococci in the past For example, Kettle's second publication (1912) written conjointly with two senior clinicians, was on the Histology of Experimental Rheumatism, and its authors came to the conclusion that the cardiac lesions induced in experimental animals by the injection of the "Diplococcus rheumaticus" of Poynton and Paine were identical with those of rheumatic fever in man Fifteen years later Kettle said "At one time I was prepared to accept the rheumacoccus, partly, perhaps, because I was rather biased in its favour, but chiefly, because I was not conversant with the histological lesions of rheumatism" Kettle never forgot that paper, there was no doubt that he had been hurried into publication by the impatience of his senior collaborators—a misfortune that is liable to happen to most of us—and that the atmosphere of the Cancer Hospital laboratory where he was working under Alexander Paine was conditioned in favour of the specificity of the rheumacoccus But the moral he drew from it all was an oft repeated dictum "Never publish a paper till you're reasonably certain that you won't regret it five years later"

Since 1912 there have been innumerable attempts, by many and various methods, to reproduce the morphological lesions of rheumatic fever in animals Although there has sometimes been similarity, there has never been identity, and that is not altogether surprising, for no disease in one species is identical with that in another and this is especially true of chronic diseases

One of the problems with regard to rheumatic fever in man is that only a small proportion (about 3%) of people with streptococcal infections develop rheumatic fever, but one attack increases susceptibility to reinfection, and antibiotic therapy of throat infections reduces the likelihood of the heart being attacked again Various long-term experiments, such as those of Murphy and Swift (1949) and Glaser and his colleagues (1956), in which repeated streptococcal infections have been induced in animals, have resulted in a small proportion developing myocardial lesions quite closely resembling the Aschoff nodule, furthermore, focal myocardial lesions can be induced by intravenous streptococcal proteolytic enzymes But the most exciting possible link is the work of Bernheimer and his colleagues (1945, 1950, 1956) with streptolysin O

About ten years ago it was shown that if you exposed an isolated frog's heart to streptolysin, nothing happened, but if the heart was washed and then treated with a second dose of hæmolysin it immediately went into systolic contraction The first dose liberates an inhibitor (probably cholesterol) but this is removed by washing and the heart is then able to react to the second dose

When this procedure was applied to mammalian hearts, the coronary arteries went into spasm, and then there was permanent and irreversible loss of myocardial contraction It was not necessary to apply two doses to release the inhibitor as was the case in the frog's hearts, but the reaction could be inhibited by cholesterol and the streptolysin had to be activated by cysteine

Going from a heart infusion preparation to a suspension of mitochondria in a Warburg flask, Bernheimer and his colleagues were able to show that preparations of streptolysin O interfered with the oxidative metabolism of the mitochondria The selective nature of the inhibition, suggested that there was interference with the action of diphosphopyridine nucleotide or co-enzyme I, and that the bacterial extract contained an enzyme which broke down the oxidised diphosphopyridine nucleotide

Here we have clear evidence of a biochemical lesion, in Peters's sense of the word, but the question remains as to how, if at all, it is related to rheumatic fever, and we must not forget that Miles (1955b) has warned us to beware of the fallacy of the appropriate substrate Nevertheless, this does offer a clue we have evidence that a streptococcal filtrate can interfere with myocardial metabolism, and, if that is so, then we have an explanation for the localisation of lesions in the myocardium in rheumatic fever without invoking immunological hyperactivity, which is probably all important for the generalised connective tissue manifestations It might be objected that these muscular lesions are irrelevant as the primary lesions in rheumatic carditis are in the interstitial tissue, but this is open to argument Some, like Murphy (1952), believe that damaged muscle fibres are the primary factor in the histogenesis of the Aschoff nodule, and even the most extreme supporters of connective-tissue alterations, such as Wagner and Tedeschi (1955) agree that there is muscle damage and that myogenic giant cells (distinct from the Aschoff giant cell) may be present in the Aschoff nodule

DIPHTHERIA

Having dealt at length with two groups of organisms in which our knowledge of the pathogenic mechanism is poor, are there any in which it is not so poor? Yes, I think there are a few Pappenheimer (1955) has made a detailed study of diphtheria toxin, which is a protein with a molecular weight of about 72,000, and has found suggestive evidence that it acts by blocking the synthesis of cytochrome C It has been known for some time that an excess of iron in the culture medium interferes with the production of diphtheria toxin, and that when toxin is produced a porphyrin pigment is also released into the medium Furthermore, it has been shown that, when excess iron is added, every four atoms of the metal inhibit the production of four molecules of porphyrin and one of toxin, if still more iron is added, instead of toxin, a respiratory pigment resembling cytochrome C appears Now cytochrome C contains four hæm radicals per moiety, so diphtheria toxin could be the protein moiety of diphtherial cytochrome C, and in a susceptible animal might block the synthesis of cytochrome C There are several other points which support this hypothesis, but it presupposes that the turnover of cytochrome C within the cell is very rapid, and there seems to be no evidence on this

TETANUS AND BOTULISM

There are a number of other bacterial toxins which, although differing markedly in their pharmacological properties from diphtheria toxin, have certain features in common with it, such as extreme potency and a long latent period before any symptoms develop, which suggests that they act not as enzymes themselves, nor by inhibiting existing enzyme systems, but by interfering with the synthesis of essential cellular constituents

I am thinking, particularly, of tetanus and botulinum toxins, the neurotoxin of Shiga, and some bacterial plant diseases Botulinum toxin is possibly the most toxic substance known 1 mg contains 1,200,000,000 M L D per kg of guineapig, and the toxic dose is believed to be about 5 molecules per nerve cell Payling Wright (1954) and his colleagues have made an intensive study of botulism and tetanus, from which it is fairly clear that, while both are strict neurotoxins, botulinum toxin acts solely upon cholinergic nerve endings of peripheral fibres, whereas tetanus toxin operates upon nerve cells in brain and cord Probably both toxins affect the synthesis and liberation of acetylcholine, possibly by interfering with choline metabolism

GAS GANGRENE

I could discuss many other infections—anthrax, cholera and its mucinase, the endotoxins of the gram-negative organisms, and the obscure problems of tuberculosis, but I would like to select as my last example gas gangrene—not only for its own interest but because it played a significant part in the development of Kettle's research interests In 1916 at the laboratory of the 3rd London General Hospital he studied gas gangrene, which had only just been recognised as an entity, and he later provided an admirable account of its histopathology for the Medical Research Council's report on anaerobic infections During this work he became intrigued with the phenomenon of defence rupture, as Gye and Cramer (1919) called it If washed spores of gas gangrene or other anaerobes are introduced into the tissues of an animal, no disease usually develops, but if a small quantity of broth culture is injected, or if washed spores with calcium or silica are introduced, fatal gas gangrene develops in twenty four hours Kettle showed that the phenomenon was not restricted to anaerobes but also occurred with streptococci and diphtheria From these experimental combinations of bacterial and non bacterial inflammatory agents, it was not a long step to the problems of the tubercle bacillus and silica, on which he made his major contribution to knowledge

Sir Paul Fildes (1927), in his studies on tetanus, elucidated the phenomenon of "defence rupture," showing that the factor which determined germination of spores and multiplication of the vegetative bacteria was a drop in the oxidation reduction potential to a critical low level This could arise as a result of ischæmia, anoxia due to proliferation of contaminating bacteria, or autolysis of dead tissue

Now in gas gangrene we have a very striking example of a disease with both local and systemic manifestations Sometimes the local lesions may appear quite trivial compared to the profound collapse with circulatory failure from which the patient dies If we examine the local site the appearances range from muscle, which is pale and does not bleed or react to stimuli, to a pultaceous pinkish mass and finally a greenish black diffluent mass associated with a large amount of exudate and gas, while there may be necrosis of the skin with bleb formation The other organs seldom show any very striking changes, apart from some fat embolism in the lungs and perhaps acute tubular necrosis in the kidneys

Microscopic examination of the muscle shows a wide separation of the fibres by an œdema of the endomysial connective tissue with a striking lack of fibrin or neutrophil leucocytes in the exudate, there is disruption of the sarcolemma and disappearance of sarcolemmal nuclei These changes are agreed by all workers, but beyond this there is disagreement both as to the degree of destruction of myofibrils and the disappearance or preservation of reticulin and collagen fibres As is usual when there is a dispute in matters of observation, it is impossible to say who is right, because the techniques of different workers vary and clearly it is unfair to compare too closely the tissue changes in naturally occurring gas gangrene in man with the alterations observed by exposing animal muscle to clostridial filtrates in vitro (Robb Smith 1945, Aikat and Dible 1956)

As there is disagreement on the nature of the local lesions, so there may also be disagreement on the mechanism by which the changes are induced, and when one considers that *Clostridium welchii* filtrate contains α-toxin, the lecithinase, θ-toxin, a possible leucocidin ϰ toxin, the collagenase, and hyaluronidase as its known components, and that the proportions of these vary from strain to strain, there is considerable opportunity for differing viewpoints However, there is no disagreement that the α-toxin or lecithinase is the principal lethal factor, with its action in the first instance on the cell membrane, whether of capillary endothelium or sarcolemma Consequent on this there will be an exudate of fluid into the ground substance already modified by the action of the hyaluronidase and the fibrinolysin postulated by Reed and his co workers (1943) Macfarlane and Dupton (1954) have shown that the lecithinase can break down the phospholipids of mitochondria with inactivation of succinoxidase, a very important link in the oxidative mechanism of the cell It is clear that a widespread intercellular metabolic disturbance of this type could well be associated with the peripheral vascular failure that is so characteristic of the disease, although Ganley et al (1955) have postulated a "circulation factor" distinct from any of the known toxins But I believe we must also pay attention to the effect of lecithinase on cytoplasmic permeability and the consequent disturbance in body-fluid distribution So far I have not mentioned the collagenase first identified by R G Macfarlane and Maclennan (1949), Evans (1947) has shown that it is not a major lethal factor, but I still feel that there is good evidence that it plays a part in the local spread of clostridial infection

Silicosis

It would have been agreeable if I could have concluded this lecture by discussing the proximate mechanisms in silicosis, but in reality we cannot add much to what Kettle and Gye (1922) said thirty-four years ago in their first paper on the subject "Just as, in a physiological sense, no material is of use for energy purposes unless it is soluble, so pathologically, with certain obvious mechanical exceptions, it is only soluble substances which can exert a substantial or a continuous effect on the tissues"

King et al (1956) have reviewed the solubility theory very carefully, and feel that, in spite of certain inconsistencies, it is the most probable, but this still [illegible] to be explained Holt and Osborne's (1953) suggestion that polymerised silicic acid might function in the connective tissue as a macromolecule analogous to a mucopoly saccharide, and so induce collagen formation, is attractive, but I feel does not altogether conform with recent work on fibrillogenesis On the other hand, MacLeod and Roe's (1956) observation that silicate in low concentration was lethal to pneumococci and streptococci and changed their reaction to the gram stain does perhaps contain a germinal idea This phenomenon could be inhibited by lecithin, choline, and substituted ammonia compounds, but not by cholesterol This might indicate a disturbance of the cytoplasmic membrane, and if such a disturbance could be substantiated one might begin to determine the biochemical lesion in silicosis

* * *

I tried to forewarn you that I would present the way in which I believe morphological pathology is exploring disease mechanisms, and the successes, limited though they may be, that have been obtained in the field of inflammation and infection I can only hope that for some of you it has raised questions to be resolved and assumptions to be tested, and is a reminder that there is still much work to be done in the way that Kettle did it

REFERENCES

Allgöwer? no

TABLE I—THE PATIENTS AND THE CONTROLS

Patients			Matched controls	
Diagnosis	Sex	Age (yr.)	Sex	Age (yr.)
Infarct 9 mos. ago	M	40	M	41
2 infarcts 9 and 17 mos. ago	M	42	M	44
Infarct 12 mos. ago	M	43	M	45
Angina for 9 mos.	M	44	M	45
Angina for 9 yr.	F	44	F	44
Two infarcts 3 and 7 mos. ago	M	45	M	46
Two infarcts 6 and 12 mos. ago	M	46	M	45
Angina for 10 yr., infarct 3 weeks ago, diabetes	M	46	M	49
Infarct 11 mos. ago	F	50	F	48
Angina for 8 yr.	M	50	M	51
Infarct 5 yr. ago	M	51	M	51
Infarct 12 mos. ago	M	51	M	51

the condition, and gross electrocardiographic abnormalities were present either at rest or after exercise. Two of these patients were in hospital at the time of the investigation.

The controls were healthy volunteers selected to correspond to the patients in age and sex. None had a history in any way suggestive of cardiac disease, but they were not otherwise investigated.

Dietary histories were taken by the same dietitian from all the people taking part in this investigation. From these histories the daily intake of calories and fat (animal and vegetable) were roughly estimated. The mean values for the coronary and control groups are shown in table II. The mean value for the intake of animal fat appears to be somewhat lower in the patients with coronary artery disease compared with the controls, but the difference is by no means significant (P=0.3). The other values are very similar in the two groups.

Methods

Collection of Blood

50 ml. of blood was drawn from the antecubital vein into acid citrate dextrose anticoagulant at least 15 hours after the last fat containing meal. The blood was kept at +4°C until required for analysis, which was never delayed longer than 24 hours.

Separation of Lipid Fractions

The blood was centrifuged to separate the red cells, which were then washed once with 0.16 *M* NaCl solution to remove trapped plasma. 20 ml. portions of both plasma and packed red cells were then added with vigorous stirring to two separate 400 ml. portions of 2 : 1 ethanol ether. After standing at room temperature for 15 hours the precipitated protein was removed by filtration, and the lipid solutions were evaporated to dryness in vacuo on a water-bath at +40°C. Before evaporation 1.0 ml. of 0.01 *M* uranyl sulphate solution was added to the plasma lipid solution to facilitate the separation of the phospholipids from the other lipid components. After evaporation the dry residue of the plasma lipids was immediately extracted with two successive 15 ml. portions of acetone.

The lipids in this fraction are called "the acetone soluble lipids of the plasma" and include principally glycerides and cholesterol esters. The lipids of the residue remaining after the acetone extraction are called "the phospholipids of the plasma". After the removal of solvent both fractions were hydrolysed by the addition of 5.0 ml. of 40% KOH and 25 ml. of 50% ethanol and heating to 60°C for 4 hours in a water bath. Unsaponified material was removed by extraction with light petroleum (40–60°C boiling range), and the fatty acids were liberated from the hydrolysate by the addition of 10 ml. of 10 *N* H_2SO_4.

TABLE II—MEAN INTAKE OF FOOD BY PATIENTS AND CONTROLS AS ASSESSED BY DIETARY HISTORIES

Group	Total calories daily	Intake of fat (g. daily)		
		Animal fat	Vegetable fat	Total
Patients with coronary disease	2372	88	23	111
Controls	2489	105	23	128

The fatty acids were isolated by three successive extractions with ether. The ether solution was then dried over anhydrous Na_2SO_4 and evaporated to dryness. Immediately after the evaporation of the ether the acids were esterified by dissolving in 10 ml. of anhydrous methanol containing HCl and heated under reflux for 2 hours. The methanol was then removed by evaporation in vacuo, and light petroleum was added, followed by a little water. The aqueous layer was twice extracted with light petroleum, and the extracts were combined, washed with dilute $NaHCO_3$ solution to remove free acid, and finally dried over anhydrous Na_2SO_4. The fatty acid-methyl ester solutions were stored at +2°C.

Fatty acids and their esters are stable when stored in dilute solution at this temperature; losses seem to take place only when they are dry and in contact with air. Before the application of the sample to the gas column the solvent was removed by evaporation on the water bath. At no time were the dried samples exposed to atmospheric oxidation for more than a few minutes.

Gas-liquid Chromatography

The samples were applied with a micro pipette to the gas-liquid chromatograph described by James and Martin (1952) for the separation of the methyl esters of long chain fatty acids. The columns used were 4 ft. long, with a stationary phase of 'Apiezon M' vacuum stopcock grease at a temperature of 197°C. The mobile phase was nitrogen, and the detector was the gas-density meter (*Martin and James 1956*).

TABLE III—FATTY ACID ABUNDANCE OF THE LIPIDS OF THE RED BLOOD CELL

Acid	Mean of 9 patients	Mean of 6 controls	(P)*
Myristic	0.85%	0.87%	0.9
Palmitic	23.0%	22.4%	0.9
Stearic	16.6%	14.7%	0.75
Palmitoleic	1.2%	1.1%	0.9
Oleic	21.3%	19.8%	0.2
Linoleic	11.8%	12.1%	0.9
Arachidonic	14.1%	13.3%	0.5

*(P) indicates the probability that the observed difference between the two means is due to chance.

The fatty acids were measured quantitatively by the triangulation technique described by James and Wheatley (1956). As a test of reproducibility three samples of the fatty-acid methyl esters from the same batch of red cells were prepared by the complete procedure just described. The three chromatograms matched one another.

Cholesterol Estimations

The total cholesterol content of the plasma was estimated by the method described by Bloor (1916). Briefly this was as follows. 1 volume of plasma was added to 25 volumes of 2 : 1 ethanol ether solution, and after being left for 30 minutes the solution was filtered and evaporated to dryness; the dry residue was extracted with three successive portions of boiling chloroform; and the cholesterol was estimated by light absorption with the use of the green colour produced on adding acetic anhydride and sulphuric acid.

Glycerol Estimations

The glyceride glycerol content of the acetone soluble fraction of the plasma lipids was estimated by the method described by Harvey and Higby (1951). In this method glycerol is estimated by light absorption, using the red colour produced by the reaction between glycerol and catechol in sulphuric acid. Glycerol estimations were made on the aqueous solution remaining after the hydrolysis and lipid extraction of the acetone soluble fraction of the plasma lipids.

Identification of Fatty Acids

The time of emergence of a homologous series of saturated fatty acids from the chromatograph column is precisely determined by their chain length (James and Martin 1956), and chemical identification was not considered necessary. The unsaturated acids were isolated and identified by chemical degradation. A preliminary account of the nature of the fatty acids present in plasma lipoprotein, neutral fat, and red blood cells has been given by James and Lovelock (1957).

TABLE IV—THE FATTY-ACID ABUNDANCE OF THE PLASMA PHOSPHOLIPIDS

Acid	12 patients	12 controls	(P)
Myristic	1·1%	1·1%	0·9
Palmitic	25·5%	26·7%	0·9
Stearic	13·4%	13·3%	0·9
Palmitoleic	1·94%	2·03%	0·9
Oleic	20·7%	20·8%	0·9
Linoleic	19·6%	18·8%	0·9
Arachidonic	9·6%	9·7%	0·9

Results

Red blood-cells.—At the beginning of the investigation the fatty-acid composition of red cells from different human sources was determined. They were remarkably constant from person to person regardless of age, sex, and state of health. A complete comparison of the fatty acids of the red cells of all of the patients with coronary-artery disease and their matching controls was not therefore made. Table III shows the fatty-acid composition of the red cells of nine patients with coronary-artery disease and that of six normal persons not of the same age and sex. The means were compared according to the '*t*' test, and the probability that the differences between the means were due to chance is shown in the table. It can be seen that the two groups are not significantly different.

Phospholipids of plasma.—Table IV shows the composition in terms of the main components of the fatty acids of the phospholipid fraction of the twelve patients with coronary-artery disease and of their matching controls. The probabilities that the differences between the mean compositions of the acids of the two groups were due to chance are also shown and again indicate that there are no significant differences between the two classes.

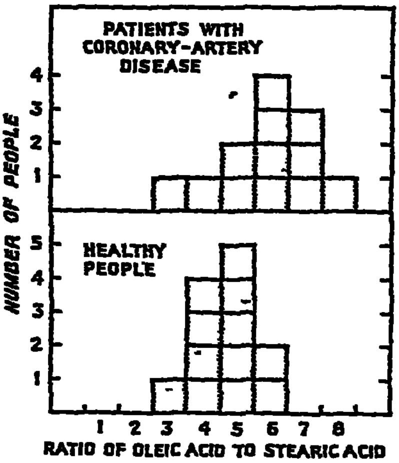
Acetone soluble fraction of plasma.—Table V shows the fatty-acid composition of the acetone soluble fraction of the plasma of the twelve patients and of their matching controls. The total cholesterol content and the glyceride-glycerol of the plasma in the two groups are also shown. The probabilities that the differences between the abundances of the components in this fraction were due to chance are shown, and, unlike the fatty acids of the red cells and the phospholipids, seem to be verging on significant differences for some of the fatty acids. Values for glyceride glycerol and for total cholesterol were not significantly different in the two groups.

Discussion

We know of only one other comparison of the fatty-acid composition of normal blood and blood from atheromatous patients—namely, that of Hammond and Lundberg (1955). Their work differed from ours in important respects: their controls and atheromatous patients were not matched for age and sex, blood was taken 3–4 hours after a fatty meal, and the analyses were done on whole plasma. In addition, the analysis was spectrophotometric, which means that groups of fatty acids of equal degrees of unsaturation were measured rather than single components as in our technique. Hammond and Lundberg found an apparent small decrease in the proportions of di- and tetra- unsaturated acids in the atherosclerotic patients; but, when these were corrected for the level of total fatty acids, there was no difference in the amount present per 100 ml. of plasma in the two groups. The main components of the di- and tetra- unsaturated acids are linoleic and arachidonic acids respectively. In our study there was no difference in the proportion of these acids found in controls and patients either in the red-cell, in the plasma-phospholipid, or in the plasma acetone-soluble fractions. Linoleic and arachidonic acids are often described as "essential fatty acids," and it has been suggested that deficiency of essential fatty acids may be a factor in the causation of atherosclerosis (Sinclair 1956). Our results do not support this idea.

TABLE V—FATTY ACIDS, CHOLESTEROL, AND GLYCERIDE GLYCEROL OF THE ACETONE SOLUBLE FRACTION OF THE PLASMA LIPIDS

Lipid component	Composition in 12 patients	Composition in 12 controls	(P)
Mean abundance of fatty acids (%)			
Myristic	3·5%	4·7%	0·1
Palmitic	23·9%	24·1%	0·9
Stearic	6·9%	7·7%	0·3
Palmitoleic	5·3%	4·6%	0·1
Oleic	38·1%	34·7%	0·06
Linoleic	12·1%	12·4%	0·9
Arachidonic	2·7%	2·6%	0·9
Total mono unsaturated acids C_{14}, C_{16}, and C_{18}	45·9%	41·6%	0·05
Other lipid components (mg. per 100 ml. of plasma)			
Cholesterol	197·0	159·7	0·5
Glyceride glycerol	4·4	4·0	0·6
Ratio of oleic acid to stearic acid	5·8	4·6	0·02



Frequency distribution of values of the oleic-acid stearic-acid ratio of the acetone-soluble fraction of the plasma lipids.

The general fatty-acid pattern in both the red-cell and plasma-phospholipid fractions is remarkably constant in spite of differences in age, sex, diet, and state of health. In the acetone-soluble fraction of the plasma most of the fatty acids are present in similar proportions in the controls and in the patients. The preliminary investigation of the fatty acids of the acetone soluble fraction of the plasma of young persons, particularly young women, showed that mono-unsaturated acids are significantly less abundant in this group than in our patients with coronary-artery disease. This observation led us to compare the proportions of the mono unsaturated C_{14}, C_{16}, and C_{18} acids in the patients and in their matching controls. The mean proportion of these acids taken together was higher in the patients than in the controls, but only at a low level of significance ($P = 0·05$). The main component of this group of mono-unsaturated acids (oleic acid) is not by itself significantly different in proportion in the two groups at the 5% level. Oleic acid may, however, reasonably be related to its corresponding saturated acid, stearic, with which it is believed to be interconvertible in the body. When the ratio of oleic to stearic acid was compared in the two groups it was found that the mean value in the patients was higher than in the controls ($P = 0·02$). A histogram of the individual values of the ratio of oleic to stearic acid for the two groups is shown in the accompanying figure.

These small divergencies in the C_{14}, C_{16}, and C_{18} mono unsaturated acids of the acetone soluble fraction would not be remarkable were it not for the contrast provided by the extreme constancy of most of the other fatty acids, and of those same fatty acids in the red cell and plasma-phospholipid fractions. It may well be that the differences would be more striking if the patients with coronary artery disease could be compared with controls whose coronary arteries were certainly healthy, for the most that can be said of our controls is that they have not yet shown any clinical manifestations pointing to this type of disease The difficulty in demonstrating differences in a small series such as this, where the controls are inevitably not "pure controls," is illustrated by the fact that the mean plasma-cholesterol level and the glyceride glycerol level were not significantly different in the two groups, although we do not question the fact that, in a much larger series, the plasma-cholesterol level has been shown to be higher in patients with coronary-artery disease

The existence of a significant difference in the ratio of oleic acid to stearic acid in the patients with coronary-artery disease suggests that the disease may be a consequence of some fault of metabolism rather than of diet as is usually held It must be emphasised, however, that the acetone soluble fraction of the plasma-lipids in which these differences are observed is a mixture of glycerides and cholesterol esters Until these two lipids can be studied separately it is unlikely that a clear picture of the differences between the patients and their controls will emerge

Summary

Gas liquid chromatography was used to determine the proportions of a range of fatty acids, from C_6 to C_{20}, in the blood of twelve patients with coronary-artery disease and in twelve controls matched for sex and age For the purpose of this analysis the blood was divided into red cell, plasma phospholipid, and plasma acetone-soluble fractions

In the red cell and plasma phospholipid fractions there were no detectable differences between the proportions of any fatty acids in the patients and their controls

In all three fractions the mean proportions of the "essential fatty acids" (linoleic and arachidonic) were about the same in the patients and in the controls Hence these observations do not support the hypothesis that deficiency of these "essential fatty acids" is a factor in the genesis of coronary-artery disease

In the acetone soluble fraction of the plasma (containing cholesterol esters and glycerides) there was some suggestion of an increase in the combined proportions of mono unsaturated C_{14}, C_{16}, and C_{18} acids in the patients compared with the controls The ratio of the most abundant of these acids (oleic) to its corresponding saturated acid (stearic) was higher in the patients with coronary artery disease The implications of this observation cannot be properly assessed without further resolution of the acetone soluble fraction into its two components, cholesterol esters and glycerides

We wish to express our gratitude to Miss J M Ingles for the dietary histories, and to the consulting physicians of University College Hospital for permitting us to investigate their patients One of us (W R T) is in receipt of a grant from the Sir Halley Stewart Trust

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HIATUS HERNIA

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Widely divergent opinions have been published by physicians and surgeons about the correct treatment of hiatus hernia This difference of views depends on the types of cases which they see Surgeons seldom see mild cases and operate on patients who have not improved with medical treatment, whereas physicians find that the average case responds to medical measures and that surgery is seldom required The present review of 87 cases of hiatus hernia and 20 with gastro-œsophageal reflux alone was undertaken primarily to assess the effectiveness of medical treatment

Material

The material consisted of 45 females and 42 males with hiatus hernia, and 11 females and 9 males with gastro œsophageal reflux alone The cases were unselected, being all those on the diagnostic index of Addenbrooke's Hospital, apart from a few patients who had died or who did not reply to the request to attend for review, All the cases had been investigated for dyspepsia, and the diagnoses had been established radiologically during the four years before review in 1954–55 All the patients were interviewed personally, except 5 who supplied information by letter

Findings

RADIOLOGICAL FINDINGS

Hiatus Hernia

Of the 87 patients 76 had sliding herniæ, 9 had large herniæ of combined sliding and para œsophageal type, 1 had a para-œsophageal hernia, and 1 a short œsophagus A similar incidence of the various types was found by Allison (1951) and Sweet (1952) All the combined herniæ and 41 of the sliding herniæ were larger than 2 5×2 5 cm (measured on the films) No correlation was found between size of the hiatus hernia and severity of symptoms, mild symptoms being associated equally with large or small herniæ All the patients with sliding herniæ had associated gastro œsophageal reflux

Gastro-œsophageal Reflux

In the 20 cases of reflux alone it was radiologically slight in 12 and gross in 8 Symptoms were severe in 11 of the 12 cases with slight reflux and in 6 of the 8 with gross reflux There was thus no correspondence between the clinical and radiological degrees of severity

RELATION OF GASTRO ŒSOPHAGEAL REFLUX TO SYMPTOMS OF HIATUS HERNIA

Intermittent and slight gastro œsophageal regurgitation is a normal event It is therefore difficult to assess the significance of gastro œsophageal reflux in the production of symptoms, and there is no agreement about the relative importance, in the production of symptoms, of a hiatus hernia and of the reflux that almost constantly accompanies it (Olson and Harrington 1948, Collis et al 1954)

In the present series there was no significant difference between the symptoms of patients with hiatal herniæ and associated gastro œsophageal reflux and those with reflux alone Œsophagitis and œsophageal spasm are considered to be responsible for the pain in both groups, and the symptoms were relieved by the same treatment (see below), which is designed to mitigate the occurrence and sequels of reflux *For this reason the symptoms of both classes of patients are considered together*

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TABLE I—SYMPTOMS

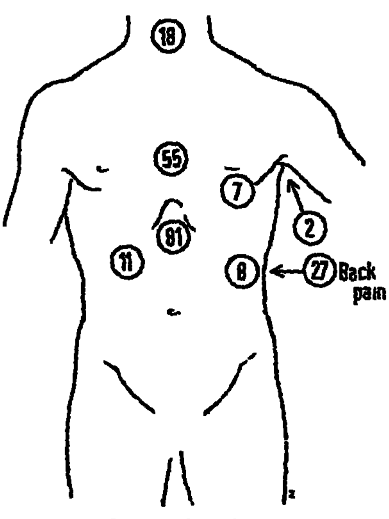
Symptoms	No of patients in whom symptom predominant	No of patients in whom symptom occurred
Pain	79	101
Isolated severe attacks of pain	4	
Regurgitation	3	62
Flatulence		69
Microcytic anæmia	5	18
Hæmatemesis or melæna	4	23
Mild symptoms, pain predominant	14	
Symptom free	2	

SYMPTOMS

Pain

Pain was the predominant symptom in 79 cases and was present in 101 of these 107 patients (table I) It occurred in the situations depicted in the accompanying figure, and many patients had pain at more than one site It will be seen that in 81 patients the pain was central and high in the epigastrium, in 55 substernal, and in 18 referred to the throat Pain in one or both arms occurred in 2 patients with cardiographic abnormalities and in 3 without evidence of coronary disease The pain was typically dull and aching The pain was worse on stooping or on lying down in 56 patients, in 61 it came on after food, within half an hour in 30 It was usually relieved by alkalis with the production of belching

Night pain was a prominent feature in 63 cases and came on an hour or more after retiring in 31 The onset of pain soon after lying down in bed has been regarded as a differential point from the night pain of peptic ulcer, but it is clear that the time-interval after retiring is not constant in the pain of hiatus hernia or reflux Lying on the right side provoked pain in 21 cases, but lying on the left side in only 6 This positional difference is probably due to the fact that, whereas the fundus of the stomach is posterior to the hiatus in the supine and left lateral positions, in the right lateral position the fundus and the hiatus are in the same horizontal plane, thus facilitating reflux (F Pygott, personal communication)



Localisation of pain

Periodicity of pain—Of the 101 patients with pain, 58 experienced exacerbations alternating with weeks or even months of freedom Such periodicity has always been regarded as characteristic of peptic ulceration, but it is evidently shared by hiatus hernia and reflux

Substernal pain suggesting angina pectoris—Isolated attacks of severe pain, such as those described by Bourne (1956) with œsophageal lesions, were initially suspected to be due to myocardial infarction in 4 cases Of these patients 1 showed definite evidence of myocardial infarction, with an almost symptomless hiatus hernia In the remaining 3 patients a hiatus hernia was responsible

Case 1—A woman, aged 44, had an isolated attack of severe retrosternal pain radiating to her back and accentuated by respiration She was dyspnœic and vomited The attack lasted three hours Myocardial infarction was diagnosed, and she was confined to bed for four weeks Subsequent electrocardiogram and radiograph of cervical spine were normal, a hiatus hernia was demonstrated She now notices substernal pain of constricting type spreading to the elbows, occurring inconstantly on exertion, and relieved by rest and by trinitrin She also complains of heartburn and retrosternal pain, worse at night

Case 2—A man, aged 60, in bed in hospital with subacute bacterial endocarditis associated with rheumatic mitral incompetence, had several severe attacks of substernal pain and dyspnœa but no pyrexia or leucocytosis Electrocardiograms were normal, but a hiatus hernia was found Since then he has had retrosternal discomfort which develops on brisk exercise and is relieved by rest

Case 3—A woman, aged 67, had an attack of severe epigastric pain spreading to the left precordium and the back The pain came on while she was sitting, and it stopped suddenly after ten hours There was no angor animi, and she has had no further symptoms An electrocardiogram was normal, but a barium meal showed a hiatus hernia

Angina of effort was present in 9 patients, of whom 7 had hiatal hernia and 2 had gastro-œsophageal reflux alone Milder varieties of pain on exertion, not typical of angina pectoris, were experienced by 11 patients, of whom 9 had hiatal hernia *and 2 gastro-œsophageal* reflux A postural régime for the hiatus hernia produced considerable improvement in 3 patients with angina and in 2 with mild effort pain

Significant abnormalities were present in the electrocardiograms of 6 of the 9 cases with anginal pain, none of the 11 patients with indefinite pains on exertion, and only 4 of the remaining 87 patients showed such abnormalities These findings suggest that hiatus hernia does not, of itself, produce angina on effort, and that when the latter is present it has some cardiac cause Baylis et al (1955) reached a similar conclusion in studies on distension of the lower œsophagus by a balloon in 8 healthy people and in 3 patients with coronary artery disease They found that distension of the lower œsophagus had no effect on the electrocardiogram of the patients with coronary artery disease, and that œsophageal pain was not associated with electrocardiographic change In their opinion the electrocardiogram offered the most reliable means of distinguishing between œsophageal and cardiac pain

Dysphagia

In 21 patients food seemed to stick momentarily behind the lower sternum on swallowing, but there was no true obstruction Pain on swallowing, also localised to the lower œsophagus, was present in 17 patients and was provoked by strong alcohol or hot fluids or foods in 11 Excessive salivation accompanied the dysphagia in 10 patients

COMPLICATIONS OF HIATUS HERNIA

Hæmorrhage and Anæmia

Hæmorrhage and anæmia are common in patients with hiatus hernia (Ritchey and Winsauer 1947, Schwartz and Blumenthal 1949) In the present series 33 patients had either frank hæmorrhage or anæmia Serious hæmatemesis or melæna took place in 15, and in 1 the hæmoglobin was reduced to 3 1 g per 100 ml A microcytic hypochromic anæmia without a history of frank hæmorrhage was found in 10 cases, in 5 of which tests for occult blood in the stools were positive A similar anæmia was also found in 8 patients with histories of frank hæmorrhage in the past

It is of considerable interest and importance that in 8 of the 33 patients with either frank *hæmorrhage or* anæmia the dyspeptic symptoms had been very slight, and in 2 cases presenting with hypochromic anæmia their hiatal hernia were entirely symptomless Large hiatal hernia showed no greater tendency to bleed than small ones

Anæmia and hæmorrhage were only recorded in cases of hiatus hernia and not in those of gastro œsophageal reflux alone. This suggests either that hæmorrhage takes place from the hernia or that œsophagitis is more severe than in cases with reflux alone.

Œsophagitis

In this series œsophagitis was reported radiologically in only 4 cases; subsequent œsophagoscopy in 1 of them revealed a high cardia and reflux of gastric contents but a normal œsophageal mucosa. In 5 other patients examined by the œsophagoscope the mucosa was normal in 3, there was general œsophageal hyperæmia in 1, and an erosion of the gastric mucosa of the hernial pouch in 1. At necropsy on 2 patients who died from unrelated causes the œsophagus was normal in 1 but showed a mucosal erosion in the other.

The demonstrated incidence of œsophagitis in this series is low because œsophagoscopy was only done on a few patients with severe symptoms and not on all patients as a routine, and radiology cannot demonstrate mild grades of œsophagitis.

ASSOCIATED DISEASES

Hiatus hernia is not infrequently found in association with other upper abdominal conditions. It has even been suggested that these promote reflex œsophageal contraction and predispose to hiatus hernia (Gilbert et al. 1946).

TABLE II—ASSOCIATION OF HIATUS HERNIA WITH OTHER ABDOMINAL CONDITIONS

—	Gilbert et al. (1946) 48 cases	Radloff and King (1947) 50 cases	Present 107 cases
Gall stones	14	4	7
Duodenal ulcer	6	3	8
Diverticulosis coli		6	6
Diverticulum of œsophagus	4	1	1
Diverticulum of duodenum		3	5
Totals	24	17	27

Table II shows that 27 of the present 107 patients had associated upper abdominal disease.

In 6 of the 8 cases with associated duodenal ulcer the symptoms were characteristic of duodenal ulcer rather than of hiatus hernia. The diagnosis of a hiatus hernia as source of hæmatemesis in 1 patient was long delayed.

Case 4.—A woman, aged 57, had had since the age of 29 left epigastric pain, worse on stooping or on lying, and coming on two hours after food and in the early hours of the morning. It was not relieved by food or by alkali. She was subject to flatulence, regurgitation, and intermittent dysphagia. Since the age of 16 she had vomited blood at intervals of several years. She underwent partial gastrectomy in 1929 at the age of 31, when a duodenal ulcer was found. She continued to have exacerbations of pain with increasingly severe hæmatemeses, latterly requiring large transfusions. In 1955 a small hiatus hernia with an œsophageal ulcer was demonstrated. Since repair of the hernia hæmatemeses have ceased and pain is much improved.

It is often difficult, too, to decide whether a hiatus hernia or the gall-bladder is responsible for the symptoms.

Case 5.—A woman, aged 53, had had epigastric pain, immediately after food, for eight years, with dysphagia and occasional vomiting. In 1949, at the age of 50, a small hiatus hernia was found, but a postural régime did not control her pain. In 1952 she had a severe attack of right upper abdominal pain with jaundice. Removal of a chronically inflamed gall bladder led to great improvement.

Case 6.—A woman, aged 72, had had for ten years pain in the epigastrium radiating to the back, worse on stooping and on lying, and coming on soon after food. She had dysphagia, regurgitation, and flatulence. Three years ago a chronically inflamed gall bladder containing stones was removed, but symptoms were unaffected. A hiatus hernia was then found, and with conservative treatment symptoms over the past years have been slight.

Case 7.—A woman, aged 59, had had epigastric pain, vomiting, and dysphagia for twenty years. Her pain was worse on lying flat and soon after food and was relieved by alkali. A normal gall bladder had been removed fifteen years before without improvement. Postural treatment for her hiatus hernia has been successful.

Treatment

The aims of treatment are the same for hiatus hernia with associated reflux as for gastro œsophageal reflux alone. They are relief or prevention of reflux œsophagitis which is believed to cause pain either as heartburn or as œsophageal spasm.

(1) Postural measures are adopted to lessen the chances of reflux. Meals are taken by the patient sitting bolt upright or even standing at first; bending forward and sitting in a crouched position are avoided, and at night four pillows are used with 4-inch blocks under the legs at the head of the bed.

(2) Causes of raised intra abdominal pressure are eliminated as far as possible. Weight reduction may be most valuable, the corsets and the bowels are kept loose, and chronic cough is treated.

(3) The acidity of the gastric juice in the lower end of the œsophagus is reduced. Persistent pain and vomiting are usually rapidly relieved by continuous mild drip with the distal end of the Ryle's tube in the upper œsophagus. After a few days the drip may be removed by day, but it should be continued by night as long as any night pain or heartburn persists. When symptoms are not severe, small frequent meals are advised, and aerated drinks, strong alcohol, and excessive smoking are forbidden. After meals magnesium trisilicate powder should be taken, preceded by a few ounces of water drunk by the patient standing up to flush through the œsophagus. A further dose should be taken at bedtime. If pain persists despite these measures, belladonna or propantheline ('Probanthine') may be helpful.

RESULTS OF TREATMENT

Medical

Of the present 107 cases 83 were treated by the full régime outlined above and were followed up after an average period of 14·7 months ($\sigma = 14{\cdot}8$). In the remaining 24 cases postural measures were not needed, either because symptoms were very mild and transient or because anæmia—rapidly corrected by iron—was the presenting feature.

In 58 (70%) of the patients treated the symptoms were well controlled; only 6 of this group were entirely free from symptoms, but the rest had only mild and intermittent dyspepsia. 12 (14%) others experienced much improvement but still found symptoms troublesome. In 13 (16%) there was no improvement, but in 8 such factors as melancholia, uncontrolled obesity, œsophageal stricture, and urethral stricture obviously contributed largely to failure of treatment.

Surgical

Surgical treatment of hiatus hernia is often contraindicated by poor general condition or by advanced age, and postoperative recurrence-rates may be as high as 30% (Sellors 1955). Surgery, however, should be considered when severe pain persists in spite of thorough medical treatment, when *hæmorrhage* is repeated, or when the hernia undergoes rupture, strangulation, or torsion. Strictures are usually amenable to dilatation (Halonen et al. 1952, McGlone and Sawyer 1953). Only 4 patients in this series were subjected to surgery: 2 are symptom free, but 1 of these still has a demonstrable hiatus hernia of moderate size; 1 patient, who survived operation, died shortly afterwards of myocardial infarction; and 1 died from mediastinitis consequent on preoperative œsophagoscopy.

Summary

87 cases of hiatus hernia and 20 of gastro œsophageal reflux are surveyed.

Medical treatment produced good results in 70% of cases, and considerable relief in a further 14%.

Surgery is seldom necessary and often impossible owing to the advanced age of many patients with hiatus hernia

I am very grateful to Dr L C Martin and Dr F Avery Jones for help and advice

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INTERMITTENT METHYLTESTOSTERONE THERAPY IN MALE SUBFERTILITY

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FOR some years it has been the practice at this clinic to treat the husband of a subfertile marriage with methyltestosterone if the quality of his semen is such that he can be regarded as partially or mainly responsible for the failure of his wife to conceive

To avoid the depressive effects of continuous treatment with androgens the methyltestosterone is given intermittently The routine is for the husband to take 10 mg of methyltestosterone daily from the sixth to the sixteenth days of his wife's menstrual cycle, the tablets being dissolved sub lingua If no conception takes place after four to twelve cycles of such treatment, the tablets are discontinued either altogether or for several months, the course then being repeated, sometimes in a higher dosage

In the cases reviewed here, all the couples made their first visit to the clinic between July 1, 1949, and June 30, 1954 Accurate information is available for at least a year, and usually for two years or longer, after the date of the first attendance at the clinic Only cases where at least two specimens of semen were examined before the husband started taking methyltestosterone have been considered The quality of the semen was assessed by the methods described by Harvey and Jackson (1945) and classified according to the mean fertility indices of the two or more ejaculates examined (Harvey 1953) The success of the treatment was measured by comparing the number of pregnancies in each fertility index class with the corresponding pregnancy rate for a larger series of cases investigated in the five years before 1949 The husbands in the control series received no methyltestosterone, but vitamin E was given to nearly all those whose semen had a fertility index below 30 This treatment had no detectable effect on their fertility (Jackson 1948)

Results

Conceptions

Reliable follow up information is available for 148 couples in which the husband was given methyltestosterone 55 of the wives became pregnant within two years of the start of the husband's treatment Half the pregnancies occurred during the first six months' treatment, the remainder being distributed fairly evenly over the following eighteen months Pregnancies are not recorded in this report if they occurred more than twenty-three months after the start of the treatment, because the conception-rate in the controls was based on a two-year period

TABLE I—INCIDENCE OF PREGNANCY IN TREATED AND CONTROL SERIES

Series	Fertility index range of husband			
	Under 30		30–49 (somewhat below average fertility)	50 or more (average to good fertility)
	Less than 10 (very subfertile)	10–29 (definitely subfertile)		
Husband receiving no methyltestosterone				
No of cases	51	90	112	286
No of wives who became pregnant	4 (8%)	20 (22%)	49 (44%)	129 (45%)
Husband receiving methyltestosterone				
No of cases	39	54	33	22
No of wives who became pregnant	16 (41%)	19 (35%)	9 (27%)	11 (50%)
No of pregnant wives expected from untreated series	3	12	14 4	9 9

The fertility indices of the semen covered a range from less than 1 to over 100, but no azoospermic donors were included Where the mean fertility index of the husband's semen is over 50, the chance of conception depends almost entirely on the wife's fertility, and treatment was given to husbands in this group only because of factors other than the quality of the semen, such as partial impotence and lack of libido Where the mean fertility index lies between 30 and 50, though the husband's slightly lowered fertility may somewhat reduce the chances of success of a subfertile wife, the male factor is seldom the principal cause of her failure to conceive It is only when the fertility index of the husband's semen falls below 30 that his fertility level becomes the critical factor in determining conception

Table I compares the number of wives who became pregnant in the two series, the couples being grouped according to the fertility index of the husband's semen

It is apparent from these figures that, whereas in the groups where the husband's semen was of fair or good quality the number of pregnancies did not differ significantly from that expected on the basis of the controls, the number of wives who became pregnant in the groups where the husband's semen may be regarded as the critical factor was more than twice the calculated expectation For the wives of the men with a fertility index under 30 the difference between the pregnancy-rates in the two series is statistically highly significant, and there seems little doubt that in these cases methyl-

TABLE II—COMPARISON OF PREVIOUS INFERTILITY OF TREATED SERIES AND CONTROLS

Series	No of years barren				
	2 or less	Over 2 to 5	Over 5 to 10	More than 10	Total
Husband receiving no methyltestosterone					
No of patients	26 (18%)	47 (33%)	58 (41%)	10 (7%)	141
No of wives who became pregnant	6	12	6	0	24
% successful	23	26	10	0	17
Husband receiving methyltestosterone					
No of patients	16 (17%)	39 (42%)	29 (31%)	9 (10%)	93
No of wives who became pregnant after treatment	11	12	10	2	35
% successful	69	31	34	22	38

Only those with a fertility index below 30 are included in this table (first two columns in table I)

TABLE III—PRE TREATMENT QUALITY OF SEMEN IN 93 MEN WITH FERTILITY INDEX BELOW 30

Quality of semen before treatment	No of men	No of wives pregnant after treatment
Density never exceeding 20 million per ml	36	13
Motility adjusted for age of specimen, equivalent to less than 10% three hours after ejaculation	39	14
Morphologically normal sperm below 35%	36	15
At least one character always below the above standards	78	29
Best value above these standards	15	6

testosterone considerably increased the couple's chances of success It is perhaps worth mentioning that in an appreciable number of cases, according to statements from both partners, the husband's coital performance was improved

To ascertain as nearly as possible whether the treated and untreated series are comparable so far as their degree of infertility was concerned, the couples in each series, where the husband's fertility index was below 30, have been grouped according to their number of years' barrenness with unprotected coitus In the methyltestosterone series this period was reckoned to extend up to the start of the husband's treatment with methyltestosterone In the controls, where methyltestosterone was not given, it was taken as extending to the date when the wife's investigation and treatment began In both series years of barrenness were reckoned from when unprotected coitus started after marriage or (in cases where there had been a previous pregnancy) after the most recent pregnancy Table II shows that the two series compare well, so far as their infertility is concerned

Change in Quality of Semen

Analysis of the quality of the semen has been confined to the 93 cases with a fertility index below 30

For those unfamiliar with the grading of semen by fertility index, table III indicates the pre treatment quality of the semen of this group of men It is based on the highest value found in the ejaculates tested

Only 48 of the 93 patients sent semen for testing after they had had some treatment, but 17 (35%) of these produced pregnancies and can therefore be regarded as a fair sample of the cases under consideration, the pregnancy rate for the whole group being nearly 38%

The change in quality of the semen is shown in the accompanying figure Of the 23 cases showing improvement in their fertility indices 8 men had a post treatment index of over 40, and 6 others of between 30 and 40 The remaining 9, though significantly better than before treatment, still had an index under 30

The following case illustrates the relation between methyltestosterone therapy and improved quality of semen

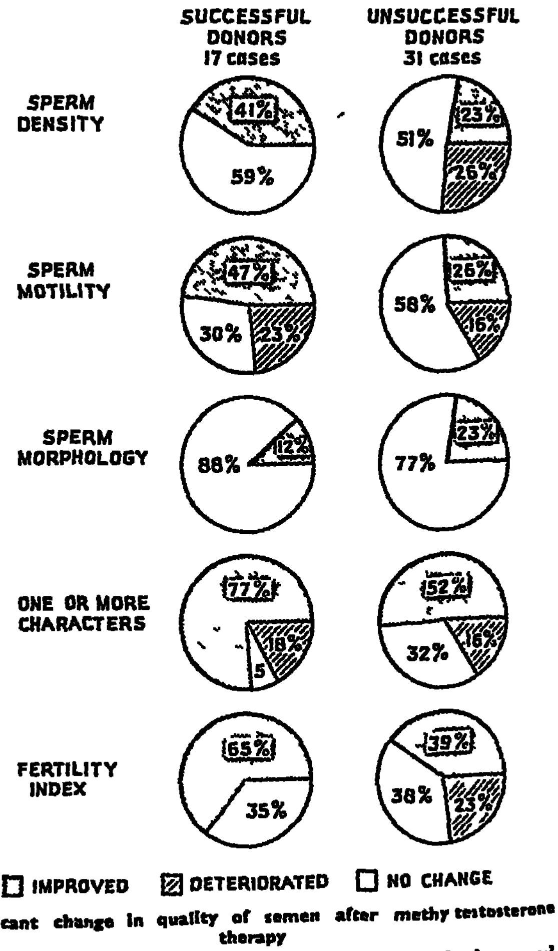
The couple were first seen in September, 1950, and the husband sent two ejaculates which had fertility indices of 25 and 26 He was then given intermittent methyltestosterone therapy, and in February, 1951 after three months' treatment, the fertility index of his semen was 41 Shortly after this, owing to family difficulties treatment was discontinued for six months In January, 1955, before treatment was recommenced, the fertility index of the husband's semen had gone down to 18 After four months renewed treatment his semen scored 63 and shortly after this last test his wife became pregnant

As is clearly shown in the figure, there are proportionately more instances of improvement in the semen of the men whose wives subsequently conceived than in the semen of those who had no success The only deterioration in semen quality observed among the successful donors was a fall in the percentage motility of the sperm, without a compensating rise in sperm density, in 4 cases, and in 2 of these the semen was not tested until after the wife had become pregnant, and two to three months after the husband had stopped taking tablets

The preponderance of cases showing improved quality of semen among the men whose wives became pregnant, compared with the unsuccessful series, is not statistically significant Had the whole group of 93 men sent post treatment semen for examination, and had the results observed on the 48 men who did so been found to hold good for the other 45, the difference between the two series would have been significant

Volume of Ejaculate

There was no indication that treatment with methyl testosterone affected the volume of the ejaculate appreciably In 3 cases (2 of which had a fertility index over 30) the volume of the ejaculate before treatment was persistently below 1 ml, and treatment was given mainly in the hope of increasing the quantity of semen produced In 2 of these cases there was no change after treatment, and in the 3rd, although the volume was nearly double that of the largest pre treatment specimen, it was still less than 1 ml



Significant change in quality of semen after methy testosterone therapy

Improvement is always assessed against the higher, and deterioration against the lower, pre treatment value Change in density, motility, or morphology is regarded as significant if the post treatment value differs from the appropriate pre treatment value by more than 20% of this value

Change in the fertility index is regarded as significant if the post treatment value differs by 10 or more from the appropriate pre treatment value. If the fertility index of the better pre treatment *specimen* is less than 5, a change of 5 is regarded as significant

In the group "*one or more characters*" deterioration means a fall in the value of one character, with no improvement in any

Fructose and Citric-acid Content of Semen

The fructose and citric-acid levels in the semen were estimated before and after treatment in 43 cases, including 15 in which pregnancy followed treatment In view of the work of Mann et al (1949) it seemed possible that men with low levels of these substances might have low androgen levels and therefore benefit from treatment with methyltestosterone, but there was no indication that low pre-treatment levels of either or both substances were related to response to treatment, nor did treatment produce any significant change in their levels in the semen There was, however, some suggestion that the ratio of the quantity of citric acid to the quantity of fructose in the ejaculate increased with treatment, and this change was more common in the successful than in the unsuccessful series Our recent work (unpublished) on partitioned ejaculates indicates that such a change is the result of an increase in the proportion of prostatic secretion in the ejaculate and of a corresponding decrease in the vesicular contribution Semen of good quality tends to contain proportionately more prostatic fluid than that with lower potential fertility, hence the observed increase in the citric-acid/fructose ratio in the semen of men taking methyltestosterone may well be associated with improvement in its fertilising-power

Discussion

The degree of improvement in semen after methyltestosterone therapy is seldom from very poor to good but rather from poor to fair or from fair to average As shown in the figure, the character least susceptible to improvement is the morphology of the sperm, and the proportion in the sperm population of those types of head-form such as pear, pyknotic, and multiple, which are known to arise in the testis (Harvey 1955), is almost unaltered after treatment Considered in conjunction with the fact that maximum improvement is often reached in three months or less, this suggests that the beneficial effect of the methyltestosterone is probably due to improved functioning of the epididymis and vas, and to more efficient ejaculation, and not to any fundamental improvement in spermatogenesis

The results observed in this series of cases can be explained by such an effect Better nourishment of the sperm in the epididymis and more efficient evacuation of mature sperm at coitus would result in improved motility, and, where sperm production in the testis is high, in increased density Where sperm production is low the elimination of accumulated postmature sperm from the ejaculate would tend to produce fewer sperm, with an improved percentage motility, a condition observed in several cases Where, however, the poor motility before treatment is due to defective development of the spermatozoa, percentage motility will not be improved by treatment with methyltestosterone, although the density may be, and the ejaculate would then actually contain more normal motile sperm, but these would represent the same proportion of the sperm population

On this view, treatment with methyltestosterone is not a cure for inherent testicular deficiency but a stimulus which enables the husband to produce the best ejaculate of which he is capable The timing of the dosage produces this stimulus at the period when the wife is ovulating By discontinuing the treatment in the latter part of the wife's menstrual cycle the potency of the stimulus is retained, and pituitary secretion is not depressed, as it would tend to be if the treatment were given continuously

Summary

Methyltestosterone was given to the husband in 93 cases of subfertile marriages in which the semen has a fertility index below 30 In 35 of these cases (38%) the wife became pregnant within two years

The success of this treatment was measured by comparing the number of pregnancies produced with that of 141 control couples in which the fertility index of the husband's semen had the same range but where he was not so treated In these cases 24 (17%) of the wives became pregnant

Analysis of the improvement in the semen after treatment of the husband with methyltestosterone shows that this hormone is not a cure for inherent testicular deficiency but a stimulus to produce the best possible ejaculate For this reason it should be given to the husband at such a time that it produces the stimulus when his wife is most likely to be ovulating During the remainder of the menstrual cycle it should be withheld so as to prevent depression of the pituitary gland and to retain the potency of the stimulus

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MECAMYLAMINE ILEUS AS A SURGICAL EMERGENCY

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THE use of ganglionic-blocking agents is becoming increasingly common in the treatment of hypertension. Recently mecamylamine hydrochloride ('Inversine'), a secondary amine, has been introduced as an improvement on the quarternary ammonium compounds hexamethonium and pentolinium The advantages claimed for this drug are complete oral absorption and more consistent control of the blood-pressure

In a single month we saw 2 patients presenting as acute surgical emergencies, owing to ileus arising from mecamylamine therapy

Case-reports

Case 1 —A man, aged 49, was admitted to hospital with suspected bowel obstruction His doctor stated that he had been under treatment for hypertension (blood pressure 200/120 mm Hg) Twelve days previously a course of mecamylamine therapy had been started, the initial dose was 5 mg b d for six days and thereafter 5 mg t i d After four days on the latter dosage the patient complained of obstinate constipation, generalised crampy abdominal pain, and vomiting The mecamylamine therapy was then discontinued In the next thirty six hours several doses of neostigmine was administered, and enemas were given, without result After this the abdomen began to swell and it became much distended No urine was passed, but, as the bladder was not distended, it was felt that this was due to the repeated vomiting

Examination

On admission the patient was thin, slightly cyanosed, with a dry furred tongue and breath smelling strongly of acetone Temperature 97°F, pulse rate 100 per minute, blood pressure 145/100 mm Hg On abdominal examination there was an old appendicectomy scar The abdomen was much distended and tympanic, with slight shifting dullness in both flanks, no tumour palpable, and no localised tenderness, a few high-pitched bowel sounds on prolonged auscultation The patient vomited dark brown fæcal-smelling material several times Serum potassium 6 7 m eq per litre Straight X-ray of the abdomen showed several air fluid levels in the small bowel Barium enema showed several diverticula in the pelvic colon but no definite evidence of a large bowel lesion, although there was a suspicious stricture-like area in the descending colon After evacuation, there was retrograde filling of one of the dilated loops of small bowel

Diagnosis and Treatment

Clinically, the diagnosis was thought to be between paralytic ileus and mechanical obstruction low in the small bowel or in the colon As the patient was markedly dehydrated, it was decided to try conservative treatment for a time An intravenous drip of saline solution was set up, and administration of penicillin and streptomycin started A Ryle's tube was passed and the stomach aspirated half-hourly Three doses of neostigmine 1 ml, followed by enemas, were given, but neither flatus nor fæces was passed After twelve hours of this treatment the patient's general condition had improved slightly, but the abdominal distension had increased, and, as there was still a good deal of foul fluid coming up the Ryle's tube, it was decided to operate

Operation and Course

On opening the abdomen through a lower midline incision a good deal of clear free fluid was found The small bowel was much distended down to the ileocæcal junction The cæcum and ascending and transverse colons looked normal The descending colon was collapsed from the splenic flexure down to the pelvirectal junction, but there was no evidence of vascular impairment and a thorough search of large and small bowel revealed no evidence of tumour or other cause of obstruction The abdomen was closed

Intravenous fluids, gastric suction, and chemotherapy were continued postoperatively, and forty eight hours after operation (four days after cessation of mecamylamine therapy) the patient had a bowel action and passed flatus

By the fourth postoperative day the distension had almost disappeared, the bowels were acting normally, and the patient was taking a light diet without nausea Unfortunately, on the fifth day, he had a presumed coronary thrombosis or pulmonary embolism and died almost immediately

Case 2 —A man, aged 60, had been in a medical unit from July 1 to 20, 1956, when he was given mecamylamine therapy for hypertension There was a long history, over ten years, of angina and cardiac asthma His general condition was good and blood-pressure on admission 240/120 mm Hg Full investigations excluded secondary hypertension Urea-clearance 57% of normal, specific gravity range of urine 1008–1015, blood urea 59 mg per 100 ml, constant slight albuminuria, intravenous pyelography showed moderate concentration He was having mecamylamine 27 5 mg daily, in divided doses, on discharge from hospital, and his blood pressure averaged 200/105 mm Hg He was readmitted to a surgical unit on the third day after leaving hospital as a case of possible mesenteric thrombosis or intestinal obstruction He complained of severe generalised abdominal pain of twenty four hours' duration and had vomited black fluid He had hiccup and had been constipated two days

Examination

On admission the patient seemed to be in pain and had a very dry mouth, temperature 98°F, and the pulse rate 70 per minute blood-pressure 240/100 mm Hg The abdomen moderately distended but not tender, bowel sounds very infrequent and high pitched He had had a total of 287 5 mg of mecamylamine over thirteen days, and this drug was discontinued Straight X ray of the abdomen showed much distension of the small intestine suggesting intestinal obstruction

Treatment and Progress

A conservative policy was decided on, and the patient was given an enema with good result By the next day his abdomen was much less distended, bowel sounds very faint but more normal in pitch He had recovered completely from the ileus by the third day, when the bowels worked normally

Discussion

In both the present cases occasional high-pitched bowel sounds were associated with severe flatulent distension of the abdomen but no tenderness Pain was a presenting symptom, and despite the history this led to suspicion of mechanical obstruction

Constipation is a well known complication of ganglionic blocking drugs Freis et al (1952) noted constipation in at least two-thirds of a series of hypertensives treated with hexamethonium, and, in addition, 4 definite cases of paralytic ileus were noted In milder cases of ileus there is abdominal distension with absence of bowel sounds, such cases usually respond to conservative treatment with an enema and parasympatheticomimetic drugs (Campbell and Robertson 1950, Lyons and Lord 1951), but deaths have been reported (Mackey and Shaw 1951, Thomas and Williams 1951)

Abdominal pain associated with intestinal distension is sometimes met with and an acute surgical emergency is simulated, as in both our cases These symptoms may suggest an obstruction so that operation is performed, as in our 1st case

Goldstone (1952) felt himself forced to do a laparotomy in similar circumstances on a patient receiving pentamethonium He found the small gut distended, while the cæcum and colon were normal in calibre The small gut, after deflation, remained flaccid and did not contract as it does after relief of the distension due to mechanical obstruction His patient died after operation

Bourne and Hosford (1951) report that at operation on a patient receiving hexamethonium in whom obstructive symptoms developed, they found œdema with distension of the small bowel but no obstruction

McCalla et al (1953) reported 2 cases of hexamethonium ileus They operated on 1 case and found the proximal small intestine and colon dilated but the distal small bowel completely collapsed This patient died, while the other patient, treated with intestinal suction and enemas, lived

Although operation on a case of mecamylamine ileus has not, as far as we know, been described there is no reason to consider this drug different in its essential action from the hexamethonium group In our laparotomy case there was collapse of the descending colon while the small bowel was much distended

It is difficult to explain these findings Motor stimulation of the intestine is generally considered to be the function of the parasympathetic system, whose preganglionic fibres terminate in the intramural plexuses, yet vagotomy does not have a pronounced effect on intestinal activity in laboratory animals

Faik et al. (1950) proved a slight decrease in tone and in the number and duration of peristaltic waves, and Alvarez (1948) clearly indicated that in man the most readily demonstrated effect was on gastric function. Sympathectomy on the other hand has little effect on the gastro intestinal tract (Craig et al 1950)

Probably the ganglionic blocking drugs act on the bowel through the intramural plexuses Locket (1951) suggested that, as ileus after hexamethonium followed only oral medication, the effect was local and associated with poor absorption and high concentrations in the gut, otherwise paralytic urinary symptoms would be expected Accumulation in one section of bowel might lead to complete arrest of both absorption and peristalsis, while the following section might show in some cases an increase in non propulsive motility and decrease in propulsion leading to pain Code et al (1952) considered at least four types of intrinsic motor activity which perform different functions—propulsion, mixing, and absorption

It would not seem necessary, therefore, to consider the action of hexamethonium outside the intestinal wall to explain why it may give rise to ileus Mecamylamine on the other hand is stated to be completely absorbed (*Lancet* 1955) *It is more difficult, therefore*, with this drug to explain the findings satisfactorily, as one would expect with high blood concentrations an overall effect on the intestine The finding of occasional high-pitched peristalsis suggests that some types of intestinal waves are still present although these are not propulsive

Summary

In 2 cases mecamylamine therapy for hypertension led to ileus mimicking intestinal obstruction

In such cases a history of recent treatment with anti-hypertensive drugs, and the finding of occasional high-pitched bowel sounds, should suggest the diagnosis

This complication should be treated conservatively

Administration of ganglionic-blocking agents should be strictly controlled, especially if renal function is impaired.

We wish to thank Mr J. C Robb and Mr R P. Smyth for their help and interest in the management of these cases

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URINARY EXCRETION OF INDIVIDUAL CATECHOL DERIVATIVES

STUDIED BY A CHEMICAL METHOD

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BY this method the catechol derivatives are adsorbed on to alumina and, after elution, are separated from one another by paper chromatography. The amounts present are assessed semiquantitatively by the fluorescence of their buffered oxidation products in ultraviolet light. Noradrenaline, adrenaline, hydroxytyramine, and dihydroxyphenylacetic acid have been detected by this method, which may be used for screening suspected cases of chromaffin tumour.

Methods

Preparation of Urine Extract

Urine is collected for 24 hours, and 15 ml of 10% sulphuric acid is added to it to ensure that the final pH is 3 5 or less. The urine is thereafter kept refrigerated until processed, which must be done within the next few days.

The preliminary procedure of adsorption on to alumina is a modification of that of Von Euler and Orwen (1955) 500 ml. of the urine, clarified if necessary by filtration is treated in a large beaker with 12 5 g of alumina (B D H , 'for chromatographic purposes') While the mixture is being vigorously stirred, 10 N sodium hydroxide is rapidly added drop by drop until the liquid, free from foam, reaches a pH of 8 7 shown by test paper (Johnson of Hendon no 8410) The end point is well defined and it is unnecessary to use a pH meter Stirring is continued for 4 or 5 minutes during which time it is usually necessary to add one or two drops more of 10 N sodium hydroxide to keep the mixture at pH 8 7

The alumina is then collected by filtration with a Buchner funnel 7 5 cm. in diameter and Whatman paper no 541, the alumina in the beaker being kept suspended to facilitate rapid filtration The time of exposure to unfavourable pH values is kept as short as possible and must not exceed 15 minutes The alumina is washed twice with quantities of 10 ml. of distilled water added to the Buchner funnel The alumina is then transferred as quantitatively as possible from the Buchner funnel to a small beaker (150 ml) without the filter paper being displaced from the funnel, and 8–10 ml of 0 5 N sulphuric acid is added to the beaker to elute the catechols. After it has been stirred for a minute the alumina is filtered off in the Buchner funnel with the same paper as before This procedure of elution is repeated twice more To the combined opalescent eluates having a pH of 2 or less is added drop by drop and with constant agitation 10 N sodium hydroxide to about pH 3 followed by about N sodium hydroxide to pH 4 0 shown by indicator paper. The solution with precipitate is then equally distributed into three 50-ml centrifuge tubes which are then filled with a mixture of equal parts by volume of ethanol AnalaR and acetone AnalaR, the filtration flask being well washed out with the solvent mixture After being stirred the mixtures are refrigerated for half an hour, and the flocculent white precipitate is removed by centrifuging The precipitate is washed with a few ml of acetone-ethanol mixture

The supernatant fluids, together with the washings, are in turn transferred to a 100 ml conical flask and distilled at reduced pressure under a stream of nitrogen at a bath-temperature of 40°C The level of the liquid is kept above that of the bath, and the flask is removed as soon as the contents are dry (Goldenberg et al 1954)

The distillation head and side of the flask are washed down with about 5 ml. of a mixture of 1 part of N hydrochloric acid in 100 parts by volume of acetone AnalaR, and this liquid is allowed to extract the residue in the flask for about 5 minutes before the faintly straw-coloured solution is transferred to a small tube graduated at 0 5 ml

The extraction is repeated three times more, the deposit being broken up if the flask is heavily encrusted. The successive extracts are evaporated down to the gradation mark under a stream of nitrogen. The tube is refrigerated, and any precipitate is removed by centrifuging at the time of preparation of the chromatogram.

Chromatography

Sheets of Whatman paper no 1 measuring 25 × 33 cm. are marked into ten vertical strips each 2 5 cm. wide, and a horizontal line is drawn a few cm. above the lower edge to mark the origins of the ascending chromatograms On each paper seven strips may conveniently be allocated to serial dilutions of one extract of urine, the remaining three being reserved for standard solutions

All additions are made from a 0 02 ml pipette specially prepared from 5 mm. external diameter 'Pyrex' capillary glass tubing drawn out to a diameter of 2 mm. at the tip and filed with carborundum. Such a pipette was made to deliver 0 25 µl. per drop.

Solutions are added to the paper drop by drop to cover the central 1 8 cm. of each strip, the row of drops being dried by cold air from an electric hair drier before the next row is applied In this way an even band not exceeding 4 mm. in width is obtained

A suitable preliminary range of quantities to apply for most urines is 0·001–0 040 ml. of the 0 5 ml. extract Standard solutions of *dl* adrenaline bitartrate (B.D H) and 3 hydroxytyramine (Light) are prepared in 0 01 N hydrochloric acid, each containing 1000 µg of the free base per ml., such solutions are kept at 4°C and renewed at intervals Noradrenaline is obtained as ampoules of the bitartrate ('Levophed,' Bayer), a fresh ampoule being opened on each occasion. Equal parts of the three standards are mixed, diluted in a mixture of equal parts of ethanol AnalaR and acetone AnalaR, and added to the paper in amounts of 0·1, 0 2, and 0·3 µg of each catechol derivative

As soon as they are prepared the paper sheets are threaded on a glass rod and suspended in a chromatogram tank measuring 28 × 26 5 cm. with a height of 38 cm. The solvent system is phenol saturated with water and sulphur dioxide added to the tank to a depth of about 1 cm, from a separating funnel immediately before use The tank is sealed and left in an unheated insulated box or cupboard overnight The solvent ascends 23–29 cm.

Spraying of Chromatogram

The papers are withdrawn from the tank and freed from much of the phenol by agitation in a dish containing 750 ml of benzene AnalaR After hanging in air for a few minutes the papers feel dry and are sprayed without delay using an all glass spray containing nitrogen from a cylinder. The spray solution buffered at pH 5·9 and made up freshly each day, has the following composition 36 ml of 0 66 M potassium dihydrogen phosphate 4 ml of 0 66 M disodium hydrogen phosphate 4 5 ml. of 6 6% potassium ferricyanide solution, and 5 ml of 40% formaldehyde solution preserved over calcium carbonate

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TABLE I—DIFFERENTIATION OF CATECHOLS

Catechol	R_F value in phenol water and sulphur dioxide	Colour reactions on spraying			
		Ferricyanide formaldehyde *		Iodine followed by Ehrlich's reagent *	Potassium iodate †
		Colour from 1 5 μg	Fluorescence in UV light 0 1 μg (unless otherwise stated)	Colour from 4 μg	
Noradrenaline	0 345	Red purple	Yellow green	Purple changing to blue green	Purple
Hydroxytyramine	0 552	Purple	,, (0 2 μg)	Orange ,, ,, dull yellow	Orange
Adrenaline	0 626	Red	,,	Red ,, ,, blue violet	Scarlet
Dopa	0 354	Red purple	,,	Red ,, ,, grey	Grey
Dihydroxyphenylserine	0 221	,,	,,		Orange
Isopropyl noradrenaline	0 670		,,	Red ,, blue violet	Red
Epinine	0 697	,,		Red blue violet	Orange
Dihydroxyphenylacetic acid	0 619	,,	,, (0 5 μg)	Bleached ,, ,, nil (10 μg)	Pale yellow
Protocatechuic acid	0 482	,,	,, (0 5 μg)	Bleached ,, ,, nil (10 μg)	Pale yellow
Band A	0 620	,,	,,	Bleached ,, ,, nil	
Band B	0 437	,,	,,	Purple ,, pale yellow	Orange
Band C	0 202		,,	Red ,, brown yellow	Yellow

* As described in text † Shepherd and West (1951)

Care is taken to saturate the paper but not to allow any running Any red or purple areas appearing at this stage are noted The paper is immediately hung inside an oven at 110–120°C and left there for exactly 5 minutes, after which it is inspected without delay in ultraviolet light A 'Mazda' lamp MBW/U in a metal case has been found suitable The spots of yellowish green fluorescence are most readily seen by transmitted light The sites and intensities of the spots of both standards and urine extract are recorded immediately because they fade appreciably after a few minutes

The adrenaline and noradrenaline standards should be just visible at a level of 0 1 μg, whereas hydroxytyramine is usually seen at a lower limit of 0 2 μg and dihydroxyphenylacetic acid at 0 5 μg Quantities as great as 1 5–2 0 μg of the catecholamines are visible as red or purple areas, and the fluorescence of such amounts remains visible for many weeks

Identification of Individual Catechol Derivatives

Identification is made by the R_F value (table I) and by comparison with the standards There is clear cut separation of all derivatives found in urine, except that very occasionally the spot of dihydroxyphenylacetic acid may be indistinguishable in position from that of adrenaline, which, however, is not usually detectable in urine If this happens, the following alternative method of identification allows the recognition of relatively large amounts of adrenaline, such as might be expected in some cases of chromaffin tumour

Three chromatogram strips are prepared as before from 1 0 μg of adrenaline standard, an amount of the urine extract calculated to contain at least 1 0 μg of the supposed adrenaline, and the same quantity of urine extract with the addition of 1 0 μg of adrenaline standard These three strips are developed according to a modification of the method of Pitkanen (1954) First the strips are sprayed with a solution composed of 36 ml of 0 66 *M* potassium dihydrogen phosphate, 4 ml of 0 66 *M* disodium hydrogen phosphate, and 4 5 ml of 0 1 *N* iodine solution After a few minutes, during which the papers are best dried under a stream of cold air, they are resprayed with a solution consisting of 4 g of *p* dimethyl aminobenzaldehyde in 380 ml of ethanol and 80 ml of concentrated hydrochloric acid Adrenaline gives a red colour with iodine, and this is subsequently changed to a distinctive blue violet at a level as low as 1 0 μg Dihydroxy phenylacetic acid first bleaches the iodine but does not give any colour with Ehrlich's reagent

Results

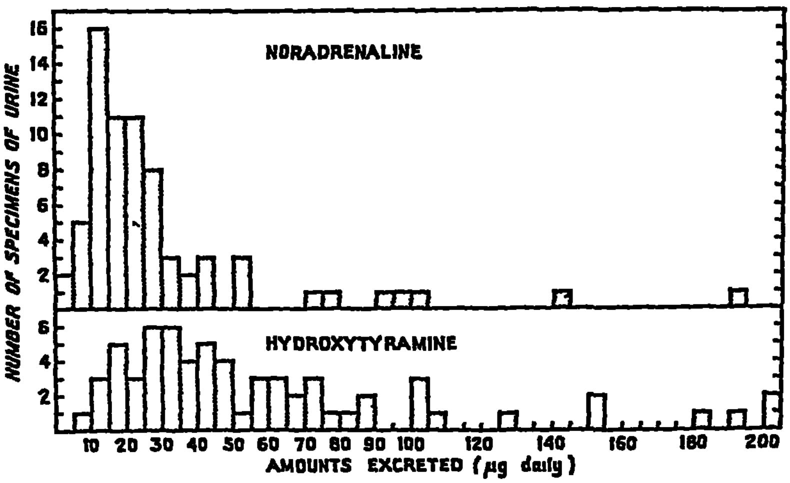
Eighty-five specimens of urine from 66 patients with either paroxysmal or sustained hypertension and specimens from 20 other persons, including some healthy people, were examined Only 1 case of chromaffin tumour was discovered (McMillan 1956)

Noradrenaline

The noradrenaline excreted in seventy one specimens of urine from 65 patients with either paroxysmal or sustained hypertension not associated with chromaffin tumour ranged from less than 5 μg to 190 μg daily (see figure) Ten specimens (14%) contained 50 μg or more daily and only three specimens (4%) 100 μg or more daily In 1 patient an output of 140 μg was associated with malignant hypertension, two specimens collected after sympathectomy showed only 24 and 44 μg of noradrenaline, the blood-pressure then being much reduced A high output of 190 μg daily was found in a case diagnosed as a hypochondriacal anxiety state, there was only 1 other patient with this condition, and in that patient the noradrenaline excretion was 95 μg daily The third highest output, 100 μg daily, was associated with severe essential hypertension None of these 3 patients was re examined, but a hypertensive excreting 90 μg daily was found on a subsequent occasion to excrete less than 30 μg 5 at least of this series were said to give positive phentolamine tests In several of the most severe cases of hypertension the patients excreted only small amounts of noradrenaline

Seven specimens of urine from the patient in whom a chromaffin tumour was confirmed at operation contained 124, 360, 370, 490, 600, 1000, and 1015 μg of noradrenaline daily, all but one of these values being much greater than any found in the rest of the series

Recorded in μg per 100 ml of urine the



Catecholamine content of unhydrolysed urine of hypertensives noradrenaline excretion of 66 patients with either paroxysmal or sustained hypertension not associated with tumour was 0 3–15 μg Seven specimens (10%) contained 5 μg or more per 100 ml. and only one specimen (1%) more than 10 μg per 100 ml The seven specimens from the patient with phæochromocytoma contained 15, 21, 40, 51, 73, 74, and 114 μg per 100 ml Non-hypertensive and healthy persons (20 people) excreted up to 64 μg daily, the urine containing 0 3–6 μg. per 100 ml

Hydroxytyramine

In sixty-four specimens of urine from 58 patients with either paroxysmal or sustained hypertension not associated with tumour the excretion of hydroxytyramine ranged from less than 10 to 200 μg daily, twenty-seven specimens (42%) contained 50 μg or more daily, and eleven specimens (17%) more than 100 μg daily (see figure) With 2 exceptions an excretion of more than 70 μg of noradrenaline daily was associated with an excretion of 150 μg or more of hydroxytyramine daily, and only 1 of the 6 patients excreting 150 μg or more of hydroxytyramine daily excreted less than 77 μg of noradrenaline (the amount in that case was 29 μg) The specimens from the patient with phæochromocytoma contained 50, 70, 92, 95, 180, 250, and 450 μg daily This relatively small increase is remarkable because the tumour contained mainly hydroxytyramine and relatively little noradrenaline The excretion of hydroxytyramine by 58 patients with either paroxysmal or sustained hypertension not associated with tumour was 0 5–18 μg per 100 ml Twenty-four specimens (41%) contained 5 μg or more per 100 ml, and nine specimens (14%) 10 μg or more per 100 ml The patient with phæochromocytoma excreted 6, 8, 8, 10, 18, 25, and 30 μg per 100 ml, and normotensive persons 0 1–10 μg per 100 ml urine

Adrenaline

Adrenaline could not be detected with certainty by its fluorescence in any of the specimens from either normotensive or hypertensive patients, corresponding to an output of less than 0 5–1 0 μg. per 100 ml in most cases It was not detected in the urine or the tumour of the patient with phæochromocytoma

TABLE II—URINARY EXCRETION OF CATECHOLAMINE IN CERTAIN HYPERTENSIVE AND METABOLIC DISEASES

Disease	Age (yr)	Sex	Noradrenaline excretion		Hydroxytyramine excretion		Adrenaline excretion	
			μg daily	μg per 100 ml.	μg daily	μg per 100 ml	μg daily	μg per 100 ml
Pre-eclampsia	20 25 31	F F F	15 11 20	1 0 7 2	15	2	<9 <6 <10	<1 <0 4 <1
Acute porphyria	24	F	22	2	44	4	<11	<1
Cushing's syndrome	22 34	F F	29 <67	5 <3	73 <130	11 <6	<7 <67	<1 <3
Hypertension (recurrent pyelitis)	38	M	11	0 5			<10	<0 5
Severe thyrotoxicosis	50	F	16	1	130	9	<11	<0 8
Coronary thrombosis with glycosuria	48	M	64	6	85	8	<22	<2
Subarachnoid hæmorrhage with hyperglycæmia	68	F	18	5	26	9	<12	<3
Diabetes and hypertension	42 42	M M	22 11	1 1	63	5	<22 <14	<1 <1
Phenylketonuria	12	M		3		9		

The values are only approximate, being correct within ± 25%

Catecholamine

Table II shows the findings in some special hypertensive states and metabolic disorders

Other Catechols

Two bands, A and C, are regularly present in urine chromatograms, a third band, B, was discovered in the urine of the patient with phæochromocytoma Some of their characteristics are listed in table I

Band A is identifiable as 3, 4 dihydroxyphenylacetic acid by R_F value and colour reactions No systematic assays were made of this substance, but it was often present in considerable amounts, which were, however, usually rather less than those of hydroxytyramine

Band B was second in prominence only to the band of noradrenaline in the urine of the patient with phæochromocytoma but was not identified with certainty in other urine though occasionally a weak fluorescent band did appear at this site Its properties (table I) and its reactions with ninhydrin, diazotised *p* nitro aniline, and potassium-dichromate solutions show it to be closely related to noradrenaline and hydroxytyramine It oxidises to a melanin like substance On incubation of a suspension of guineapig liver with noradrenaline, hydroxytyramine, and adrenaline separately and subsequent purification of the catechols by adsorption on to alumina and chromatography it was found that a substance indistinguishable from band B was present among the derivatives of adrenaline and noradrenaline but not of hydroxytyramine It was never traced in urine to which large amounts of known catecholamines had been added at any stage during concentration A catechol derivative with an R_F similar to band B (Crawford 1951) is *α* ethyl noradrenaline, but this substance has not yet been investigated

Band C must be carefully distinguished from noradrenaline It is almost always present and is sometimes very prominent, amounting to the equivalent of 200 μg of noradrenaline daily The amount does not appear to correlate with that of noradrenaline and hydroxytyramine in the urine of either normal or hypertensive people, and relatively little was present in any of the specimens from the patient with phæochromocytoma The band was never produced by adding known catecholamines to urine or by treating them with organic solvents or exposing them to alkali The substance forming band C is not precipitated by barium hydroxide solution at pH 5 and is not adsorbed on to ion exchange resin 'IRC 50' It is not destroyed by acid hydrolysis at pH 1 0 Although its R_F resembles that of 3, 4 dihydroxyphenylserine, unlike this substance it has not given any colour reaction with ninhydrin Catecholglycollic acid would probably have a higher R_F than has band C

Discussion

A simple chemical method of detecting increased urinary excretion of catecholamines by patients with phæochromocytoma has been urgently wanted The symptoms of phæochromocytoma are varied and mimic those of other diseases No reliable diagnostic test with a sympatholytic drug is yet known, and drugs stimulating secretion of the tumour carry a grave risk to the patient Assay of the urine is the most valuable procedure, biological assay, which has almost always to be used, has obvious disadvantages, and simplifications introduced into the method lead to further loss in specificity and to the risk of false results Chemical assays previously published depend entirely on fluorimetry of a solution containing a mixture of catechols The disadvantages of this are that the equipment required limits the practicability of the assay to a few centres, and the fluorescence is not specific for any one catecholamine and is liable to be affected by the presence of other substances

The fluorescence methods fall into two groups those depending on the reaction of ethylene diamine with the catechol group, and those depending on the formation of fluorescent derivatives on oxidation Von Euler et al (1955) reported that the ethylene diamine method of Natelson et al (1949) gave for urinary catechols calculated as noradrenaline values which were 10–100 times those obtained biologically, the results with hydrolysed urine being even worse Such interference was attributed to acidic catechols formed by degradation

Weil Malherbe (1956) assayed the hydroxytyramine of alumina adsorbed urine by subtracting the sum of the values obtained for noradrenaline and adrenaline by the methods of Lund (1950) or of Von Euler and Floding (1955b), which measure the fluorescence of catecholamine oxidation products, from the values obtained by the ethylene diamine method (Weil-Malherbe and Bone 1953), a necessary preliminary being the separation of acidic from basic catechols on ion-exchange resin This method is unsatisfactory in that it involves many manipulations and depends on the complete removal of all acidic catechols and on a complete lack of fluorescence of hydroxytyramine on oxidation, in accordance with the concept that only compounds with the side chain containing a β OH group and a H at the α C atom can fluoresce appreciably in the reaction Von Euler and Floding (1955a) stated that hydroxytyramine did fluoresce weakly and reported (Von Euler and Floding 1955b) some discrepancy between biological and chemical assays for which the reason was unknown

In the present method catechols such as dihydroxyphenylacetic acid and even protocatechuic acid gave oxidation products of similar colour and fluorescence as did true catecholamines treated with buffered ferricyanide solution The inference must be drawn that no assay using a mixture of catechols can be relied on

Burn and Field (1956) describe a chemical method using ethylene diamine for the diagnosis of phæochromocytoma Urine from healthy people gave extinction values in colorimetry which were equivalent to as much as 50 µg of noradrenaline per 100 ml of urine, the same extract showing less than 5 µg per 100 ml by bio-assay These workers recommend that urine with higher extinctive values than this should be submitted to biological assay for confirmation of phæochromocytoma No mention was made of hydroxytyramine

Chromatographic separation is more satisfactory with phenol water sulphur dioxide than with n-butanol acetic acid water (4 1 5) When adrenaline and noradrenaline were chromatographed in the former solvent and the paper was then cut horizontally at 1-cm intervals, the catecholamine content of each strip being determined by a quantitative method with phospho tungstic acid reagent (to be published), the recovery of noradrenaline averaged 91 7% in seven determinations (range 84–102%, standard deviation 5 49) and of adrenaline 96 4% in nine determinations (range 87–112%, standard deviation 6 85) The figures for hydroxytyramine were similar Omission of sulphur dioxide or substitution of phenol 0 1 *N* hydrochloric acid reduced the yield of adrenaline to 29–62%

Similarly, quantitative assays showed that the recovery of catecholamines added to urine which was then adsorbed on to alumina, concentrated, and chromatographed was 90% for noradrenaline and 85% for adrenaline The alumina has been found to vary, and it is advisable to check every new batch

The original spray solution of Shepherd and West (1953) proved unsatisfactory in that the fluorescence faded very rapidly as melanin derivatives were formed, and hydroxytyramine often did not fluoresce at all Of several buffer systems investigated, phosphate at pH 5 9 proved best because very small amounts of the catecholamines were visible and both the red colour of the oxidation products and the fluorescence were visible for many weeks

The method described here is relatively rapid, a result can be obtained in little more than 24 hours from receipt of the specimen Its chief disadvantage is that fluorescence is measured arbitrarily by visual comparison with standards and the results are only partially quantitative Against that, the individual catecholamines are assessed separately, and the method has shown that no less than six catechol derivatives may be excreted in the urine

Summary

A method is described for the separate assessment in urine of the following catechol derivatives noradrenaline, adrenaline, hydroxytyramine, and dihydroxyphenyl acetic acid

Two unidentified substances were found one occurred regularly in all urine, often in large amount, the other was present in very great amount in a case of phæo chromocytoma

The method requires no expensive apparatus A result may be obtained in little more than 24 hours

The results of the assay of 105 urine specimens from hypertensive and other persons are presented

I am much indebted to Prof F S Fowweather and Dr A Jordan for their interest and encouragement, Dr Jordan for his careful criticism of this paper, the many clinicians of the United Sheffield Hospitals and elsewhere for their cooperation, Dr H Blaschko for the gift of 3, 4 dihydroxyphenyl serine, Dr G B West for epinine, and Dr R Dahlbom, of Astra Ltd, for 3, 4 dihydroxyphenylacetic acid

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UTERINE ELECTROLYTES IN PREGNANCY AND LABOUR

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It is generally accepted that potassium deficiency is associated with hypofunction of both striated and smooth muscle, leading, for example, to paralytic ileus Pregnancy introduces to the maternal organism two new factors which tend to drain more potassium than usual from the body the storage of minerals in the fœtus, and the increased production of steroids, which might lead to renal loss of potassium Furthermore, intense muscular work and possibly anoxia may lead to a local loss of potassium from the cells of the myometrium, if this loss is not made good it will inevitably affect further contraction (Szent Gyorgi 1951) We therefore tried to follow changes in intracellular electrolytes and water in the myometrium during pregnancy and labour (especially prolonged inefficient labour) in groups of patients sufficient for statistical analysis though small

Methods

All the material was collected during uterine surgery for other reasons Blood was withdrawn for analysis usually just before *operation* Since local trauma may lead to loss of potassium from cells, care was taken to take the biopsy specimens rapidly from fresh tissue. Samples of skeletal muscle were taken from the rectus abdominis muscle during laparotomy, and myometrial samples were taken from the outer muscle layers in the lower uterine segment. In all the cases the anæsthetic used was ether.

The patients were selected so as to exclude obvious metabolic disturbances—e.g., diabetes mellitus, congestive heart-failure, and toxæmia—which might influence the composition of the tissues. A control group of 10 patients undergoing hysterectomy was selected for base-line non-pregnant values. In no case was there any reason to believe that any local pathology had influenced results in the controls, but the indications for hysterectomy meant that the controls were older than the pregnant women, although we tried to counteract this as much as possible by selecting patients aged 46 years or less.

A second group of pregnant women was selected consisting of patients who underwent cæsarean section for either disproportion or placenta prævia 2 to 3 weeks before the onset of labour was due, to illustrate the myometrial changes due to pregnancy alone.

A third group consisted of patients in ineffective active labour who had to undergo cæsarean section usually because of disproportion and failure to engage at a trial of labour. All of this group had been in active labour for at least 6 hours, and would presumably illustrate the effects of extreme muscular contraction on the composition of the myometrium. A fourth group consisted of 10 women with prolonged ineffective labour, who had not reached full cervical dilatation in 36–72 hours of labour and whose contractions were judged to be infrequent, ineffective, or abnormal. All of them had already had their membranes ruptured either naturally or manually and had received 'Pitutrin' without the desired effect. Cæsarean section was indicated for the safety of both mother and child.

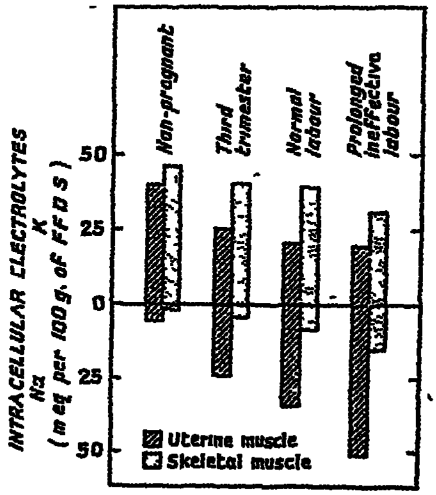
Every attempt was made during the course of labour to maintain an adequate intake of calories and fluids to prevent dehydration.

Analytic Methods.—The tissue samples were rapidly blotted of excess blood, obvious fat was quickly removed, the samples were placed in weighing flasks, and their fresh weights were determined. They were then left to dry overnight in a drying-oven set at 90–100°C. After their dry weight had been recorded, the samples were ground to powder, and a weighed portion was extracted with petroleum ether to remove neutral fat and lipids and then reweighed. The remaining fat-free dry solids (F.F.D.S.) were then extracted in an appropriate volume depending on the weight of the sample and on the sensitivity of the methods (usually 2–5 ml.) of 0.1N H_2SO_4. Cl was estimated after 3–5 days' extraction either by the 'fast green" microdiffusion method (Gordon 1952) or by amperometric titration with a dropping Hg calomel electrode system with 0.02N $HgNO_3$ (Kolthoff and Miller 1941). Na and K were estimated in appropriate dilution with a single-ended Zeiss flame photometer using interference filters. Calculations were based on the Cl assumption as applied by Darrow and outlined in numerous sources (Cort 1955). All the calculations are in terms of m.eq. or ml. per 100 g. of F.F.D.S., and all the serum levels are in m.eq. per litre.

Results

The results are summarised in the accompanying figure. The physiologically important results from each group are averaged. In view of the difficulties always encountered in selecting such groups, particularly of different ages and with different dietary histories, it is surprising to find such significant differences in intracellular K and Na. Intracellular water showed smaller changes than did Na.

Effects of Pregnancy Alone.—Skeletal muscle tended to contain less intracellular K and slightly more intracellular Na in pregnancy. Its extracellular composition, however, remained normal. The myometrium showed statistically significant changes, a loss of K and a sharp gain of intracellular Na and water. The increased amounts of extracellular Na, Cl, and water in the uterine samples presumably reflects merely the increased blood volume of the pregnant uterus.



Results of electrolyte analyses.

Effects of Normal Labour.—At this period of pregnancy, an average of 2–3 weeks later than in the previous group, there was a greater tendency to a generalised K deficiency, with a further loss of muscle K and gain of Na. The greatest extra-uterine changes during labour were the development, in most of the patients, of extracellular metabolic acidosis (high Cl, low HCO_3) and dehydration (higher serum-Na level, lower muscle-water values). Myometrium, in common with skeletal muscle, showed a further loss of K and gain of Na and water in cells. "Total base," estimated by the sum of Na and K, also increased in cells. The relative diminution of extracellular space in the myometrium, compared with the pre-labour gravid uterus, may be the result of cellular swelling or of muscular contraction.

Effects of Prolonged Ineffective Labour.—As might be expected, this group showed the most extreme changes of all, both in uterine and skeletal muscle. Skeletal muscle showed a clear picture of mild or moderate K deficiency, reflected by a tendency to hyponatræmia, hypochloræmia, and a high extracellular Cl : HCO_3 ratio (Cort and Matthews 1954, Cort 1955). Myometrium showed an even greater loss of K, with a gain of Na, water, and "total base," which resembled in degree what happens to tissues when the active transport of Na is blocked by cold, anoxia, enzyme poisons, &c. (Davies 1954, Cort and Kleinzeller 1956). Because of the design of the experiment, it was impossible to obtain the dietary history of the patients throughout pregnancy and to make rough balance studies to ascertain K balance. The incidence of prolonged ineffective labour did not correlate with either Hb level or hæmatocrit during pregnancy or with the rate of weight gain (toxæmia had been excluded from this series).

Discussion and Conclusions

It seems that the increased opportunities of losing potassium during pregnancy (fœtal and perhaps urinary losses) may cause a deficiency of potassium by the end of pregnancy, and that this deficiency is not evenly distributed, being more pronounced in the myometrium than in skeletal muscle. From the purely obstetric point of view this loss of potassium might be expected to prejudice the ability of the myometrium to contract, and it suggests that, in the women investigated, the intake of potassium was insufficient during pregnancy. The general stress and intense myometrial activity during labour could be expected to exaggerate the loss of potassium at the end of pregnancy. Moreover metabolic extracellular acidosis was also present in nearly all the patients during this period, a factor which per se can lead to a loss of cell K Anoxia and the production of adrenal hormones during labour may also change the electrolyte pattern in the myometrium Intracellular K is associated with glycogen, and West and Cervoni (1955) have shown (in the rat) that œstrogens increase the amount of glycogen in the myometrium, whereas uterine contractions and anoxia decrease it Biopsy specimens in the present investigation were seldom large enough to permit glycogen analysis as well as electrolyte analysis, but it might well be that changes in uterine glycogen would parallel those in uterine K

It is impossible to say whether the changed electrolyte pattern found in the myometrium of patients with prolonged ineffective labour was a cause or a result of the abnormal labour We rather think that it is both The intracellular hyponatræmia and overhydration of the myometrium suggest that local anoxia, affecting the transport of Na, may also be present If this is true, the calculations would contain a greater error than is usually attributed to the Cl assumption It is furthermore not known how well the Cl space calculation agrees with other extracellular-fluid markers in the myometrium, but the changes in intracellular K and Na recorded here are sufficiently significant to render it doubtful whether error associated with any extracellular-fluid marker would negate the changes found

Our results are, of course, preliminary, and further work will be required to elucidate the mechanisms involved in these changes and the possible clinical application It would probably be useful to repeat the investigation in animals under more controlled conditions and to investigate further the possible occurrence of K deficiency in pregnancy and the possibility of treating prolonged ineffective labour by the rapid deposition of K in the cells, by for example, infusion of glucose, K, and insulin

Summary

Biopsy specimens from uterine and skeletal muscle were analysed from the following groups of patients non-pregnant, in the third trimester of pregnancy before the onset of labour, during active labour, and during prolonged ineffective labour

All the samples were taken during uterine surgery for other reasons

Pregnancy per se was associated with a significant loss of myometrial K and a gain in cell Na, water, and total base in the uterus There were slight changes in the same direction in skeletal muscle (rectus abdominis)

Normal labour caused a loss of K and a gain of Na, water, and total base in myometrium

Prolonged ineffective labour was associated with the most severe changes of the above type in the myometrium, and was also associated with clear signs of K deficiency in skeletal muscle and in the extracellular fluid

Normal labour often produced a metabolic acidosis

We wish to thank Mr M Noble, F R C S E, for initially suggesting the importance of this study, and Dr S Franz and Dr L Vojta for their kindness in permitting us to investigate their patients and for assisting in the investigations Particular thanks are due to Miss D Rosicka for invaluable technical assistance

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LEPTOSPIROSIS IN ENGLAND DUE TO FOREIGN SPECIES

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Broom stated in 1951 that all cases of leptospirosis then recognised in this country had been due to *Leptospira icterohæmorrhagiæ* or *L canicola* He further investigated the sera from 642 cases of aseptic meningitis in which viral infection had been excluded and found 17 cases of Weil's disease and 8 of canicola fever but no evidence of infection with "foreign" leptospiræ, of which *L bataviæ*, *L grippotyphosa*, *L pomona*, and *L sejroe* were chosen as a representative series Since that time the Wellcome Research Institute has acted as the Leptospira Reference Laboratory for the Public Health Service covering England and Wales, and Broom (personal communication) states that none of the "foreign" species has been identified as the causal organism of disease in this country until the present case

Case-report

A Malayan engineer, aged 32, left Malaya by air on Sept 3, 1955, and arrived in this country the following day During the previous 6 months he had worked on the foundations of a new bridge at Ulu Selangor, a swampy region of Central Malaya He was admitted to this hospital on Sept 20 with 7 days' history of malaise, anorexia, and absolute constipation He had had occasional slight headaches but no muscle or joint pains and no photophobia He had not noticed any reduction in the volume of his urine but said that it had been dark

On admission his temperature was 103°F, pulse rate 104, and respirations 20 a minute He had moderate conjunctival suffusion, no anæmia or jaundice, no glandular enlargement blood-pressure 140/95 mm Hg Heart sounds normal, no murmurs Chest clear Liver impalpable but spleen enlarged two finger breadths below the costal margin, firm, and not tender No neck rigidity Kernig's sign negative No other abnormality in the central nervous system

Investigations —Hb 94% (13 9 g per 100 ml), white cells 17,300 per c mm (neutrophil polymorphs 80%, lymphocytes 14%, monocytes 6%), no malarial parasites, blood culture negative, urine contained albumin, occasional red cells and leucocytes, and amorphous debris, no organisms seen and sterile on culture Widal test positive to a titre of 1 in 160 for *Salmonella typhi* and *S paratyphi-A* H agglutinins and to 1 in 80 for *S paratyphi B* H agglutinins It was negative at all dilutions for O agglutinins and for *Brucella abortus* and *Br melitensis* These results were compatible with the patient's T A B vaccination a month before leaving Malaya The Wassermann reaction of the blood was negative Liver function tests thymol turbidity 10 units, thymol flocculation +++, Takata Ara reaction ++, van den Bergh negative direct and indirect, serum bilirubin level 0 4 mg per 100 ml, serum alkaline phosphatase level 7 4 units No ova, cysts or parasites were seen in the stools, and no pathogenic organisms grew on culture Dr Broom, at the Wellcome Research Institute, made leptospira agglutination tests and reported that the patient's serum agglutinated *L grippotyphosa* to a dilution of 1/3000, *L icterohæmorrhagiæ* to 1/300, and *L canicola* to 1/300 there was no agglutination of *L bataviæ* or of *L sejroe* When the tests were repeated 10 days later, agglutination of *L grippotyphosa* was maintained at a titre of 1/3000, whereas the others had fallen to 1/30 These results established the diagnosis of leptospirosis due to *L grippotyphosa*, a serotype endogenous in Europe and Asia and carried by the field mole

Progress —Clinically the infection was mild, with none of the severe muscle and joint pains and meningeal or renal symptoms sometimes seen in this disease The patient felt well after a few days, though pyrexia persisted for a further 12 days—i e, 19 days from the onset of symptoms Liver function tests 2 months after the onset were thymol turbidity 7 units, thymol flocculation ++, Takata Ara reaction +, serum bilirubin level 0 6 mg per 100 ml, serum alkaline phosphatase level 6 4 units

Comments

Leptospirosis is relatively common among British troops in Malaya: 160 confirmed cases in 1954 and more than 200 in 1955 The incubation period is usually given as 4–12 days (not less than 10 in the present case) and with the increasing use of air transport it is surprising that more cases due to foreign species have not occurred in this country This, and an equally surprising low reported incidence of canicola fever in view of the 30–40% infection-rate among dogs in this country, are probably explained by the benign and self-limiting nature of leptospirosis and a consequent reluctance to pursue difficult and prolonged investigations Thus leptospirosis was not specifically excluded in 113 cases of "pyrexia of unknown origin" reported by Reid (1956), though 41 remained undiagnosed. Alston and Broom (1949) drew attention to the resemblance of the meningeal form to non-paralytic poliomyelitis, and Ramsay (1955) reported 4 such cases of canicola fever where the presence of mild conjunctivitis and nephritis prompted further investigation.

Summary

All cases of leptospirosis previously reported in this country have been due to either *L icterohæmorrhagiæ* or *L canicola*

A case due to a foreign species, *L. grippotyphosa*, is described

It is again suggested that the true incidence may be greater than that reported

I thank Dr. Alexander Kahan for permission to publish and Dr J C Broom for the agglutination tests.

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FAILURE OF PROPHYLACTIC ORAL PENICILLIN TO INHIBIT A HUMAN LABORATORY CASE OF LEPTOSPIROSIS

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THIS case seems worth reporting because of the unusual mode of infection and also because of the failure of a prophylactic course of penicillin to prevent the disease

The strain involved (R 43676) was isolated in Malaya from *Rattus rattus argentiventer* It belongs to the *javanica* serogroup, but its serological reactions are not identical with those of either *Leptospira javanica* or *L poi* (the two members of the group already known) The accidental infection took place during the preparation of a homologous antiserum for further investigation of the antigenic constitution of the strain

Case-report

The patient, a man aged 50 is a chief laboratory technician with many years experience of handling cultures of leptospires. On Oct 18 1956 a syringe containing 10 ml of living culture slipped from his hand as he was on the point of inoculating a rabbit In an attempt to prevent the syringe from being shattered on the floor and disseminating the culture widely he put out his foot to try to break its fall. The syringe must have dropped almost vertically point downwards for the needle passed through the leather upper of his shoe and penetrated his foot The needle snapped off at the mount so only a very small quantity of culture could have been injected (Incidentally, the syringe did not break.)

The Illness

A small and slightly lacerated wound was found on the dorsum of the foot and was immediately swabbed with spirit. As a prophylactic measure it was decided to give penicillin by mouth, and the first dose, 1,000,000 units, was administered within an hour of the accident Thereafter penicillin 500,000 units was taken 6-hourly to a total dosage of 6,000,000 units. The wound healed by first intention, but on the 8th day after the accident it became red and sore with puffiness of two toes, though there was no general disturbance On the 9th day the patient had flatulent indigestion, relieved by sodium bicarbonate, and on the 10th day he felt feverish and had severe headache In view of the history he was admitted to hospital on the same day

On admission his temperature was 99°F and pulse-rate 88 He was a fit-looking man with a slightly furred tongue but with no conjunctival injection, neck stiffness, or glandular enlargement There was a tender area of erythema about ½ in. in diameter on the dorsum of the left foot but no abnormal physical signs were found anywhere else The liver and spleen were not palpable, Kernig's sign was negative, and the urine contained no albumin

Next day he complained of severe general malaise with headache and pain behind the eyes. His temperature rapidly rose to 103°F and his pulse-rate to 105 Neck stiffness was present He was immediately treated with oxytetracycline 250 mg 6-hourly for five days His malaise and temperature persisted for 72 hours, after which his general condition rapidly improved, and his temperature returned to normal At no stage was there any diminished secretion of urine

Laboratory Investigations

A blood-culture in glucose broth gave no growth after 6 days The blood-urea level was 21 mg per 100 ml, hæmoglobin 102% and leucocytes 6750 per c mm (differential count normal) Lumbar puncture on the 3rd day produced clear cerebrospinal fluid under a pressure of 90 mm. water, with a free rise to 140 mm on Queckenstedt's test, and containing 1 cell per c.mm. protein 15 mg per 100 ml., and sugar 67 mg per 100 ml. The urine showed no abnormality Tests for bile salts and bilirubin were negative Urobilinogen was present in normal amounts

Two samples of venous blood were taken on the 1st day of illness and one was injected into a guineapig and a golden hamster intraperitoneally Next day blood-cultures were made in Korthof's medium from the second sample, and serum was removed for agglutination tests. Leptospires were seen in the blood-culture after incubation for 7 days The remainder of the blood was treated by the method of double centrifugation described by Ruys (1933), and a few motile leptospires were seen microscopically in the final sediment

Four days after the animals were inoculated numerous leptospires were visible in the peritoneal fluid of the hamster but not in that of the guineapig The hamster was killed next day, and the strain was cultured from the heart blood. The guineapig never showed signs of infection either during life or at necropsy 3 weeks later

The serum taken on the day of onset contained no agglutinins for strain R 43676 A sample obtained on the 12th day of illness agglutinated strain R 43676 to a titre of 1/3000, and a specimen taken about 10 weeks later to 1/1000

Comment

Although a short incubation period has been reported in some laboratory infections of leptospirosis, the period of 10 days in this case is within the usual range There is thus no indication that the administration of penicillin even delayed the onset. There is ample evidence from experiments on animals that a course of penicillin begun soon after infection. prevents the development of the disease. Failure in the present instance may have been the result of too small a dosage, too short a course, or a combination of the two factors

The clinical picture differed from that seen in either classical Weil's disease or infection with *L canicola* in that there was no evidence of either renal or hepatic involvement There was no meningitis and no conjunctival injection The appearance was that of an acute uncomplicated septicæmia

Treatment with oxytetracycline may or may not have modified the course of the illness.

Summary

A laboratory worker contracted leptospirosis from an accident in which the needle attached to a syringe containing live culture pierced his shoe and penetrated his foot

Oral penicillin to a total dosage of 6,000,000 units in 3 days did not prevent the onset of leptospirosis

The infecting strain was obtained in culture from the blood and indirectly by inoculating a golden hamster

The clinical picture suggested acute septicæmia rather than leptospirosis

Treatment with oxytetracycline may or may not have modified the course of the illness

REFERENCE

Ruys, A C (1933) *Ned Tijdschr Geneesk* 77, 3654

Reviews of Books

The Gist of Obstetrics

H B ATLEE, M D, F R C S, F I C S, head of the department of obstetrics and gynæcology, Dalhousie University, Halifax, Nova Scotia, Canada Springfield, Ill Charles C Thomas Oxford Blackwell Scientific Publications 1957 Pp 327 45s

THIS is something quite different The author has given up systematic lectures to undergraduates, and his book has developed from a set of notes which he hands out to his students The title is appropriate, because details have been kept to a minimum and the style is more like that of a novel than of a textbook On the important principles of obstetrics, instruction is clear and dogmatic and often phrased in such a way that the student is unlikely to forget it The book is essentially practical and the line drawings are clear and self-explanatory The student should not rely on it as his only book of reference—it is not intended as such—but both he and the practitioner will find it a very useful practical guide and they will enjoy reading it Teachers will find in it many expressive phrases that they can borrow The bleeding of placenta prævia is " quiet and sneaky " Of transverse lie, " the disasters arising out of this presentation can all be avoided by early diagnosis It is when the baby's little hand has come through the vulva to wave at you that you are friendless in Gaza "

Essentials of Physiology by Bainbridge and Menzies

10th ed Edited and revised by H HARTRIDGE, M A, M D, SC D, M R C P, F R S, emeritus professor of physiology, University of London, J L D'SILVA, M B, PH D, D SC, M R C P, professor of physiology in the University of London at the London Hospital Medical College London Longmans, Green 1957 Pp 506 36s

THERE has been no new edition of this work since 1940 Owing to changes in these sixteen years the book has had to be vigorously revised and largely rewritten The editors have done remarkedly well to cover the essentials in a bare 500 pages Inevitably the subject is treated dogmatically, but, as the editors state, their aim was to write a book for the ordinary medical student—that is, one who will attend lectures and practical classes where the variations and uncertainties of biological work will be pointed out The student will be glad to have this book for summarising and revising the subject The writing is clear and straightforward, and many of the illustrations are new

The Dramatic Universe

Vol I *The Foundations of Natural Philosophy* J G BENNETT London Hodder & Stoughton 1957 Pp 534 42s

THE author's intention is to " explain the universe "—a task rejected as unprofitable by many modern philosophers—and he shows great learning and ingenuity Since it has so far seemed impossible to elucidate a mechanical structure of the world and all that therein is which satisfies not only observation but common sense he proposes, instead of the usual dualist solution of the problem, a schema based upon a fifth dimension of " eternity " Unfortunately, though he sees the whole domain of forest far clearer than most of us, he labels the individual trees with names not commonly in popular or scientific use This has been a difficulty with many a cosmogonist, and arises from the poverty of dead and living languages · he must either coin new names or pay old ones extra and make them mean what he likes Even the glossary might be more helpful to the novice—for example, " Corpuscle The bipotent state of hyle Compromises electrons, positrons, photons, neutrinos and mu-mesons " Inevitably, perhaps, a great deal of the book is hard to follow, but the subject is a suitable one for study by the thoughtful and inquisitive

Analytical Pathology

Treatises in the Perspective of Biology, Chemistry, and Physics Edited by ROBERT C MELLORS, M D, PH D, assistant professor of pathology, Cornell University Medical College, Sloan Kettering Division, New York New York, Toronto, London McGraw Hill 1957 Pp 477 90s

THIS curious subtitle seems to mean that these eight essays, or surveys, dealing with pathological subjects are concerned to show how biochemistry and some biophysics can be correlated with morbid anatomy, experimental pathology, and even therapy When the reader ventures beyond this discouraging title, he will find the essays rewarding, they are relatively short and contain a remarkable amount of information Some of the chapters are simply reviews—with all the dullness of style that we have come to expect in this sort of article But others are readable and intelligent syntheses

The chapter on the biology, biochemistry, and pathology of cancer by the editor is one of the best, and the chapter on macrocytic anæmia by John F Mueller and Richard W Vilter is also particularly well done, it starts with a discussion about nucleotides and how folic acid and vitamin B_{12} are concerned with their metabolism, and progresses via some mention of megaloblasts to the actual treatment of the anæmias The chapter on the adenohypophysis by Agnes B Russell deals with recent histochemistry as well as with experimental work in animals

The other surveys are on arteriosclerosis and hypertension by John W Gofman, inflammatory and vascular diseases of the glomerulus by David B Jones cholæmia, ascites, and hæmorrhagic phenomena in liver failure by Oscar B Ratnoff, abnormal hæmoglobins by John J Will, and the rôle of connective tissue in hypersensitivity by Bernard M Wagner All have their good points, and workers in the particular fields will be sure to find some original way of looking at and putting together the material available Each chapter has a summary or a paragraph setting out its conclusions, and most of them have an extensive bibliography

Handbuch der Orthopädie

Vol I *Allgemeine Orthopädie* Edited by Prof Dr G HOHMANN, Munich, Prof Dr M HACKENBROCH, Cologne, Prof Dr K LINDEMANN Heidelberg Stuttgart Georg Thieme 1957 Pp 1186 D M 178

THIS beautifully produced book is the work of its editors and some 20 co-authors It is the first of four volumes which are designed to replace the classic German " handbook " of Joachimsthal, now past its fiftieth birthday Nothing comparable has been produced in Germany since then, and with the vast increase in knowledge during this century the demand for such an edition cannot be doubted

It contains a series of up to-date essays surveying in general terms the whole of orthopædics including long chapters on physiotherapy British readers will note with interest the stress laid on the logical inclusion of trauma in the orthopædic field, in Europe opinion has not advanced so far down this road as in Britain or America Discussion of treatment has been reserved for later volumes, which makes for heavy reading in the first but does not detract from its high quality

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Contemporary Rheumatology (Amsterdam Elsevier London Cleaver Hume 1956 Pp 654 95s)—The proceedings of the European Rheumatology Congress held in Holland in 1955 have been published under the editorship of Prof J Goslings and Dr H van Swaay.

THE LANCET

LONDON SATURDAY, APRIL 6, 1957

The Staphylococcus Plague

REGULAR readers of medical journals seldom have to wait long for an account of some more or less grave episode of staphylococcus cross-infection in a hospital The latest instance in our own columns was last week's report by Dr GRESHAM and Dr GLEESON-WHITE of staphylococcal bronchopneumonia Of course there has always been staphylococcal cross-infection in hospital, and the nasal-carrier rate has always been greater in hospital staff than in the general population, but this discrepancy has increased dramatically in recent years Bacteriologists with fewer hæmolytic-streptococcal epidemics to investigate, now have more time for staphylococci, and a growing number of bacteriologists have profited from the invaluable work on phage-typing at Colindale But unfortunately, there is no reason to believe that the problem of staphylococcal cross-infection in hospital is being artificially inflated by these factors We face, indeed, a hospital plague It is properly the duty of a hospital authority to maintain a clean and wholesome sick-house and many hospital authorities would probably be bewildered at suggestions that they may be failing in this respect Yet they are In olden days people were afraid to enter plague-houses Nowadays, if they knew all the facts, they might justifiably hesitate to run the risk of being operated on or delivered within even pleasant-looking hospitals, for these, no less than the obviously unattractive ones, may at any time be stricken by an outbreak of our modern plague—virulent staphylococcal cross-infection

It is hard to see an easy, early, or complete remedy, but there is much that should be done, and some of it is fairly obvious and far from difficult if we abandon some of our thoughtless habits We should clearly begin with a ruthless examination of our use of antibiotics When these drugs were introduced the fear was expressed that general practitioners would misuse them and thus spoil their efficacy by fostering resistant bacteria and sensitising patients Ironically, whatever general practitioners may have done in this respect, the effects of misuse are clearest in hospitals The trouble is not, as was feared, that insufficient therapy leads to the emergence of resistant variants of a sensitive strain of staphylococcus in the individual patient, but that antibiotic-resistant staphylococci prevail in the hospital population—attendants as well as patients In hospitals uncritical use of antibiotics for every imagined reason, and for none at all, has so led to the replacement of sensitive staphylococci by naturally resistant and apparently hardier strains which are normal inhabitants of the nose—even of people who have never been treated with an antibiotic This is the heart of the problem

Individual hospital clinicians practise restraint in prescribing antibiotics, but their wise conduct may have disappointingly little effect unless all the staff of a unit—indeed perhaps all the staff of a hospital—adopt the same policy. The surest way of ensuring agreed action is by regular meetings of a cross-infection committee in each hospital We need to notify each one of these infections to a responsible centre of information in the hospital, to study the bacteriology and epidemiology of each episode, and to discuss whether and how further episodes may be prevented In some hospitals—too few by far—cross-infection committees do useful work in this way and even act as a forum at which a policy for the use and non-use of antibiotics may be worked out Such a committee also has a notable educative value For example, some hospital doctors (including many of the residents, who often do much of the prescribing) are probably unaware of the harm that may be done by some of the antibiotics and antibiotic combinations that have recently been introduced—to the dismay, it may be said, of the more responsible advisers of the drug firms themselves There is no justification for giving penicillin and streptomycin together almost as a routine This powerful combination should be used only with good reason—for example in resistant forms of endocarditis In many hospitals, thanks to intelligent and planned restraint, it is still impossible to isolate an erythromycin-resistant staphylococcus In such hospitals an acute life-endangering staphylococcal infection may confidently be treated, without waiting for sensitivity tests, with erythromycin, and it is with this object that some hospital staffs have voluntarily restricted their use of this valuable drug This limitation is hard on the manufacturers of erythromycin, as we have said before, and there may be a case for compensating firms which produce an antibiotic too valuable for general abuse But it is harder still for such firms to see appearing on the market drugs that have few if any virtues peculiar to themselves and will assuredly do harm if they are used widely enough to produce cross resistance to erythromycin This criticism does not apply to such genuinely new antibiotics as novobiocin and vancomycin.

Restraint in the use of antibiotics is not our only weapon against the plague of staphylococcal and of other cross-infections We cannot afford universal air-conditioning in hospitals, but every surgical unit should have an air-conditioned room for its wound dressings (it is certainly no longer possible to find a word to say for the practice of dressing open wounds in general wards) We need to get rid of operating-theatre suites whose air-flow comes from the wards and corridors, or from the anæsthetic room or sterilising-room into the theatre itself, we need to deal with 'sterilisers" that do not sterilise or that may—because of absent or deficient air-filters—contaminate after sterilisation We need to be sure that wards and operating-theatres have a decent flow of fresh air even if it is not fully controlled and conditioned, for there are many wards and theatres in which the atmosphere of still over-heated air may favour cross infection We need to find acceptable ways of sterilising blankets regularly or to devise new kinds of blankets that can be sterilised by steam By such methods, but above all by constant awareness of the risk of cross-infection and determination not to abuse antibiotics, we can surely begin to lift this modern plague from our hospitals

Cæsarean Section

CÆSAREAN section may be preferred as a seemingly easy alternative to vaginal delivery (though for different reasons) by both obstetrician and patient Yet the maternal mortality for this operation is still about ten times greater than that for vaginal delivery, and in Brooklyn, New York, in 1937–50 cæsarean section was a constant factor in about 20% of all puerperal deaths[1] The features which have contributed to the progressive decrease in maternal morbidity and mortality from cæsarean section—including the use of blood-transfusion, antibiotics, and ergometrine—have also reduced the risk of vaginal delivery D'ESOPO[2] reported that complications of cæsarean section in 1000 cases at the Sloane Hospital, New York, included the following puerperal infection, 107, wound infection, 29, surgical shock, 27, thrombo-embolic disease, 24, burst abdomen, 2, intestinal obstruction, 2, damaged bladder, 1, hæmorrhage requiring hysterectomy, 1 MARSHALL and COX[3] reported that of 7762 cæsarean sections in nineteen British teaching hospitals during 1943–47 the maternal mortality was 0 99% Such figures are a corrective to the view that cæsarean section is preferable to any obstetric operation other than the simplest type of low forceps and that all other methods of delivery will become obsolete[4 5]

The classical cæsarean section, which has many disadvantages, has been largely replaced by the lower-segment operation In the classical approach the fœtus is extracted feet first and commonly takes deep inspiratory gasps before delivery is complete, liquor amnii is thus aspirated into the respiratory passages and fatal atelectasis may result The incision, in the anterior uterine wall, is subjected to intermittent tension with each "after-contraction" of the puerperium This leads to the formation of a gutter on the under-surface of the scar which may be the starting-point of rupture in a subsequent pregnancy[6] The uterine scar is exposed to the peritoneal cavity, and gut may become adherent and later strangulate Nevertheless the occasional surgeon working under emergency conditions finds this the easier operation, and for his patient it may be the safer WATERS[7] advocated an extraperitoneal approach, to reduce the risk of disseminating intra uterine infection, but the operation is difficult, and has been abandoned in this country Occasionally the bladder is damaged, commonly the peritoneum is opened, and the incidence of serious infection is not reduced

Many of the difficulties and dangers of the lower-segment operation can be avoided by careful attention to technique[8]

The bladder is kept empty by an indwelling rubber catheter The peritoneum over the lower segment is incised transversely near the upper limit of its loose attachment, and the bladder is pushed down by very gentle finger separation A midline catgut traction-suture is inserted in the lower segment, which is incised progressively with a scalpel while the muscle is pulled away from the fœtal head When the amniotic sac is opened the incision is completed by separating the transverse fibres with digital stretching With a finger in the infant's mouth the head is rotated occiput posterior, the chin is hooked out over the upper uterine flap, and the head is delivered slowly by flexion with the hand A head impacted in the pelvic brim can be freed by mild Trendelenburg tilt Intravenous ergometrine 1 0 mg is given and spontaneous expulsion of the placenta is awaited Meanwhile lateral traction sutures are placed in the lower segment incision Commonly the placenta is delivered by cord traction, but in cases where the uterus is atonic this results in profuse hæmorrhage from the placental site Continuous sutures in the lower segment may cause severe ischæmia and the formation of a weak scar, interrupted sutures of fine catgut are preferable Aspiration of blood and liquor which have spilled into the peritoneal cavity will reduce the incidence of postoperative distension of the bowel Intravenous fluids are not given as a routine, but where much blood-loss is expected, as in placenta prævia, an intravenous drip should be set up before operation Prophylactic antibiotics are administered where sepsis is expected—particularly after prolonged labour with ruptured membranes

The risk of ruptured uterus after cæsarean section is increased by each subsequent pregnancy and vaginal delivery, by high parity, by multiple pregnancy, large fœtus, and hydramnios, and by implantation of the placenta beneath the scar[9] In many clinics in the U S A a cæsarean-section scar is regarded as an absolute indication for terminating further pregnancies in this way, and in 1954 in Brooklyn 38 7% of cæsarean sections were done for this reason[10] This will not completely eliminate the risk of scar rupture, since 25% of ruptures following the lower-segment operation and 50% of ruptures following the classical operation take place before the onset of labour

Rupture of the classical scar is more dangerous to both mother and child DEWHURST[11] reports that in 762 pregnancies of women who had undergone the classical operation the scar ruptured in 17 cases (2 2%) In 100 reported cases where the scar ruptured, the maternal mortality was 5% and the fœtal mortality 73% In 40% of all cases the placenta overlies the scar After rupture the uterus contracts and retracts, the amniotic sac ruptures, and often the placenta and fœtus are partly expelled into the peritoneal cavity, hæmorrhage from the placental site is profuse, and the patient presents the picture of severe shock She has severe continuous abdominal pain and tenderness, the fœtal heart cannot be heard and the fœtal parts may be easily felt Intermittent labour pains usually cease, and there may be slight vaginal bleeding The fœtus dies from cord compression, placental separation, and maternal cardiovascular collapse

Rupture of the lower-segment scar is less dangerous and less usual DEWHURST[11] reports 8 cases in 1530 pregnancies (0 5%) Rupture may be gradual and unaccompanied by dramatic symptoms Even where symptoms and signs are more pronounced and the peritoneum is involved, the fœtus is usually—but not always[12]—retained in utero, the placenta is rarely involved, and bleeding is usually slight The fœtal loss is consequently less (12 5%) and in this country no maternal death has been recorded In the presence of a lower segment scar, therefore, the mode of delivery will depend largely on the indication for the first cæsarean section If this was on account of a recurring cause, such as contracted pelvis or diabetes mellitus, an elective lower-segment cæsarean section is indicated Otherwise vaginal delivery, carefully supervised in hospital, with facilities for immediate transfusion and operation, is to be preferred The second stage of labour should not exceed fifteen minutes, and if necessary,

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[1] Gordon C A *Amer J Obstet Gynec* 1952 63 284
[2] D'Esopo D A *Ibid* 1950 59 77
[3] Marshall, C M Cox L W Transactions of the 12th British Congress of Obstetrics and Gynæcology 1949, p 30
[4] Harris J M Rosenblum G Glusburg B L Stolman, B D, Steinman M S *West J Surg* 1951 59 137
[5] Cosgrove, S A *Amer J Obstet Gynec* 1950 59 104
[6] McIntyre D *Proc R Soc Med* 1924 17 131
[7] Waters E G *Amer J Obstet Gynec* 1915 49 739
[8] Russell, J K *Lancet* 1955 ii, 322
[9] Lennie R K Barry A *Brit med J* 1956 i 65
[10] Gordon C A *Amer J Obstet Gynec* 1957 73, 65
[11] Dewhurst C J *J Obstet Gynæc Brit Emp* 1957, 64, 113
[12] O'Dwyer J P *Lancet* 19[illegible] ii 324

very is hastened by episiotomy and forceps It is e to palpate the lower segment with two fingers to clude late rupture during fœtal expulsion

uspected rupture of the scar is best treated by esuscitation and immediate laparotomy—especially f labour is established After delivery of the fœtus and placenta, either the uterus is repaired and the fallopian tubes ligated, or, in the more severe case, subtotal hysterectomy is undertaken

Half the fœtal deaths in deliveries by cæsarean section are attributable to the risks inherent in the operation itself In Brooklyn in 1954 there were 2693 cæsarean sections 2714 infants were delivered with 44 stillbirths and 90 neonatal deaths—a perinatal mortality-rate of 49 4 per 1000 live and still births, which represents an incidence about 55% above the general perinatal mortality for New York city (GORDON[10]) We should therefore hesitate before deciding on cæsarean section solely in the interests of the infant

Progress in Argentaffinomatosis

ARGENTAFFINOMATOSIS—the syndrome resulting from the secretion of 5 hydroxytryptamine by argentaffinomas—is now familiar, though rare In cases of obscure cyanosis or flushing and in pulmonary stenosis, it is accepted that abdominal carcinoids come into the differential diagnosis, and the estimation of urinary 5-hydroxy-indole acetic acid is established as a valuable diagnostic measure[1 2] But of the underlying biochemistry and physiology of the process much remains to be learnt

One of the most interesting aspects concerns the source of the 5-hydroxytryptamine (5-H T) Metabolic studies on relatively large series of patients in Bethesda[3] and Glasgow,[4] supported by the use of isotope-labelled tryptophan,[3] have shown very clearly that the 5 H T is derived from tryptophan In some cases a very large proportion of the normal dietary intake of tryptophan is diverted to this process, and this, combined with the diarrhœa often present, leads to a considerable risk of a nicotinic acid/tryptophan deficiency[4] The conversion of tryptophan to 5 H T seems simple enough Oxidation of tryptophan at C 5 produces 5-hydroxytryptophan, and loss of CO_2 from the carboxyl group produces the corresponding amine, 5-H T GADDUM and GIARMAN[5] demonstrated the presence of a decarboxylase which accomplished the second part of this process and showed that its distribution corresponded fairly well with the sites of formation of 5-H T The first part remains elusive The tryptophan oxidase that would produce 5-hydroxytryptophan has never yet been demonstrated in animal tissues Tryptophan incubated with rat liver slices, for instance, undergoes no 5 hydroxylation One of the cases in the Glasgow series[4] was therefore of especial interest, for 5 hydroxytryptophan in substantial quantities appeared in the urine, apparently from renal metastases of the tumour This is valuable confirmation of the reality of the postulated route of formation DALGLIESH and DUTTON go further, and deduce that the tumour, and so presumably the normal argentaffin cells from which the tumour has arisen, must be capable of this essential 5-hydroxylation of tryptophan SJOERDSMA et al[3] failed to demonstrate such an action in tumour tissue, but so fruitful is this hypothesis that their findings should be re-examined It follows if DALGLIESH and DUTTON are right, that the major function of the argentaffin cells is not the local release of 5-H T (though this may be one of their functions) but the manufacture of its precursor, 5-hydroxytryptophan, for circulation to various other cells which decarboxylate it and turn it into the active hormone Among other things, this would account for the fact that though 5 H T is produced apparently by several different kinds of cells, no other kind of tumour produces excess of it The body's total production of 5-H T is presumably limited by the availability of the precursor, and only the argentaffinoma can produce excess of the precursor The elimination of 5-H T by oxidation to 5-hydroxy-indole acetic acid (5-H I A A) is effected by an amine oxidase present especially in the lungs MACFARLANE et al[2] made the interesting suggestion that some of the discrepancies between the intensity of symptoms and the level of hormone production (one of their patients excreted 600 mg of 5-H I A A a day but had no relevant symptoms except slight diarrhœa) might be accounted for by an adaptive rise in the amine-oxidase content of the lungs But this possibility has been eliminated by DAVISON and SANDLER,[7] who showed that the lung amine-oxidase remains at normal levels The relation to 5-H T. secretion of the most striking feature of the syndrome—the vasomotor changes which account for the flushing and cyanosis—is uncertain[4]

Nothing further seems to have been learnt of the origin of the endocardial lesions Their constant appearance downstream from the main tumour masses makes it difficult to believe that we are not seeing a direct effect on the endocardium of some toxic material produced by the tumour But what[2] 5-H T seems the only possible answer, yet no action of 5-H T that would account for its damaging the endocardium is known Its presence in high content in the platelets does not seem to damage them, and there is no evidence from the few adequate post-mortem studies reported[8-10] that platelet deposition or thrombosis play any part One can only assume that 5 H T in high concentration has some unrecognised action on the endocardium, or that some unrecognised secretion of the tumours is the culprit Even that most satisfactory observation of GOBLE et al[11]—namely, a substantial removal of 5-H T from the blood during its passage through the lungs in one patient (thus accounting, it seemed for the difference between the lesions in the left and right hearts)—has been challenged by SJOERDSMA et al,[3] who found no difference between the 5-H T content of pulmonary-artery blood and femoral-artery blood Among confusing observations it is a relief to find in the Glasgow series studies of gastric function (high pepsin

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1 Page I H, Corcoran A C, Udenfriend S, Sjoerdsma A, Weissbach H *Lancet* 1955 i 198
2 Macfarlane P S, Dalgliesh C E, Dutton R W, Lennox B, Nyhus L M, Smith A N *Scot med J* 1956 1 148
3 Sjoerdsma A, Weissbach H, Udenfriend S *Amer J med* 1956 20 520
4 Smith A N, Nyhus L M, Dalgliesh C E, Dutton R W, Lennox B, Macfarlane P S *Scot med J* 1957, 2 24
5 Gaddum J H, Giarman N J *Brit J Pharmacol* 1956, 11 88
6 Dalgliesh C E, Dutton R W *Biochem J* 1956 64 481
7 Davison A N, Sandler M *Clin chim acta* 1956, 1 450
8 Spain, D M *Amer J Med* 1955 19 366
9 Goble A J, Hay, D R, Hudson R, Sandler M *Brit Heart J* 1956 18 544
10 Smith J P, Campbell A C P *J Path Bact* 1956, 72 673
11 Goble A J, Hay D R, Sandler M *Lancet* 1955 ii, 1016

and low acid) and of renal function (inconstant oliguria) with results that fulfil physiological prediction. The increased production of 5-H T in response to reserpine is also not unexpected, but the failure of 5-H T antagonists to influence the syndrome is hard to account for. It is especially disappointing to find a failure to confirm Bleehen's[12] report of an alimentary stimulus to 5-H T secretion, in which we once[13] thought we saw evidence of an intermediary hormonal mechanism.

This syndrome is only one of the many aspects of the biochemistry and pharmacology of the aromatic amino acids in which, largely under the influence of chromatographic methods,[14] rapid advances are being made. Two recent studies remind us that the aromatic amino acids and their derivatives should not always be considered separately: first, the description by Waldenström et al.[15] of an argentaffinoma which appears to secrete large amounts of histamine as well as 5-H T, and second, the demonstration that 5-H T metabolism is involved in phenylketonuria.[16] We might also note the claim of Boyland and Williams[17] that some normal urinary indole derivatives may be carcinogenic for the bladder.

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[12] Bleehen, N M Ibid, p 1362

[13] Ibid, p 1369

[14] Dalgliesh C E Biochem J 1957 65 21P

[15] Waldenström, J, Pernow, B, Silwer, H Acta med scand 1956, 156 73

[16] Pare C M B, Sandler M, Stacey R S Lancet, March 16, 1957, p 551

[17] Boyland, E, Williams, D L Biochem J 1956, 64 578

Annotations

THE BOMB TESTS

On his return from Bermuda, the Prime Minister declared that the forthcoming tests of thermonuclear weapons at Christmas Island in the Pacific would be "so small and on such a restricted scale that they cannot really add to anything that would be dangerous to the world"[1], and on Monday he said he was satisfied that the radiation effects would be insignificant. The most likely interpretation of "small" is that the bombs will contain only a lithium-deuterium mixture detonated by an "ordinary" atomic bomb, and that the mass of uranium which gave earlier hydrogen bombs their enormous power, and which was responsible for most of the radioactive contamination they caused and are still causing, will be omitted or much reduced. If that is in fact what is planned, the new tests will generate much less radioactivity than previous thermonuclear explosions, and immediate fears about their consequences will be eased.

Small "clean" bombs may have been the Government's intention all the time, and the outcry at home and abroad against the tests may have forced it to disclose what they hoped to keep secret. On the other hand, a small explosion would be something of an anticlimax: one of the main reasons for having the tests (and it is a reason which, in the Government's view, may outweigh potential dangers) is presumably to demonstrate that Britain possesses a weapon of devastating and deterring power; and, as Mr Angus Maude puts it,[2] "the peculiar effectiveness of the H bomb as a deterrent . . . is that it is a total destroyer." Before the Bermuda conference, few people doubted that at least one full scale hydrogen bomb was on the programme for Christmas Island, around which an enormous danger area had been outlined. With a wider realisation of what radioactive fallout may conceivably do and, more specifically, of the ignorance of the ultimate effects of even small doses of strontium 90 on bone and blood, opposition to continued nuclear tests has hardened. And the Government may have been constrained by the vehemence of the protests to modify the tests.

For those who fear, as we do, that the radioactive accumulation from thermonuclear explosions may be near the danger point, there can be little lasting comfort in the news that British bombs are small bombs, while the action of other countries remains in doubt. The only course that does not involve risks which, in relation to mankind as a whole, are utterly unjustifiable is for the three governments so far concerned to stop thermonuclear explosions of all kinds. Proposals for limiting or abandoning tests have had to be revised because it is now apparently possible to hold tests in secret. Nevertheless, we hope the Government will now press forward with negotiations—and with a far greater sense of urgency than they or other governments have shown in the past. Putting the risks at their lowest, continued explosions of megaton bombs can hardly fail in the end to kill a certain number of people by giving them bone tumours that they would not otherwise have had; at worst, accumulated fallout could be responsible for a great many early deaths from malignant disease or other hazards of internal or external radiation of which we know even less—premature ageing is one. Those who are unconcerned at the way bombs have been exploded in recent years are fortified by the belief that the present rate of firing can be continued for a long time without seriously endangering anyone's health. They put their faith (as Mr Macmillan seems to do) in the hypothetical existence of a threshold below which no harm is done. In this belief they may be right; but what matters now is that no one can yet say for certain that they are not very wrong.

EPILEPSY, MIGRAINE, AND SUBARACHNOID HÆMORRHAGE

In the past two decades the syndromes associated with intracranial angiomas have been more clearly defined. This clarification has been largely due to the introduction by Egaz Moniz, in 1929, of cerebral angiography, which enables the condition to be unequivocally diagnosed in most cases. In 1936 Tönnis[1] reported 22 cases investigated in this way. Most of these were studied in Olivecrona's clinic, and in 1948 Olivecrona and Riives[2] reviewed a further 43 cases. Of these, 17 had epilepsy, usually with focal features, as the initial symptom, while subarachnoid hæmorrhage occurred first in 12. The two cardinal clinical features[3] of the condition—focal epilepsy, which may precede other signs by years, and recurrent intracranial bleeding—were thus clearly established. Olivecrona noted one other presenting feature: hemiplegia, either sudden from intracerebral hæmorrhage or insidious by direct involvement of cerebral tissue in the angioma. Mackenzie[4] added episodic headache as a common initial symptom (present in 12 of his 50 cases), and he emphasised that the association of migraine, focal epilepsy, and subarachnoid bleeding which Adie had remarked on in 1930 was sometimes part of the angioma syndrome. Paterson and McKissock,[5] in a careful study of 110 cases, found that 38% presented with subarachnoid hæmorrhage, 26% with epilepsy, 21% with headaches (of episodic "migrainous" type in 15%), and 7% with progressive hemiparesis—thus confirming once more the importance of the triad of subarachnoid hæmorrhage, epilepsy, and "migraine" They observed in 14% of their cases dementia, which Olivecrona had noted to a mild degree in as many as 50% of his Discussing the mode of progression of angiomas they pointed out that, although not neoplastic, these abnormalities can become truly progressive space-filling lesions as small recurrent hæmorrhages result in the formation of cerebral cysts or false aneurysms

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[1] Times March 28 1957

[2] New Scientist March 28 1957

[1] Tönnis W Gefässmissbildungen und Gefässgeschwülste des Gehirns Leipzig 1936

[2] Olivecrona H Riives J Arch Neurol Psychiat 1948 59 567

[3] Cushing H Bailey P Tumors Arising from Blood Vessels of the Brain Springfield Ill 1928

[4] Mackenzie I Brain 1953 76 184

[5] Paterson J H McKissock W Ibid 1956 79 233

These lesions are liable to cause severe disability or even death by sudden severe hæmorrhage or gradually increasing impairment by recurrent epilepsy and dementia Treatment is therefore important Olivecrona was a pioneer in establishing the possibility of radical excision, and McKissock undertook this in almost a third of his cases Ligation of feeding-vessels is less satisfactory and may damage normal brain tissue by general changes in cerebral blood-flow The value of X-ray treatment, in vogue for many years, is dubious, though Potter[6] has recently suggested that it may help It is evident that if these lesions are progressive, as McKissock believes, then prompt diagnosis should be followed by surgical treatment Angiography, the diagnostic linchpin, should always be considered in subarachnoid hæmorrhage, focal epilepsy, and even migraine

RESCUE IN THE MINES

AFTER a mining accident, rescue workers have often to contend with extreme heat and humidity in an atmosphere in which they must use breathing apparatus No laboratory conditions can simulate all facets of an underground disaster, but men can be set equivalent tasks in conditions of high temperature and humidity, like those encountered underground, and they can wear various forms of rescue apparatus while doing them By such means, an attempt has been made to establish limits of tolerance for typical members of rescue teams under anticipated rescue conditions The memorandum by Lind et al,[7] published by the National Coal Board, contains detailed physiological data and consequent recommendations for the guidance of those concerned with rescue teams

The investigation was in two parts, carried out at Oxford and Doncaster The subjects were underground workers, divided into two age groups, 19–31 and 39–45 The Oxford programme was intended to assess the intrinsic individual variations of the subjects, and to compare the reactions of the two age groups to a standard task under hot and humid conditions while not wearing rescue apparatus At Doncaster the men were given a work routine representing a rescue in a mine, to estimate "tolerance-time" in various saturated environments, and to determine any differences in reactions between the two age groups and between men normally employed on different types of mine work In these Doncaster tests the men wore one of two different types of apparatus commonly used in rescue operations

As might be expected, the physiological data show that the older men are less adaptable to stress, for example, their rectal temperature and pulse-rate rose more than those of the younger group under identical conditions But in spite of this, age did not affect the tolerance time, and men from the older group could work hard in hot wet surroundings for as long as the younger men There was no evidence that men in a particular class of pit work were any better or worse physiologically at rescue work than those doing other jobs

On the basis of these data, the National Coal Board memorandum recommends safe working times for rescue teams for a given temperature and humidity—the "confidence limit" If a team exceeds this limit, the possibility of collapse of any member with a low heat tolerance increases No routine medical examination can assess an individual's heat tolerance, and until a suitable heat selection test has been devised, Lind et al think that rescue workers should face hot conditions on their routine practices, so that "heat-intolerant" men may be detected

Though only two instances are reported in the memorandum, tolerance is lowered by minor infections (such as mild food-poisoning and an early head cold) Such minor ailments may prove serious under stress

An appendix to the memorandum sets out the recommendations arising out of the investigations, with details of the precautions to be observed in the conduct of rescue operations, and tables of maximum safe periods of exposure under various specified wet and dry bulb temperatures

NEW SALARY-SCALES FOR DENTAL TECHNICIANS

THE new salary-scales for dental technicians employed in hospitals and local-authority health services[1] probably offset the rise in the cost of living since the previous scales were put into effect, but the remuneration of skilled technicians still seems inadequate, compared with, for example, that of many grades of local-government employees Moreover, the "differential" between the salary of a technician immediately on completion of his apprenticeship (£430, rising step-wise to £535 after six years) and that of a chief technician of many years' experience in charge of a technical staff (£545–760 according to length of service and size of staff) hardly seems to take account of the considerable responsibility involved in the latter post

PRIMARY HEPATIC CARCINOMA

THE incidence of primary carcinoma of the liver judged by necropsy findings, has increased distinctly in recent years Thus, at the Mayo Clinic in 5976 necropsies reported in 1926 the frequency was 0 083%,[2] whereas in 16,303 necropsies reported in 1947 the frequency was 0 19%[3]—more than double that observed twenty years earlier Similarly in Vancouver[4] the incidence doubled in twenty years

These and other figures show that primary carcinoma of the liver is still rare in North America and Europe, but in Oriental countries it is three to four times as common as in the Occident, and in parts of Africa it is no longer rare, the incidence being highest in members of the Bantu tribe The report of the South African Institute for Medical Research[5] that primary carcinoma of the liver was present in 39 56% of all necropsies, and the observation that this tumour constitutes 86% of all primary carcinomas in the natives in the gold mines of the Witwatersrand,[6] are overwhelming evidence of the importance of local factors in this disease The relative importance of racial and environmental factors is still not clear, but the pronounced tendency for the incidence to decrease among Oriental and African immigrants to North America suggests that environment may be the more significant factor, and the most important environmental variable is probably the diet

The relation of dietary deficiency to cirrhosis in both man and laboratory animals is now well established The association of primary carcinoma with cirrhosis of the liver is equally well established cirrhosis is present in about 80% of cases of hepatocellular carcinoma and in about 30% of cases of cholangiomatous carcinoma In under-privileged communities the high incidence of primary hepatic carcinoma is doubtless attributable mostly to the high prevalence of hepatic cirrhosis. The enhanced incidence of primary carcinoma of the liver in North America and Europe during the past decade is paralleled by an enhanced frequency of hepatic cirrhosis. MacDonald's figures from the Boston City Hospital,[7] for example, show that, whereas in each decade from 1917 to 1946 hepatic cirrhosis was found in about 8% of all necropsies, in the eight years from 1946 to 1954 this figure was almost doubled; and primary carcinoma of the liver increased correspondingly from 0.34% to 0.72% of all necropsies. It is unlikely that the enhanced prevalence of cirrhosis in these areas is due to lowering of the nutritional status.

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[6] Potter J M Ann R Coll Surg Engl 1955 16 227

[7] Lind A R Weiner J S, Hellon R F, Jones R M, Fraser D C Reactions of Mines Rescue Personnel to Work in Hot Environments Medical Research Memorandum no 1 National Coal Board Medical Service Pp 68 10s Obtainable from the board at Hobart House Grosvenor Place London, W 1

[1] P T B circular 70

[2] Counseller V S McIndoe A H *Arch intern Med* 1926 37 363

[3] Horne, R M, Kernohan J W *Ibid* 1947 79 532

[4] Strong G F Pitts H H *Ann intern Med* 1932 6, 455

[5] Charache H *Amer J Surg* 1939 43 96

[6] Berman C Primary Carcinoma of Liver London 1951

MacDonald finds that of seven varieties of cirrhosis into which the cases were classified, two account for most of the increase—namely, nutritional cirrhosis, whose increase is almost certainly the result of increased alcohol consumption, and healed yellow atrophy, an increase of which was to be expected in view of the widespread epidemics of infective hepatitis in recent years. A surprising finding, however, is the frequency with which primary carcinoma develops in the liver scarred as a result of acute yellow atrophy. Mallory[8] reported in 1932 that carcinoma developed in 3 out of 46 cases of healed yellow atrophy, compared with 4 out of 49 cases of hæmochromatosis and only 5 out of 454 cases of other varieties of cirrhosis. MacDonald has now found carcinoma in 13% of 222 cases of healed atrophy, the frequency among cases of other forms of cirrhosis, excluding hæmochromatosis, remaining at the usual low level of about 2%. The reason for this enhanced tendency towards malignant change in the liver after recovery from acute massive necrosis is unknown. Discovery of this reason might throw much-needed light on the mechanism of the well known sequence of injury, repair, hyperplasia, neoplasia that takes place not only in the liver.

METHONIUM AND PULMONARY DISEASE

THE development of pulmonary disease in hypertensive patients treated with methonium was noted by Doniach et al.,[9] and Perry et al.[10] now report the results of further investigations into this matter. They examined post mortem the lungs of two groups of patients in whom an anatomical diagnosis of arteriolar nephrosclerosis had been made. The first group of 67 patients had never been treated with methonium compounds; the second group of 27 patients (who died later than the first) had all received at least 30 g. of methonium salts in their last month of life. The groups were comparable in age and type of disease. It was found that the lungs of a proportion of the patients in both these groups showed fairly constant histological features—intra-alveolar fibrin masses, with a striking tendency to fibrous organisation, and hyaline-like membranes lining the walls of alveolar ducts and atria. But the lungs in the methonium-treated group were almost twice as often affected as those in the untreated group (59% compared with 34%). This condition, termed "fibrinous pneumonitis" by Perry et al., has been observed in uræmia[11 12] and rheumatic fever,[13-15] and in order to separate if possible the effects of uræmia from those of methonium therapy an analysis was made of the clinical findings in 59 patients in the two groups who had been diagnosed during life as suffering from malignant hypertension (supine diastolic pressure greater than 120 mm. Hg at rest, hæmorrhagic and exudative retinitis with papillœdema, and severe renal disease). 19 of these patients belonged to the methonium-treated group and 40 to the untreated group. Whereas fibrinous pneumonitis was not found in untreated patients whose non-protein nitrogen never exceeded 60 mg. per 100 ml. plasma (normal 25 mg. per 100 ml. by the method used), it was seen in 9 methonium-treated patients with non-protein-nitrogen levels below this figure. It was inferred from these results that methonium compounds, like the retained nitrogenous products of uræmia, may precipitate in hypertensive patients an attack of fibrinous pneumonitis.

Doniach et al.[9] do not consider that this lung condition can be attributed directly to methonium; they think that its probable basis is pulmonary œdema, due to attacks of left-sided heart-failure, modified by intermittent lowering of the blood-pressure by the drug. Perry et al.[10] investigated the effects of a raised pulmonary capillary pressure by examining post mortem the lungs of 39 patients who died from severe, or moderately severe, mitral stenosis. They did not discover fibrinous pneumonitis of any extent, though they found small patches of it in 18% of cases. Epstein and Greenspan[16] similarly examined the possibility that heart failure was responsible for the "fibrinous pneumonitis" sometimes associated with rheumatic fever, by looking for the characteristic but non-specific pathological picture in the lungs of 59 patients dying of pulmonary congestion caused by hypertension, coronary thrombosis, or mitral stenosis without active rheumatic infection. The only instance they found was in a patient with hypertension complicated by uræmia. Perry et al. could also find no clinical evidence of left ventricular failure in patients with fibrinous pneumonitis: dyspnœa was usually relieved, not exacerbated, by putting the patient supine, and circulation times and venous pressures were relatively normal. The most striking clinical feature in these attacks was the rapid respiration rate, and, since the minute volume was often much increased in the presence of a normal carbon-dioxide content, pH, and oxygen saturation of the arterial blood, interference with blood gas exchange by the fibrinous pneumonitis was the most likely explanation of the respiratory distress. Perry et al., therefore, believe that methonium salts, like uræmia and rheumatic fever, may cause fibrinous pneumonitis by damaging the pulmonary capillaries so that they leak exudate into the alveoli; and they do not think that left-sided heart failure is an important factor, although it is admittedly difficult to exclude it altogether.

Whatever the exact ætiology of fibrinous pneumonitis in methonium-treated hypertensive patients may prove to be, it is well to remember that this condition may easily be overlooked as a cause of respiratory distress, since physical signs are few, even when chest films show widespread changes in the lung fields.

REMUNERATION

A DECISION to recommend refusal to cooperate with the Royal Commission on the remuneration of doctors and dentists was reached by the council of the British Medical Association on Wednesday, March 27. This news was given at a press conference on the following day, when it was announced that the council is also recommending that the association should institute its own comprehensive review of State medical services, with the aim of eradicating "those faults of the present system which cause dissatisfaction to the public and frustration to the profession." Lay persons of high standing are to be invited to sit with medical members on the committee of inquiry. Both these recommendations are to be put to the association's representative body on May 1.

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Special Articles

DAY HOSPITALS AND NIGHT HOSPITALS IN PSYCHIATRY

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A DAY hospital is a place in which patients spend a substantial portion of their waking time under a therapeutic régime and from which they return to their own home or hostel to sleep at night. Soviet Russia has had day centres as departments of its neuropsychiatric dispensaries at least since 1942. In the Russian centres the emphasis is on occupation and rehabilitation for work, although hospital facilities are also provided (Wortis 1950). The first day hospital in the English-speaking world was started in Montreal (Cameron 1947, 1956), as part of a psychiatric teaching hospital, the Allan Memorial Institute. Since then only two have established themselves firmly in North America, one in the Montreal General Hospital, a large general hospital with a psychiatric department (Moll 1953a and b), and one in the Menninger Clinic, Kansas (Law 1947, Barnard et al. 1952). Several attempts in State mental hospitals in the U.S.A. have proved abortive. But the idea is spreading, and a day hospital operating successfully among primitive people in tropical Africa has lately been described (Lambo 1956).

In England the first day hospital was started in London as an independent institution unconnected with any existing hospital (Bierer 1951). Since then the number has slowly increased. Some follow the original London model (Aron and Smith 1953), some—such as the Bethlem and Maudsley ones—the Montreal pattern. Some cater for specialised groups of patients, such as old people (Cosin 1955) or chronic unemployable neurotics (W. Mayer Gross, personal communication). They differ in outlook and methods. There is no uniformity, for example, in the amount of time that each patient spends at the day hospital. In some, as at Oxford, one afternoon a week may be thought adequate for some patients (Cosin 1955), in others, as at Bethlem and the Maudsley, five days is the minimum for all patients.

Bethlem and Maudsley Day Hospitals

Bethlem Royal Hospital and the Maudsley Hospital together form a postgraduate teaching hospital which caters for all types of psychiatric illness except uncomplicated mental deficiency. Although administratively one hospital, the buildings are 8½ miles apart. The two day hospitals, one at Bethlem and one at the Maudsley, function essentially as wards whose special characteristic is that the patients go home each evening. In other words patients can readily pass from the conventional inpatient wards to the day hospital and from the day hospital to the inpatient wards as their condition requires. In practice, however, most of the day-hospital patients spend their illness in the day hospital and are not transferred to or from the ordinary wards. All the diagnostic and therapeutic facilities of the joint hospital are open to them, and the only forms of psychiatric treatment which it has proved impossible to undertake in the day hospital are deep insulin coma, continuous narcosis, and neurosurgery. Each day hospital takes 30 patients at a time and has some 100 to 150 admissions a year.

The Maudsley day hospital was opened in May, 1953, and is within the grounds of the hospital in the ground-floor and basement of a Victorian house which had been used as a nurses' hostel (Harris 1954a and b). The day hospital at Bethlem was opened in April, 1956, and is housed in a pavilion which used to belong to a sports club (Harris 1956). Each has a large room where men and women patients can mix and undertake group activities, such as discussions, games, and play-readings. There are two smaller rooms, one for men and one for women, where the more ill patients can spend their time quietly without too much social pressure. Two rooms for doctors, an office for the nurse in charge, and lavatories complete the indoor accommodation. There is also a tennis court and grounds in which the patients can walk and play. The Bethlem day hospital, which is farther from the main hospital and therefore has to be more self-contained, also has a kitchen, extra interviewing-rooms for psychologists and social workers, and a hut for the administration of electroconvulsion therapy, with a waiting-room, treatment-room, and recovery-room.

The day hospitals are open from Monday to Friday and closed on Saturday and Sunday. The patients arrive about 8.30 A.M. and leave about 5.30 P.M., or at times that fit their relatives' hours of work and convenience. They pass their day in much the same way as the patients in the less acute conventional wards, the morning generally being given over to occupational therapy and the afternoon to group activities. But the programme at the day hospital is readily varied to meet the need of individuals. For example, those unsuited for group activities continue with occupational therapy in the afternoons. Shopping parties, in the company of a nurse, enable patients whose families are all out at work to return home with the household supplies. If a night sedative is needed it is handed to a relative who sees that the patient takes it at home.

Staff

The medical care for each hospital is provided by a senior psychiatrist (giving one session a week), a full-time registrar or psychiatrist in training, and one or at times two clinical assistants. The nursing care is provided by a doubly qualified ward sister and two junior nurses, who are staff nurses or student nurses according to the training situation at the hospital at the time. The part-time services of a clinical psychologist, a psychiatric social worker, and an occupational therapist are also available. Nurses find work in the day hospitals congenial, because the simple type of organisation and absence of bed linen and other stores relieves the ward sister of administrative duties and enables her to give the greater part of her time to the patients directly. As there is only one shift, the nurse is in close contact with the whole of the patients' hospital life, and this increases her sense of responsibility and personal influence. The relatives chat and ask advice when they bring and collect the patients, so that the nurses are brought into the family situation as well.

Patients

In selecting patients one of our chief criteria has been that the patient must be so ill as to need admission to a hospital bed if the day hospital did not exist. We have closely adhered to this: all our patients are so far incapacitated by their illness as to be unable to work or lead their normal lives and most are unfit to be left alone at home during the daytime. On the other hand the patient must not be so disturbed as to be too difficult for his family to manage at night or for them to bring him and fetch him. He should not live much more than half an hour's journey away, for arrangements will break down if too much travelling is involved. Sensible, stable relatives, with affection and concern for the patient, who are willing to play an active, supporting rôle, are a very great help, and in their absence day-hospital treatment is likely to prove difficult, though success has been achieved in some unfavourable family situations. Harassed, overworked housewives, with no one to take their burdens, who try to cram their housework in during the evenings, do not do well and usually have to be admitted as inpatients With experience we have found that a very large proportion of potential inpatients can be treated on day hospital lines, and the pressure of recommended admissions is now greater on the Maudsley day hospital than on the wards

Advantages of the Day Hospital

The advantages of day-hospital treatment are economic and social It has been found at the Maudsley that the running costs of a 30 place day hospital are roughly one third of those of a 30 bedded ward, and Montreal experience is similar There is only one nursing shift instead of three and no bed-linen or dormitory space are needed Also kitchen and domestic staff are needed for only a short time The saving in capital costs is even greater, for new building is unnecessary and existing buildings can be adapted Thus the day hospital at Bethlem was bought, reconditioned, furnished, and equipped for little more than the cost of one bed in a new hospital

The patient keeps his place in the family—a very important matter for the middle aged and elderly who form the bulk of the day-hospital clientèle Such people's homes tend to disintegrate if they are brought into hospital as inpatients

Treatment tends to be shortened, for it is no longer necessary to test the patient's reaction to his normal environment by sending him home for half days and then weekends 60% of patients in the Maudsley day hospital suffer from depressive illnesses and two groups of depressed patients, under the same physician and matched for severity and other relevant features were compared One group was treated for the whole period of the illness in the day hospital and the other in the inpatient wards, and the average stay of the day-hospital group was between two and three weeks less than that of the inpatients (M J Craft, personal communication)

Some women present an intractable social problem, because owing to phobias or other symptoms they cannot be left alone and there is nowhere for them to go while their husbands or other relatives are at work In the absence of the day hospital they must be admitted into hospital (with the risk that their homes will break up), or their husbands must give up their jobs, which usually causes poverty, resentment, and unhappiness These patients are successfully handled in the day, hospital, though many require long treatment—up to one or even two years

Other people whose difficulties the day hospital has solved include a woman who might have lost the custody of her child if she had left home altogether, and a hallucinated paranoid patient who refused to stay as an inpatient but attended the day hospital until she recovered, so that certification was avoided

Night Hospitals

At the Montreal General Hospital there is a night hospital to which the patients come after their day's work, they spend the evening there, have any necessary treatment, and then sleep until it is time for them to go to work the next morning (Moll 1955) The Maudsley night hospital, which opened in August, 1956, is not for patients undergoing active treatment but for those who have partially recovered and are working though not secure enough to live in ordinary lodgings or hostels For many years it has been the practice in the joint hospital as in several other psychiatric hospitals, to allow suitable patients to go out to work and return to the hospital in the evenings Their adjustment to the outside world is easier if they can make it in two instalments, first to the job and then to normal living conditions These patients are now collected in the night hospital, which uses the day hospital accommodation as sitting rooms and the bedrooms upstairs for sleeping—an economical use of this Victorian house One nurse stays on from the day hospital to receive them on their return from work, they see their doctor once a week, and they attend the evening amusements and social events arranged for the inpatients if they wish There are 14 bedrooms—one floor for men and one for women Patients usually settle in their jobs and leave the night hospital after a *few* weeks

Comment

These developments are in line with the feeling which is growing up, not only in psychiatry but in other branches of medicine also, that patients are sometimes isolated in hospital more often and for longer than is necessary Social considerations and the possible harmful effects of a stay in hospital are receiving more attention

Varying patterns of day hospital can be designed to suit different types of parent institution In the new Montreal General Hospital inpatients and day patients share the same psychiatric ward, and this model might well be copied by psychiatric departments of general hospitals in this country, which are usually situated in large centres of population and are therefore better placed than most mental hospitals to run day hospitals

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FREEZE-DRIED BONE-GRAFTS

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TUTOR AND SENIOR REGISTRAR IN ORTHOPÆDICS

P M Yeoman
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SENIOR LECTURER IN BACTERIOLOGY

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A I S T
TECHNICIAN

SCHOOL OF MEDICINE, LEEDS

A BANK of freeze dried bone established in Leeds in April, 1955, has supplied grafts to about 80 patients, of whom 46 are reviewed here, the remainder having been operated on too recently for final radiological assessment

Collection and Preparation of Bone

Bone is taken from donors aged up to 30 A considerable amount of cancellous bone is obtained with the minimum of difficulty from the lower end of the femur and the upper end of the tibia The limb is draped as for

Short-term clinical results, the ease and convenience of use, and the shortening of operating-time resulting from the use of freeze dried bone, in our opinion, justify the wider application of this method

We are indebted to the Board of Governors of the United Leeds Hospitals for a grant towards apparatus, expenses, and maintenance of the bank One of us (K Z) has been in receipt of a grant in aid of expenses by the Medical Research Council We are indebted to Mr A B Pain and Mr J M P Clark for their support and encouragement in this venture and for allowing us to record the clinical results All the patients in this series were under their care

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OXFORD PLANS

AFTER nearly five years of close study a subcommittee of the board of governors of the United Oxford Hospitals has worked out a plan which is described as "not a directive to expand but a demonstration of the boundaries within which it would be advisable to confine future expansion "[1]

The group of eight hospitals combined under the National Health Service Act to form the United Oxford Hospitals now has some 1260 beds These hospitals provide $1^1/_2$ million people with general medical and surgical services, while in some specialties such as plastic surgery and neurosurgery the population served may be as big as 5 million

The oldest of these hospitals is the Radcliffe Infirmary, which was opened with two wards in 1770 as an integral part of the faculty of medicine in the university The munificent endowment of more than £2 million from Lord Nuffield in 1937 established the Nuffield chairs and departments of medicine, surgery, obstetrics and gynæcology, and anæsthetics, and later at the Wingfield-Morris Hospital a chair of orthopædics The Nuffield Provincial Hospitals Trust established later the professorship and department of plastic surgery These new units primarily for research and postgraduate teaching had to be integrated with the existing organisation of a county hospital Then the clinical school was given great impetus in 1939 by the war time need of students completing their medical course out of London This complexity made imperative an examination of the medical work and teaching, research, and nursing services and of the board s relations with the regional board and other bodies

The main development is envisaged at the Radcliffe Infirmary, which is to be enlarged from 498 to 733 beds Each specialty in the divisions of medicine, surgery, obstetrics and gynæcology, and laboratories is discussed in turn, and the dental requirements are considered separately The Nuffield departments are to be integrated geographically and their consultants will be members of the hospital "firms", and it is proposed that one consultant in each specialty should be part-time to promote closer professional contact with the general practitioners The laboratories are now scattered and poorly housed, these need new buildings, and some units such as the Nuffield department of anæsthetics will have their own The outpatient department, at present sadly inadequate, will need a new block

The Churchill Hospital will be increased from 283 beds to some 440, and the neurological, respiratory and dermatological units will be here The Slade Hospital may be used for convalescents The Cowley Road Hospital will continue to accommodate the elderly sick, both acute and long term Large capital expenditure is turning this hospital, once a workhouse with a visiting doctor, into a modern geriatric unit, including a rest home and a day hospital The Eye Hospital, modernised between 1948 and 1950, needs only minor modifications

As regards medical teaching the subcommittee remarks that perhaps if the preclinical students were better informed about the fundamental research work carried out in the clinical departments, more of the abler students might take their clinical course in Oxford The preclinical departments are closer in both situation and organisation to the other scientific university departments than to the clinical school

It is not easy to balance the essential work to be done by the nurses and their own welfare and educational needs, and the subcommittee suggests that a director of nurse training should coordinate the theoretical and practical sides of their training

This stimulating report ends with a firm statement that the basic aim of its recommendations has been to ensure a steadily rising standard of hospital care, and that "there must never in a teaching hospital be any conflict between the claims of research and teaching, on the one hand, and the care of the patient, on the other"

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[1] Future Development of the United Oxford Hospitals Report by the Chairman s subcommittee of the board of governors

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NATIONAL HEALTH SERVICE ESTIMATES

THE estimated total net cost of the National Health Service in England, Wales, and Scotland in 1957–58[1] is £550,136,745—an increase of £21,236,715 on the cost in the present year Of the estimated gross total of £630,196,495 in the coming year, the hospital services take up £404,442,415—an increase of £17,744,900 This increase is mainly accounted for by increases of £11,011,000 in the allotment to revenue accounts (total £371,537,000) and of £5,622,000 to capital accounts (£20,524,000)

The cost of the general medical, dental, pharmaceutical, and supplementary ophthalmic services in 1957–58 is estimated at £177,641,830—an increase of £3,208,175 This increase is due mainly to increases of £2,831,500 in the cost of general dental services (total £38,526,500) and of £1,415,000 in the cost of general medical services (£67,214,000)

Public Health

Accidental Deaths

PROVISIONAL figures of deaths from accidents are to be published monthly in the *Registrar-General's Weekly Return* Detailed figures of accidental deaths during each quarter will continue to be published regularly in the *Registrar-General's Quarterly Return* The first of these monthly reports appears in the weekly return for March 30, which gives the following figures for January, 1957

The total number of accidental deaths was 1377 Of the 730 deaths from home accidents, 481 were due to falls There were 413 deaths from road accidents, 219 of which were of pedestrians Deaths due to other transport accidents numbered 51 Deaths from all other accidents numbered 183

Of the 1377 deaths, 97 were of children under fifteen years of age and 766 were of persons aged sixty five or over

Eire in 1956

In Eire last year[2] the birth-rate was 21 0 per 1000 population, and the death-rate was 11 7 per 1000, the death rate from all forms of tuberculosis was 0 24 per 1000 The maternal-mortality rate was 0 82 per 1000 births registered The infant-mortality rate was 36 and the neonatal-mortality rate 23, per 1000 births registered

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[1] Civil Estimates for the year ending March 31 1958 Class V Health, Housing and Local Government H M Stationery Office Pp 155 7s

[2] Quarterly report on Births Deaths and Marriages December quarter 1956 and yearly summary 1956 Government Publications Sale Office G P O Arcade Dublin Pp 30 6d

In England Now

A Running Commentary by Peripatetic Correspondents

ALL honour to your Dip Ski correspondent returning prize-laden to these shores from the Alpine snowfields, his malleoli intact, all cares blown away from his 50-odd years. Alas, I have a different story to tell. My roaring 40s seem to be giving way prematurely to the frailer 50s. My muscular tone is not what it was for retention of an upright posture, or for much else.

As this is the season for travellers' tales, I will simply say that I have just come back from a mountain-rescue course high in the Norwegian snows. It was a fine mixture of first-aid and survival techniques. Praying fervently against a personal need for first-aid, I concentrated wholeheartedly on survival. Although no slalom certificates adorn my desk, I have a pretty little silver snowflake badge in my lapel. It seems I went in deeper and oftener than anyone else.

One of our exercises was to build an igloo and prove our worth by spending the night in it. There were six men and a girl in my group; so out we went on to the mountain, and spent the afternoon cutting snow-blocks with a saw. By 6 P.M. the igloo was made and we all crawled inside. Although the aperture was none too generous for my statistics, a friendly Scandinavian shove on the buttocks finished the job. We crouched together by candlelight over our tins of soup while the thermometer remained immovable at −12°C. The Norwegians bobbed in and out to pay social and other calls around the neighbouring igloos. I could not be bothered to thaw out my frozen boots, so I perched crosslegged on my little nest of fir branches and bowed international good will to passers-by. About 9 P.M. the last of my companions came to roost and sealed up the doorway with a huge snow-block. They dressed or undressed for bed as fancy pleased, wriggled into their sleeping-bags, and with a final round of wisecracks snored happily off into oblivion.

It was my fate to try out a paper casualty-sack instead of a proper sleeping-bag. As sleep appeared unlikely I resigned myself to a twitching vigil. At 1 A.M. signals started thawing their way from the hypogastrium through my semi-frozen spinal cord. At 2 A.M. the afferent warning-system was red hot. The cerebral cortex wondered what to do. A rather brash association-area cell suggested airing my proudly learnt phrase-book question *Hvor er et Toalett?* But the answer was too obvious. Gents' or Ladies, there were none. I crawled out of my paper torture-bag and squeezed into my frozen boots. Six Norwegians stirred uneasily in their dreams. I lit a candle and crept on all fours over their bodies to the door. A pretty question then arose: should I leave the candle inside the igloo to find my way back, or should I take it in case I froze up? My previous efforts with a blowlamp on British plumbing had been so disastrous that the candle seemed best as a homing beacon. I tugged at the snow-block door in vain; we were frozen into our ice-chamber. My elbow knocked over the breakfast billycan. Greta alone turned over and groaned. The thought of having to enlist the fair help of the only Norwegian with any reflexes left sent a panic surge of adrenaline to heave away the snow-block and dive towards the night.

I started the second stage as an R O A with extended legs, a malpresentation which jammed at the igloo brim. Involuntary fœtal cries awoke the rest of the litter. They stared with sleepy incredulous eyes at to what from their angle was a mad English breech. My polyglot repetition of "Toilett! Toilet!" produced only shrieks of bawdy merriment.

A further interchange of simple guide-book phrases resolved their doubt as to whether I was coming or going. I rather feared that they might try to hook out a leg, but after much bearing down from the fundus, a cry of *En, To, Tre!* produced a strong contraction, and I was delivered into the same old cold hard world. That mountain snowfield looked very beautiful under the full moon. Sixty seconds later I had the strange experience—like running back a bizarre midder teaching film—of returning as a high forceps retrograde R O P, given a slick internal version, and commanded to close the so-and-so cervix until reveille sounded full term.

* * *

We had always thought that curfews were only to be found in textbooks of medieval history, but they are quite the fashion again these days. We had one in our part of the Orient when we had our bit of rioting last autumn, and one or two people found it highly embarrassing.

For example, there was the inpatient in one of the local hospitals who leaned so far out of the window to see how the riots were getting on that he fell out into the street. He hammered at the doors in an endeavour to get in again, but received no sympathy from the doorkeeper, who stoutly maintained that his orders were to admit riot casualties only—and the patient obviously didn't come into that category. The police who found him in the street outside the hospital, however, took an entirely different view. They considered his story that he had fallen out of a hospital window improbable. Unfortunately he had a bandage round his head owing to a bit of surgical treatment: to the police this was clear evidence that he had been taking part in the riots—and here he was breaking the curfew! So off he went to gaol, and it took him a couple of days to convince the authorities of his innocence.

A more proper respect for the law was shown by a small boy who was on probation. He had to report to the police-station every Thursday. On the Thursday in question the police-station happened to be in the centre of what was almost a pitched battle, but the boy boldly made his way there through shot and shell (or whatever it was that they happened to be using at the time) and presented himself in the proper manner. If his delinquent tendencies can be controlled that lad should go far.

* * *

However much I eat I am still hungry in my stomach and I still lust for food in my mind. I cannot sate appetite either physically or mentally, though normally I am bored by food. Today for lunch, until now always a very light meal, I ate 1 lb of fat ham with a 2½ oz slab of butter on my bread, ½ oz of olive-oil on my lettuce, and some apples. I ceased eating not because I had scoffed 3000 calories but because I felt filled, though still hungry. Now, half an hour later, even the pleasurable feeling of being full has faded away. I should like another lunch. I hanker for food as I go to sleep, I yearn for food as I wake. As I enter the Royal Society of Medicine library I catch myself looking to see if there is any food about though in twenty-five years I have never seen even a sweet there. I shall myself now go out to post this to *The Lancet* purely as an excuse to pass a shop where I can buy four smoked buckling and two large Belgian sausages to add to my light afternoon tea. Prednisone tablets at £6 a hundred may be nothing to the N H S, but the appetite they induce is bankrupting me.

* * *

Jane was a bright young lady of 3½ years who peered through the bars of the cot and never missed anything that went on in the ward. When she had been there for two or three months, and was by far the oldest inhabitant of the ward, the pædiatrician suddenly struck his brow with his palm and declaimed: "Jane must have occupational therapy." The registrar and houseman set to work, and at last persuaded the unwilling occupational therapist to venture into the children's ward—an unprecedented feat.

Next day the houseman called on Jane, and found her with a little tin on her knees. The tin was neatly labelled "Occupational Therapy". "What's this, Jane?" he asked.

"Rubbish," she said.

* * *

Do they really mean it?—In the paper on Papworth's results (*Lancet*, March 9, 1957, p. 521) the following frank marital statistics are given:

Reasons for Leaving Prematurely

409 (47%) ended their training prematurely for the following reasons:

To take other work	120
To a different training course	23
Marriage	15
Other domestic troubles	61

Letters to the Editor

THE HUMAN USE OF ^{22}Na

SIR,—Dr Martin and his associates in your last issue draw attention to the great advantages of the use of ^{22}Na in the study of sodium metabolism There is no doubt that it could be of the greatest assistance in the investigation of many clinical problems They rightly comment on misgivings about the use of this long half-life isotope in man Clearly, the danger depends on the extent to which it may be retained in the body

In the course of an experiment in September, 1955, on one of ourselves, after a dose of 50 microcuries of ^{22}Na, we followed changes in sodium metabolism using both the cumulative balance technique and the whole body counter In addition we attempted to study sodium exchange in the patella by an external counting technique The results suggested that a small portion of the dose was taking part in an extremely slow exchange with a fraction of the sodium in bone

The external counting technique indicated that the effective half life of the ^{22}Na in the body at the end of fifty days was approximately ten days This method was not sensitive enough to give an accurate measurement of the residual activity of the body after a long period Observations have been made, however, in the high-pressure ionisation chamber system of the Department of Medical Physics at Leeds The following figures have been obtained with this instrument by Dr P R J Burch, Medical Research Council fellow

Days after injection of ^{22}Na	*Body content of ^{22}Na*
256	0 055 µc
290	0 052 µc
469	0 031 µc

We are grateful to Dr Burch for allowing us to quote his observations

The results suggest that the body retained over a long period about 0 1% of the injected dose, which has a biological half life of approximately one year

The radiation dose involved in this test is of the order of 0 8 rads to the whole body from the radiosodium undergoing turnover in the extracellular fluid For the very slow phase in bone, the dose is bigger, but if it be assumed that the specific activity of that sodium in the bone involved in the long term exchange approximates to that of the plasma at its highest value, a dose of 14 0 rads appears to be the upper limit in the small volume of bone in which the ^{22}Na is deposited

This radiation dose is in the range which may be hazardous, though the matter is at present controversial Nevertheless, the dangers associated with long-continued irradiation of bone are well recognised

In view of these results it would seem advisable in future to limit the use of this isotope in clinical investigation to special circumstances where information essential for treatment of the patient is not otherwise available

Sheffield

H MILLER
D S MUNRO
G M WILSON

HOSPITAL MEDICAL RECORDS

SIR,—Dr Skelton (March 30) urges the permanent preservation of hospital records and X-ray films and concedes that "the practical problem revolves around the question of space required for their storage"

This 560 bedded general hospital stores the X ray films of five years on 876 cubic feet of steel shelving costing £240 in a permanent brick building (with steam heating) of 2600 cubic feet capacity, estimated to cost £500–600 and representing approximately 7% of the cubic capacity of the X-ray department

These figures give some idea of the magnitude of the problem and the expense involved should be equated to the intangible value of the records preserved While hospitals are urgently requiring more space, the claim of the patients is greater than that of the records

Ashford Hospital,
Middlesex

J A BROCKLEBANK

DISCREPANCIES IN THE ERYTHROCYTE-SEDIMENTATION RATE

SIR,—In their paper of Feb 2, Dr Alexander and Mr Andrews make no reference to previous work on this subject

When Westergren [1–3] adapted the sedimentation test of Fahraeus,[4] he showed by careful experiments that a tube of 200-mm length and 2 5 mm bore was adequate for the sedimentation of blood using 3 8% sodium citrate solution as anticoagulant Wintrobe [5] introduced the hæmatocrit tube for determining the packed cell volume of blood and for this purpose a solid anticoagulant had to be used He first used potassium oxalate but subsequently [6] used the ammonium and potassium oxalate mixture of Heller and Paul [7] to obviate correcting for the shrinking of the erythrocytes caused by the former anticoagulant Wintrobe suggested that the hæmatocrit tube could also be used for determining the erythrocyte sedimentation rate (E S R) and correcting for anæmia, but it is now evident that not sufficient experiments were carried out to ascertain that the tube length and bore were adequate for the sedimentation of blood when the anticoagulant was changed from 3 8% sodium citrate solution to solid oxalate mixture

One of the first to doubt the advisability of using oxalated blood for determining the E S R was Schuster,[8] who showed that sedimentation was irregular when the bore of the tube used was less than 3 5 mm and when a high red cell count was combined with rapid sedimentation Schuster also described a lag in the sedimentation of oxalated blood Others [9–12] subsequently reported anomalous E S R readings using the Wintrobe method and were of the opinion that the original Westergren method gave a better indication of the clinical state of a patient

Goldberg and Conway [12] showed that the factor concerned in the irregular sedimentation was that of dilution, for when oxalated blood as used in the Wintrobe method was diluted with isotonic saline, E S R readings were similar to those using the Westergren method I observed similar irregularities with both heparinised and oxalated blood in Westergren tubes, and showed that this was due to a prolongation of the aggregation phase of sedimentation As this phase was observed to end suddenly with the formation of large rouleaux aggregates and followed by rapid sedimentation, I considered that it was due to a metastable state and suggested that the condition might be a hysteresis phenomenon [13] Alexander [14] showed that a delay in sedimentation may be caused when the tube wall above the meniscus of the blood is not previously wetted—the "reflux factor" Subsequently, Lewi and Clarke [15] showed that this phenomenon occurred when the packed cell volume and the "rouleaux formation intensity" of the blood are both high

On the Continent, irregularities in the sedimentation of undiluted blood have been studied by Östner,[16] Horányi,[17] and Mårtensson and Hansen [18] The last mentioned have termed these irregularities the "reversed E S R" because the sedimentation of undiluted blood is often less than when diluted with isotonic saline They have also shown that the bore and length of the Wintrobe tube is inadequate for the sedimentation of undiluted blood and that for unimpeded sedimentation the tube bore has to be at least 5 mm and the length greater than 200 mm

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2 Westergren, A *Ergebn inn Med Kinderheilk* 1924 26 577
3 Westergren A *Nord med Tidskr* 1937 13, 913
4 Fåhraeus R *Acta med scand* 1921 55 1
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6 Wintrobe M M, Landsberg J W *Ibid* 1935 189 102
7 Heller V G Paul H *J Lab clin Med* 1934 19, 777
8 Schuster N H *Lancet* 1939, i 873
9 Sinton J R *Brit med J* 1948 i 391
10 Gilmour D Sykes A J *Ibid* 1951 ii 1496
11 Goldberg, S, Glynn L E, Bywaters E G L *Ibid* 1952 i 2[illegible]
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13 Duxbury McD *Acta med scand* 1954 150 263
14 Alexander W D *Brit med J* 1953 i 433
15 Lewi S Clarke K T *Ibid*, 1954 ii 36[illegible]
16 Östner K *Acta med scand* 1942 127 suppl p 7
17 Horányi M *Klin Wschr* 1943 22 3[illegible]9
18 Mårtensson F H Hansen H A *Acta med scand* 1953 146 161

For the past two years we have been determining the E S R by both the Westergren (3 8% sodium citrate solution) and Wintrobe (heparin) methods We have found many discrepancies between the two readings—invariably there is a delay in sedimentation in the Wintrobe tube As also observed by Dr Alexander, we find that these discrepancies are not confined to any specific disease They occur when the "rouleaux formation intensity" and the packed-cell volume are high The conditions that frequently have a potentially high E S R, and in which we have found discrepancies, are rheumatic fever, rheumatoid arthritis, tuberculosis, and multiple myeloma On several occasions a case of myeloma has first been suspected when there has been a gross discrepancy between the two methods We consider that the Westergren method gives a better and more reliable indication of the clinical state of the patient We use the Wintrobe method as well, partly for interest and partly so that a correction for anæmia can be obtained

Pathology Department,
Chase Farm Hospital,
Enfield Middlesex
McD DUXBURY

REFLECTIONS ON CIRCULATORY CONTROL

SIR,—I should like to express my firm endorsement of Dr Brown's remarks (March 23) on the use of hypotensive anæsthesia in neurosurgical practice

From 1949 to 1952 in the Bristol Neurosurgical Unit, hypotensive anæsthesia by arteriotomy, or occasionally by ganglion-blocking drugs, was used in selected cases of (1) cirsoid aneurysms and aneurysms of the main cerebrovascular tree, and (2) vascular tumours, or tumours in which considerable intracranial tension was already present, and in which the diminished hæmorrhage and brain shrinkage achievable might be an advantage

From the beginning of 1953 till now normotensive anæsthesia, but with the addition of controlled respiration by mechanical means, and latterly the routine use of premedication with hypertonic sucrose solution whenever there was papillœdema, has been used in almost all our craniotomies Postoperative recovery has been more rapid, and cerebral œdema either during or after operation has virtually disappeared The operating conditions obtained by simple light anæsthesia, elevation of the head end of the table, and controlled respiration have been as good as—and often much better than—those obtained with safe degrees of arterial hypotension, the period of reactionary oozing which tends to follow restoration of normal blood-pressure, and which must surely be a reaction to relative ischæmia, is not seen, and wounds do not now need to be reopened for the removal of postoperative clot

The brain in a vascular sense resembles an incarcerated hernia Strangulation, caused by failure of adequate venous drainage due to compression of veins, leads to a neurosurgical emergency Owing to the use of scalp and diploic channels as emergency drainage in many cases of cerebral tumour, venous impairment is made worse by craniotomy until decompression is achieved

Manually assisted respiration alone aids in avoiding congestion If mechanical respiration with negative phase apparatus is used, intracranial tension can be reduced below preoperative level, and often without recourse to lumbar or ventricular drainage, The arterial vascularity of the brain appears unimpaired, and blood-pressure is maintained Hypertensive patients with evidence of arteriosclerosis can be anæsthetised thus, be allowed to remain hypertensive, and bleed no more than normotensive patients

The fatal lesion is compressive ischæmia In the presence of this threat, it does not seem wise to reduce arterial blood pressure until decompression has been achieved (when it is no longer necessary anyway) if comparable results can be obtained by any other means In cases where there is no intracranial lesion, the use of hypotension in anæsthesia for particular types of surgery may well be justified, though personal experience has shown that what is applicable to neurosurgery is also applicable to other cases in which a relatively bloodless field is required

Frenchay Hospital,
Bristol
P L F MORTIMER

INSULIN TREATMENT OF SCHIZOPHRENIA

SIR,—I, too, would like to congratulate Dr Ackner and his colleagues on one of the first truly scientific attempts to assess the value of deep insulin therapy in schizophrenic patients (March 23)

There is, however, one reason for reserving judgment on this controversial subject, and that is the short follow-up period, which, it seems, never exceeded 2 years, and in some cases was only 6 months

If this and similar investigations show that deep insulin treatment has no specific effect in schizophrenia, and it is discarded wholesale by mental-hospital staffs, I hope that one aspect of this particular study will be borne in mind—that each patient received active therapy and enthusiastic attention The danger seems to be that deep insulin therapy will be discarded and nothing put in its place, except perhaps a half-hearted trial of some of the new drugs, such as chlorpromazine, which may or may not be successful

London, S W 16
R D WATSON

SIR,—In the interesting report by Dr Ackner and his colleagues of a controlled trial of insulin in schizophrenia, the analysis does not permit any unique conclusion It shows both that the results could have been due to chance and that the failure-rate, in terms of not being discharged, was, most likely, almost halved in the insulin group

Consider the nature of the data, and, for simplicity, consider only the failures, and suppose the control sample, with 10 failures out of 25 to be typical, so that one need only consider the sub-set of possible trials of the form

	Control group	*Insulin group*
Discharged	15	$25 - a$
Not discharged	10	a

where a is the number of failures in the insulin group

Now the proportion of failures in the insulin group is $a/25$ and the failure-rate, compared to that in the control group, is $a/10$ Yet even if insulin did halve the failure rate ($a = 5$) the result would not be "significant" Significance would only be demonstrable if a were equal to 3 or less, in which case the failure-rate would be reduced to the spectacular figure of 12% or less, and few exponents of insulin therapy would regard such a claim as reasonable Indeed, were insulin that good, it is unlikely that there would be sufficient expert disagreement for a trial to be considered appropriate Even if insulin were to halve the failure rate a trial of twice the size would be about as likely as not to fail to detect a "significant" therapeutic advantage

Conclusions from such analyses of such data on trials of practicable size under conditions which justify a trial (e g, expert disagreement) will almost always be either that there is no difference, or that there is a difference, but that it could easily have been due to chance (i e, it is not "statistically significant")

It is not altogether unfair to term this the heads I-win tails you lose technique of therapeutic trials In diseases in which there is so little to measure or enumerate, it seems very questionable whether such a trial can reveal therapeutic advantages with the precision of the casually acquired beliefs of experienced observers

Although experience is frequently fallacious, judgment is often impossible

Birmingham, 15
J H EDWARDS

UNMARRIED PARENTHOOD

SIR,—Now that we have completed the circuit of the course, may I revive the matter which initiated the correspondence? Dr Hamilton (March 30) makes the critical point of it: every child has the right to be conceived in love, born in happiness, and nurtured in security. A great deal of human coition takes place, and will quite certainly continue to take place, in circumstances which, within marriage or outside it, do not fulfil these conditions. It is possible to ensure that in a proportion of these cases, at least, coition will not be followed by conception. It seems to me that if we are really concerned with the rights of the child, we should attempt to ensure that this is so. If we are not concerned very much about the rights of the child, but very greatly concerned to preserve a particular doctrine of conduct, we shall wish to limit the availability of contraceptive knowledge so that we can continue to appeal to the rights of the child when appeals to the beauty of holiness wear thin. It seems to me that while we may well hold our own conclusions upon the doctrine of conduct, we ought not to let our zeal for it increase the number of unwanted children among those who find our doctrine unconvincing; by withholding contraceptive knowledge in the interests of sacramental marriage, we shall certainly not stop human beings from coition in a very wide range of contexts. By providing it, we might even make more of these contexts sacramental, instead of psychologically and morally negative.

Loughton Essex **ALEX COMFORT**

RUPTURE OF THE PREGNANT UTERUS

SIR,—I was most interested in the 3 cases of ruptured uterus reported by Mr Higgins (March 23). His opinion that a change may be appearing in the commoner causes predisposing to uterine rupture is one which I have held myself for some time.

The tragic ætiology of the accident in the past has often been the neglected transverse lie, the unrecognised hydrocephalic, or the unsuspected pelvic contraction in the multipara—abnormalities which are more frequently recognised now and appropriately dealt with before there is any danger. There has always been, however, a group of patients—previously a small group but now relatively much larger—in which no major fault had been present to explain why the uterus ruptured. In this group a weakness of the uterine muscle may have arisen from a cervical tear, or following difficult manual removal of an adherent placenta, or, as Mr Higgins suggests, following traumatic curettage. Such a weakened area might give way during a labour only slightly more difficult than usual, perhaps due to no more than a large child or a degree of extension of the head, two abnormalities which were illustrated by Mr Higgins's first case.

As a further illustration of the changing ætiology of uterine rupture, I would like to quote some figures previously reported.[1] Between 1951 and 1955, in Sheffield, 8 cases of uterine rupture were seen in the Jessop Hospital for Women and the City General Hospital. In only 1 was the rupture due to a neglected transverse lie; in 1 it was due to an attempt to deliver the impacted shoulders of a baby weighing $11\frac{1}{2}$ lb; in 1, to a previous Fothergill colporrhaphy; in 1 to a pregnancy in a rudimentary uterine horn; in 1 to previous fundal perforation during curettage; and in 3 the rupture was unexplained in multiparous patients.

I think that the importance of the changing ætiology lies in the need for us to think of the possible diagnosis of rupture of the uterus under different circumstances than in the past. When signs of shock appear in a patient with obstructed labour due to transverse lie or gross disproportion, the diagnosis of rupture of the uterus can usually be made without difficulty. When, however, collapse occurs without any apparent reason in a seemingly normal labour—or even in pregnancy, as in 2 of Mr Higgins's cases—the suspicion of uterine rupture may not so easily arise in our minds; the absence of the common ætiological agents of the past may delay the correct diagnosis in favour of, say, accidental hæmorrhage or adrenal hæmorrhage, with the result that operation may not be performed in time.

I think Mr Higgins's paper has given us valuable additional information on the present-day ætiology of this serious accident.

Department of Obstetrics and Gynæcology
Jessop Hospital for Women
Sheffield **C J DEWHURST**

OBSTETRIC FLYING-SQUADS

SIR,—Mr Telfer Gray (March 30) should realise that seven years in one mission hospital provides only a parochial picture of a vast problem. I did not visit the Bolobo area, and have no information of the Bayanza or the Wadia whom, I suspect, he served. My safari was to visit personally the authorities upon the subject of my research and the tribal villages of the people over a wide area of the Belgian Congo and Central and East Africa. We do not form our own opinions from a six months' investigation, but we acquire and profit by the expert knowledge of local witnesses.

My statement, that postpartum hæmorrhage is almost entirely absent in uncomplicated labour among unurbanised tribal Africans (March 23), is amply justified by the evidence that I have upon this subject and the status of those who generously gave their time to help me in this investigation. If Mr Gray could study these original documents he would appreciate the limitation of his experience and withdraw his uncalled-for imputation that I imagine Africa to be an obstetric Utopia.

Chichester **GRANTLY DICK-READ**

AN ADJUSTABLE SPLINT FOR FRACTURES INTO THE KNEE-JOINT

SIR,—I was interested to see a modification of my splint by Mr Tupman (March 23). Several similar alterations have already been suggested by other users of this method. When this form of traction and splintage was originally devised and published, it was my deliberate intention to keep the apparatus as simple as possible so that it might be readily assembled from existing materials. I have, moreover, continued to use this method unmodified to my satisfaction since that time, although I agree that there are certain slight disadvantages in the maintenance, to which Mr Tupman refers. Like him, I have found the method particularly valuable in the treatment of injuries in the neighbourhood of the knee-joint, and indeed I know of no other method by which bony union can be quickly obtained with good alignment while preserving an excellent range of knee movement.

I am hoping shortly to publish my own modification of the splint which resembles in some ways Mr Tupman's but over which it has certain advantages—namely, retention of the simple "rigging" and incorporation of a hinge at the knee which adjusts itself to the alteration in the axis of the knee during movement. I still prefer to use skeletal traction through a Steinmann pin in the upper end of the tibia, but I agree that strapping traction is a perfectly satisfactory alternative.

I firmly believe, however, that modifications of the splint are of themselves of little importance compared to the underlying principle involved in its use—namely, early return of synergic muscle action, which promotes rapid bony union and retains a supple and powerful lower limb.

London, W 1 **GEOFFREY R FISK**

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[1] Dewhurst C J J Obst Gynæc Brit Emp 1956 63 12

EPIDEMIC VERTIGO

SIR,—Your excellent annotation (March 16) has prompted me to review my own thirteen cases seen over the past 5 years in the southern part of the New Forest, in an area extending from Christchurch to Southampton

There has been at least one case every year, including two so far this year Five were in men and eight in women Three were aged 30–39, one, 40–49, six, 50–59, and three, 60–74 Coryza preceded the illness in four cases, and the onset was fairly evenly distributed throughout the year

Five patients had headache, eight nystagmus (obtained sometimes only in certain positions of the head), one fever, five tinnitus, and one diplopia The blood (leucocyte and differential counts) and the cerebrospinal fluid were normal in the four cases in which these examinations were made An electro-encephalogram in one case showed "minimal non-specific dysrhythmia—insufficient to give opinion"

Promethazine 8 chlorotheophyllinate ('Avomine'), given first at the suggestion of Dr E W Deane, of Christchurch, has been successful in the treatment of three cases and in some further cases treated by Dr Deane

All the patients were widely distributed and none had any known association with another But one reported that her daughter and son-in-law, all living in the same house, had suffered from similar symptoms of shorter duration in the preceding week, and one (a Customs officer) reported similar symptoms in three fellow officers with whom he worked

In five cases there was a relapse after some days of freedom from vertigo

Lymington Hospital,
Hants

R J McGILL

SECRET REMEDIES

SIR,—In his erudite and derisive lecture, to the Royal Society of Arts on Quacks Through the Ages (mentioned on p 223 of your issue of Jan 26), Mr Dickson Wright defined a quack as "one who sells a secret remedy" Some such remain among us, who blend a variety of pigments with their pills, dispensed as triplets, anonymous and unobtainable by prescription to patients or family doctor On a different plane, there is still, even in conventional practice, a tendency to cover the label on prescribed proprietary preparations, which practice might well be relegated to a past era of mystery and mysticism in medicine I recognise that this would make it more difficult to satisfy the patient who travelled several thousand miles to this country to receive the same treatment as had been successful with his friend and which, he thought, was called "placebo"

London, W 1

S LEONARD SIMPSON

A MISSED FRACTURE

SIR,—I cannot agree with Dr. Stone (Feb 2) that a coroner has "no power to criticise anyone" Coroners have always reserved to themselves the right to criticise those whose negligence or lack of foresight has contributed, however slightly, to the death under investigation Nor do I endorse his final opinion that the public has no right to expect "completeness"—perhaps "thoroughness" would have been a happier word—in the examination and treatment of patients referred by their own doctors to the casualty department of a general hospital

When an elderly person falls sufficiently heavily to break an arm, the possibility of a concomitant fracture of hip or femur should never be overlooked I think the coroner was perfectly justified in directing his criticism towards the casualty officer concerned The family doctor's duty ended when he recognised the need of hospital treatment for his patient, and the casualty officer's duty surely includes the elimination of likely complications—which do not embrace "a host of other possibilities" such as diabetes mellitus or carcinoma of the sigmoid colon Had the old lady, in fact, died from any such condition the coroner would not have seen fit to offer any criticism at all Dr Stone's indignation is, I feel, misdirected, and his closing remark something of a non sequitur

Komani Hospital,
Queenstown, Cape Province
South Africa

R DINGWALL KENNEDY

CARDIAC ARREST

SIR,—The recent report by Bencini and Parola of the efficacy of pneumomassage in maintaining the circulation despite cardiac arrest[1] recalls some speculations that several of us indulged in some years ago

Deterred by technical considerations from attempting massage by intermittent pressure within the pericardial sac, we considered the effect on the circulation of intermittent pressures within the thoracic cavity We know that forced respiratory movements against the resistance of a closed glottis, or of a mercury manometer, can raise the intrathoracic pressure to nearly 100 mm Hg Of course intra abdominal pressure is also raised to the same degree, and this pressure tends to propel blood away from the heart, towards the head and extremities, in the great veins as well as the arteries Such pressure might be expected to empty the entire left heart Possibly such intermittent forced expiratory movements against resistance could maintain some cerebral circulation, in a manner analogous to electrophrenic respiration

The experiment we envisaged consisted in supporting the chest and abdomen of the animal whose heart was stopped, with either a close fitting (possibly pressurised) cuirass or tight bindings, while applying intermittent pressures of about 150 mm. Hg to a tight fitting endotracheal tube at a rate of about 120 per minute, and recording arterial and venous pressures in the neck or thigh

So far as we know this has not yet been tried

Livernois Clinic
Detroit 10 Michigan, U S A

SAM I LERMAN

PENICILLIN IN THE TREATMENT OF LACTATIONAL BREAST ABSCESS

SIR,—Dr De Jode's article (March 16) confuses an already difficult situation I refer to the respective values of penicillin therapy for severe staphylococcal infection, in hospital and in domiciliary practice

Many workers are aware of the limitations of such therapy within the hospital environment, but observant general practitioners remain pleasurably surprised at the continued success of this drug in their practice More recently, articles dealing with the subject of staphylococcal ecology show that the success or failure of the treatment is largely dependent upon the source of infection, and many general practitioners are well aware of this

Surprisingly, Dr De Jode does not comment on his finding that 71% of breast abscesses occurring in mothers confined at home were due to penicillin-insensitive staphylococci Epidemiological studies show that the frequency of penicillin resistant staphylococcal infection runs pari passu with the extent of the nasal carriage of resistant strains of the causal organism In this part of the world 10–25% of the general population carry in their noses penicillin resistant staphylococci, whereas large hospital communities show a frequency which varies between 50 and 70% It is therefore reasonable to assume that Dr De Jode's group of "home confinements" is not representative of the general population, or that the bacteriology of these cases requires further elucidation It would be useful to know, for instance, by which method the in-vitro sensitivities were determined.

Dr De Jode suggests that it is reasonable to restrict the use of penicillin to those cases of breast abscess following home confinements—with 71% penicillin resistance—where "there is therefore a reasonable chance of dealing with an organism sensitive to penicillin," thus illustrating the uncertainty of conclusions drawn from records of this kind Perhaps it would have been more useful to emphasise the fact that, in this series of cases, the average duration of penicillin therapy was only $3^1/_2$ days

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[1] Bencini A Parola, P L *Surgery*, 1956, 39, 375, see *Lancet*, 1956 ii, 1201

Department of Bacteriology,
University of Aberdeen

H G SMYLIE

VITAMIN B_{12} IN PSORIASIS

SIR,—Several reports have been published recently on the efficacy of vitamin B_{12} in certain skin diseases and particularly in psoriasis Muscardin[1] has treated 31 patients with psoriasis and reports that a dose of 1000 µg daily for ten to twelve days produced an "excellent" result in 7 patients, and "good" results in 12, and on the whole those patients who had itching were helped most

We have used vitamin B_{12} in these doses for ten days on 12 patients suffering from psoriasis The first patient treated, in an acute and exfoliative stage, did improve rapidly Five months later, however, the same patient had an exactly similar episode, and the vitamin B_{12} seemed to have no appreciable effect, though given in the same dose for the same length of time

The other 11 patients treated were "paired" with patients suffering from the same type of psoriasis, one group was given vitamin B_{12} and tar ointment, the other group tar ointment only No appreciable difference was noted, either in speed of recovery or in well being, in the two groups

My thanks are due to Dr Alice Carleton who permitted me to treat the patients

Oxford.

SUZANNE ALEXANDER

CYTOLOGICAL DETECTION OF UTERINE CANCER

SIR,—I am sorry to see you have once more launched into the common confusion and arguments about the "true value" of cytological detection of uterine cancer The last time you did this[2] both Dr Osborn and myself were moved to protest Last April[3] I was content to see you on the right lines at last when you opened another leader with the sentence "Incredulity has delayed the development of exfoliative cytology in this country" Your leader of March 23 still bristles with misunderstandings, some of which I hope you will allow me to help to clear up

The main reason, you say, for views differing on the value of the method is that many reports do not make it clear how often cytology has really helped to make a diagnosis I agree that too many reports are presented with a final "percentage accuracy," which has already been exploded by Howard Taylor, jun, of New York, as meaningless, but our Edinburgh reports have been based *solely* on how often cytology has helped, and our last published total was of 9910 cases of gynaecological outpatients, screened by gynaecologists, with 98 cases discovered which would otherwise have been missed[4] Our series from a contraceptive clinic and from general practitioners is excluded Only two-thirds of these were cancers in situ, and the remaining third were invasive growths No cases of clinically obvious cancers were included in these numbers as cytology cannot accelerate their diagnosis

When we have been in doubt as to whether we have "surprised" the gynaecologist with a positive report, we have asked him and during our earlier years we had access to his letters to the practitioners who referred cases in the first place and this told us whether he suspected the cervix or not, where it was not otherwise clear When, as has occurred, two senior gynaecologists disagreed about the naked eye appearance of the cervix, the case has not been counted When, as has occurred, a senior gynaecologist has described a cervix as "looking benign, but should have biopsy," who should say whether he has been suspicious or not? This question of "clinical suspicion" seems to be the crux of the difference between the Birmingham and Edinburgh figures You state "it was not certain that [the Edinburgh] patients had always been subjected to as searching a clinical inquiry as those of McLaren et al" I can relieve this uncertainty by stating quite confidently that *none* of our patients was subjected to as searching a clinical inquiry and questionnaire

We have in fact been treated to descriptions of cervices on many occasions which show that the clinician is trying to have it both ways, and we realised before our first report, in 1951,[5] that correlation of our results with clinical suspicion was too dependent on subjective impressions for useful assessment—even when dealing with the most experienced gynaecologists, as the degree of suspicion is too easily influenced by the history

Dr Bamforth,[6] at the meeting (quoted in your leader) at the Royal Society of Medicine in November, 1955, stated that by "unsuspected" is meant "no biopsy would have been taken except for the positive report on the vaginal smear" This is excellent, though it is better still to include the gynaecologist's opinion of the cervix The appearance of the cervix on speculum examination must come into the question of clinical suspicion McLaren,[7] at the same meeting, was anxious for a definition of the "surprise" discovery of an unsuspected case, mentioning the symptom of post coital bleeding as being very important The implication is that the cervix looks different if the beholder knows the patient has had post coital bleeding In the *management* of a case he is right, for an erosion of the cervix associated with leucorrhœa in a girl of 25, is cauterised without further ado by most gynaecologists, whereas the same appearance in a woman of 55 with post coital bleeding, naturally gives rise to clinical suspicion We believe that "clinical suspicion" is too subjective to be the sole criterion of assessing the method, whose "true value," if there be such a thing, may be entirely personal to one or other group of gynaecologists It would be interesting to know, in McLaren's series, how often clinical suspicion proved groundless, yet led to hospital admission, anæsthetics, biopsies, and curettage

In parenthesis, although Dr Bamforth has a definition for the unsuspected cervical cancer, he later refers to Wachtel's 7 "unsuspected" cases of carcinoma of the uterus, without any definition What is an unsuspected case of body carcinoma? Surely only the pre menopausal cases? Are we not properly trained to suspect every case of post menopausal bleeding with a healthy cervix as a possible body carcinoma in need of urgent diagnostic curettage?

Your last paragraph makes a practising gynaecologist and cytologist feel very old It is acknowledged, and always has been, that the method must never become a substitute for clinical investigation I would assert that no cytologist or pathologist has ever claimed that it could, or should, but clinicians would often like to take short cuts, and this advice should be directed to them In cases of clinical suspicion, with negative cytology, our reports repeatedly warn the clinician to ignore the cytology report, and investigate along traditional lines

In spite of McLaren's expression of perplexity and your own query as to the "true value" of the method, he gave the only answer himself when he called it "a laboratory test of considerable importance" We will progress further if we leave it at that and get on with it There is no doubt whatever that the method has come to stay in spite of all the self torturing of those with the time for elaborate questionnaires The method is not, and in this country never has been, "research," for it was well established in America before it was started in Britain, but it can be used for investigation of the natural history of cancer, once it has been learnt, which is a different matter

Edinburgh

A F ANDERSON

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[1] Muscardin L *Cron Idi* 1956 5-6, 115
[2] *Lancet* 1953 i 779
[3] *Ibid* 1956 i, 489
[4] Anderson A F *J Obstet Gynaec, Brit Emp* 1956 63 139
[5] Anderson A F Grant M P S McBryden R M *Proc R Soc Med* 1951, 44, 308
[6] Bamforth J *Ibid* 1956 49 215
[7] McLaren H *Ibid* p 251

INFUSION NEEDLES

SIR,—As a house surgeon whose patients specialise in small veins and whose "drips" occasionally exhibit a poor sense of occasion, in not knowing when not to stop, I would prefer a smaller needle for use with the giving set

Even a makeshift syringe needle, when used for the same purpose, seems less likely to cause thrombosis, and the standard giving set needle is cruelly oversize, except perhaps for giving blood

DAVID FURNISS

St James s Hospital
Leeds 9

PEDICULOSIS CAPITIS

SIR —In their article of Feb 23, Dr Nelson and Mr Cromie refer to reinfestation taking place mainly in the family circle It would be interesting to have details of the treatment given to these cases in the first instance

It is commonly supposed that preparations such as dicophane application *B.P C* need only be left in contact with the hair for 24 hours, in fact the directions given in the *National Formulary* include the sentence "Do not wash the hair during the next 24 hours" This is too short a period and at least 7 days contact should be allowed None of the residual insecticides is effective against nits and it is only by allowing time for the nymphs to hatch and come into contact with the insecticide that a complete kill can be ensured

Our experience in the Army is summed up in the following passage from the *Manual of Army Health*, 1954

> "The most efficient method of treating head lice is to apply a persistent insecticide and leave it there for a week, the hair should not be washed during this period"

W M McCUTCHEON

London S W 1

REACTIONS AFTER TRANSFUSION

SIR,—In a leading article in 1955[1] you noted that 1–2% of all patients transfused with blood were liable to reactions other than those due to mistakes in blood-grouping or cross-matching techniques You added that 1–2% of recipients had urticarial and other allergic reactions, while 2–5% had febrile reactions, and you remarked that different workers had sought in various ways to reduce the frequency of the reactions, either by sedation or by giving an anti-histamine The choice of anti-histamine and the mode of administration are still undecided Since reading your leader, I have always advised that patients to be transfused, other than under a general anæsthetic, be given a sedative and oral anti histamine, the choice of drugs used being governed by the wishes of the clinician concerned The routine technique for all cross matches performed under my direction has included the use of a saline and albumin technique at room temperature, as well as saline, albumin, and indirect anti-globulin techniques at 37°C Moreover, a smear of the blood to be given has always been stained with methylene blue and examined microscopically to exclude any possible infection of the bottle concerned

Over a period during which 2295 pints of blood were administered, 16 patients had rigors, 4 pyrexial reactions of over 100°F and 2 urticaria Checks of the group, the cross match tests and the possibility of infection or hæmolysis in the bottle of blood on return to the laboratory were all invariably negative 2 patients, both treated at the beginning of the period under review, had had two reactions at the commencement of a transfusion, despite the transfusion of fresh blood, sedation, and the administration of an anti histamine It was decided to treat these patients with chlorpheniramine maleate, 10 mg to be introduced into each bottle immediately before use This technique enabled us to transfuse these cases repeatedly (3 times and 4 times respectively) without further incident It was decided thereafter to transfuse all patients who had previously had a transfusion reaction in the same way, having excluded any possibility of blood-group incompatibility It should be emphasised that this use of chlorpheniramine maleate was reserved only for those who had had such transfusion reactions

During the period under consideration, 90 bottles of blood containing chlorpheniramine maleate were administered, and of these 88 were accompanied by a perfectly uneventful course, with no sign of reaction whatever The other 2 produced febrile reactions of 99 8°F and 100 2°F respectively, but neither patient had a rigor The first patient was not again transfused, and the second, after 2 transfusions of washed red cells in saline, which gave no reaction, was later successfully transfused with whole blood, again accompanied by chlorpheniramine maleate

While this small series cannot pretend to be anything more than a limited examination of the problem, it nevertheless suggests that chlorpheniramine maleate can make it possible to transfuse patients who might otherwise prove resistant to such therapy Such results are in accordance with those of Simon and others[2–7]

I am grateful to the clinicians of Westminster Hospital for their most helpful coöperation in collecting this series, as well as to Messrs Allen & Hanburys for the provision of chlorpheniramine maleate in the form of 'Piriton Maleate' 10 mg ampoules

K GOLDSMITH

John Burford Carlill Pathological
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[1] *Lancet*, 1955, ii, 180

[2] Simon S W, Eckman W G *Ann Allergy*, 1954, 12, 182

[3] Frankel D B, Weidner, N *Ibid* 1953 11 204

[4] Offenkrantz F M, Margolin S Jackson, D *J med Soc N J* 1953 50 253

[5] Tuft L *In* Current Therapy Philadelphia 1954, p 564

[6] Wilhelm R E *J Mich med Soc* 1954, 53 651

[7] Winter, C C, Taplin G V *Ann Allergy* 1954, 12, 717

PHENYLBUTAZONE IN SUPERFICIAL PHLEBITIS

SIR,—I should like to draw attention to the remarkable effect of phenylbutazone in cases of superficial thrombophlebitis In a series of 23 cases results have been highly gratifying, and it has been possible to reduce very considerably the length of the illness

The patients treated can be divided into two groups

15 patients had acute superficial phlebitis without ulceration The effect of phenylbutazone in these cases was dramatic Pain relief was quickly obtained, and inflammation subsided rapidly All cases cleared up within five days, and patients were ambulant soon after treatment began

8 patients were subject to periodic mild attacks of superficial thrombophlebitis, leading to shallow but painful ulceration of the leg Such cases previously took four to six weeks to heal, but with phenylbutazone they cleared up within ten days

This series is admittedly not large enough for statistical comparison with similar cases admitted to hospital for conservative treatment, but the results are so striking that I feel they should be made known at once A wider trial seems highly desirable

R O GILLHESPY

Dudley Road Hospital
Birmingham

GOVERNMENT AND PROFESSION

SIR,—In his letter last week, my neighbour, Dr John Fry, deplores the manner in which the profession's claim has been presented I agree that the claim should have been associated with an expressed desire to examine defects in the existing service He does not, however, stress sufficiently the fundamental defect in the scheme from which the present weaknesses spring, nor do the remedies he suggests all appear pertinent to the issue

The defects arise, as far as general practitioners are concerned, from the fact that the majority are attempting, valiantly if inadequately, to stretch old conditions of practice to meet the demands of a new age—an age that is characterised by an increased understanding of the individual in health and disease together with a changed sociological outlook that demands the national application of this knowledge The family doctor's increased area of responsibility is indicated by the widely varying demands for advice made by his patients He daily dispenses pædiatric guidance, support for the adult neurotic, care for the aged, some measure of health instruction, in addition to his constant therapeutic attack on established disease Obstetric management has moved far beyond the immediate demands of a successful confinement The single handed practitioner must rarely succeed in providing this comprehensive service His difficulties are lack of time and often inadequate facilities, together with insufficient auxiliary help

The basic need seems to me, therefore, to be that of stimulating group practice, not merely in the sense of multiple partnerships but in that of a coordinated effort with each of the group accepting special responsibilities With this should go the organisation of suitable premises and the employment of ancillary help

Financial injections should not therefore be aimed at keeping alive outmoded conditions The suggestion that a system of "merit awards" would promote a more desirable practice organisation will not "meet the bill" Sheer lack of cash would prevent the young practitioner, and for that matter most single-handed doctors, however enthusiastic, from qualifying for such an award If incentives to joint practice were coupled with a mode of remuneration that paid adequate regard to the expense factor and thus promoted capital investment, good practice would be furthered Among other benefits might be the disappearance of what is surely an anomaly—the "assistant without a view"

The suggestion that periodic examinations throughout life be stimulated by additional payments is surely of limited value It would promote a niggardly approach to, say, pædiatric and geriatric care Where a practice is known to provide, for example, a satisfactory pædiatric clinic, then much more will be accomplished in the way of supervision during childhood than by periodic examinations Not only would the early detection of disease be forwarded, not only would some degree of health instruction be provided, but the chance created to influence the emotional climate in the home where this is needed Similarly, given adequate practice organisation, proper supervision could be maintained throughout life It is surely the continuity of contact with his patient that is the general practitioner's special asset

Local health authority clinics must inevitably disappear with the extended care undertaken by the improved organisation of practice This would release the various local authority auxiliary services for their better employment by the G P The one feature of the school health service that seems to be valuable and should be retained is the advice given by the examining doctor to the individual school head This should prove, however, no great administrative hazard

If specific efforts are to be stimulated by extra fees then the most pertinent one appears to me to be that already suggested in your editorial columns—namely, the domiciliary care of the acute sick

My theme, therefore, is that, given the right conditions of practice, current weaknesses will tend to disappear Even if there is no general support for this approach, surely we can agree that publicity should be given to the profession's good will towards the N H S and, as an earnest of this good will, to our desire to examine and remedy its defects

Beckenham, Kent. D I FINER

SIR,—How right Mr Patey is to suggest, in his letter of March 23, that it is time that discussions between the doctors and the Government should include matters other than salaries However, I cannot agree that granting to patients who consult their doctor outside the National Health Service the right to N H S prescriptions is a desirable reform Surely the most important matter for the doctors to discuss with the Government is how to reduce the bill for prescriptions on the N H S, which during the past year has increased by £5 million If some way could be found to eliminate prescriptions for medicines which could not conceivably do any good to the patient, enormous sums of money would be saved and the doctors should deservedly get a rise out of the savings

Unnecessary prescribing arises because the patient has grown to expect a prescription, and the doctor feels obliged to fulfil the patient's expectations The remedies are *twofold* First, the general practitioners must be courageous and tell the patients the truth They might be encouraged to do this if their salaries were made more independent of the number of patients on their books Secondly, an attempt must be made to reduce the demands of patients I suggest, as a start, that a meeting be called of the editors of all journals that publish sections on health and beauty The editors' attention should be drawn to the undesirability of encouraging readers to make self-diagnoses and then demand the latest drug from their doctors The Radio Doctors must have done untold good to the anti-medicine cause in their time

London, N 12 PETER N CAMPBELL

SIR,—As one who has always liked general practice and who has always held that the general practitioner could conform to the highest standards of *family* medicine, I find your leaders on the proposed withdrawal, to secure justice for ourselves and for the standards of practice, at once biased and inaccurate *Findings* such as these, if true, are a sorry condemnation of your journal, which should surely uphold the standards of general practice if not the just remuneration of the practitioners responsible for the maintenance of such standards

We are not planning a strike The word denotes a *total cessation* of work, whereas we unanimously intend to care for our patients as before, but under different financial and administrative arrangements

We are not using politics or political force We are opting out of the N H S because our employers consistently refused to recognise the Spens and Danckwerts judgments, just as their predecessors had done

Unlike the striking artisans, we are mainly concerned with securing such additional monies as will pay our vastly increased practice expenses and enable us at the same time to improve our medical service to the community

Your underlying implication that we are lowering our medical traditions and social esteem is bitterly resented inasmuch as its manifest untruth will not prevent some splitting of our professional ranks nor some bolstering up of the present Government In fact, your leader last week is itself a potential political weapon and in no way a help in the maintenance of medical traditions and standards or efficient care of the community

Manchester J G O'SULLIVAN

SIR,—Few can be feeling happy about the outcome of the B M A 's present plan for a doctors' "strike" A better idea would be to pull out the key men at a bottleneck—the teachers of and examiners in anatomy and physiology There are so few of these that the rest of the profession could afford to subsidise them indefinitely

This would take a few years to work but in the end the pressure would be irresistible In the meantime, it would have the advantage of diverting some thousands of young men and women from an overcrowded profession, where they are *not* wanted, to more useful occupations

Clifton Bristol, 8 GEORGE L ALEXANDER

Parliament

Nuclear Hazards

In the course of his report on the Bermuda talks to the House of Commons on April 1, the Prime Minister said that nuclear power was the basis on which Britain's defence plans must at present rest The only question that remained therefore was whether the process should be brought to fruition or whether we were to hesitate at the last stage when the necessary tests had to be made before production was carried out He recognised that the Opposition asked him to abandon the tests from sincere and conscientious motives, but did they accept the logical consequences of abandoning the weapon ? This, he said, would mean permanency of conscription and the need to raise far larger armies

Turning more particularly to the question of limiting the tests he said that late in December Sir Anthony Eden had been working on proposals to limit the tests even outside a general disarmament agreement, but he had to tell the House that a simple agreement, such as the Government then had in mind, as to the permissible yield of fissionable material without any detailed arrangements for control would not work The scientist was always ahead of the politician What might have seemed possible some months ago was now confirmed as not being watertight The proposals were based on the assumption that the total yield of the explosion was a reasonable measure of the fission products discharged into the atmosphere It was now clear that that was not necessarily the case He was assured by our own scientists as well as by the Americans that there was no feasible method of properly measuring at a distance how much of the yield of a particular explosion was due to fission and how much was due to fusion Our scientists believed that a deliberate attempt to run a test explosion in such a way as to avoid detection would almost certainly be successful So far as we knew, no such attempt had been made On the other hand, there had been instances in which our scientists were unable to be certain whether an explosion had taken place or not For these reasons they had agreed at Bermuda that the original approach would not do But it would be an error to say that the Bermuda communiqué once more attached the concept of test-limitation to a comprehensive disarmament agreement It said that it must be accompanied by general nuclear control Such a system would at least have to include watertight measures of policing any test-limitations which might be agreed upon The President and he had agreed to go a step further while waiting for any general agreement They said that they would " conduct nuclear tests only in such manner as will keep world radiation from rising to more than a small fraction of the levels that might be hazardous "

So far as our own tests were concerned he had been asked to say that there would be no perceptible radiation outside the test area He was satisfied from the medical and biological point of view that the radiation effect of this explosion would be insignificant

The closest watch was being kept on possible dangers to human health and we had regular and up-to-date measurements External radiation, which constituted the main genetic hazard, was not in any sense a new kind of hazard, and, only a small proportion of it was attributable to bomb tests Natural sources of radiation, were estimated to give an average dose of $^{1}/_{10}$ roentgen a year, or 3 roentgens during the thirty years of an average reproductive life Modern civilised man had added by his own inventions, to the amount of dosage received in a normal lifetime, and especially in recent years These included X rays, and such things as luminous watches, and the development of atomic energy in industry All these new man-made sources of radiation gave us an additional dosage which, in this country, was reckoned to add at least a quarter to the 3 roentgens we already received from the natural background Unless, therefore, we were prepared to abandon X rays in medical treatment and many other features of our civilisation, we must expect to be exposed to about 3$^{3}/_{4}$ roentgens each every thirty years

It was estimated that, if test explosions go on at the same rate as in the past few years, in the course of a long time the external radiation from fallout would build up to an exposure per generation of not more than $^{1}/_{100}$ part of what man would receive in the same period from natural sources alone To this $^{1}/_{100}$ of the 3 units, which was the most from the explosions up to now, the explosions we proposed to make shortly could add not more than a small fraction of the total explosions already made by Russia and the United States

Apart from the external radiation to which bomb-tests made a very small contribution, there was the internal radiation due to the absorption into the body from food or drink of substances such as strontium 90 which were part of the fallout It was fair to say that the average levels of strontium 90 at present measured in human bone in the United Kingdom were less than 1 unit and that was 100 times less than what, in the view of the Medical Research Council, was the maximum allowable concentration in bodies of individuals of the population

The Government took this matter very seriously They would keep it under continuous review in the light of any new advance, both in this country and elsewhere But he believed that we should add very little to this danger by the test we were about to make and we should gain enormously in strength and in the defence of our country

Other aspects of this problem were raised at Question Time The questions included the following

Dr Barnett Stross asked the Minister of Health by how much the expectation of life was reduced as a result of exposure for ten years to the maximum permissible ionising radiation to which workers in radioactive substances may be exposed —Mr Dennis Vosper replied There is very little evidence regarding the possibility that exposure to radiation may affect the expectation of life in man, and it is therefore impossible to estimate the effect in this respect of any particular dose The present recommended maximum permissible levels have been chosen as providing a substantial margin of safety below the minimum dose known to produce any effect Dr Stross Is it not suspected, however, that 10 or 15 years' work at the maximum permitted dose would reduce the expectation of life by about 18 months ?—Mr Vosper There is a great variety of medical opinion about this I would not wish to accept that estimate as being the correct one It could well be less

Dr Stross asked the Minister whether he was aware that ground bone meal was used as an ingredient in some food for children and invalids , and what research was being conducted on the presence of radioactive strontium in cattle whose bones are so used —Mr Vosper replied I understand that treated bone meal is used in very small quantities in some cereal foods mainly intended for infants No measurements of the level of strontium 90 in cattle bones have been carried out in this country but there is evidence that the levels are comparable to those in milk Dr Stross In view of the fact that strontium is taken up in bone just as calcium is taken up in bone, is it not desirable that ground bone should not be used in any food for invalids and infants unless we know exactly whether it is safe or not ? Is the Minister not aware that the bones of sheep, in Wales in particular, are said to be very highly contaminated with radioactive strontium ?—Mr Vosper Watch is being kept on this matter mainly in connection with the effect on milk I am sure that the Medical Research Council is concerned about this and that advice will be given if necessary

Mr Somerville Hastings asked the Minister whether he would inquire of the Medical Research Council to what extent the thermonuclear bombs so far exploded had resulted in a tendency to increase mutations and, in consequence, the number of deformities in the human race during the next 1000 years —Mr Vosper replied I am advised that, while all radiation does affect human mutation rates, our present knowledge of the subject shows that compared with the radiation to which man is already exposed, the additional amount which has been produced by the thermonuclear bombs so far exploded is so small that the genetic effects would be insignificant Mr Hastings Does the Minister realise that scientific opinion is changing very rapidly in this direction ? Has his attention been called to a report on the genetic effects of radiation by the World Health Organisation, from the Press release of which I quote as follows

> " all man made radiation must be regarded as harmful to man from the genetic point of view "

Whilst the harm may not be very great, at any rate as we see it at present, is it not perfectly clear that harm is bound to follow ?—Mr VOSPER The hon Member asked me to inquire of the Medical Research Council, and he will know that the committee, in its report last year referred to the fact that an increase of only 1% of that from normal sources could be expected From my further inquiries, I understand that that estimate is still reasonably accurate Dr SUMMERSKILL Is the Minister satisfied in always quoting from the report of June 1956, in view of the fact that this committee was convened in 1955 and Professor Haddow himself has been making public statements that there has now been a shift in emphasis since June, 1956 ?—Mr VOSPER I thought I had made that clear I have made inquiries of the Council as to its present attitude, and it confirms that the report still holds good

QUESTION TIME

Remuneration

Mr ARTHUR BLENKINSOP asked the Prime Minister whether he would make a statement on the form of any interim award to general practitioners in the National Health Service pending the longer term review being undertaken by the Royal Commission —THE PRIME MINISTER I have nothing to add to the reply I gave on March 19

Mr BLENKINSOP May I ask whether the right hon Gentleman would not now make some suggestion to clarify the statement which he himself made in his letter ? Does he not realise that no one in the House supports the point of view expressed by the doctors, who so far are refusing to submit evidence to the commission ?—THE PRIME MINISTER I can only say that I hope to make a statement shortly

Mr HENRY HYND asked the Minister of Health what arrangements were now being made to deal with the situation which would be created by the proposed withdrawal of doctors from the National Health Service —Mr VOSPER At the moment, I do not wish to add anything to the statement made by the Prime Minister on March 12 Mr HYND Is it not very desirable, in view of the serious effects which will arise if this dispute is allowed to develop, that something should be prepared now to meet that contingency ?—Mr VOSPER I have read that it is suggested that doctors may withdraw from the National Health Service on Oct 2 My right hon Friend said that he would make a further statement in due course, and the hon Gentleman could deduce that that would probably be before Oct 2

Mr K ROBINSON Would the Minister convey to the leading members of the medical profession that this suggestion in the view of most people, including many who are sympathetic to the doctors' claims, is both irresponsible and ridiculous ?

Leukæmia

Mr BLENKINSOP asked the Minister to what extent there had been an increase in deaths from leukæmia over the past 30 years —Mr VOSPER replied In 1923 the number of deaths certified as due to leukæmia (including aleukæmia) was 552 representing a death rate of 14 per million persons living In 1955 the number of deaths was 2224 and the rate 50 per million Mr BLENKINSOP In view of the serious increase which is taking place and the anxieties there are about the possible future growth of this disease, does the right hon Gentleman accept responsibility for giving advice to the Prime Minister about the possible effects of future hydrogen bomb tests, in view of the clear indication that these tests, on whatever scale, are bound to have an effect upon the strontium of the body ?—Mr VOSPER I think the hon Member should not come to too rapid conclusions A great part of this increase took place in the years 1925–45 There are a number of causes contributing to the increase Of course, the matter is very much in my mind and in that of my right hon Friend

Mr B HARRISON Would the Minister make sure that the most modern equipment is available for X ray photography and that this photography is not a cause of the increase in leukæmia ?—Mr VOSPER I think it may well be a cause, and it is, in fact, being investigated by the committee under the chairmanship of Lord Adrian

Merit Awards

Mr J W W PEYTON asked the Minister on what basis merit awards were made to consultants, by whom such awards were recommended, and to what extent regional hospital boards who had to meet the cost were consulted —Mr VOSPER replied Awards are made for professional distinction and on the basis that 4% of consultants receive awards at the rate of £2500 a year, 10% awards at the rate of £1500 a year, and 20% awards at the rate of £500 a year The recommendations are made by the Advisory Committee on Distinction Awards In view of the basis of the committee's recommendations, regional hospital boards are not consulted upon them Mr PEYTON Does not the Minister feel that there is considerable need for wider knowledge of how this committee makes its awards ? When the award is a continuing one, does it not involve considerable uncertainty among consultants and the medical profession generally ?—Mr VOSPER I am aware that some concern has been expressed about this matter before As I understand it, the whole idea of the awards is that they are on a professional basis

Mrs BRADDOCK Is the Minister aware that, in the early stages of this scheme of merit awards, the details of those who obtained them used to be submitted to the management committees of hospitals, and that that has ceased to be done ? Is it not a fact that at no time are the names of those who receive merit awards submitted to or known to the hospitals in which they are employed ? Will he reconsider the position to see whether it is not wise to start reissuing the names of those who receive merit awards to the hospital management committees concerned ?—Mr VOSPER It is several years since the names were disclosed I understand that the change was made in the interests of patients and not necessarily of the consultants concerned Of course, I will look at it again, but I think the disadvantages would outweigh the advantages

Medical Officers of Health

Mr R S RUSSELL asked the Minister whether he had yet reached a decision on the recommendation of the Guillebaud Committee that the medical officer of health, or one of his staff, should be given an honorary appointment on the medical staff of a hospital , that he should be a member of the medical staff committee , and that he should take charge of outbreaks of infection —Mr VOSPER replied After consulting the bodies chiefly interested, I have decided not to adopt this recommendation Hospital authorities have already been advised of the desirability of medical officers of health being members of group hospital medical committees, and of medical officers of health of sanitary districts being members of control of infection committees at hospitals In my view, arrangements of this kind contribute more satisfactorily to the link between the different parts of the health service which the committee had in mind than formal appointments as they proposed

Lung Cancer and Diesel-engine Fumes

Mr G WILSON asked the Minister to what extent continuing investigation indicated that diesel fumes are responsible for the increasing incidence of lung cancer —Mr VOSPER replied The investigations being made under the auspices of the Medical Research Council into the nature and effects of the exhaust products of diesel engines have provided no evidence to support the suggestion that these fumes are a cause of cancer I hope this statement will remove any misunderstanding which may have arisen as the result of a reply which I gave to a supplementary question on Feb 4[1]

Bath's Mineral Waters

The MINISTER OF HEALTH, in answer to a question, said that the content of the mineral waters at Bath was known and there was no evidence that it would be harmful in pregnancy

Dental Courses

In 1956, of dental courses given under the National Health Service in England and Wales, 41 6% were for patients under twenty one and 1 4% for expectant and nursing mothers

Blood Donations

In England and Wales during 1956 the number of blood donations was 803 522 compared with 759 571 in 1955

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[1] See *Lancet* Feb 9, 1957, p 328

Obituary

FRANCIS CYRIL OLIPHANT VALENTINE

F R C P.

After a short illness, Frank Valentine died on March 27 at the London Hospital Except during the war, nearly all his work in bacteriology and chemotherapy was done there, and it was done in the best tradition of London Hospital pathology His gently spoken opinions carried much weight, and he will be remembered, too, with much affection

Born in Dundee in 1897, he was at Winchester from 1911 to 1916 He then held an Artillery commission until the beginning of 1919 when he went to Magdalene College as a scholar Both at Cambridge and at The London he showed exceptional ability, and in the natural course of events he became house-physician to the medical unit, first under Charles Miller and then under Prof Arthur Ellis Two qualities which impressed his friends even at this stage of his career were his care in everything he undertook and his sympathy with his patients But he did not like "dealing with" people, and probably he did not really enjoy medicine, except on its scientific side, till in 1925 he took a post in the pathology department as an assistant to H M Turnbull In 1926 he spent a year at the hospital of the Rockefeller Institute in New York, where he worked with Prof T M Rivers on the influenza group of bacilli, and on his return to the London Hospital he joined Philip Panton in the clinical laboratories

When I went to the London Hospital in 1926, writes S P B, Frank Valentine was at the beginning of his career as a specialist in pathology Deriving his inspiration from Panton in all probability, he found greater interest in the application of pathology to the diagnosis and treatment of disease than in the study of its more academic aspects He had set himself to become what for want of a better term we call a clinical pathologist and he was a member of the staff of the clinical laboratory It was to this department that I went as a Freedom research fellow, and I soon learned that he was not only a delightful and cultured person but possessed a keen intelligence and an inquiring mind, discussion of my research problems with him was most profitable Later when, on the retirement of G T Western, Valentine took charge of what was then known as the inoculation department, he and I became more closely associated By then I had succeeded Bulloch in the chair of bacteriology, and traditionally the two departments were linked

But it was during the war that I first learned fully to appreciate Valentine at his real worth He had been put in charge of one of the emergency laboratories in the London Hospital sector, and when Panton went to the Ministry of Health and I took over his duties as sector pathologist I paid regular visits to Valentine's laboratory at Claybury Hospital I was greatly impressed by his quiet efficiency, his skill in improvisation, and the breadth of his knowledge And much of this knowledge was the outcome of his own experience not just what he had learnt by reading For me those visits were both a pleasure and an education

After the war Valentine returned to The London to become director of the department of chemotherapy, and later a university reader in that subject This did not really represent any fundamental change in his work it merely recognised the change of emphasis from immunotherapy and prophylaxis to chemotherapy which, from the discovery of the sulphonamides, had taken place over the war years As a member of the staff of Professor Bedson's department he took his share in the teaching of microbiology, with advantage to the students and pleasure to himself And he continued with his investigations which from before the war had been particularly concerned with the staphylococcus and its role in disease The last of his papers to be published in this journal was a study of the survival of bacterial species under bacteriostasis, and, though some were academic in that they were an end in themselves, the majority had the welfare of the patient as their principal objective In 1954 he was responsible, with Dr R A Shooter, for the third edition of *Recent Advances in Chemotherapy* (vol III) and it was characteristic that he not only checked every fact in his section of the book but undertook special experiments to make sure that the information was completely reliable With the increase in the number of chemotherapeutic agents available to clinicians, he was drawn more and more back into clinical work, and his helpfulness and sympathy made him one of the best loved members of The London's staff As one of his friends there says, "people are inclined to underestimate the importance of quiet unaggressive colleagues who are without malice and maintain in the background a standard of honesty in personal relationships not attained by all of us Frank had this sort of influence at The London" Away from work, he fished in Scotland and played bridge and golf, winning the founder's cup at Sunningdale in 1937 from a handicap of 9

In 1931 Dr Valentine married Freda, daughter of the 8th Earl of Lanesborough She survives him with two sons

GEORGE FREDERIC STRONG

M D Minn, F R C.P, F R C P (C), F R A C.P, F A C P

Dr Strong, professor of clinical medicine in the University of British Columbia, Vancouver, died on Feb 26 in Montreal, where he had gone to preside over a meeting of the National Heart Foundation He was a past president of the American College of Physicians

He was born in 1897 of Canadian parents at St Paul, Minnesota, and he was educated at the University of Minnesota, graduating M D in 1921 A year of his training was spent at the Vancouver General Hospital and he decided to settle in that city In 1926 he was appointed to the staff of the Vancouver General Hospital He was for many years director of the heart station of the hospital and it was as a cardiologist that he was best known, but he had also published a 25-year study of carcinoma of the liver and he was keenly interested in reablement

He had played an important part in the founding of the University of British Columbia, and it was appropriate that he was invited, in 1951, to become its first professor of clinical medicine He was also the first Canadian to become president of the American College of Physicians, holding office from 1955 to 1956 He was an honorary graduate of the universities of Laval, British Columbia, and Toronto and a fellow of the Royal Colleges of Physicians of London and of Australasia

D P writes

In Vancouver Strong was a leader in all things medical He fostered and launched the Western Rehabilitation Centre, one of the best equipped centres for the treatment of post-poliomyelitis and paraplegic cases on the Continent He was able to raise money for such a project and get together an outstanding committee of lay people because of the respect and trust the public had for him He inspired the British Columbia Cancer Foundation and raised large sums for it He was founder and chairman of the medical board of the British Columbia Medical Research Institute While president of the Canadian Medical Association he travelled from coast to coast lecturing and urging that more facilities for the rehabilitation of the handicapped be provided He had a real interest in England and the British Empire Last year he visited Australia and New Zealand as the president of the American College of Physicians, and on more than one occasion he visited Britain.

He was a first class internist and heart specialist, and his services were much in demand He was a very human man and his patients loved and trusted him for he gave them confidence, and seemed to understand the psychological side of their illnesses Before any major medical move took place here, the question always was "What does Fritz Strong think of this project ? " We will miss his kind heart, honest counsel jovial personality, and courageous leadership

Dr Strong leaves a widow and a daughter His only son was killed during the war while serving with the R C A F

KIYOSHI SHIGA

Professor Shiga will be remembered for his discovery of the dysentery bacillus that was named after him

He was born in 1870 the son of Shin Sato, a Samurai In 1886 he was adopted by Tasuku Shiga and the same year began his studies at the Imperial University in Tokyo After graduating he became an assistant at the Institute for Infectious Diseases in Tokyo, and it was in 1897, while he was working under Professor Kitasato, that he made his *observations on the dysentery* bacillus In 1901 he was sent by the Japanese government to Europe and he worked with Ehrlich in Frankfurt and later with Kossel at Heidelberg With Ehrlich he published experimental work on the chemotherapy of trypanosomiasis In 1909 he was sent on a scientific mission to India In 1912 he visited Europe again and for a year studied the chemotherapy of tuberculosis under Ehrlich He continued this work in Japan In 1920 he was appointed professor of bacteriology in the Imperial Keijo University in Korea

After the first world war, in 1924, Shiga attended some international conferences in Switzerland and then came to London to visit the National Institute for Medical Research, the Lister Institute, and the Wellcome Physiological Laboratories In 1929 he was appointed president of the Imperial University in Korea While he was in Korea he made a special study of leprosy and the culture of the lepra bacillus In 1931 he returned to Tokyo where he acted as consultant to the Kitasato Institute In 1936 he was appointed an official of the Imperial household

After the late war he retired to his native province, and he died peacefully at his villa at Sakamoto on Jan 25

RICHARD CHRISTOPHER CLARKE

O B E , T D , M B Brist , F R C P

Dr Richard Clarke's death on March 23, at the age of 71, breaks an association of nearly fifty years with the Bristol Royal Infirmary As student, resident, and honorary he served the institution with loyalty and devotion until he retired from the active staff in 1918 Despite his attachment to the traditions and history of the Bristol Royal Infirmary he had the vision to see the advantages to the Bristol Medical School which would follow from the amalgamation of the clinical schools at the Royal Infirmary and General Hospital, and he was one of a small group who planned and worked towards this end, which was achieved in 1940

He was educated at Clifton College and the University of Bristol, and he took his clinical course at the Middlesex Hospital in London After qualifying in 1910 he held a series of house-appointments at the Bristol Royal Infirmary

Even as a student he was an enthusiastic member of the Territorial Army, enlisting as a private in the Bristol Rifles, and in the 1914–18 war he served with the R A M C , for the greater part of the time with no 19 casualty-clearing station, and for his services he was appointed O B E Some twenty years later in his presidential address to the Bristol Medico Chirurgical Society he gave a vivid description of his struggles and achievements with the medical problems of the war in France

In 1913 he had been appointed assistant physician to the Bristol Royal Infirmary, and after he was demobilised he returned to Bristol to take up this appointment and resume his private practice in Bristol In 1921 he was appointed full physician In 1931 he was elected F R C P

During the years between the wars he served with the Territorial Force as medical officer to the 4th Gloucesters until in 1937 he was gazetted colonel to command the reconstituted Second Southern General Hospital In the late war he was in charge of a hospital with the Mediterranean Expeditionary Force

In 1925 he became a member of the Bristol Zoo Council, and three years later was elected chairman For the next thirty years he derived great pleasure from planning the development of the gardens and the care of the animals His disregard of convention served him well By discarding the traditional methods of coddling the inmates and by his early realisation of the importance of vitamins, nutrition, fresh air, and the avoidance of infection he had great success in maintaining the health and vigour of the animals, particularly the larger primates Perhaps two of his greatest achievements were the rearing of that fine gorilla Alfred and the birth of the first chimpanzee in this country

C B P writes

"As a physician Richard Clarke was an individualist, an original thinker, and something of an iconoclast as is shown by one of his earlier papers entitled *The Teething Myth* Though perhaps never recognised as a pædiatrician he was always keenly interested in infant welfare and the diseases of children and for many years ran an infant welfare clinic at the Royal Infirmary As soon as a department of child health was established in the university he endowed a prize in this subject His mercurial and vivacious personality endeared him to colleagues and students, and in fact to all with whom he came in contact We shall all miss his visits to the Royal Infirmary which he served so well"

Dr Clarke leaves a widow, a son, and two daughters

BERNARD ROWORTH TURNER

B A , M B Camb

Dr B R Turner, who died on March 20, went to Oundle as a general practitioner at the beginning of the century and settled there for the rest of his life, building up a fine practice in the school, the town, and the surrounding country, a farming area and a region of many great houses He was educated at the University of Cambridge and King's College Hospital, qualifying in 1802

C E N writes

Dr Turner owed his success to his personal qualities He was a good sound doctor, without any intellectual pretentions, and he never played at surgery, but he had two outstanding qualities he liked and understood people, and he knew when illness was serious When a case was within his scope, he dealt with it with confidence and efficiency when he thought it was beyond him, he had no hesitation in referring it to the expert, and he recommended the right expert He was a wise counsellor and a personal friend to all his patients That would not be a bad description of a good doctor, and he was a very good doctor , the kind which comes to mind on reference to "the family doctor," of which flower of the profession he was an outstanding example

He worked hard and conscientiously, but he found time to enjoy life Good food and drink, exercise, and the open air life he loved He played a good game of bridge (and of tennis in his younger days), he always had at least one dog in the car with him, and he was always ready to stop and talk His chief pleasure in life was people, and he had a wonderfully cheerful disposition, with a lasting almost boyish zest for life which was extremely attractive Some at least of it was the result of courage, for he had not always had the easiest path He was absolutely genuine, without pretentions, and with a deep underlying humility his attitude that the person he was talking to was more competent than himself to speak of this or that was no affectation It was no wonder he was so loved, and when people laughingly said that B R T stood for brotherly love, relief, and truth, they were being neither sarcastic nor pretentious

HILBRE HAMILTON WATTS

M B Lpool

Dr Watts, who died at his home in Hertford, on March 21 at the age of 41, was the elder twin son of Mr A T Watts, the founder of Kingsmead School Hoylake He was educated at Monkton Combe School and before starting medicine at Liverpool in 1930 he held a post with Imperial Chemical Industries for a short time At the university he made his mark on the rugger field and in the activities of the Student Christian Movement and Evangelical Union He qualified in 1942 and was house-surgeon to Prof Charles Wells at the Royal Southern Hospital, Liverpool, before being called up to the R A.M C While on active service in India he was stricken with poliomyelitis which left him severely crippled When he was able to start medical work again he found surgery too strenuous, and turned to pathology, but it did not satisfy his real zest for life Finally, after holding a registrarship in clinical medicine at the Royal Southern Hospital, he decided to enter general practice He was an assistant in Birmingham or a time and three years ago joined a partnership in Hereford

T L S writes

It will not be for his doctoring or his prowess on the rugger and cricket field that Hilbre Watts will be remembered, but rather for his deep abiding faith in God and His purpose Throughout his life he strove to influence others by his example, in particular through the Crusader groups which he led, first at Hoylake and then in Hereford and through the S C M and Evangelical Union at the university He overcame the physical handicaps which followed his illness with an inner reserve of courage and never complained, though for one who had been so active in outdoor sports his disability was particularly irksome At his funeral service in Hereford tribute was paid to his great contribution to the spiritual life of the city

Dr Watts leaves a widow and two young daughters

LAWRENCE WILLIAM CANN

M B Lond , D P H.

Dr Cann, pathologist to the Ashford County Hospital, Middlesex, died at the age of 56 on March 11 He qualified from Guy's Hospital in 1924 and was for a time assistant pathologist at Guy's, and while there he collaborated with De Navasquez in the preparation of a paper comparing the value of the Wassermann and Kahn reactions For some years he gave up medicine and only returned because of the need for pathologists during the war He joined the Emergency Pathological Service at Ipswich and was soon transferred to Ashford, where he played a vital part in building up the laboratory from small beginnings He gave particularly valuable service in visiting the smaller, outlying hospitals and seeing patients, in consultation with members of their staffs

W F H writes

Bacteriology was Lawrie Cann's main interest, and on any point raised, no matter how obscure, he would be sure to remember some relevant paper The details he could find at a moment's notice in his index This he kept up to date by constant revision—going through the old papers, rejecting selecting, and annotating He was an enthusiast in all matters relating to bacteriology A chance remark would set off a train of thought on which he would ponder for weeks, forming and if possible testing, theories

Cann was foremost a deeply religious man He thought much and read widely about the religions of mankind but his faith remained a simple one, free from creeds and dogmas and best expressed in his own words 'The Lord knows best', He had known for many years that he had severe mitral and aortic lesions the result of acute rheumatism, but he never let this knowledge interfere with what he conceived to be his duty And his duty to Cann was not only what he was paid for Even in the last year or two he insisted on undertaking far more than his share of the ever increasing burden of work

He sought no popularity but he became extremely popular with all sorts and conditions of men He has kept up correspondence with almost everyone who had worked in the laboratory He was a very modest man, and partly because of this, and partly because he thought of people as individuals and not in groups, he was content to exert his influence locally

He was always exasperated by rigid rules, particularly by the rigid salary scales of the ancillary workers in the laboratory "Here is a man" he would say, for example who has served this hospital for years He has a wife and family Surely we can pay him more Surely we can make him a senior' He would know quite well that there was no vacancy for a senior but that was a matter of small import to Cann I will not say that life in the laboratory with him was always blissfully peaceful, but then probably the last thing he sought was peace, not because he was a man of war or liked strife, but because he felt that we were not entitled to the joys of peace till every wrong was righted But he enjoyed life to the full He was a happy man with a keen sense of humour He enjoyed reading He appreciated music and the arts Pictures both ancient and modern had a great appeal He was very fond of flowers, particularly the less sophisticated varieties He loved children, but curiously, though always kind and gentle to them, he was not very fond of animals, he could be deeply moved by the beauty of an anemone but not by the grace of a pony in action He was a very sociable man Though he rarely gave formal invitations he always delighted to welcome the casual caller He dearly loved a party Above all he was a family man His chief delight was the time he spent with his wife and family, playing with the younger ones, talking to and reading with those older, and if we sometimes felt that he was too ready to involve them in his quixotic acts of self-immolation it was always with their consent, for every important action was discussed with them and agreed upon

Dr DESMOND FARIS

P M -B writes

The antimalarial measures which Faris organised and devised with such enthusiasm, together with Dr J W Scharff in the early 'thirties are generally recognised as an outstanding achievement in malariology and one which has played a great part in converting Singapore, and indeed Malaya in general, into the health resort that it has now become Malaya owes him another debt in the fine work that he did for its university He threw his heart into this task. He made a most admirable dean who, by his charm and accessibility held the various races and cliques together To visitors to Singapore he showed unbounded kindness and hospitality, and encouraged their interest in the everyday life of his university He did much for the dignity and efficiency of this growing institution, and his influence will remain as a binding tie among the racial rivalries of Singapore

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Appointments

FARRER J A. M B Melb assistant county M O and school M O Settle division of Yorkshire

McDONAGH, T P M B Edin D P H M O H Keighley and divisional M O West Riding of Yorkshire

O DOHERTY N J M D M R C P I resident house surgeon The Hospital for Sick Children Great Ormond Street London

ROLFE M G, M B Camb F.F A R C.S , D OBST consultant anaesthetist, London Hospital

Manchester Regional Hospital Board

JOHNSON G T M D Lond M R.C O G F F A R C S consultant obstetrician and gynaecologist West Manchester hospitals

JONES L G G M R C P F assistant venereologist Manchester area

SHERRAH DAVIES, EVAN M B Camb F R C S D M R T assistant radiotherapist Christie Hospital and Holt Radium Institute, Manchester

TRICKEY E L M B Lond F R C.S consultant traumatic and orthopaedic surgeon Ashton Hyde, and Glossop Hospitals

Colonial Appointments

CAREY ELLEN M B N U I D P H health officer British Guiana

DUNN W M B D OBST M O silicosis medical bureau Northern Rhodesia

GARROD J M B M B Belf D T M & H director East African leprosy research centre East Africa High Commission

GROVE WHITE R J M D Dubl M R C P E medical superintendent Trafalgar Home Singapore

HART ROSEMARY M D Lond M R C P specialist (physician) Gold Coast

KHOO FUN YONG M B D M R.D senior radiologist (diagnostic) Singapore

KNOWLES H E M R C.S D M R D radiologist Fiji

MACCULLOCH C M M B Sheff M O silicosis medical bureau Northern Rhodesia

McPHERSON H J M B D O specialist ophthalmologist (grade A) Selangor Federation of Malaya

MADGE F H M B Lond surgeon specialist Mauritius

MEARNS A W M B Glasg D P H senior M O H Jamaica

NORMAN WILLIAMS C M M B Edin. D T M & H D P H M O Western Nigeria

ROBERTS A B M R C.S M O South Pacific health service British Solomon Islands Protectorate

SAMARASINGHE C F P L M S D C H D T.M & H D P H M O H Gold Coast

SMITH I D M B Dubl M O St Vincent Windward Islands

SMYTH N P B L.P C P I M O Kenya

TOAL KEVIN M B N U I M O South Pacific Health Service British Solomon Islands Protectorate

VAN DER KAAY H J, M D Amsterdam D T M & H D M J M O Western Nigeria

WALKER A J M D Lond M R.C P D P H M O Northern Nigeria

WESTWOOD D A M B Edin M O Kenya

Notes and News

NEW RATES FOR HOSPITAL STAFF

REGULATIONS[1] authorising an increase of 10% from April 1 in the salaries of all hospital doctors and dentists up to the grade of senior registrar were published last week An interim adjustment of salaries for these grades had been promised by the Prime Minister earlier last month The number of doctors and dentists affected in hospitals in England and Wales is about 8500

The new rates per annum for whole time appointments (with the old in parentheses) are

Senior registrar £1210 in first year (£1100), £1320 in second year (£1200), £1430 in third year (£1300), £1540 in fourth and any subsequent year (£1400)

Registrar £935 in first year (£850) £1061 10s in second and any subsequent year (£965)

Junior hospital medical officer commencing at £852 10s (£775) and rising by annual increments of £55 to £1182 10s (£1075)

Senior house officer £819 10s (£745)

House officer £467 10s for first post held (£425), £522 10s for second post held (£475), £577 10s for third and any subsequent post held (£525)

The total cost of the increases will be in the region of £900,000 a year

A statement issued last Monday by the British Medical Association criticised the Government because "no negotiation or even discussion took place before the increase of 10 per cent was decided on, although on February 20, Lord Salisbury, in the House of Lords, promised that the increase would be 'negotiated through the established Whitley [Council] machinery'—a promise repeated by the Minister of Health in the Commons on March 4" This, the statement continues, is "a flagrant breach of the pledge given to the hospital doctors in 1949 that no changes would be made in their terms and conditions of service without discussion in Whitley The manner of making this increase is naked dictation and nothing else"

EFFECTS OF RADIATION ON WOUND HEALING

SOVIET surgeons have lately been studying, by means of experiments on animals, some of the problems which may arise for the surgeon when irradiation damage is combined with mechanical trauma Prof N E Blenov[2] describes experiments in which guineapigs and rabbits were wounded after irradiation at doses of 400r and 600–800r respectively In the first experiment, 243 guineapigs were used, and it was found that wounds made half an hour after irradiation took, on an average, two days longer to heal In another experiment, 195 guineapigs were used and wounds were made three, six, twelve, and twenty four hours after irradiation There was primary healing in 30 out of 84 irradiated animals, and in 29 out of 51 controls (The "missing" animals appear to have died, there are no figures indicating the relative mortality of irradiated animals and controls) When suppuration followed, it became apparent several days later in the irradiated animals Similar experiments were done giving the animals streptomycin or penicillin—both locally and systemically These antibiotics assisted local healing but did not alter the overall mortality

Another series of experiments showed that irradiation delayed formation of callus in closed fractures in rabbits (112 irradiated, 24 controls) In open fractures too, callus formation was delayed, and there was a higher incidence of osteomyelitis and suppuration in the irradiated animals Blenov concludes that if a surgical operation must be done after exposure to irradiation, the sooner it is done the better, and surgical interference should be small and as gentle as possible He also concludes that wounds should be covered with sterile dressings (i e, not left open) and the limb immobilised Stitches should be left in place for at least three or four days longer than usual and fractures immobilised in plaster for at least two weeks longer Blood transfusion three days after irradiation helped healing and recovery from radiation sickness, and combined with the administration of streptomycin it lowered the mortality rate

Prof B M Chromov[3] investigated methods of cleansing wounds contaminated with radioactive material Wounds 2 cm long were made in the backs of rabbits and immediately contaminated with 20 microcuries of radioactive iodine isotop (^{131}I) Two hours later, the wounds were thoroughly excise and irrigated with various solutions (physiological saline, 3% soap, and 0 5% aqueous iodine) Thorough excision was foun to remove a third of the radioactive material, or half th material when combined with irrigation

UNIVERSITY APARTHEID

IT has been found that the parts of the Separate Universit Education Bill[1] dealing with the Natal non European medica school and the Fort Hare Native College would have t be submitted to a select committee, which would mea long delay before the Bill was finally passed The South African minister of education has accordingly withdrawn i and will introduce an amended Bill to establish university apartheid this session, leaving Fort Hare and the Natal medical school till later

The *Times* (April 2) reports that the students' representativ council of Stellenbosch University have issued a statement approving the principle of university apartheid but with a rider saying that this was not a direct endorsement of the government's Bill

NEW ORIENTATIONS IN RENAL DISEASE

MOST clinicians probably think of the kidney as primarily an organ of excretion The physiologist on the other hand pictures it as a homœostatic organ regulating the distribution of water and electrolytes in the body This conception, although not new, is exerting a growing influence on clinical medicine, as is evident from the latest issue of the *British Medical Bulletin*,[2] which is devoted to the physiology and pathology of the kidney The 16 articles, written by clinicians and edited by Prof Robert Platt, reveal how much has been added to our knowledge of the kidney in recent years

Flame photometry, chromatography, and the discovery of aldosterone have focused attention on the renal tubules, and have given a great impetus to the study of water and electrolytes R A McCance and E M Widdowson describe the homœostatic function of the kidney in the newborn O Wrong reviews the problems of dehydration and œdema with special reference to the kidney's rôle in the volume control of body fluids D A K Black and E W Emery, and M D Milne, R C Muehrcke, and B E Heard consider the complex relationships of the kidney in potassium metabolism, H Harris explains the significance of certain rare renal amino acidurias, M G McGeown and G M Bull discuss the pathogenesis of renal calculi and S W Stanbury in what is perhaps the outstanding essay of a distinguished collection throws new light on the way in which the failing kidney affects calcium metabolism and causes renal osteodystrophy

These metabolic studies are supported by new information about structure E M Darmady and F Stranack give an account of the technique of microdissection, which enables the morbid anatomy of an entire nephron to be examined in detail, while C R Macpherson and A G E Pearse show how the enzyme systems of the kidney can be studied histochemically In the living patient a new aspect of structure is being revealed by the radiologists, R S Murray and G C Tresidder describe what can now be learned from renal angiography while R E Steiner describes renal venography

Treatment and prognosis receive less attention than other aspects but C Wilson and D G Abrahams discuss the use of hypotensive agents in renal hypertension and J R Squire J D Blainey and J Hardwicke review the prognosis and treatment of the nephrotic syndrome which now has no less than fourteen known causes

The rôle of the kidney in hypertension remains obscure but M A Floyer and J M Ledingham describe some new advances in experimental hypertension The problem of the kidney in old age is represented only in so far as it affects the rat although pioneer studies in man have been reported in this country[3] It is none the less of great interest to learn that G C Kennedy has shown how senile changes in the rat's kidney can be accelerated both by overfeeding and by unilateral nephrectomy

This is an outstanding number of the *Bulletin*

A FILM ON EPILEPSY

People Apart is a 35 minute sound film about epilepsy It was made by Guy Brenton, who, with Lindsay Anderson wrote and directed the successful documentary *Thursday's Children* The medical supervision was by Dr Christopher Ounsted Most of it is a convincing account by patients of the illness seen from their own point of view, telling how it has affected their lives and work None are professional actors, but most speak fluently and attractively There is no sentimentality or pathos, but no attempt to gloss over their handicaps

Other parts of the film give some account of the nature of the disease Cerebral dysrhythmias are likened to the convulsive movements of a spraying hose which has been up and the depicted writhings of the hose strikingly counterpoi

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1 The National Health Service (Remuneration and Conditions of Service) Amendment Regulations 1957 S I 1957 no 491

2 Blenov N E *Chirurgia* 1956 11 46

3 Chromov, B M *Ibid*, p 61

1 See *Lancet* March 30 1957, p 675

2 *Brit med Bull* 1957 13 no 1

3 Olbrich O Ferguson M H Robson J S Stewart C P *Edinb med J* 1950 57 117

the writhing of a patient in a major fit, which is shown in two or three sequences—a very severe fit which might be considered unsuitable for showing to a general audience Electro-encephalography, as shown, appears a rather frightening business

The main purpose of the film which was made for the British Epilepsy Association, 27, Nassau Street, London, W 1, seems to be to show that epileptics are ordinary people and generally employable It is unlikely to reach a wide public, but it is hoped that teacher s training colleges and welfare organisations will profit by it

JOURNAL ON MENTAL DEFICIENCY

THE first number of the *Journal of Mental Deficiency Research*, sponsored by the National Society for Mentally Handicapped Children, is to appear this spring Articles on all aspects of mental deficiency will be included, but there will be a medical bias and much of the space will be allotted to papers reporting original research.

The Journal will be administered by an advisory committee under the chairmanship of Prof L S Penrose F.R.S with Dr B W Richards as editor It will appear twice a year in the first instance The cost will be 7*s* 6*d* ($1 50) per issue Subscriptions should be forwarded to the Publishing Manager Mr A Highfield 10, Shendon Way Sevenoaks Kent. Inquiries and contributions should be addressed to Dr B W Richards St Lawrence s Hospital Caterham Surrey

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University of London

Dr Katharine Lloyd-Williams has been elected dean of the faculty of medicine for the remainder of the period 1956–58, in succession to the late Prof W G Barnard

Dr Charles Harris has been reappointed deputy vice-chancellor for 1957–58

Royal College of Physicians of London

Prof G W Pickering will deliver the Croonian lectures on Tuesday and Thursday, May 14 and 16 at 5 P.M, at the college, Pall Mall East, S W 1 He will speak on the regulation of body temperature in health and disease

Sydney Body Lecture

Sir Hugh Linstead, M.P, will give this lecture at the General Hospital, Southend on-Sea, on Friday, April 12, at 8 30 P M He is to speak on human relations in and around the health service

Royal Society of Health

At a meeting of this society to be held at 90, Buckingham Palace Road, London, S W 1, on Wednesday, June 12, at 2 30 P M, Dr F G Spear will speak on the effects of radiation

Mental After Care Association

The annual meeting of this association will be held at Caxton Hall, London, S W 1, on Tuesday, April 16, at 3 P M, when Lord Pakenham will speak

Biochemical Society

A joint meeting of this society with the Societe Belge de Biochimie will be held in the department of biochemistry of the University of Oxford, on Friday and Saturday, April 12 and 13

Russian Tuberculosis Conference

A conference for all tuberculosis workers in the U S S R will be held in Moscow from June 9 to 15 1957, inclusive The agenda includes epidemiology of tuberculosis in the U S S R, vaccination and immunological problems anti bacterial therapy, and surgical treatment Visitors will be welcome, and further details may be had from Dr Lapina, director, Tuberculosis Division of the Ministry of Health Moscow

Medicinal Chemistry

A symposium on this subject is to be held by the Chemical Society, the Institute of Petroleum the Royal Institute of Chemistry, and the Society of Chemical Industry at the University of Manchester on Tuesday, April 16 at 9 30 A M The speakers will include Dr H C Carrington Dr A Spinks, Prof Henry McIlwain D SC Mr R B Rodnight Prof Franz Bergel, F R I C Dr A L Walpole and Dr Harold Jackson Further particulars may be had from Dr M G T Burrows, Murgatroyd s Salt & Chemical Company Ltd, Elworth, Sandbach Cheshire

Society for Cultural Relations with the U S S R

On Tuesday, April 9, at 8 P M, at 14, Kensington Square London, W 8, Dr Fedor Syrovatko, professor of obstetrics and gynæcology at the central medical postgraduate school in Moscow, will speak on Soviet work in the relief of pain in childbirth

Agricultural Research Council

Dr J W Howie, professor of bacteriology in the University of Glasgow, has been appointed a member of the council in place of Prof J S Young who has resigned

Group and Social Psychotherapy

A course on this subject will be held by the Institute of Social Psychiatry in collaboration with the Group Analytical Society from July 22 to 29 at Moor Park College, Farnham, Surrey Further information may be had from the institute, 9, Fellows Road London, N W 3

Advisory Committee on the Handicapped

The Minister of Health has announced that this committee to consider the health and welfare of the handicapped will meet under the chairmanship of Mr Edward Evans, M.P The 19 other members include the following doctors Dr T M Cuthbert, Sir Harry Platt, F.R C S, Prof A B Semple. and Dr J A L Vaughan Jones

Tribute to Sir Ernest Rock Carling

In celebration of Sir Ernest s 80th birthday on March 6, some of his friends held a dinner in his honour last Monday at the Royal College of Surgeons

Sir Stanford Cade, who presided, spoke of him as a man scrupulously punctilious in his life as a surgeon and a doctor, regarded with veneration, respect, gratitude, and affection With continuity of purpose in a varied career, he had always seemed to his juniors a little different from other surgeons, but forty years ago he had looked exactly as he did now Sir Adolphe Abrahams suspected that Sir Ernest, besides serving medically in the South African war and the two world wars, had been active in the Crimea and even the Indian Mutiny At Westminster Hospital, in whose new building he had been the dominating factor, he had gained eponymous immortality through the naming of a ward, but there was not a stone in the structure that did not bear the imprint of his personality Even if he had shown complete ineptitude in every other capacity, he would have earned lasting fame as a surgeon by his indefatigable generosity, his judgment and his skill His sympathy and skill had also been at the service of the profession through the Medical Protection Society Sir Clement Price Thomas said that his old chief had " meant an enormous amount in my life ' he remembered how when juniors made mistakes, it always turned out that Sir Ernest himself had made bigger ones

Sir Ernest quoted Kipling to the effect that no satisfaction on earth compares with that of approval of one s work by fellow workers, but he feared that a higher court would be more concerned with what he had *not* done—with the opportunities missed At least he could not be reproached he felt, for basking in the reflected glory of his former students and he went on to speak of the contributions of each of them and of what he owed to his colleagues at Westminster and to other members of the company—to Sir Henry Dale, who introduced him into the Medical Research Council, to Sir Wilson Jameson who sent him to the Home Office, to Sir John Charles his chief there to Sir George North for his association with the work of the General Register Office to Sir Landsborough Thomson, of the M R C, and to many others present, including some of those who have worked with him on radiological problems—W V Mayneord, B W Windeyer E E Pochin W P Grove Lord Amulree, J S Mitchell M Lederman, and D W Smithers The peak period of his life had, he thought, been during the war, when he had a share in the invaluable contribution made by the Medical Research Council, and the Atomic Energy Commission had given him his most interesting ten years

A presentation of inscribed cuff links was made to Sir Ernest, and Professor Mayneord handed him a book sent to their chairman emeritus by the International Commission on Radiological Protection—a body whose pre-eminence was largely due he said to Rock Carling s guidance The evening ended with a toast proposed by Sir Ernest, to Private Secretaries and Personal Assistants, whose work, he believes, all too seldom gets the recognition it deserves He coupled it with the name of his own secretary, Miss Barrie

Register of Nursing Research

The council of the Royal College of Nursing proposes to maintain a register of nursing research The librarian would be glad to receive information from individuals or organisations about completed work or work in progress The address of the college is Henrietta Street, London, W 1

Vocational Rehabilitation of the Disabled

The Government propose to accept a recommendation on the vocational rehabilitation of the disabled adopted at the 38th session of the International Labour Conference in 1955 (Cmd 111) The law and practice of the United Kingdom is generally in accordance with the provisions of the recommendation

International Society of *Bioclimatology* and *Biometeorology*

This society will hold its first scientific congress in Vienna from Sept 23 to 27 Further particulars may be had from Dr S W Tromp, Hofbrouckerlaan 54, Oegstgeest, Leyden, Holland

London College of Osteopathy

The Leverhulme Trust Fund is providing scholarships to enable qualified medical men and women to study osteopathy at this college The next course begins on Oct 8, and particulars may be had from the secretary of the college, 24, Dorset Square, London, N W 1

André Mayer Fellowships

The Food and Agriculture Organisation will offer six to eight of these fellowships in 1957 for research in agriculture, agricultural economics and statistics, fisheries, forestry, and nutrition Further information can be had from the secretariat of the F A O National Committee for the United Kingdom, c/o the Ministry of Agriculture, Fisheries and Food, Whitehall Place (East Block), London, S W 1

Portrait of Sir Geoffrey Keynes

The Osler Club held a ' cardiac surgery evening " on March 26 in honour of Sir Geoffrey Keynes's 70th birthday On behalf of the club Dr W S C Copeman, the president, presented him with his portrait by Mr Gilbert Spencer, A R A, who was present In a short address Sir Gordon Gordon Taylor extolled Sir Geoffrey's achievements in surgery, letters, art, bibliography, and the ballet Sir Russell Brock then spoke on the history of cardiac surgery and was followed by Sir Henry Souttar, Dr A H T Robb Smith, Sir Zachary Cope, and others The company included the presidents of the three Royal Colleges and of the Royal Society of Medicine

The Family Doctor in New Zealand

Sir Charles Hercus, dean of the Otago Medical School, in an oration to the biennial conference of the New Zealand branch of the British Medical Association in Wellington, said that the family doctor was becoming the pivot of the national health service People were looking to him as consultant in daily life as well as in the treatment of disease, and he was showing an increasing interest in preventive medicine In physiology, bacteriology, obstetrics, pædiatrics, and psychiatry, as well as in preventive medicine, we have endeavoured to give effect to this recommendation Unfortunately, in the young graduate's period of compulsory training in hospitals this aspect is almost entirely subordinate to clinical work His contact with the home and the team of workers concerned with the welfare of the family is broken For a considerable period of his postgraduate training there is a regrettable separation from the home environment where all the factors leading to ill health are to be found Some method has yet to be found to overcome this important gap in the doctor s postgraduate training '

ADDENDUM *Fractures of the Femoral Neck* —Dr D B Murray and Mr Stuart Young, whose article appeared in our issue of March 23 have asked us to say that they are particularly grateful to Mr William Sillar, who operated on many of the patients for offering these cases for review They would also like to acknowledge the detailed medical evaluation by Dr James Buchanan of Dr Laurence Scott's medical unit during 1954 and 1955

Changing Demands of Modern Work and Control

The Ergonomics Research Society is to hold a symposium on this subject at the University of Bristol from April 8 to 11 Further particulars may be had from Dr O G Edholm, department of human physiology, M R C Laboratories, Holly Hill, London, N W 3

Sir Philip Manson Bahr has been awarded the Emile Brumpt prize for 195[illegible] by the Faculty of Medicine and the Institute of Tropical Medicine of Paris

Brigadier G T L Archer, Q H S the Army's director of pathology is visiting the United States at the invitation of the U S Department of Defence to discuss Anglo American research in military preventive medicine

Diary of the Week

APRIL 7 TO 13

Sunday, 7th

UNIVERSITY COLLEGE HOSPITAL MEDICAL SCHOOL University Street, W C 1

10 15 A M Dr W N Goldsmith, Dr P J Hare Common Affections of the Hand (Clinical demonstration for general practitioners)

Tuesday, 9th

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields W C 2

5 P M Mr H T Shaw Radical Surgery in Cancer of the *Extrinsic Larynx and Laryngopharynx* (Hunterian lecture)

ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W 1

8 P M *Psychiatry* Dr Denis Parr Homosexuality in Clinical Practice Dr Peter Scott Some Forensic Aspects of Homosexuality

Wednesday, 10th

UNIVERSITY OF LONDON

4 P M (Middlesex Hospital, W 1) Prof R M Janes (Toronto) Cancer of the Lung—Certain Consideration in its Diagnosis

ROYAL SOCIETY OF MEDICINE

4 30 P M *Physical Medicine* Dr Graham Weddell Dr G Gordon Dr R M Mason Referred Pain

5 P M *Epidemiology and Preventive Medicine* Dr A M McFarlan Dr R Irene Hutchinson, Dr R L O Williams Transmission of Infection

Thursday, 11th

ROYAL COLLEGE OF SURGEONS OF ENGLAND

5 P M Mr A A Jefferson Pituitary Chromophobe Adenomata and Rathke Pouch Cysts (Hunterian lecture)

ALFRED ADLER MEDICAL SOCIETY

8 P M (11, Chandos Street, W 1) Dr John Cowie The Delinquent Girl

BRITISH INSTITUTE OF RADIOLOGY, 32, Welbeck Street W 1

8 P M Dr Macdonald Critchley *Clinical Aspects of Tuberose Sclerosis*, Dr J J Y Dawson Tuberose Sclerosis with Special Regard to Pulmonary Changes, Dr P H Whitaker Radiological Changes in Tuberose Sclerosis

MANCHESTER MEDICAL SOCIETY

7 P M (Liverpool Medical Institution, 114, Mount Pleasant Liverpool, 3) Joint Meeting with Liverpool Society of Anaesthetists *Anaesthetics* Dr A L Stead Pre and Post operative Care of the Newborn Dr Mark Swerdlow Respiratory Effects of Thiobarbiturates

Friday, 12th

ROYAL SOCIETY OF MEDICINE

5 15 P M *Radiology* Dr J H Middlemiss Sickle Cell Anaemia Dr A A Donaldson Percutaneous Vertebral Angiography by the Atlanto occipital Approach

VICTOR HORSLEY MEMORIAL LECTURE

5 30 P M (B M A House, Tavistock Square, W C 1) Sir Geoffrey Jefferson, F R S Sir Victor Horsley—His Life and Work

INSTITUTE OF NEUROLOGY, The National *Hospital* Queen Square W C 1

5 30 P M Dr E J Moran Campbell Pulmonary Physiology and Artificial Respiration

INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330, Gray's Inn Road London W C 1

5 30 P M Dr Imrich Friedmann Chemotherapy in Ear, Nose and Throat Diseases

BRITISH TUBERCULOSIS ASSOCIATION

10 45 A M (School of Geography Mansfield Road Oxford) Opening of two day meeting

Births, Marriages, and Deaths

BIRTHS

NORMAN —On April 1 to Dr [illegible] Rainsbury wife of Dr I J Norman of 31 Court Road Eltham—a second daughter

DISEASE AND POPULATION*

A LESLIE BANKS

M A. Camb , M.D Lond , F R C P , D P H

OF LINCOLN'S INN, BARRISTER-AT-LAW,

PROFESSOR OF HUMAN ECOLOGY, UNIVERSITY OF CAMBRIDGE

IN medieval times the pattern of disease was such that a physician trained in an Eastern city could practise his art in Europe, subject only to the restrictions of language and certain modifications due to climate

The average expectation of life from birth in Europe did not exceed 19 years, and in the big cities was at times considerably less (Sand 1952) The biological balance was one of high birth-rates, high death-rates especially in infancy, diseased adults, and few old people

The underlying causes are sufficiently well known War, pestilence, famine, and the mass movements of people all predisposed to the great epidemics Severe malnutrition, bad housing, and lack of cleanliness encouraged the spread of disease, and parasitic infestations, both major and minor, were universal Above all were the effects of ignorance and superstition

The Changing Picture in the West

In Western Europe this pattern began to change about 250 years ago, and subsequent developments may be traced in four stages Firstly, the slow improvement in economic and social standards extending over the 17th, 18th, and 19th centuries resulted in increased wealth, better housing, improvement in the standard of nutrition, and a general awareness of the desirability of conserving life Secondly, from about the year 1848, came a deliberate and sustained attack on the faulty physical environment The quantity and quality of water supplies, the proper disposal of sewage, and improvement of housing and working conditions all received attention Next, towards the latter part of the 19th century, may be seen increasingly successful attempts to control the biological environment, beginning with the recognition of the nature of infection and the segregation of infectious cases in "isolation" hospitals Intensive study of the causes of the various infectious diseases led to effective measures for their prevention

The fourth stage—the improvement of the social environment—has reached its peak in the present century, with the organisation of health and welfare services on a national scale In this country, for example, the National Health Service, National Assistance, comprehensive education, housing and town planning, smoke control, the protection of water sources by river boards, and the safeguarding of the quality and quantity of food have all reached full development within recent years Above all, countries like our own can now rely on accurate statistics and stable government

Some of the results are quite extraordinary In England the year 1856 was a good one (Farr 1858) Potatoes were 26 lb for 1*s* in the wholesale market, and beef and mutton 5½*d* per lb The population of England and Wales was 19 million with a birth-rate of 34 5 and a death-rate of 20 5, but 20% of all deaths were due to acute fevers, and 25% of all deaths occurred in the first year of life In that year 94,000 infants died "Consumption," with 49,000 deaths, accounted for 12 7% of the total mortality Included in the principal causes of death were cholera, smallpox, typhus, and dysentery The average expectation of life from birth of the most favoured classes was only about 45 years, but, even so, the population was rapidly increasing, in spite of emigration It is worthy of note that 170,000 people emigrated in 1856 of whom 80,000 were Irish and 72,000 English and Welsh

Turn now to the year of my birth, in London in 1904 According to the report of the medical officer of health it was a hot dry summer, and "during these months there was consequently a great increase in infant deaths, due to epidemic diarrhœa" The infant-mortality rate was 155 per 1000 live births as compared with 24 9 today, and one seventh of all deaths were due to infectious disease Although the birth-rate was falling it was still high as compared with the present day, and so also was the death-rate The expectation of life from birth was now 40–45 years for all classes 90% of the London schoolboys examined in that year had dental caries and in 70% this was serious Ringworm was common and the report recognised want of cleanliness and lack of food as the principal evils of children (London County Council 1904)

Today the picture is again different The death-rate is low (11 7 per 1000), and so also is the birth-rate at 15 0 Children and adults are healthy, and the proportion of people aged 65 and over has risen to 11%, compared with 5% in the year 1901 The principal causes of death are those of middle life, with cardiovascular disease and cancer in the lead The death-rate from infection is insignificant, but there is increasing preoccupation with mental stress and illness, and with the neurotropic viruses

It seems clear that we can expect relatively little further improvement in our vital statistics, unless it becomes possible to prevent or cure cancer and circulatory diseases, and indeed we must expect, in our type of society, to face an increasing burden of the elderly infirm due to the numbers now surviving to later life

Disease in Underdeveloped Areas

We can be said to live in two worlds Approximately one-sixth of the population of the world are now healthy, and wealthy, although perhaps not particularly wise They are able to control their environment and, even more important, their rate of reproduction They have adequate food, shelter, and medical care

Before proceeding further, to discuss the so called underdeveloped areas of the world, it is necessary to stress the fallibility of the statistics Adequate statistics are available for about one-third of the world, rough estimates obtain for another third, while the statistics for the remainder are generally inadequate (United Nations 1952) It should be noted, also, that much of the data on which reliance is placed today was collected in the years immediately after the war It is possible, therefore, that this reflects the fluctuations following the second world war and does not truly mirror the conditions which would prevail in times of stability

The population of the world in 1954, according to the United Nations Statistical Office, was 2652 million (United Nations 1955) More than half (1451 million) lived in Asia, the remainder being distributed as follows

Europe	404	million
America	357	"
Africa	210	"
U S S R (not included in Europe or Asia)	214	"
Oceania	14	"

In parts of Asia and Africa the disease picture resembles that of medieval Europe, for the individual may suffer from five or six diseases The people are at risk from the killing diseases of temperate climates in addition to "tropical" diseases Severe malnutrition is common, and added to this are the harsh physical environment, poverty and ignorance, bad housing, and often the crumbling of the ancient social patterns Birth-rates are high, but so are death rates, and the natural picture of population has been one of slow increase with sharp cuts due to famines or epidemics

That was the picture in many areas until about ten years ago Indeed, the year 1947 may be considered, like the year of the Black Death, a turning point for the world, for it was then that the first effects of the mass attack on malaria became apparent

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* Abridged from an address given to the Science Masters' Association on Jan 3, 1957

It is now possible to launch attacks on disease at national and international levels, and on several fronts at the same time Environmental sanitation is rapidly being improved, and especially the chlorination of water-supplies, so that cholera, dysentery, and enteric fever, are declining in importance Malaria, predominantly a disease of rural areas with 300 million cases a year in the world and 3 million deaths, is now being attacked through the mosquito at a cost of 15–50 cents per head In Ceylon in one year, 1947, the death rate was almost halved from this cause alone Yaws, which affects most land areas between the Tropics, can be cured by one injection of penicillin at a cost of 2 dollars per head Tuberculosis, the greatest killer of all, is now being assailed in many ways, including immunisation with B C G

Bilharzia, estimated in 1947 to affect 114 million people (Stoll 1947), is receiving increasing attention, and so also is hookworm, which by reason of its distribution from 36° north to 30° south of the Equator can affect half of the inhabitants of the world Trachoma, a serious cause of blindness in both arid and wet tropical and subtropical regions, is readily amenable to modern therapeutic and preventive measures

Malnutrition, as evidenced by beriberi, pellagra, scurvy, rickets, and nutritional anæmia, in addition to protein deficiencies under various titles such as that of kwashiorkor, is now being treated on a vast scale by the provision of vitamins and dried milk

The results are, at first sight, catastrophic, for, while death-rates are being cut by half, birth-rates remain high or are rising Examples of the high birth-rates prevailing in various parts of the world are the following

Venezuela	in 1955	47 1
Mexico	in 1954	46 4
Ceylon	in 1955	37 9
Chile	in 1955	35 0
India	in 1955	30 5

The corresponding rate for England and Wales is 15 per 1000 population

Many more people are now surviving to adult life and reproductive ages as a direct result of the control of the killing diseases But other factors are at work also The control of famine, the reduction of losses in small and local wars, improved transport and communications, rising economic standards, education, and good government, are all playing a part

Problems of Population

In Puerto Rico the expectation of life at birth has increased by over one year per annum since 1940 This is at least twice, and often three times, as high as the maximum national rates ever recorded in the populations of the West Even so, the Puerto Rico rates were doubled by Japan between the years 1947 and 1950 and trebled by Ceylon between the years 1946 and 1949 (Stolnitz 1955)

In India the infant mortality rate in 1910 was 260 per 1000 live births In 1951 it had fallen to 116 If this rate can be reduced to 35 within the next twenty years, as seems possible, it will have fallen from 260 to 35 in seventy years

In Brazil the crude death rate for 1940–50 was between 19 and 20 per 1000, whereas the birth rate for the same period was between 43 and 44 The rate of natural increase was 23 per 1000, and the expectation of life from birth has risen to 42 or 43 years

In the Sudan the pilot census of 1953 showed a crude death rate of 37 per 1000 and a birth-rate of 56 per 1000

Many parts of the world are, therefore, able to demonstrate changes in their vital statistics over a period of ten to fifteen years which took us seventy or more years to accomplish They can, in fact, go on and beat the Western figures for low death-rates because of their high proportion of young people

It is at first sight odd that Oceania should have the highest rate of increase at 2 5% per annum, but this is explained by immigration The United States of America and China come next with an increase of 2% per annum followed by Asia, Africa, and the U S S R with about 1 5% per annum Europe is well behind with 0 7% per annum

The average world population increase is about 1 5% per annum, and when it was thought that food production was only increasing at the rate of 1% per annum (0 04% in the Far East), the picture gave cause for immediate alarm The latest reports of food production, both as to quantity and stability of output, are more reassuring (Food and Agriculture Organisation 1956) Even so, after allowing for all statistical fallacies, 100,000 births a day are something to be reckoned with

The most recent World Health Organisation statistics show a tendency to stabilisation of birth and death rates in the period 1951–55, with a slight overall decrease (World Health Organisation 1956) The infant mortality rate is declining rapidly, and in 1955 Sweden set up a new record with 17 infant deaths per 1000 liveborn This is the lowest rate ever recorded in the world, and can be contrasted with 422 per 1000 in Maceio in Brazil in 1943 and 353 in Saigon in Vietnam in 1947 As the improvement of infant mortality rates turns on such matters as family income, feeding, housing, sanitation, the working conditions of women, and the control of mass diseases including malaria, it is a reliable indication of the measure of improvement of those conditions also

It should be remembered that only certain countries have an immediate population problem Egypt, for example, is heavily overpopulated, whereas Iraq and Persia are not In general, the problem appears in its most acute form in islands Quality, as well as quantity, is involved The fertility of the people of agricultural areas is particularly affected, and that of market gardeners and paddy and coconut workers in Ceylon is now 40% higher than that of the people of Ceylon as a whole That is, of course, primarily due to the control of malaria

When discussing the growth of population it is tempting to blame the doctors for upsetting the balance of Nature, and it is often forgotten that the people are themselves demanding the prevention of disease There are many other factors involved, besides the advance of medical science There is, for instance, the cultural pattern which demands large families , the duty, often reinforced by religion, to perpetuate the family , and the need of agricultural peoples, using primitive methods, for large families if they are to survive The removal of taboos on sexual intercourse, which in some parts of India covered as many as 120 days in a year (Chandrasekaran 1954), must also be taken into consideration It is possible also that the biologists may, as a result of their studies of population changes in animals, have something to contribute to our knowledge of the natural rhythm of growth of human populations

Population Control

The most obvious remedy is some form of birth control which would be widely acceptable The various methods include total abstention from sexual intercourse , partial abstention by the rhythm method, which requires an ability to count, the wish to cooperate, and some elementary knowledge of biology , mechanical methods which require a trained physician working in maternity and child welfare centres (which do not yet exist in many areas) and the "little pill," containing some substance which will interfere with the maturation of the sex cells or embryo If and when, the latter becomes available it will need to be tested manufactured on a commercial scale, and sold at prices which the people can afford—its use being acceptable to them

We must face the fact that there is no short cut, and that the present rapid growths of population will involve a period of turbulence and instability for the areas concerned for perhaps fifty years or more

Meanwhile the results of the medical advances have not all been bad Malaria control has resulted in large tracks of land being brought into cultivation, and the improved health of the workers has meant increased production, both of food and of industrial products The control of hookworm alone is said to increase the working efficiency of affected people by 25% or more, and similar results will attend freedom from other diseases The people most concerned are those living in the rural areas of the world and responsible for the production of food Improvements in transport and communications mean, in turn, the possibility of improved distribution of food

There is also the changing attitude towards women, with outlets other than marriage, in the fields of teaching, nursing, and industry Nor must it be forgotten that the means to combat ignorance and prejudice are becoming increasingly available, both by the extension of formal education and by the radio and television

Conclusion

The first and most urgent need is to obtain true and reliable statistics of population and of food production, so that we may have an accurate world picture There is also an urgent need for combined action to study the problems of areas where the pressures seem to be greatest The persons required for such investigations include geographers, biologists, agriculturists, economists, veterinarians, anthropologists, administrators, and medical men

Until we have full knowledge of the problems of population growth it will be as well to observe the ancient maxim, "festina lente," for the happiness of a people does not necessarily turn only on an increased expectation of life

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in the 50 years of sexual activity, a healthy man produces a trillion sperms—to produce 4 children on the average 250,000,000,000 per child To gain an idea of what a trillion really means is like trying to encompass the magnitude of the national debt But let us try On Feb 10, 1938 the editor of the *Baltimore Sun*, concerned with the growing number of persons on the Federal payroll, then 1,000 000 published on the editorial page what looks like a blank, but actually contains a newspaper half tone of 1,000 000 dots —1,000 rows of 1 000 dots each A lot of dots! However, to represent the number of sperms a man can produce in a lifetime would require a million editorial pages like this The paper necessary to produce 1,000,000 such pages would require 5 acres of forest trees Let me however inject at this point that this selfsame man also has a quadrillion of brain cells which are always available for the exercise of reason and self control!—Dr CARL G HARTMAN, *Trans Amer gynec Soc* 1956, 79 xcviii

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REDUCED EFFECT OF HETEROLOGOUS INTRINSIC FACTOR

AFTER PROLONGED ORAL TREATMENT IN PERNICIOUS ANÆMIA

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ORAL administration of vitamin B_{12} plus intrinsic factor represents a rational treatment of pernicious anæmia, and this combination has come into wide use in the past three or four years With such treatment, however, in some cases a good initial response has been followed by a decrease in hæmoglobin level and red-cell count (Mollin and Ross 1954, Meulengracht 1955, Norregaard 1955, Lowenstein et al 1956)

In the past two years we have observed this phenomenon several times Occasionally, the blood status may be improved by increasing the dosage, but usually the oral treatment has to be supplemented by injections Vitamin B_{12} intramuscularly or liver preparations with vitamin B_{12} have always resulted in hæmatological remission Fig 1 illustrates this form of response in one of our patients

Using ^{60}Co-labelled vitamin B_{12} we have investigated the absorption of vitamin B_{12} and the effect of intrinsic factor in different groups of patients with pernicious anæmia As a result of this investigation, we have demonstrated the reason why oral treatment fails in some patients

Material and Method

Our series of patients may be divided into three groups A, untreated pernicious anæmia, B, injection-treated, with vitamin B_{12} or liver preparation, C, orally treated for six months to four years with preparations containing hog pyloric mucosa plus vitamin B_{12}

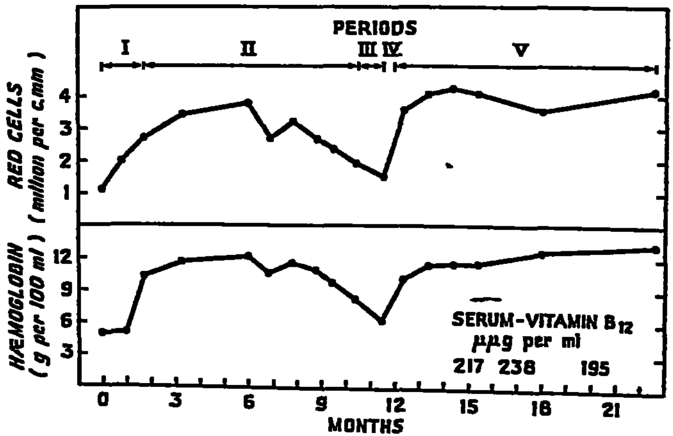

Fig 1—Blood findings and treatment in case of pernicious anæmia.

Period I 'Cycoplex' 6 capsules daily Period II. cycoplex 2 capsules daily Period III cycoplex 6 capsules daily Period IV liver extract intramuscularly for six days (a total amount of 540 μg vitamin B_{12}) Period V 'Exopylorin' 5 g daily (1 capsule of cycoplex contains vitamin B_{12} 5 μg plus dried hog pyloric mucosa 50 mg 5 g exopylorin contains 3 5 g dried total hog pyloric gastric wall plus 1 5 g dried liver residue from manufacture of liver-extracts)

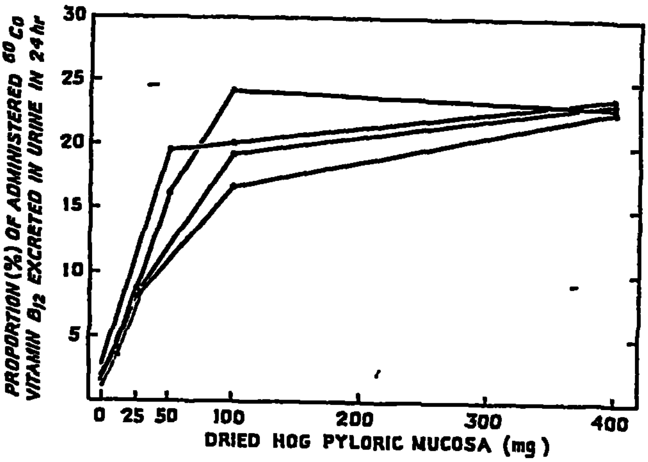

Fig 2—Urinary excretion in Schilling test performed with different amounts of hog pyloric mucosa in 4 patients with untreated pernicious anæmia

The method used in the investigation was the Schilling (urinary excretion) test 0 5 µg labelled vitamin B_{12} (0 1 µC) is given by mouth, and two hours later 1 mg unlabelled B_{12} is injected intramuscularly, urine is collected for twenty four hours All patients had a normal kidney function as measured by endogenous creatinine clearance In healthy subjects we had previously found by this technique a urinary excretion of 10–38% of the dose In patients with pernicious anæmia the excretion ranged from 0 to 8%

Results

Fig 2 shows the results in untreated patients (group A) A dosage response curve was plotted for the preparation dried hog pyloric mucosa An increased dose of intrinsic factor was found to give a larger urinary excretion, indicating increased intestinal absorption This "stoichiometric" relationship applies only, however, up to a certain limit If the amount of intrinsic factor is increased beyond this limit, there will be only a slight increase in the absorption of vitamin B_{12} These results confirm previous findings

In the same way, we studied 2 patients who had been on injection treatment for more than three years (group B) Fig 3 indicates that these patients show the same absorption as untreated patients

On the other hand, the study of 9 patients who had been on oral treatment (group C) for six months to four years gave quite a different result Fig 4 shows that of these 9 patients 7 exhibited an absorption of vitamin B_{12} which, with the same dose of intrinsic factor, was decidedly inferior to that found in groups A and B Only 2 patients of group C showed the same absorption as groups A and B Of the 7 patients with poor absorption only 3 had been showing a falling hæmatological status for some months The duration of the disease did not appear to be of decisive significance

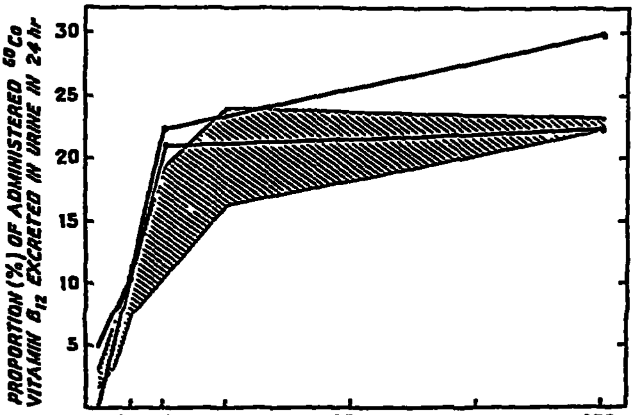

Fig 3—Urinary excretion in Schilling test performed with different amounts of hog pyloric mucosa in 2 patients with pernicious anæmia treated by injection for three years (Hatched area represents values for 4 untreated patients)

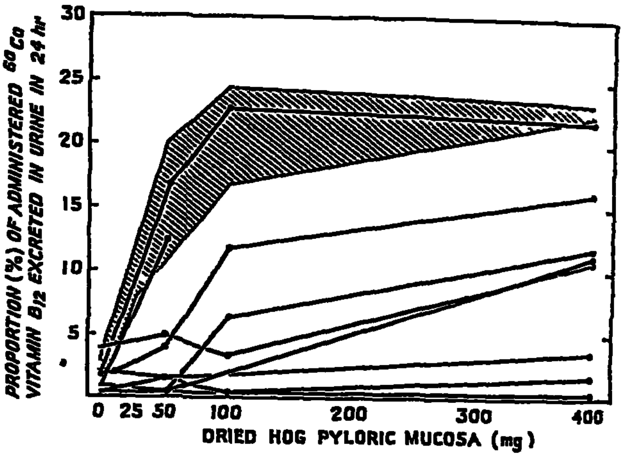

Fig 4—Urinary excretion in Schilling test performed with different amounts of hog pyloric mucosa in 9 patients with pernicious anæmia, orally treated for a half to four years (Hatched area represents values for 4 untreated patients)

In addition to these 9 patients, we studied 6, also on oral treatment They are not included in fig 4, as they had only a few doses of intrinsic factor, but the results were exactly the same

URINARY EXCRETION IN SCHILLING TEST PERFORMED WITHOUT INTRINSIC FACTOR AND WITH TWO DIFFERENT SOURCES OF INTRINSIC FACTOR FIGURES ARE PERCENTAGES OF ADMINISTERED ^{60}Co VITAMIN B_{12} EXCRETED IN URINE IN TWENTY FOUR HOURS

Patients	Intrinsic factor		
	None	400 mg dried hog pyloric mucosa	100 ml human gastric juice
Orally treated pernicious anæmia	1 7 0 0 3 7 0 6 1 8	0 1 8 3 7 11 2 11 6 16 4	21 0 23 4 15 5 30 1 22 0 18 8
Untreated pernicious anæmia	1 7 0 7 2 7	22 6 22 2 23 2	20 9 24 3 20 7

The intrinsic factor preparation used in these experiments was not highly purified We therefore repeated the experiments, using a highly purified preparation of intrinsic factor also made of hog pyloric mucosa In untreated and injection treated patients 2 mg of this preparation gave maximal absorption of vitamin B_{12} whereas in orally treated patients even 4 mg gave very poor absorption

As far as we know, this finding has not previously been reported It raises numerous new problems of theoretical and practical interest

All commercial stomach preparations are made of hog stomachs, so the intrinsic factor administered in treatment is of heterologous origin Our orally treated patients with poor absorption were therefore given human intrinsic factor in the form *of 100 ml human* gastric juice administered with the labelled vitamin B_{12} The results are given in the accompanying table, which shows that after administration of human intrinsic factor there is no demonstrable difference between orally treated and untreated patients

2 patients of group C were also given 100 ml human gastric juice, but neutralised to pH 7 This resulted in exactly the same good absorption as administration of acid gastric juice Conversely, we were unable to increase the absorption of B_{12} in group C by adding 100 ml 0 1 *N* HCl plus pepsin to the hog pyloric mucosa preparation

At present we cannot explain these phenomena Possibly the intramural "intestinal acceptor" postulated by Glass et al (1954) is affected by long term treatment with heterologous intrinsic factor

Summary

In patients with untreated pernicious anæmia the absorption of vitamin B_{12} can be considerably increased by quite small amounts of hog pyloric preparations

After treatment for some time with preparations of vitamin B_{12} plus pyloric mucosa, this absorption is more or less distinctly "blocked" in some cases The cause of the "block" is not yet known, but it is not present when homologous intrinsic factor is administered

This "block" is presumably the cause of the failure in some cases of oral treatment with preparations of vitamin B_{12} plus intrinsic factor.

We wish to thank Dr Lester Smith of the research division, Glaxo Laboratories, for supplying part of the labelled vitamin B_{12}, and Medicinalco Ltd and Gea Ltd, both of Copenhagen, for liberal supplies of the intrinsic-factor preparations This study was supported in part by the Statens Videnskabsfond, University of Copenhagen

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CLINICAL STUDIES OF THE HYPOGLYCÆMIC ACTION OF THE SULPHONYLUREAS

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CARBUTAMIDE (N (*p* aminophenylsulphonyl) N^1 [*n*-butyl] urea) and tolbutamide (N (*p*-tolylsulphonyl) N^1 [*n* butyl] urea) in a dosage of 20–80 mg per kg of body-weight daily (Bertram et al 1955, Franke and Fuchs 1955, *Deutsche Medizinische Wochenschrift* 1956) reduces the blood sugar level in healthy people and some diabetics

Several points in carbohydrate metabolism have been suggested for the action of these sulphonylureas they may reduce the absorption of carbohydrate from the gut (Friedlich et al 1956), stimulate the secretion of insulin from the pancreas (Kracht and Rausch Stroomann 1956), enhance the action of insulin in the tissues by inhibition of the enzymes which destroy insulin (Mirsky et al 1956), depress the secretion of the hyperglycæmic factor, glucagon, from the α cells of the pancreatic islets, or inhibit hepatic glucose-6-phosphatase with the result that the breakdown of glycogen to glucose is reduced (Hawkins et al 1956)

Most of these hypotheses are based on experiments with large doses in animals We undertook the following studies to determine whether evidence for any of them could be obtained in man

Investigation

To investigate different aspects of carbohydrate metabolism the following tests were made before, and repeated during, treatment with the sulphonylureas

(1) Carbohydrate digestion and absorption were investigated by using a standard breakfast test (Duncan 1947) and by oral and intravenous glucose tolerance tests

(2) Sensitivity to the action of insulin was investigated by combining an injection of soluble insulin with the above mentioned tests

(3) The arteriovenous difference in blood-sugar levels was measured during the glucose tests

(4) Because of its bearing on the arteriovenous difference the peripheral blood-flow was measured in the forearm

(5) Possible alteration of intermediary carbohydrate metabolism was investigated by measuring the level of α keto acids in the blood during the tests

(6) Glycogenolysis in fasting patients was investigated by injecting a test dose of glucagon intravenously

Clinical Material

29 patients, with fasting blood-sugar levels above 100 mg per 100 ml, were selected from the Guy's Hospital diabetic clinic because it seemed likely that they would respond to the hypoglycæmic agents, or because diet and insulin had not controlled their diabetes

The group consisted of 17 females and 12 males aged 16–82 (mean 61) The average duration of diabetes was 6¹/₂ years 11 patients were obese and 7 thin 20 of them had complications of diabetic origin 10 had diabetic cataracts, 7 diabetic retinitis, 10 vascular disease, 3 albuminuria and 11 neuropathy

Each patient was studied in hospital for at least three weeks The diet which had been prescribed at the clinic was continued in hospital Its preparation was supervised by a dietitian Any insulin required was given as the soluble preparation two or three times a day

Laboratory Methods

Routine

The 24-hour urinary excretion of glucose was measured by the quantitative Benedict (1911) method, and colorimetric estimations of glycosuria and acetonuria were made at 4 hour intervals throughout the day. Samples of capillary blood were taken each day at 2 30 P M for estimation of the blood sugar level by the Schaffer-Hartmann method as described by King and Wootton (1956) The patients were weighed and had their blood-pressure recorded every day, and, when carbutamide was given, its concentration in the blood was estimated daily Blood-counts, including a platelet-count, were done before and during treatment

Experimental

After at least 5 days' acclimatisation to the hospital, control tests were made in different patients In each test the patient fasted overnight (16 hours) and in the morning remained quietly in bed No therapeutic insulin was given on the morning of the tests Samples of fasting capillary blood was taken for estimating blood-sugar levels, and venous samples were drawn without stasis from an antecubital vein for measuring blood-sugar and blood α-keto acid levels by the method of Friedemann and Haugen (1943) Carbohydrate alone or with insulin was given in one of three ways 50 g

TABLE I—EFFECT OF SULPHONYLUREAS ON FASTING BLOOD-SUGAR LEVEL

Case no	Sex	Age (yr)	Age at diagnosis (yr)	Fasting blood sugar level	
				Before S urea	% reduction with S urea
1	F	78	56	234	61
2	F	75	75	220	61
3	M	57	52	154	60
4	F	67	67	320	58
5	F	38	20	285	57
6	M	40	36	201	56
7	F	70	62	200	55
8	F	82	81	245	53
9	F	73	60	337	51
10	F	65	60	126	45
11	F	63	57	145	39
12	F	16	12	307	37
13	F	62	59	195	37
14	M	82	82	104	37
15	F	74	74	145	37
16	M	55	54	139	36
17	M	34	34	225	31
18	F	76	74	184	30
19	F	59	51	246	29
20	M	81	79	114	24
21	M	55	33	303	18
22	M	58	58	126	17
23	M	50	43	179	8
24	F	62	62	250	6
25	F	69	60	346	3
26	M	71	66	280	1
27	M	64	63	140	0
28	F	47	30	170	−1
29	M	43	33	246	−11

of glucose dissolved in water was given by mouth, or 20 g. of glucose was given as 50% solution intravenously, or a carbohydrate meal was eaten. In the insulin tests soluble insulin (7 units) was injected intravenously as the glucose was administered or immediately after the test breakfast. Capillary blood was taken at 15-minute intervals for the first hour and at 90 minutes. A second venous sample was drawn for estimating blood-sugar and blood-α-keto-acid levels at 1 hour. In the glucagon tests 1.0 mg. of glucagon was injected intravenously, and capillary blood for estimating blood-sugar levels was obtained at 15 minute intervals for an hour and at 90 minutes after the glucagon had been given. Initial doses of 3.0–4.0 g. of sulphonylurea were followed by 2.0–3.0 g. daily, until the levels of sugar in blood and urine fell. The dose was then reduced as necessary to prevent hypoglycæmia. If the level of glucose in blood and urine had not fallen after 3 days, the dosage was raised to 3.0–4.5 g. daily to achieve the required effect. The tests were then repeated in the same patients at least 7 days after the start of sulphonylurea treatment.

In certain special investigations described the forearm blood-flow was measured in conjunction with capillary blood sugar estimations. The blood-flow was determined with a venous occlusion plethysmograph (Grant 1938) operated at 34°C. Three blood-flow determinations were made before each capillary sample was withdrawn. In some patients forearm blood-flow was measured in the early afternoon before and during sulphonylurea treatment.

Results

Clinical Findings

It is not our purpose to describe the clinical aspects of this study. Our findings agree with those of the symposia published during 1956 in the *Deutsche Medizinische Wochenschrift* (1956), *Canadian Medical Association Journal* (1956), *British Medical Journal* (1956), and *Metabolism* (1956).

Blood sugar

A hundred carbohydrate tolerance tests of various types were made. The most obvious change in 22 of 29 patients during sulphonylurea therapy was *a fall in the fasting blood sugar level*. In table I we have arranged our patients in order of % fall in fasting blood sugar levels. We have arbitrarily classified those with a *fall* of more than 15% as having reacted (cases 1–22). This classification is not intended to imply that the diabetes of the patients who react could be controlled satisfactorily by sulphonylurea compounds either alone or in conjunction with insulin. We now know that in only 12 of these patients was sulphonylurea of practical value in their prolonged management.

Table II summarises the mean capillary blood sugar levels in the various tests carried out in the patients who responded. The lower level of fasting blood sugar during treatment is not associated with any marked change in the mean rise, or fall, of blood sugar during the tests. The sulphonylureas caused no significant difference in the reduction by insulin of the hyperglycæmia following the oral administration of glucose or the standard breakfast, but *in the intravenous glucose insulin test* the changes in blood sugar level at 60 and 90 minutes, taken together, were significantly different during treatment ($p = 0.05$).

The arteriovenous differences of blood sugar levels, in both the fasting state and at 1 hour during the various tests, were so variable that it would only be misleading to present them as indicating the peripheral uptake of glucose. This question is discussed later.

TABLE II—BLOOD-SUGAR AND BLOOD-KETO-ACID LEVELS IN VARIOUS TESTS BEFORE AND DURING SULPHONYLUREA TREATMENT

Test		Case nos	Blood sugar level (mg. per 100 ml.)					Mean rise in blood α-keto acid level at 60 min. (mg. per 100 g.)
			Mean fasting	Mean change at				
				15 min	30 min	60 min	90 min	
1 *Oral glucose*	Before During	3, 7, 11, 12, 17, 18	211 136	+61 +58	+92 +78	+150 +135	+130 +126	0.18 0.01
2 *Oral glucose and insulin*	Before During	1, 3, 7, 11, 12, 13, 17, 18, 21	211 128	+1 +2	+19 +36	+80 +66	+83 +78	0.70 0.63
3 *Insulin response from 1 and 2*	Before During	3, 7, 11, 12, 17, 18		62 48	13 39	86 85	57 75	
4 *Intravenous glucose*	Before During	4, 5, 6, 14, 15	226 100	+116 +121	+99 +96	−56 −57	−13 −35	0.03 0.13
5 *Intravenous glucose and insulin*	Before During	4, 6, 11, 15, 22	176 105	−80 −92	−53 −47	−30 −11	1 −21	0.72 0.13
6 *Breakfast*	Before During	2, 8, 10, 16, 19, 20	177 94		−86 −73	−125 115	−133 −118	
7 *Breakfast and insulin*	Before During	2, 8, 10, 16, 19, 20	177 109		−69 −58	−80 +86	−52 −81	

Blood-α-keto acids

The mean fasting level of blood-α-keto acids before treatment was within normal limits (0 96 mg per 100 g) There was a small but statistically significant (p = 0 02) fall to 0 86 mg per 100 g during sulphonylurea therapy The changes in the α-keto acid levels at 1 hour in the various glucose-tolerance tests are shown in table II All are within normal limits, and none of the changes observed after therapy is statistically significant It is concluded that small changes in the fasting level of blood α-keto-acid may take place during sulphonylurea treatment, but further studies are required to define which α-keto-acids are affected

Peripheral Blood-flow

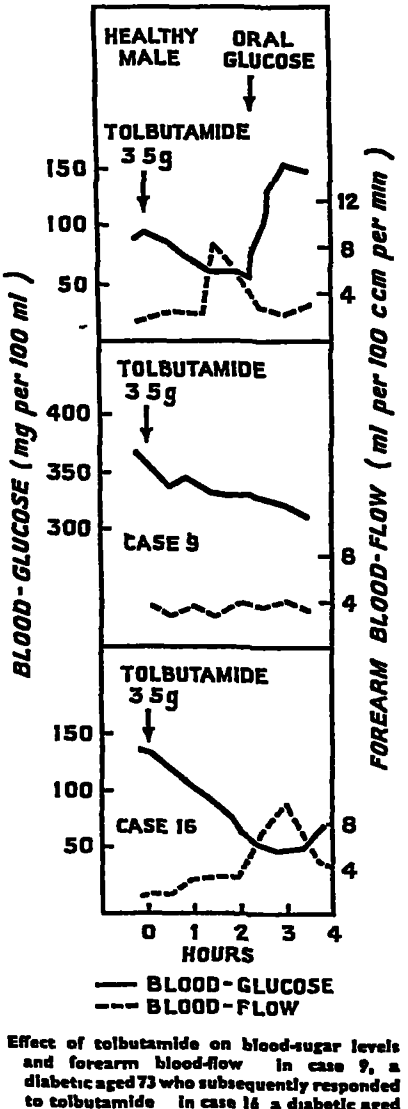
The following studies stemmed from the appreciation that changes in peripheral blood-flow must be taken into account if arteriovenous differences are to be regarded as an indication of the rate of uptake of glucose by the tissues

The forearm blood-flow was measured in 7 diabetics before and after more than 7 days' treatment with tolbutamide There was an increase in resting flow from a mean of 2 06 to 2 87 ml per 100 ml of forearm a minute For the group of patients this evidence of vasodilatation is just statistically significant (p = 0 05) This finding obviously complicates the interpretation of any arteriovenous differences in blood-sugar levels

The possibility *that tolbutamide* has a vasodilator effect was investigated The effect of 3 5 g of tolbutamide on the blood-sugar level and forearm blood-flow during the first 4 hours after its ingestion was observed in 3 fasting persons a diabetic aged 73 (case 9) who did not develop hypoglycæmia during this time, a diabetic aged 55 (case 16) who did, and a healthy male, who also developed hypoglycæmia The results of these tests are shown in the accompanying figure

In the elderly diabetic the blood sugar level fell only from 370 to 315 mg per 100 ml, and there was no significant change in blood flow

In the other diabetic the blood-sugar level fell from 145 to 55 mg per 100 ml, when the forearm blood-flow abruptly increased three fold and then returned to normal as the blood sugar level rose again



Effect of tolbutamide on blood-sugar levels and forearm blood-flow in case 9, a diabetic aged 73 who subsequently responded to tolbutamide in case 16 a diabetic aged 55 who responded more rapidly and in a healthy male

TABLE III—MEAN BLOOD SUGAR LEVELS IN GLUCAGON TEST BEFORE AND DURING SULPHONYLUREA TREATMENT

—	Mean blood sugar level (mg per 100 ml)					
	Fasting	Change at				
		15 min	30 min.	45 min	60 min	90 min
Before	216	—43	+62	+62	+52	+31
During	105	+44	+59	+69	+39	+23

In the healthy male the blood sugar level fell from 90 to 56 mg per 100 ml There was an abrupt fourfold increase of forearm blood-flow at the low blood sugar levels 50 mg of glucose was given, and the blood-sugar level promptly rose to 140 mg per 100 ml with a concomitant decrease in blood flow The blood sugar level subsequently fell (not shown in the figure), indicating that the tolbutamide was still active

We, like others, have observed a similar vasodilatation not only during hypoglycæmia caused by insulin but also during the infusion of adrenaline However, we are careful to attribute the vasodilatation only to the general response to hypoglycæmia, since Ginsburg and Paton (1956) have reported it in hypoglycæmic adrenalectomised patients Though tolbutamide does not immediately cause vasodilatation, the possibility that its prolonged administration is associated with vasodilatation requires further investigation

Glucagon Tests

The fasting blood sugar level is probably maintained by the continuous breakdown of hepatic glycogen to glucose—a breakdown in which the enzyme glucose 6-phosphatase is concerned The results of some experiments on animals suggest that the sulphonylureas inhibit glucose 6 phosphatase, and the results of the tolerance tests do not contradict this hypothesis We tested the facility with which glycogen is broken down to glucose, before and after sulphonylurea therapy, by observing the hyperglycæmic effect of 1 mg of glucagon on 9 patients who responded to sulphonylureas by a fall of fasting blood-sugar level The results are given in table III, which shows that, after treatment, there is a slight reduction of the hyperglycæmic effect of glucagon towards the end of the test, but none of the changes is significant We therefore conclude that further studies are unlikely to show any significant effect of sulphonylurea on the hyperglycæmic response to 1 mg of glucagon

Discussion

The results of our glucose-tolerance tests are essentially similar to those reported by other workers (Duncan et al 1956, Fajans et al 1956, Purnell et al 1956, Renold et al 1956)

The breakfast and the glucose tolerance tests show that the sulphonylureas neither retard the digestion of carbohydrates nor impede the absorption of glucose Furthermore, such actions would not explain the fall of blood sugar level when these compounds are given to fasting people

Phosphorylation and dephosphorylation of glucose take place in the liver and in the cells lining the intestines The fact that the absorption of glucose is unaltered shows that the sulphonylureas do not interfere with the action of glucose 6 phosphatase in the gut wall Unaltered glycogenolysis after the intravenous injection of glucagon indicates that the glucose 6 phosphatase of the liver is not blocked either

We have little evidence that the sulphonylureas affect the action of injected insulin Response to insulin can be judged by the alteration of the oral glucose curve when insulin is given The absence of any significant change in this during sulphonylurea treatment argues against enhanced insulin action (table II) On the other hand, during sulphonylurea treatment the action was achieved at a lower level of blood-sugar, which fact might mean that the insulin was more effective We find it difficult to accept this proposition We would expect an enhanced insulin action to alter the form of the glucose insulin curves In fact the sulphonylureas regularly produce lower but otherwise unchanged oral glucose insulin curves Therefore we are not persuaded that they render insulin more effective by suppression of insulinase or by interfering with insulin binding in the plasma

The only significant change in the various tolerance tests during sulphonylurea therapy took place at 60 and 90 minutes in the intravenous glucose insulin tests, when the blood sugar level was falling below the fasting level The records of Cox et al (1956) show a similar effect

This inability to regulate a falling blood-sugar level during treatment could be due to increased secretion of insulin or to a failure of the adrenal or pancreatic hyperglycæmic mechanisms Loubatières (1946) first suggested that the sulphonylureas act by stimulating the secretion of insulin Since we know that our patients were sensitive to insulin we cannot reconcile his hypothesis with the unaltered tolerance of oral and intravenous glucose during treatment Furthermore, the changes in fasting level of blood α-keto-acids was in the reverse direction to that observed after the injection of insulin The persistence of the diabetic form of glucose tolerance during treatment is evidence that the sulphonylureas do not truly correct the diabetic state, which fact is pertinent to the question of their ultimate place in the treatment of diabetes mellitus

The sulphonylureas do not act by blocking either adrenal or pituitary hormones There is evidence that they lower the blood-sugar level in patients with pituitary insufficiency and in patients with Addison's disease (Goetz et al 1956) and in hypophysectomised and in adrenalectomised animals (Houssay and Penhos 1956) Moorhouse and Kark (1956) have shown that the hyperglycæmic response to 1 mg of adrenaline is unaltered by tolbutamide, and we have shown that the adrenaline-like reaction to hypoglycæmia caused by tolbutamide occurs as readily as when the hypoglycæmia is caused by insulin

There remains for discussion the possibility that the sulphonylureas affect the production or action of glucagon Our patients showed no change in the hyperglycæmia after the administration of 1 mg of glucagon, indicating that there was no gross inhibition of the response to this large dose Similar results showing that the action of such doses of glucagon is not affected are mentioned by other workers (Moorhouse and Kark 1956, Volk et al 1956) We cannot draw any conclusion about the production of glucagon, there being no reliable method of estimating glucagon levels in man We had hoped to derive some information from our measurements of the arteriovenous differences in blood sugar levels because Elrick (1956) had shown that the administration of glucagon increased that difference We noted a statistically insignificant decrease of the arteriovenous difference at 1 hour in most tolerance tests after the administration of sulphonylurea Unfortunately no definite conclusions about the production of glucagon can be drawn from these results because the arteriovenous difference must depend on the peripheral blood flow, and we cannot be sure that this was the same when each test was repeated Clearly, if the action of the sulphonylureas on glucagon is to be settled by measuring the uptake of glucose more elaborate techniques than have been used hitherto will be required

Thus we have no evidence that the hypoglycæmic action of the sulphonylureas is mediated by any of the mechanisms so far suggested by the results of experiments on animals Although some of our findings might be construed as arguments that the sulphonylureas enhance the action of insulin, our present view is that the predominant changes occur in the mechanisms controlling the fasting blood sugar level, and that all other factors are essentially unaffected

Summary

The effect of 7 days' treatment with sulphonylurea (with and without insulin) on various carbohydrate tolerance tests, arteriovenous differences in blood sugar levels, blood-α-keto acid levels, peripheral blood flow, and the hyperglycæmic response to injected glucagon were studied in 29 diabetics

In 22 patients the fasting blood sugar fell more than 15% The only significant ($p = 0\ 05$) change after treatment in the various tests was in the intravenous glucose tolerance test, where the blood sugar level fell below the fasting level at 60 and 90 minutes

There was a significant ($p = 0\ 05$) increase in the forearm blood flow during treatment Such changes in peripheral blood flow complicate the interpretation of arteriovenous differences in blood-sugar levels There was a small but significant ($p = 0\ 02$) fall in the fasting level of α keto acids

The hyperglycæmic response to 1 mg of glucagon injected intravenously was not significantly changed after treatment

The hypoglycæmic action of the sulphonylureas in diabetics does not appear to be mediated by any of the mechanisms so far suggested by the results of experiments on animals

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BENIGN MYALGIC ENCEPHALOMYELITIS

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REPORTS have lately appeared of several similar outbreaks of acute paretic illness, of which four occurred in Britain, and the term "benign myalgic encephalomyelitis" has been suggested for this condition (*Lancet* 1956) In one of these outbreaks infectious diseases staff in a Coventry hospital were affected when nursing similar cases admitted as poliomyelitis from the surrounding area in the summer of 1953 (Macrae and Galpine 1954), in three of the staff an electromyogram was taken and an abnormal discrete pattern found Ramsay and O'Sullivan (1956) describe cases seen in an area in north-west London and give details of abnormal electromyograms

We report here 7 further cases which arose sporadically in the Coventry area in 1956 They gave clinical and electromyographic findings which recalled those of the paretic cases seen in 1953

Case 1, female, married, aged 22, admitted July 10 as ? paralytic poliomyelitis, discharged July 26

Case 2, female, married, aged 20, admitted July 13 as ? paralytic poliomyelitis, discharged Aug 14

Case 3, male, unmarried, aged 17, admitted July 20 as ? paralytic poliomyelitis, discharged Aug 24

Case 4, female, married, aged 44, admitted Aug 29 as pyrexia of unknown origin, discharged Sept 14

Case 5, male, married, aged 33, admitted Sept 25 as ? paralytic poliomyelitis, discharged Oct 18

Case 6, male, married, aged 28, admitted Sept 27 as ? paralytic poliomyelitis, discharged Oct 8

Case 7, female, married, aged 40, admitted Oct 6 as ? meningitis, discharged Nov 9

General Clinical Description

Early symptoms included mild sore throat, lassitude, drowsiness, vomiting, nuchal pain, backache, giddiness, and headache Slight or moderate stiffness was variably found in the neck or in the back, with or without Kernig's sign, but in case 2 these signs were altogether absent In case 6 muscle tone was diffusely increased in the paretic right arm In case 5 spasm developed in the left calf Muscle tone in the affected limbs did not otherwise seem abnormal

Paresis was found in all the cases It was diffuse and tended to fluctuate and shift In cases 1–6 it varied in onset from the first to the fifth day of disease In case 7 there was a history of weakness and clumsiness in the left arm for the preceding 2 months, hindering her domestic activities and occasionally making her drop things (This patient had the blood picture of glandular fever but was apyrexial, small lymphatic glands were palpable in the neck only increase of symptoms with vomiting, severe occipital headache, and slight nuchal rigidity prompted her admission to hospital as ? meningitis) In several cases weakness affected two or three limbs, tending later to predominate in one, in other cases one limb alone was weak The limbs predominantly affected were right leg (2 cases), left leg (3 cases), right arm (1 case), and left arm (1 case) Ability to use a limb ranged from frank immobility to slight reduction in power detectable on careful testing against resistance and accompanied by aching, "heaviness," and undue fatigability Inadvertent muscular action in an apparently paralysed limb was seen in case 1 During recovery case 2 was startled by a transient nocturnal increase of paresis in the legs Complaints were made of "slight cramps," "spidery" or "wormy" sensations, and of a limb disturbing rest by "jumping" Fasciculation was observed in case 3, the patient also complained of transient dyspnœa and intermittent diplopia 3 patients had difficulty in starting micturition, and 1 had incontinence of urine Slow coarse intention tremor was seen in several cases

Tendon-reflexes were brisk and equal Plantar responses were flexor but tended to be feeble and indeterminate in affected limbs The superficial abdominal reflexes were present Paræsthesiæ, diffuse aches, and muscle tenderness occurred In case 1 (see below) cutaneous and deep anæsthesia was found in the paretic limbs generally and an area of hyperæsthesia in one axilla In case 6 hypoæsthesia was found in the affected right arm from mid-forearm downwards together with a degree of astereognosis in the right hand Case 5 had hyperæsthesia over the extensor surface of the upper arms Case 2 complained of photophobia and hyperacusis and vague abdominal tenderness with pain on deep inspiration Several patients complained of diminished mental grasp, which returned in convalescence

No enlargement of liver or spleen was found Small shotty lymphatic glands were palpated in the posterior cervical triangles in cases 1, 3, and 7 (mentioned above) They were smaller, for example, than those of a typical case of rubella Cases 6 and 7 were apyrexial Case 4 had a continued pyrexia (reaching above 103°F) for five days In other cases low intermittent pyrexia (99–100°F) occurred

All the patients were ambulant when discharged after a hospital stay of from eleven days to five weeks All except case 5 were available for follow-up in the third month from admission At this time recovery appeared satisfactory in cases 2 and 3 Aching, "heaviness," or pins and needles in the affected limbs, especially after use was variously complained of by cases 1, 4, 6, and 7 Full power had returned in case 4, but there was slight reduction of power against resistance in case 1 (dorsi flexors of left foot), case 6 (right arm), and case 7 (left arm) A fine tremor showed in the right hand of case 6 after brief exertion, and his right arm, if forced to give way, did so in a cog-wheel fashion

Illustrative Case-record

Case 1 is representative clinically and remarkable in having been admitted for a similar illness in 1953

A married female textile machinist, aged 22, developed a mild sore throat which cleared in two days Three days later she had headache and pain at the nape of her neck, giddiness, lassitude, hot and cold "flushes," aching in her right arm, and difficulty in gripping things, her legs became heavy and hard to lift, and cramps and profuse sweats occurred She lost power in the involved limbs and was admitted as a case of paralytic poliomyelitis

Previous Illness

Three years previously (1953) she had been admitted with a similar history (as were many others at that time) Her legs alone were involved at first, but shortly after admission her recti abdominis muscles became weak, dyspnœa developed and a cabinet respirator was prepared for her She improved, however, and it was not used. Her cerebrospinal fluid (C S F) was normal Within six days some recovery was evident in her abdominal muscles and legs and on discharge a fortnight later she was clinically normal An appointment was made for her follow up but she felt so well that she did not keep it From that time until the present illness she had not complained and did not have any comparable illness Several weeks after her discharge in 1953 cases of a similar kind began to occur among the nurses of the hospital, and in retrospect the original diagnosis of paralytic poliomyelitis was altered to that of an unknown infection simulating that illness

Examination

On admission she was apyrexial, anxious, rational, and coöperative and mentioned that she had had "polio" three years previously She complained of headache, numbness, and inability to lift her right arm and both legs Just before admission the affected limbs had been aching, and she was relieved when this gave way to numbness Slight nuchal rigidity and a positive Kernig's sign were present Abdominal reflexes were elicited but were weaker than normal, and vague abdominal pains were complained of Tendon reflexes were exaggerated Cutaneous sensibility to touch, pain, and temperature and position sense were absent in the right upper and both lower limbs, and firm pressure over the Achilles tendons did not cause pain There was hyperæsthesia in the right axilla The plantar responses were inconclusive Shotty glands were palpated in the posterior cervical triangles Incontinence of urine occurred in the ambulance and twice after admission

Progress

During her stay in hospital the patient had low irregular pyrexia (99 2°F being the highest recorded) Within two days sensation and much power had returned to her arm, next day her left leg was greatly improved, and by the next her right leg had also become normal This was the order in which the limbs had become affected Sensation both superficial and deep was restored, and she could walk unaided She commented spontaneously that her concentration was bad and that she felt depressed although she had not previously been that way inclined Diplopia and "spots before her eyes" were other features and they cleared up within a few days On discharge seventeen days after admission she appeared to have returned completely to normal

Follow up several weeks later showed, however, that there was slight weakness of the dorsiflexors of the left foot when tested against resistance The patient received physiotherapy, and on further follow up two months later weakness was still just detectable, but she was without disability

Investigations

Blood —If 2500 per c mm is taken as the lower limit of normal of absolute numbers of neutrophils (Dacie 1956), 2 patients had neutropenia, 2 others less than 3000 per c mm, and the highest number found was 3068 per c mm In 2 cases occasional atypical lymphocytes were found In case 7 the blood picture of glandular fever was found total leucocytes 5600 per c mm (lymphocytes 35%, atypical lymphocytes 28%, glandular fever cells 28%, monocytes 9%) A month later the glandular fever cells had disappeared The Paul Bunnell test was + 1/128 (after absorption + 1/80, ± 1/160) and later + 1/256 Erythrocyte sedimentation rates and liver function tests were normal in all the cases

C S F —Cell counts and protein and sugar values were normal except for a slight increase of protein in 3 cases (60, 50, and 80 mg per 100 ml)

Electrodiagnosis —Stimulation of the external popliteal nerve in the 5 cases having weakness of the tibialis anticus muscle showed retention of nerve conduction, muscle response being brisk Electromyography with needle exploration of the muscles showed no fibrillation potentials or other signs of spontaneous activity, in all the cases grouping and reduction in number of the motor unit potentials on volition were found Some potentials were polyphasic and often of very large amplitude

Electro encephalography was performed in cases 1, 2, and 3 and was normal in 1 and 3 Case 2 showed a basic alpha rhythm of 10 cycles per sec in the postcentral leads at potentials up to 50 µV This rhythmic activity was disturbed at times by irregular slower activity (about 7 cycles per sec) of low amplitude this being more noticeable in the transverse leads These minor irregularities were deemed to be within normal limits

Virus investigations made in cases 1, 2, and 3 did not reveal the presence of any cytopathogenic agent in the fæces and serological tests for poliomyelitis were negative

Discussion

These 7 cases, though resembling those seen in the outbreak of "poliomyelitis like illness" in Coventry in 1953, were less severe than some in that year The kaleidoscopic clinical picture did not hide their similarity to each other Laboratory investigations were, as in 1953, largely unrewarding, but case 7 showed the hæmatology of glandular fever Neurological complications occasionally develop in glandular fever (Fullerton and Smith 1951), but in this case it seems likely that the weakness in the left arm (of two months' standing) preceded the mononucleosis Bowie (1954) regards sporadic glandular fever as a syndrome occurring in people appropriately sensitised by a previous infection and reinfected "with the same or a closely allied organism" 2 other patients had atypical lymphocytes In the C S F the cytology was normal, but in 3 patients the protein content was a little increased As in all previously reported series virus investigations were negative

Electromyography was abnormal in all the cases, recalling that of the Coventry outbreak in 1953 and that described by Ramsay and O'Sullivan (1956), who compare their findings to the so-called myelopathic pattern of early motor involvement at cord level described by Bauwens (1955) Nevertheless the characteristic clinical or electrodiagnostic picture of lower motor neurone degeneration did not develop as in prolonged paralysis in paralytic poliomyelitis, and, in the 3 cases so tested nerve conduction remained good

Electro encephalograms were obtained in 3 cases, although these were all within normal range, 1 showed minor irregularities similar to those mentioned by Ramsay and O'Sullivan (1956)

The anomalous clinical picture and negative or minimal laboratory findings in some instances aroused suspicion of hysteria Against this is the cumulative weight of such considerations as the underlying consistency in the clinical picture, the local prevalences, the lack of general correlation with the hysterical temperament, the pyrexia of some patients and the abnormal electromyographic findings The latter are of particular value in confirming the presence of an organic lesion (*Lancet* 1956)

Summary

5 cases of suspected paralytic poliomyelitis, 1 of suspected meningitis, and 1 of pyrexia of unknown origin admitted to a Coventry hospital in 1956 provided grounds for a diagnosis of "benign myalgic encephalomyelitis" One patient had had a similar illness in 1953 In another patient there was laboratory evidence of glandular fever Electromyography gave in all the cases an abnormal pattern with grouping of action potentials

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SURGICAL TREATMENT OF LARGE AIR CYSTS OF THE LUNG

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> " . . and if the air blown into any lobe will not be expelled thence by the natural tone or muscle of the bladders, that the lobe may again subside of itself, 'tis certain that some injury is done to the ventiducts; the bladders are either broken, and admit air into the membranous interstices, or else they are over distended like a hernia in the peritoneum; and this will produce an inflation of the whole substance of the lungs, and that a continual compression of the air and blood vessels, which will produce a constant asthma."—Sir JOHN FLOYER, *Treatise of the Asthma*, 1698

Sir John's account of the development of "windy tumours" in the lungs cannot, except in details, be greatly improved upon today.

Air cysts of the lung are not common. They may be small or they may fill one side of the thorax. However large they are, the disability they cause may be negligible or it may be severe. When disability is present, it is uncertain how much of it is due to the cyst, how much to associated lung disease, and how much to the combined effect of the two. It is not known whether the cysts will get bigger or not. These uncertainties and the severe breathlessness of some of the patients have made surgeons and physicians reluctant to advise surgical treatment.

We believe that the success attending surgical treatment of carefully selected patients with large cysts of the lung is not sufficiently well known. This may be because the number of reports of cases so treated is small. Ten authors have described surgical treatment of a total of 88 patients, resulting in "improvement" in 82 (Abbott et al. 1953, Allbritten and Templeton 1950, Clagget 1949, Cook and Blades 1952, Crenshaw and Rowles 1952, Dugan and Samson 1950, Head and Avery 1949, Naclerio and Langer 1947, Santy et al. 1955, Weisel 1955). None of these authors give precise indications for the selection of the individual case for treatment. We will describe the surgical treatment of 21 adults with large air cysts of the lung, and we will try to show how those patients for whom the operation is both necessary and reasonably safe may be selected from the clinical and radiological findings.

Diagnosis

Diagnosis of air cyst of the lung may be made by radiological examination alone. The cyst may be discovered unexpectedly following inspection of the chest radiograph of a patient diagnosed as suffering from "chronic bronchitis and emphysema" because he complained of chronic productive cough, breathlessness, and wheeze. It may be seen on the radiograph of a patient with spontaneous pneumothorax. Occasionally it is seen on the routine film of symptom-free people.

The clinical and radiological findings in our patients are summarised in table I. Most of the patients had been breathless for many years. Spontaneous pneumothorax was common.

The radiograph of the chest showed the cyst, sometimes mediastinal shift, sometimes herniation across the anterior mediastinum, and usually evidence of disease in the rest of the lung. The cyst was located by abnormal radiolucency caused by the absence of vascular shadows and by the smooth outline of the cyst wall. Sometimes a thin cyst wall was difficult to see even on tomograms. Often it was better seen on the lateral film or on a film taken in expiration.

Bronchograms sometimes helped to define the limits of the cyst. They showed compression of the lung and distortion of the bronchi around the cyst. They gave some information about the health of the rest of the bronchial tree. Bronchograms are a great help in making the occasionally difficult distinction between a large cyst and spontaneous pneumothorax. Our experience has been that where the diagnosis was in doubt the lesion was a large cyst.

During fluoroscopy, the cyst and more obstructed parts of the lung darkened (emptied themselves of air) slowly or not at all during forced expiration. In some cases where obstructive lung disease was much more advanced in the lung with the cyst, the mediastinum swung to the sounder (less obstructed) side. This swing was better seen with a column of barium in the œsophagus. General obstructive lung disease was accompanied by slow and incomplete darkening (emptying) of the whole lung field and slow and limited movement of the domes of the diaphragm.

Fluoroscopy used in this way gave an indication of the severity and distribution of obstructive lung disease. We were able thus to make a rough guess at the contribution of each lung to total ventilation. It was established that the side of the chest to be opened in each patient was doing less than half of the total ventilation. In 8 cases bronchospirometry was used to confirm this.

Selection for Operation

All the patients chosen for operation were breathless. Their cysts occupied at least a quarter of one lung

TABLE I—CLINICAL, RADIOLOGICAL, AND SPIROMETRIC FINDINGS

Case	Age	Sex	Effort tolerance		Sputum		No. of spontaneous pneumothoraces	Cyst size	Forced expiration volume (c.cm. in 1 sec.)	Vital capacity (c.cm.)
			Grade	Duration (years)	Grade	Duration (years)				
1	51	F	4	10	trace			one half	770	1600
2	55	M	5	18	+ + + +	4		one half	970	2640
3	41	F	5	15	+			two thirds		1500
4	49	M	4	7	+ + +	7		one half	30*	
5	60	M	3	1				three quarters	1170	2370
6	50	M	5	4	trace			one half	640	2030
7	60	M	4	10	+ +	12	1	two thirds	510	1780
8	46	M	4	6	?	?		one	19*	
9	57	M	3	10	+ + +	20		one half	1500	3100
10	58	M	5	25	+ +	25	1	two thirds	32*	1950
11	55	M	5	6	+ + +	6		one half	660	1240
12	65	M	4	8	+			one		1900
13	47	M	3	12	+	12		one quarter	840	2340
14	56	M	0				2	one third		
15	26	M	1	?			2	one third		4200
16	52	F	5	5	+ +	7	1	one third	36*	1500
17	45	M	4	20	+ + + + +	20		one third	39*	2620
18	29	M	2	3	+		3	one quarter	80*	2760
19	64	M	6	7	+	7		one third		1700
20	59	M	4	4	+	25		one quarter	48*	2400
21	52	M	3	9	+	9	2	one third	27*	2400

* Maximum breathing capacity (litres per min.)

Sputum: + = an egg-cup a day; + + + + = a cup a day.

Duration: Time in years since symptoms of effort intolerance or expectoration first appeared, irrespective of severity.

Effort tolerance grade:
0 = No disability
1 = Cannot hurry on hills
2 = Cannot hurry on level
3 = Cannot keep up with others on level but can walk any distance own speed
4 = Cannot walk 500 yards or 20 min. slowly
5 = Cannot walk 100 yards or 5 min. slowly
6 = *Bedridden*

The horizontal line separates those with a cyst occupying half or more of one lung field (above) from those with a cyst occupying less than half of one lung field (below).

field on the radiograph In 3 patients repeated spontaneous pneumothorax was the main indication for surgery Breathlessness, however, severe, was never alone a contra indication

A number of patients with cysts occupying more than half of one lung field were refused operation because they were not breathless

Only 1 breathless patient with a large cyst was refused operation On fluoroscopy the cyst was found to be on the better ventilated side, and this was confirmed by bronchospirometry The other lung had been severely damaged by pneumonia Operation may be reconsidered should breathlessness become more severe

The Operation

Anæsthesia

To prevent dangerous expansion of the cyst and further embarrassment to the lungs "positive-pressure" ventilation was not used until the chest was opened An attempt was made to keep the partial pressure of alveolar carbon dioxide near that to which the patient was accustomed Hypoventilation might exaggerate the carbon dioxide retention which was already present Hyperventilation may so far reduce the partial pressure of carbon dioxide in the blood that spontaneous breathing may be slow to re establish itself (Atherstone 1956)

Surgical Details

A posterolateral approach was used in all save 1 patient in whom cavity drainage was performed When the chest was opened, an attempt was made to assess the condition of the whole lung Often before this could be done the cyst had to be incised because the lung was so voluminous that it herniated through the wound as soon as the pleura was opened Two anepithelial cysts (Belcher and Siddons 1954) were encountered in this series, in these the blood supply was ligated and the cyst was removed intact In 1 case, cavity drainage as recommended by Head and Avery (1949) was established in two stages and the tube was left in situ for a long period In the remaining 18 patients, cysts and a varying degree of emphysema were found Where one or more cysts were present and particularly where the lobe concerned appeared to contain areas of normal alveoli the procedure described by Naclerio and Langer (1947) was carried out the visceral pleura which formed the outer wall of the cyst was removed, the air leaks from the underlying lung were sought and oversewn, and the raw areas were approximated This was done on eight occasions On the other hand, where the whole lobe was destroyed by generalised alveolar breakdown, where all the intersegmental planes were disrupted, and where it was possible to express air from one end of the lobe to the other, resection was carried out One segmental resection, eight lobectomies, and one pneumonectomy were performed

As it was felt that these patients were suffering from mechanical rather than from nervous or reflex disorders, the vagotomy recommended by Abbott et al (1950) was not carried out

Postoperative Care

Drainage tubes were used in all cases and continuous suction was applied at once In most patients there was a considerable air leak from the cut lung surfaces in the period immediately after the operation In only 1 patient did it persist for more than a few days In this case an empyema which developed was successfully treated by simple drainage In the remainder the tubes were removed on an average five days (maximum nine) after operation

To reduce the risk of carbon dioxide narcosis, oxygen was not given as a routine and heavy sedation was avoided Only 1 patient, treated early in the series, died shortly after operation The lung on the unoperated side was too diseased to support life by itself In no other case was there any cause for alarm

Results

Of the 21 patients treated, 9 were enormously improved and 8 claimed moderate or slight improvement (*table II*) All who claimed improvement said they were last as well between three and fifteen years ago 1 patient died four days after operation before operation he had been breathless even in bed, and both lungs had been severely damaged by disease A large cyst was present

TABLE II—CLINICAL, RADIOLOGICAL, AND SPIROMETRIC FINDINGS BEFORE AND AFTER OPERATION

Case	Cyst size	Sputum		Effort tolerance grade		Forced-expiration volume (c cm in 1 sec)		Vital capacity (c cm)		Last as well (years ago)	More than 1 st weight gain	Assessment †
		Preop	Postop	Preop	Postop	Preop	Postop	Preop	Postop			
1	one half	trace	trace	4	3	770	945	1600	2140	6	+	E
2	one half	++++	trace	5	3	970	1600	1600	3240	2	+	E
3	two thirds	+	trace	5	0		1760	1500	2680	15	+	E
4	one half	+++	++	4	3	30*	52*			6	+	E
5	three quarters	trace	trace	3	0	1370	1600	2370	2410	5	+	E
6	one half	trace	trace	5	2	640	830	2030	2360	5	—	E
7	two thirds	++	++	4	2	810	1200	1780	2570	10	++	E
8	one	?	?	?4	?1	19*	48*	1940	2400	6	—	E
9	one half	++−	+	3	2	1500	1840	3100	3380		—	E
10	two thirds	++	+	5	4	32*	22*				++	M
11	one half	+++	+	5	4	660	660	1240	1720	1	++	M[1]
12	one			4	4						—	S[3]
13	one quarter	+	+	3	3	840	1050	2340	2240	6	—	S
14	one-third	trace	trace	0	Worse							Worse[4]
15	one third	trace	trace	1	0		3860	4200	5560			S
16	one third	+−	+	5	4	1670	1780	1500			Loss 4 st	S
17	one third	++++	+++	4	4	39*	30*		2620	20	—	S
18	one quarter	+	trace	2	2	80*	118*	2700	2700		—	S
19	one third	−		6	Died						—	Died[2]
20	one quarter	+	+	4	4	48*	45*	2100	2000		—	S
21	one third	+	−	3	3	27		2400			—	S[5]

Grading and volumes as in table I * Maximum breathing capacity (litres per min)
† E = enormous improvement M = moderate improvement S = slight improvement

1 Died following spontaneous pneumothorax on other side some months after operation
2 Died four days after operation
3 Died some months after operation of unknown cause following initial improvement
4 Died from glioma some months after operation
5 Cavity drainage

The horizontal line separates those with a cyst occupying half or more of one lung field (above) from those with a cyst occupying less than half of one lung field (below)

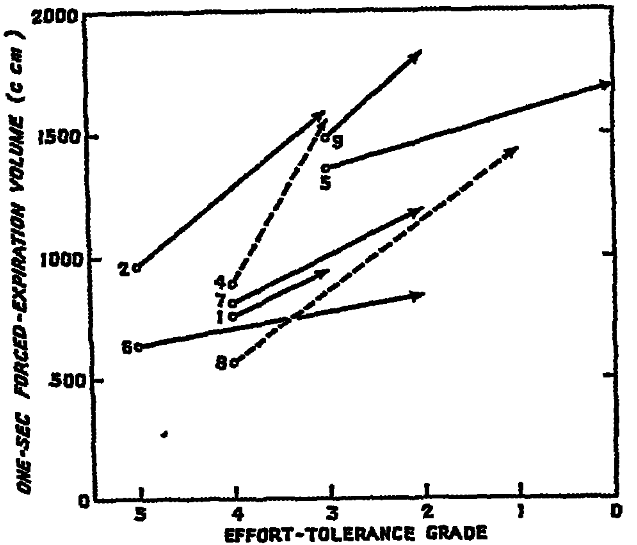

Fig 1—Change in effort tolerance grade and one-second forced-expiration volume after removal of lung cyst Second measurements made about three months after operation Broken line indicates that forced-expiration volume is calculated from M B C Case numbers correspond to those in table II

on each side The efficiency of the lung on the unoperated side had been overestimated

3 other patients died, none as a result of operation 1 with severe hypertension died from an unascertained cause six months after an operation which had been followed by considerable initial improvement A patient with severe hypertension but few symptoms was operated on because of recurrent spontaneous pneumothorax he became worse with hemiplegia and died two years later from a spontaneous pneumothorax on the unoperated side 1 patient whose condition was unchanged by the operation died later from a brain tumour

Assessment of Results

Change in effort tolerance—Change in effort tolerance is the best way of assessing the value of an operation intended to improve it An attempt was made to assess effort tolerance from the answers to standard questions put to the patient before and after operation Effort tolerance was then graded as in table I In 15 patients, including the 9 who claimed "enormous improvement," their grading was roughly confirmed This was done by one of us walking with them before and after operation, on the level and up stairs The changes experienced by the patients are shown in table II Those we considered "enormously improved" are indicated

Change in lung function—Objective evidence of any change in lung function which might be associated with any change in effort tolerance was sought from timed ventilation studies (table II) The change in one second forced expiration volume seen in tests before and after operation have been graphically related to the change in the effort tolerance grade after removal of the cyst in 8 of the 9 patients who claimed enormous improvement (fig 1) The increase in timed expiration volume is seen to be related to the increase in effort tolerance This was independent of season

Change in bronchial disease—6 of the patients claiming "enormous improvement" regularly brought up large amounts of sputum (an egg cup to a cup a day) before operation Since operation 5 of them bring up less than an egg cup a day, except after head colds The 6th patient reports no change in the quantity of his sputum All patients who "improved enormously" noticed a big reduction in their wheeze, and this is confirmed by the improvement in one second forced expiration volume

Improvement in well-being—The patients who enjoyed an improvement in effort tolerance also reported an improvement in well-being Here are typical expressions of this

"Much more energetic Last as well five years ago"

"Much better My ankles do not swell any more"

"Life worth living now I used to see my doctor every week Now I haven't seen him for a year, except socially"

"Was suicidal for two years My depression now gone More buoyant Last as well ten years ago"

"Sputum much less Surprise my wife by going to sleep without a wheeze"

"No comparison, a different man now Even acquaintances notice the improvement Can run for a bus now Have not done this for three years '

"Twice as fit Last as well ten years ago Much more energy Circulation much better Hands and feet no longer get cold"

"For five years *I could not walk more than one hundred yards* without a stop Before I left hospital I was able to run upstairs with less trouble than the physiotherapist Circulation much better Hands and feet do not now get so cold"

"They've got my wheeze upstairs," (i e, in the operating-theatre)

Weight change—In 8 patients there was simple objective evidence of this improvement in well-being They gained at least one stone in weight during the six months following operation This was maintained on leaving hospital

Effect of cyst size on the result—All the cysts occupied more than a quarter of one lung field on the radiograph 12 patients had cysts occupying a half or more than a half of one lung field 9 of these 12 patients with the bigger cysts were the ones who "benefited enormously"

Disability before operation—Only 3 patients had little disability before operation Repeated spontaneous pneumothorax was the reason for operating on them The rest were disabled, some severely (see table I) None of these patients were able to walk at a normal pace 7 were unable to walk a hundred yards 7 patients were able to blow between 450 c cm and 1000 c cm only in the first second of forced expiration This might be compared with maximum breathing capacities in the range 15–30 litres a minute The remarkable improvement experienced by some of the most disabled will be noticed (table II)

Follow-up—All patients were followed up for at least three months 4 were followed for one year and 5 for two years or more In all cases where it occurred "enormous improvement" in effort tolerance and well-being was noted soon after operation—within three months In all cases this improvement has persisted apart from temporary setbacks in bad weather and during bronchial infection

Timed ventilation increases were at their maximum about three months after operation Most of our recent follow-up measurements are lower than the maximum values About half the gain has been lost, but this may be due to winter We have not yet been able to complete our study of weather and time change We believe this fall may prove too big to be explained by weather changes alone

DISCUSSION

The disability in patients with large air cysts of lung is due to mechanical interference by the cyst with the ventilation of diseased lungs The cyst and lungs are too big for the thorax As soon as the chest is opened the cyst balloons through the incision The anæsthetist immediately notices an improvement in the patient's condition and ventilation This has often been reported (Atherstone 1956, Dugan and Samson 1950)

Compression may prevent ventilation of relatively healthy lung near the cyst Respiratory effort is wasted in changing the volume of the cyst The existing tendency of the damaged lungs to trap air is increased Some of the tidal volume is lost to the ventilation of the cyst

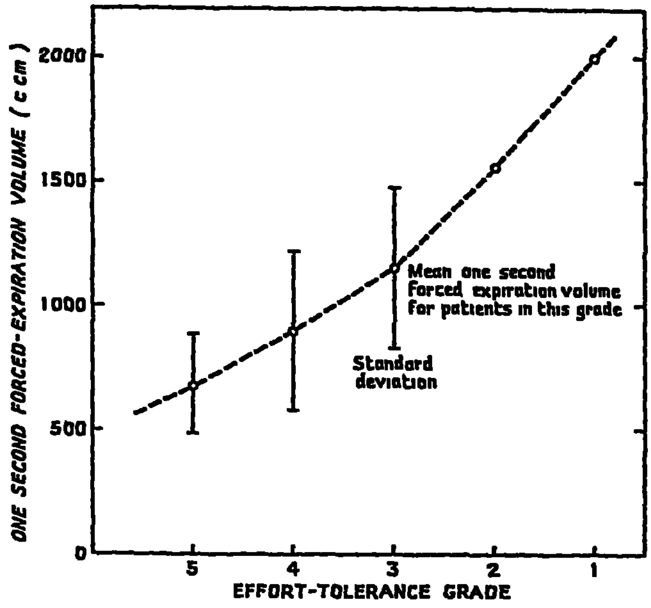

Fig 2—Relationship between effort-tolerance grade and one-second forced expiration volume in 150 patients with chronic obstructive lung disease

The bronchial leak into the cyst was found at operation to be fairly large in some patients and small in others

If the lungs are healthy, a cyst may encroach on two thirds of one lung field and the patient yet be symptom-free Breathlessness, when present, must therefore be related to general disease of the lungs The more diseased they are the less are they able to carry the extra burden of the cyst It follows that the larger the cyst and the more breathless the patient, the more seriously must operation be considered. Our experience has confirmed this

2 patients with very large cysts (half of one lung field) but no symptoms were tested Timed ventilation measurements were almost normal in one and about two thirds presumed normal in the other There is no evidence that the disease is progressive in these patients Even should they deteriorate nothing is lost by waiting

As, over the years, diseased lungs gradually lose their efficiency, there comes a time when small deteriorations cause disproportionately large losses of effort tolerance The mean difference in one second forced-expiration volume between normal people and our grade 3 patients (those unable to walk with others on the level but able to walk any distance) is 2500 c cm The mean difference between our grade 3 and our grade 5 (patients unable to walk one hundred yards slowly) is only 450 c cm This difference was found in a study of over 150 patients with bronchial disease in our laboratory

Similarly, it would be expected that small increments of lung efficiency, signalled in our patients by small increments in the one second forced expiration volume, might be followed by a disproportionately large improvement in their effort tolerance This, we believe, explains in part the "enormous improvement" enjoyed by our 9 patients

In 150 patients with bronchial narrowing or obstruction as a feature of their chronic lung disease, we have compared their effort tolerance graded as described (table I) with their one second forced expiration volumes (Smart and Capel 1957) There was a clear relationship between the two (fig 2) In 8 of our 9 patients who "improved enormously" the increase in one second forced expiration volumes for the increase in effort tolerance grade claimed by the patient was what would have been expected if this relationship held true for them This suggests that the improvement is proportional to the relief of airway obstruction

As we believe the disability to be due to mechanical interference with lung ventilation, we see no place for pulmonary plexectomy in treatment Those who have reported most benefit from this manœuvre found it largely in those patients from whom the cyst had been removed as well Their reported improvements with plexectomy seem to be comparable to ours without it

The comparative safety with which these often dangerously disabled patients may be operated on is not unexpected The patient with respiratory insufficiency is never so well off as he is temporarily during the controlled ventilation of anæsthesia The patient with a large cyst improves as soon as his chest is opened The operation is technically fairly simple A critical burden is removed so increasing the patient's ventilation reserve Our "enormously improved" patients claimed benefit even during the first few days after operation

Conclusions

As radiological diagnosis may be difficult, a close study should be made of the chest radiographs of all breathless patients before they are labelled "chronic bronchitis and emphysema"

In 8 of the 9 patients who were "enormously improved" there was direct and indirect evidence that this improvement was related to relief of chronic obstruction of the airways It may be that the presence of a large cyst in the thorax can aggravate the general narrowing of the bronchi of lungs already diseased

Surgery should not be considered in symptom-free patients Resection is dangerous in very breathless patients when fluoroscopy (and bronchospirometry if available) show the cyst to be on the more efficiently ventilated side of the chest Open drainage may be proved to be of value in these cases

Surgery should be considered in all breathless patients who are found to have an air cyst of the lung occupying at least a third of one lung field on the chest radiograph The larger the cyst and the more breathless the patient the more urgently is surgery required

Summary

(1) 21 patients with large air cysts of the lung (occupying more than a third of one lung field) were treated surgically

(2) Clinical and spirometric findings before and after operation were recorded

(3) The operation proved both simple and safe

(4) 9 of the patients were "enormously improved"

(5) It is concluded, with one reservation that the larger the cyst and the more breathless the patient the more seriously must operation be considered

We wish to thank Dr J Smart for his advice, for his assistance with the pulmonary function studies, and for referring patients to us We also wish to thank the other physicians who referred patients

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RECTAL BIOPSY AS AN AID TO THE DIAGNOSIS OF AMŒBIC DYSENTERY AND ALLIED DISEASES OF THE COLON

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In the routine diagnosis of dysenteriform diseases, which falls to the lot of the tropical physician, it is advisable to have as many strings to one's bow as is possible

It is a fact that, generally speaking, little crucial information can be garnered either from the patient's history or from physical examination of the abdomen In patients hailing from the East, in whom a whole series of differing diagnoses have been made from time to time, and an equal number of varying treatments prescribed, it is a recurrent perplexity to disentangle the probable course of events So often the diagnostician is faced by the same story of repeated fæcal examinations positive for amœbæ one day and negative the next—a discrepancy which has given birth to the widespread and popular belief that the causal organism disappears from the intestinal tract directly the patient passes from the tropics to temperate zones, only to reappear in reinforced numbers immediately on his return to the endemic areas If the fæces contain no active amœbæ or cysts, little will be gained from even the most skilful microscopic examination of them

In consulting practice, it is not possible to admit to hospital for long and elaborate laboratory tests every patient who complains of an intestinal upset It is therefore desirable to devise a technique whereby a positive and reliable diagnosis may be arrived at with the minimum expenditure of time In this paper we describe the method we have routinely used for the past few years, and broadly summarise the results obtained. We are encouraged to do so by the success of this technique

The diagnosis of amœbic dysentery may be very simple, on the other hand it may be and often is, the very reverse *Entamœba histolytica*, in its habits may be likened to a Scarlet Pimpernel of tropical medicine—" here today and gone tomorrow " It is this cyclical appearance of the organisms which renders routine diagnosis such a chancy affair Because of the sporadic nature of the infection and its confinement for the most part to the large intestine, no reliable intradermal or serological diagnostic tests have been evolved, and the diagnosis ultimately depends, therefore, on identification of the causative organism In such diagnosis the discovery, in a preparation, of one authentic *E histolytica* is as important as that of a dozen or more

Rectal Biopsy

The sigmoidoscopic appearances of amœbic lesions on the bowel will have been often described In the acute stage they are often obvious and characteristic, but in the chronic stage they may be difficult to detect In some cases the points of entry into the mucosa are so minute as to escape detection and in others active and typical amœbæ have been identified in preparations from the normal mucosa From the diagnostic viewpoint it is fortunate that *E histolytica* is a parasite of the large intestine and is apt to favour the lowest part of the bowel—the rectum in particular The lesions are therefore readily accessible, and through the proctoscope biopsy scrape preparations are easily and painlessly obtainable The rectum proper extends for 5 in , of which $4\frac{1}{2}$ in can be viewed through the proctoscope

The technique is simple, and skill in its application is readily acquired The instrument used does not conform to the common model designed for the treatment of hæmorrhoids or examination of the lower bowel, but has been designed for this specific purpose It is a tubular rectoscope, 6 in in length by $\frac{5}{8}$ in in diameter, and is provided with a suitable handle

After lubrication with ' K-Y Jelly ' (*not* petroleum jelly which tends to spoil the preparation), the tube, which has previously been warmed in water, is inserted and gently pushed up so as to permit examination of $4\frac{1}{2}$ in of the rectum The importance of pushing the instrument home lies in the fact that the part of the mucous membrane coming into contact with the end of the tube bulges into it, presenting a suitable surface for biopsy scraping An area of the mucosa can be viewed at the upper limit of the tube range, and other areas as the instrument is being slowly withdrawn For illumination a dental lamp provides a full, evenly distributed illumination and is known as the ' Straight Illuminator Lamp ' It is fitted into a long flex attached to a battery It is not necessary as a routine to use a magnifying eyepiece

Biopsy material is obtained by scraping the suspected area of the mucosa with a long handled Volkmann spoon The stem is 16 in in length and the diameter of the cup $\frac{1}{2}$ in It is important that the edges of the spoon should not be so sharp as to unduly lacerate the tissues A sample of the diseased mucosa is obtained by side-to-side movement of the base of the spoon impinging against the interior of the proctoscope By these means a definite slice of the mucosa comes to lie in the hollow of the spoon this is removed directly, with the aid of a matchstick, on to a microscope slide, and a " squash preparation " is produced by pressing down with a no 1 $\frac{3}{4}$-in -square coverglass

The specimen is first quickly examined under a low-power lens and then with the $\frac{1}{6}$ in It is essential that the microscope should always be handy, for the preparation *must* be fresh and *the cells must be seen in the living state* An interval of 5–10 minutes is fatal to success since the finer appearances of the mucosal pattern deteriorate with great rapidity *No normal saline or other diluent should be added* The addition of vital stains do nothing to assist in the interpretation of the appearances which must be assessed with the tissue in a fresh and undamaged state The condenser should be racked down so as to be able to obtain clear definition of the outlines of the intestinal cells

Macroscopic Appearances of Amœbic Lesions

In the main the lesions of amœbic dysentery seen in the rectum conform to those seen higher up in the sigmoid colon

In the acute stage, small, discrete, flat depressions, with undermined edges and hæmorrhagic margins, can be distinguished Submucous telangiectatic hæmorrhages are often seen in their vicinity In our experience it is rare to be able to recognise the classical diamond shaped amœbic ulcer in this situation More usually the changes are very superficial and range from small granulations to hyperæmic patches

In the chronic stage the changes are so minute and so superficial that they may escape detection The actual depressions in the mucosa may be so shallow that it requires oblique illumination, as Cropper (1945, 1951) has emphasised, to show them up By punch biopsy he has shown that the cavity of such a lesion extends down to the muscularis mucosæ beneath the superficial glands In 1937 one of us (P M -B) described the mucosa as " pock marked " and as resembling the lesions produced by the nibbling of " microscopic mice " (fig 1) It is to Cropper that we are indebted for the expressive terminology in which he compares the pin-point craters to those of bomb craters as seen in aerial photographs The small ones upon which we place particular emphasis give what he terms a "pigskin appearance" or minute scattered pits, resembling pinpricks on a plasticine surface Cropper has demonstrated their microscopical structure by "punch" biopsy It is necessary to differentiate this pathological picture from the regularly disposed openings of Lieberkühn's *glands in the lower* rectum

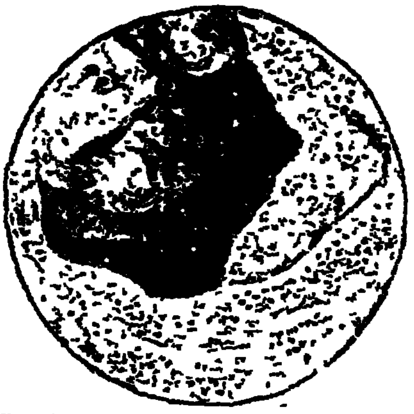

Fig 1—Proctoscopy of rectum chronic amœbic dysentery "Pigskin pittings"

Microscopic Appearances in Scrape Preparations

The Normal Picture

A preparation of normal mucosa shows the crypts of Lieberkühn with their contained columnar cells spread out in a symmetrical mosaic pattern when spread out on a slide (fig 2) The boundaries of the glands can be envisaged outlined with capillary vessels and encompassing (besides the normal cells) goblet cells, lymphocytes, and occasionally eosinophils

Amœbic Lesions

In biopsy scrapings under the microscope, *E histolytica* in the active and cystic stage can readily be picked out from the midst of the necrotic debris by its refractile and shiny appearance (fig 3) There is something crystalline about it which makes it stand out, so to speak, from the surrounding cells To make recognition absolutely certain, the organisms should protrude pseudopodia and perform amœboid movements They can easily be induced to do so by warming the slide (No elaborate apparatus is necessary, placing the slide for a few minutes on the microscope lamp base suffices) We would draw attention to the fact that cysts of the non pathogenic amœbæ, such as *E coli*, *E nana*, and *Iodamœba butchlii tend to adhere* to the mucosal surface and may be demonstrated in this situation We have also found therein ova of ascaris ancylostoma, *Schistosoma mansoni*, *Tænia saginata*, and oxyuris, besides adults of the latter worm

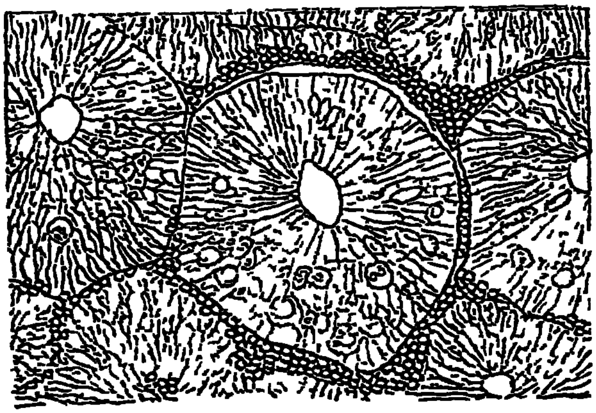

Fig 2—Normal rectal mucosal pattern

Bacillary Dysentery

A recurrent difficulty in tropical practice is the differentiation of mild attacks of bacillary dysentery from those of the amœbic form, and to obtain some positive evidence as an aid to treatment For this purpose the history and physical examination, however thorough, may yield remarkably little information Microscopical examination of the fæces may also provide little, and cultural methods are on the whole too long, too tedious, and too uncertain, while serological reactions are subject to the same drawbacks and are usually unreliable

The proctoscopic appearances of these post-bacillary cases are superficial and slight Usually the mucosa has an angry and lack-lustre appearance at the most small, deep red, strawberry-like granulations are visible On the other hand, the cellular changes in biopsy preparations are very helpful to the trained eye The diagnostic sign consists in the recognition of minute granules in the columnar cells They are of a protein nature, and are coarser and more irregularly disposed than the finer ones only detectable under the $^1/_{12}$ in lens in normal biopsy preparations Frequently, too, small necrotic foci within the crypts of Lieberkühn may be demonstrated (fig 4) These intracellular changes are not found in amœbic dysentery

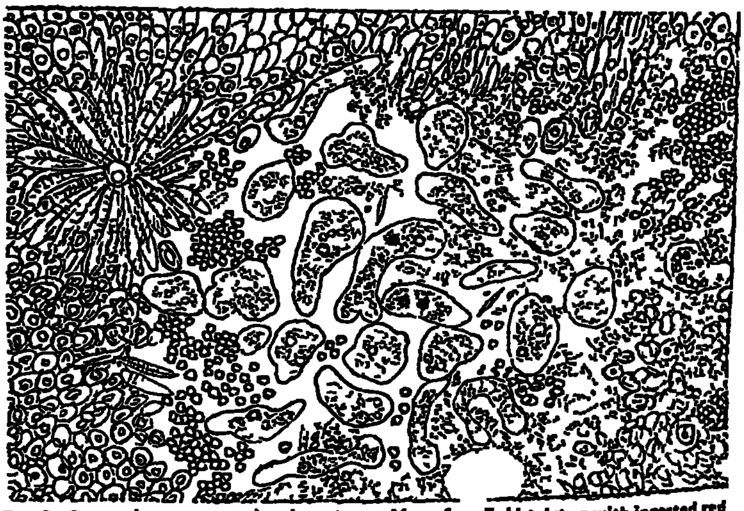

Fig 3—Scrape biopsy amœbic dysentery Many free *E histolytica* with ingested red cells and Charcot-Leyden crystals in a case with no amœbæ or cysts in the fæces

Ulcerative Colitis

It is not always easy to separate the mucosal lesions of ulcerative colitis from those of the bacillary dysenteries We have come to regard the deep red-porter colour of the granulations and the general angry look of the mucosa as being suggestive In biopsy material the picture is that of advanced coagulative necrosis of the crypts and contained cells, together with aggregations of leucocytes and macrophages (fig 5) We have also observed on one occasion a curious phenomenon of autolysis of the cells under the high power of the microscope This consists of minute spirochæte like filaments, undergoing active undulating movement and breaking down into minute granules as depicted in fig 6 This seems to indicate a necrotic process which is peculiar to ulcerative colitis It is possible that this phenomenon can be demonstrated solely in fresh preparations Our experience agrees with the statement that the essential lesion of ulcerative colitis, as seen in rectal biopsy material appears to be an excessive destruction of undifferentiated cells leading to secondary infection (Lumb and Protheroe 1953) The "strawberry lesion" of Shera (1955), confirmed by Thomas (1956), is in our opinion indistinguish

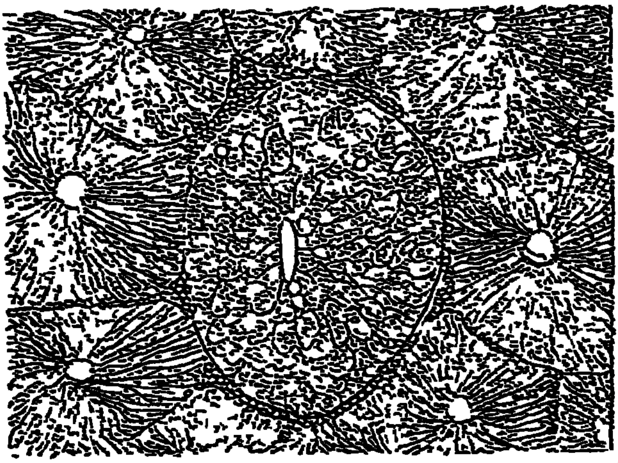

Fig 4—Rectal biopsy showing granular cells in a convalescent case of bacillary dysentery

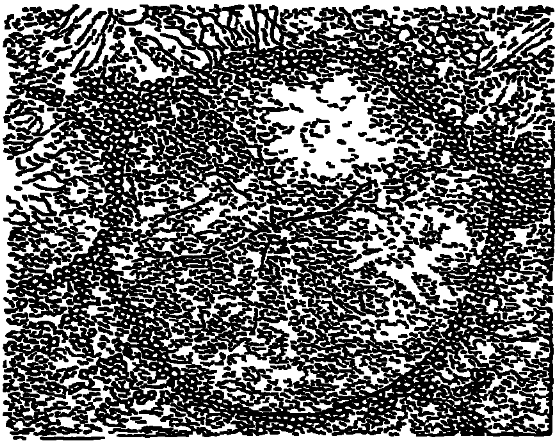

Fig 5—Rectal biopsy showing necrosis and autolysis of cells in acute ulcerative colitis.

able from that of ulcerative colitis with a superadded spirochætal infection In this connection we would draw attention to the appearances illustrated in fig 6, which though obviously of protoplasmic origin bear a close resemblance to massed spirochætes

Mucous Colitis

This and other forms of disturbance of colonic function associated with oversecretion of mucus are often met in the diagnosis of the dysenteries. Here the proctoscope reveals a pale and puckered mucosa overlaid with a patina of adherent mucus In this condition biopsy preparations are very helpful in firmly establishing diagnosis The hypersecretion of mucus can readily be seen in the goblet cells of the follicles, which are swollen with mucin and present a characteristic picture which in our opinion, is reliable in this common condition (fig 7)

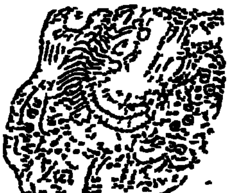

Fig 6—Autolysis of cells of Lieberkühn in acute ulcerative colitis producing an appearance resembling massed spirochætes

Tropical Sprue

Though the diagnosis of tropical sprue can usually be reached from a physical examination of the patient, from examination of the blood-cells and from analysis of the fæces proctoscopy provides very considerable assistance, especially in borderline cases The mucous membrane has a dull surface and is usually pale rose pink When mopped with a cotton-wool swab, the surface is not easily damaged (as it is in bacillary infections) and presents a fine beaded surface Usually pale cream-coloured fæces can be seen adherent to the mucosa Biopsy scrapings usually show a regular mucosal pattern, but small nests of fine granules are visible between the crypts, possibly indicating the presence of some mild toxic agent

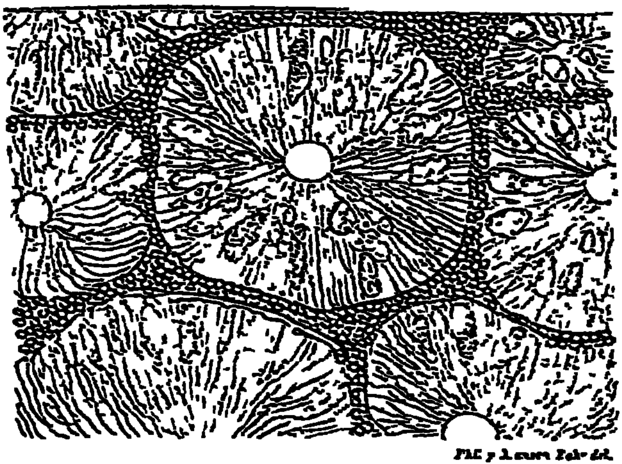

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Fig 7—Rectal biopsy pattern of mucous colitis showing excessive secretion of mucus by goblet cells in the crypts

Amœbic Dysentery . Value of the Method

To compare the microscopical findings in direct examination of the fæces and in proctoscopic scrape preparations we present 30 positive consecutive cases of amœbic dysentery. In these the infection was acquired in the following places

British Guiana 1, Burma 3, Ceylon 1, Egypt 3, England (indigenous case) 1, Far East 2, Iraq 3, India 6 Indo China 1 Italy 2 Malaya 1, Natal 1, Pakistan 1, Venezuela 1, West Africa 3

Examination of the fæces showed *E histolytica* cysts in 16 cases vegetative forms in 5, and both in 2 No amœbæ or cysts were found in 7

In all 7 cases with negative fæces active vegetative *E histolytica* were found in proctoscopy scrape preparations In these 7 there was a previous history of amœbic dysentery in 4, previous diarrhœa and abdominal discomfort in 2, and no previous history of dysentery or diarrhœa in 1

Proctoscopic scrape preparations from the 30 patients showed active vegetative forms of *E histolytica* in 13 and cysts in 2 In 24 of the patients proctoscopy showed the typical red, inflamed or pitted mucosa In 6 the mucosa looked normal, 2 of these exhibited vegetative forms of *E histolytica* in scrape preparations

Of the 30 patients, 15 gave a previous history, or presented positive signs and symptoms, of amœbic dysentery, and 8 of previous or present diarrhœa In 7 there were no previous or present symptoms or signs of diarrhœa or dysentery

The special proctoscope is made by Messrs. Vann Bros the lamp by Messrs John Bell & Croyden, and the Volkmann spoon by Messrs Allen & Hanburys

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THIRTY-MINUTE SCREENING TEST FOR PHÆOCHROMOCYTOMA

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The estimation of urinary catecholamines is now generally accepted as the most reliable diagnostic test for phæochromocytoma, being more specific (and involving less inconvenience and risk to the patient) than the provocative tests and tests with adrenolytic agents sometimes used

The normal urinary excretion of catechols by resting patients is about 15–30 µg per 24 hours, of which about 80% is noradrenaline (Von Euler 1955), excretion by people engaged in normal daily activities is about twice as high Goldenberg et al (1954), in a study of thirteen normotensives and thirty five patients with essential hypertension, found that it was never more than 100 µg , other workers, however, have reported somewhat higher normal values, the extreme range being 15–185 µg (Burn 1953, Pekkarinen 1954, Von Euler and Floding 1955)

In cases of chromaffin-cell tumours a striking increase is seen Although a 24 hour urinary excretion of only 190 µg has been reported by Goldenberg et al (1954) and one of 180 µg by Burn (1953), the amount excreted is usually about 10–100 times the normal and may be as much as 9000 µg —representing a secretion of about 200 mg per day (Von Euler 1955) The increase is most often in the noradrenaline, though cases have been described in which adrenaline secretion was also greatly increased (Holton 1949, Engel and Von Euler 1950, Goldenberg and Rapport 1951, Burn 1953, Von Euler and Floding 1955)

Several methods (Engel and Von Euler 1950, Lund 1952, Goldenberg et al 1954, Pekkarinen 1954, Moulton and Willoughby 1955, Von Euler and Floding 1955) are now available for estimating urinary adrenaline and noradrenaline For various reasons these are beyond the scope of the average hospital laboratory The semi quantitative method described here, based on the Lund (1952) procedure for separating catechols and developing fluorescent products with ferricyanide (Ehrlen 1948), is designed to detect the presence of more than 180 µg of catechols in a 24 hour collection of urine, without differentiating them as noradrenaline and adrenaline The test can be carried out in about half an hour and can be used as a routine test in any laboratory having an ultraviolet lamp Several specimens can be tested at once with little extra expenditure of time or effort

Procedure

Measure a tenth of the 24 hour collection of urine (filtered if necessary) make up to 200 ml with distilled water, and pour into a 250 ml beaker Add 2 g of aluminium oxide (this need be weighed only once and can be measured subsequently by volume with a small graduated cylinder) and 0 5 ml of 1% phenolphthalein, then add 20% NaOH drop by drop stirring thoroughly with a thick glass rod until a definite pink colour persists (pH about 8 4–8 5) Continue stirring for about a minute, then allow the aluminium oxide (with adsorbed catechols) to settle (The heavy aluminium oxide sediments very rapidly, and no centrifuging is necessary at this stage)

Pour off the supernatant fluid and precipitated phosphate (most of which remains suspended in the supernatant) as completely as possible without disturbing the aluminium oxide, then wash by adding about 200 ml of distilled water, stirring allowing to settle and pouring off the water

Rinse the aluminium oxide into a 15 ml centrifuge tube with small amounts of distilled water, centrifuge for about 2 minutes at 2500 r p m , drain off the water, and dry the inside of tube with filter paper

Add 5 ml of $N/5$ H_2SO_4 to the tube, mix thoroughly with a glass rod and by shaking, and centrifuge again for 2 minutes at 2500 r p m

Pipette 3 ml of the $N/5$ H_2SO_4 eluate into a 'Pyrex' tube containing 3 ml of 2% $NaHCO_3$, mix by shaking, then add 0 5 ml of 0 25% potassium ferricyanide, and mix again After 2 minutes add 1 ml of a mixture containing 9 parts of 20% NaOH and 1 part of 2% ascorbic acid (freshly made), mix, and centrifuge briefly

Pour the supernatant into a flat bottomed tube of non fluorescent glass and examine under ultraviolet light

Under these conditions preparations from normal urine show faint green fluorescence, whereas those from urine having an abnormally high catechol content show an intense bright green fluorescence For comparison a standard representing about 180 µg of catechols in 24 hours is prepared as follows to 100 ml of normal urine (containing about 4 µg of total catechols) add 50 µg of noradrenaline and make up to 200 ml with distilled water, extract catechols as described above and dilute the $N/5$ H_2SO_4 eluate with 2 parts of $N/5$ H_2SO_4 3 ml of this solution (which is stable for at least a month in the refrigerator) is used in developing the fluorescence as described above

Normal urine can readily be distinguished from urine containing 180 µg or more of catechols per 24 hour collection, and the approximate catechol content of the specimen to be analysed can be calculated by diluting the standard until the fluorescence equals that of the specimen to be analysed (total catechols in 24 hours = 180/D, where D = dilution necessary) , or, in a positive test, by diluting the specimen to be analysed to match the standard

If the volume of the urine is greater than 2 litres, 200 ml should be used and a suitable correction applied

Notes on Reagents

The aluminium oxide (chromatography grade) should be washed by shaking 200 g in a litre of hot *N*HCl, rinsing free from acid with several changes of distilled water, and drying The ascorbic acid should be kept in the ice compartment of the refrigerator, and the ferricyanide in a dark bottle The other reagents are stable

Preservation of Specimens

The catecholamines are stable in acid solution specimens not analysed immediately can be kept in the refrigerator for about a week without loss of activity if acidified to pH 5 or lower by addition of about 1 ml of concentrated H_2SO_4 A 24 hour specimen is advisable in so far as there is a diurnal variation in the excretion rate, the night excretion rate being significantly lower than the day excretion rate (Burn 1953, Von Euler et al 1955, Elmadjian et al 1956) , in severely paroxysmal cases, however, a single specimen taken following an attack may be more informative

Results

The method has been applied to the urine of 70 hypertensives suspected of having phæochromocytoma 69 of them were negative, giving approximate values of 15–132 µg (average 46 µg) of catechols per 24 hours The remaining patient, from whom a phæochromocytoma was later removed at operation, excreted about 1500 µg per 24 hours This value was in close agreement with those obtained subsequently on the same specimen by biological and colorimetric methods 10 days after operation this patient's excretion of catechols had decreased to about 75 µg per 24 hours

As a further check on the efficiency of this method of detecting increased urinary excretion of catecholamines, specimens of urine taken from athletes after strenuous physical exercise were tested These always showed the expected increase above the pre exercise values (Von Euler 1955), the approximate contents ranging from 75–210 µg per litre, with an average of 117 µg

I am indebted to Prof E J Conway, F R S , to the Rockefeller Institute for Medical Research and to the Medical Research Council of Ireland for facilities granted

References at foot of next column

FŒTAL BLOOD IN GENITAL HÆMORRHAGE DUE TO PLACENTA PRÆVIA AND ABRUPTIO PLACENTÆ

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It is generally agreed that, in cases of hæmorrhage due to placenta prævia or abruptio placentæ, maternal blood is lost from the ruptured uterine or decidual vessels, but the suggestion has been made (Macafee 1949, Busby and Neal 1951) that a proportion of the blood lost may come from the fœtal blood-vessels of the placenta, and that this loss may even suffice to cause anæmia of the newborn We report here the results of an investigation undertaken to establish whether genital bleeding due to placenta prævia or to abruptio placentæ carries fœtal blood as well as maternal blood Such an investigation is made easier by the fact that maternal blood does not contain more than 2% of fœtal hæmoglobin (alkali denaturation method, Singer et al 1951), whereas fœtal blood contains 50–100% (Walker and Turnbull 1955)

To determine the variations in amount of fœtal hæmoglobin in the blood of healthy women at term, clotted venous blood of 113 healthy women at term was examined by the method of Singer et al (1951) In 5 pregnant women with external bleeding due to placenta prævia, and in 2 women with abruptio placentæ, fœtal hæmoglobin was estimated in blood clots expelled vaginally before and during labour and, at the same time, in clotted maternal venous blood All the women were in the last month of pregnancy except 1 woman with abruptio placentæ in the seventh month

The clotted venous blood of 113 healthy pregnant women at term contained 0 3–2 3% (mean 1 4%, standard deviation ±0 53, and standard error ±0 081) of fœtal hæmoglobin In all 5 women with placenta prævia and 2 with abruptio placentæ the expelled blood contained more fœtal hæmoglobin than did the maternal venous blood, the differences between the two levels ranging being 0 8–2 3% (see table)

These results seem to show that the blood lost in the separation of the placenta in placenta prævia and in abruptio placentæ consists partly of fœtal blood, indicating that fœtal vessels have been damaged The amount of fœtal blood lost in this way was but small in the 7 women examined and was not large enough to cause anæmia of the newborn, it did not exceed 3–4 ml per 100 ml On the other hand, it has been suggested that, in rare cases of placenta prævia with marginal insertion of the cord, a large umbilical vessel may rupture, giving rise to considerable loss of fœtal blood (Wickster and Christian 1954)

FŒTAL BLOOD IN EXTERNAL GENITAL HÆMORRHAGE DUE TO PLACENTA PRÆVIA AND ABRUPTIO PLACENTÆ

Case no	Diagnosis	Fœtal Hb in expelled blood (%)	Fœtal Hb in maternal venous blood (%)	Difference (%)
1	Placenta prævia	4 1	1 8	2 3
2	,, ,,	4 3	2 2	2 1
3	,, ,,	3 0	1 1	1 9
4	,, ,,	3 5	2 3	1 2
5	,, ,,	2 1	1 3	0 8
6	Abruptio placentæ	3 5	1 8	1 7
7	,, ,,	3 8	2 2	1 6

Summary

In 5 cases of placenta prævia and 2 cases of abruptio placentæ the amount of fœtal hæmoglobin in blood-clots expelled vaginally before and during labour was estimated

In all 7 cases the expelled blood contained 0 8–2 3% more fœtal hæmoglobin than did the mother's venous blood

It therefore appears that, in the external genital bleeding of placenta prævia and abruptio placentæ, small amounts of fœtal blood are usually lost, though not enough to cause anæmia of the newborn

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PREDNISOLONE SNUFF IN HAY-FEVER

A CONTROLLED TRIAL

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The efficacy of systemic cortisone, hydrocortisone, and corticotrophin in suppressing the symptoms of hay-fever is now well established (Toogood 1956) More recently there have been reports of good results following the use of oral prednisone and prednisolone in nasal allergy (Arbesman and Ehrenreich 1956, Brown and Seideman 1956, Feinberg and Feinberg 1956)

Since the systemic administration of all these drugs may produce undesirable side-effects, the advisability of their use in hay-fever has been questioned and Friedlander (1956) recommends that the treatment of hay fever with both the newer and the older steroids be restricted to severe cases which have not responded to other therapy However, the topical use of prednisolone in solution was effective and free from side effects in 30 patients with nasal allergy treated by Anderson and Ogden (1956) in a controlled trial Similarly Herxheimer and McAllen (1956) record the absence of side effects when using hydrocortisone snuff for the treatment of 24 patients with pollen hay-fever, 23 of these patients had 'excellent relief of symptoms, but the trial was uncontrolled

We present here the result of a small controlled trial in which patients with hay fever were treated by inhalation of either prednisolone snuff or an inert snuff containing lactose

Method

46 patients (23 males and 23 females), aged 12–54, entered the trial. All had a typical history of hay-fever, the duration of the disease varying from two to twenty years. 10 patients also had bronchial asthma.

A positive reaction to skin testing with mixed grass-pollens was obtained in each case. 18 patients had previously received one or more courses of pollen desensitisation, but none had received this treatment for at least a year.

The material for trial was supplied in two sets of capsules: one set contained 1 mg. of prednisolone with 144 mg. of lactose, and the other set 145 mg. of lactose only; the average size of the particles was 20 μ. The actual content of the capsules was not known until after the results had been assessed. The patients were arranged in pairs according to age and sex and were allotted to one of two groups at random.

A nasal insufflator was used to apply the snuff to each nostril in turn. The capsules were pierced at both ends with a household pin and inserted in the insufflator; pressure on the bulb produced a fine spray, and wastage was minimal. The patients were requested to use one capsule twice daily, dividing it as equally as possible between the nostrils. In no case was there initial difficulty due to blockage of the nose, but several patients using the control snuff complained that, after they had used the insufflator, their nostrils became obstructed. Anti-histamine tablets of chlorprophenpyridamine maleate ('Piriton') 4 mg. were provided, and the patients were instructed to use one or more of these tablets if the nasal insufflations did not control the hay-fever. Each patient was provided with a diary and asked to keep a daily record of (1) the presence or absence of hay-fever, and (2) the number of anti-histamine tablets used.

Diaries were kept from May 18 to July 7, 1956, and the trial was divided into three periods: (1) the fortnight beginning May 18 was used to assess the severity of symptoms in each group, no snuff being administered but anti-histamine tablets being taken as required for relief of symptoms; (2) from June 1 to June 30 the patients used the insufflator and took tablets of chlorprophenpyridamine maleate if their symptoms were not relieved; and (3) from July 1 to July 7 anti-histamine tablets alone were used.

RESULTS OF A CONTROLLED TRIAL OF PREDNISOLONE SNUFF IN HAY-FEVER COMPARED WITH RESULTS OBTAINED IN 18 PATIENTS TREATED BY POLLEN DESENSITISATION

Patients	—	Period in 1956					
		May 18–31		June 1–30		July 1–7	
		Hay-fever days	Anti-histamine tablets used	Hay-fever days	Anti-histamine tablets used	Hay-fever days	Anti-histamine tablets used
Group A (prednisolone snuff) 18 patients (9 male and 9 female) aged 12–54	Total	47	56	134	97	22	39
	Mean	2.6	3.1	7.4	5.4	1.2	2.2
	Range	0–11	0–20	0–21	0–31	0–6	0–21
Group B (control snuff) 20 patients (9 male and 11 female) aged 12–55	Total	54	64	285	460	62	85
	Mean	2.7	3.2	14.2	23.0	3.1	4.2
	Range	0–12	0–21	0–30	0–96	0–7	0–19
Group treated by pollen desensitisation 18 patients (8 male and 10 female) aged 15–50	Total	4	6	84	101	21	35
	Mean	0.22	0.33	4.7	5.6	1.2	1.9
	Range	0–1	0–3	0–22	0–22	0–7	0–11

Results

Only 38 of the original 46 patients completed the trial. The 8 patients not included in the final assessment were rejected for the following reasons: 4 patients did not keep records; 2 devised their own treatment and did not adhere to the rules of the trial; 1 had persistent nasal blockage due to non-allergic disease in the nose; and 1 died in a motor accident.

There were 18 patients (9 male and 9 female) in group A (prednisolone) and 20 patients (9 male and 11 female) in group B (control). 7 patients in group A and 11 patients in group B had previously undergone pollen desensitisation.

During the initial observation from May 18 to May 31 the 18 patients in the prednisolone group (A) recorded 47 days on which hay-fever symptoms occurred, and required 56 anti-histamine tablets (means 2.6 hay-fever days and 3.1 tablets). In the control group (B) the 20 patients recorded 54 days' hay-fever (mean 2.7 days) and took 64 anti-histamine tablets (mean 3.2 tablets). The severity of the hay-fever in each group thus appears to be very similar.

From June 1 to June 30, during which time nasal therapy was given, the patients in group A (prednisolone) had 134 days of hay-fever (mean 7.4 days) and used 97 anti-histamine tablets (mean 5.4 tablets), whereas the patients in group B (control) had 285 days of hay-fever (mean 14.2 days) and used 460 anti-histamine tablets (mean 23.0 tablets).

Comparison of the two groups during this period of nasal therapy shows that the difference between the number of hay-fever days is not statistically significant ($P=0.05$), but that there is a significant advantage to the patients treated by prednisolone as regards the use of anti-histamine tablets ($P=0.01$). However, the number of hay-fever days merely indicates the presence or absence of symptoms and takes no account of their severity; it can therefore almost certainly be assumed that the quantity of anti-histamine tablets used provides a better indication of the efficacy of treatment.

6 of the patients in the control group (B) complained that use of the insufflator irritated the nose, and 3 thought that the snuff initiated attacks of hay-fever. Because of this 2 of the latter gave up using intranasal therapy a few days before the end of June. No side-effects, either local or general, were noted by the patients inhaling prednisolone snuff (group A).

During the first week after stopping insufflations (July 1–7) there was no significant difference between the groups. The patients who had been using prednisolone snuff (group A) had 22 days of hay-fever and used 39 anti-histamine tablets (means 1.2 days of hay-fever and 2.2 anti-histamine tablets), whereas the patients inhaling control snuff (group B) had 62 days of hay-fever and required 85 anti-histamine tablets (means 3.1 days and 4.2 tablets). If the hay-fever days recorded by each group are compared, $P=0.05$; similarly the difference between the number of anti-histamine tablets used is not statistically significant ($P=0.3$).

The patients' own assessment of the efficacy of treatment was recorded in each case. Of the 18 patients inhaling prednisolone snuff (group A) 16 thought that the treatment had been most effective, 1 considered it to have been fairly effective, and 1 considered it to have been of little value. The 20 patients of the control group (B) had different views: only 7 thought that the snuff had been effective, 2 considered it to have been fairly effective, but 11 said categorically that it was "no good."

The 10 patients with bronchial asthma (4 male and 6 female) were divided equally between each group. Of the 5 patients in group A (prednisolone) 2 recorded improvement in their asthma and had almost complete relief of hay-fever symptoms. In group B (control) 2 patients thought that their asthma had improved, but only 1 of this pair felt that the hay-fever had benefited from the snuff

While this trial was in progress a further 18 patients (8 male and 10 female, aged 13–50) with hay-fever were under observation in our clinics They had all been treated by pollen desensitisation and were provided with anti-histamine tablets (chlorprophenpyridamine maleate 4 mg) for relief of symptoms Although they do not form a control group, we recorded the results of their treatment for comparison with our other patients Desensitisation had continued until the end of May, 1956, and from May 18 to May 31 these 18 patients recorded 4 days of hay-fever (mean 0 22 days) and used only 6 anti histamine tablets (mean 0 33 tablets) From June 1 to June 30 they had 84 days of hay-fever and used 101 anti-histamine tablets (means 4 7 hay-fever days and 5 6 tablets) During the first week in July they had 21 days of hay-fever (mean 1 2 days) and used 35 anti-histamine tablets (mean 1 9 tablets) 14 of these patients commented that they had been almost completely free from hay-fever, and 4 had experienced fairly good relief of symptoms

The results are summarised in the accompanying table

Discussion

Although we deliberately administered a small dose of prednisolone to avoid the possibility of undesirable side-effects, our results suggest that the inhalation of prednisolone snuff is a promising method of controlling the symptoms of hay fever The 1956 hay-fever season was unusually mild, but this circumstance applied to both groups of patients, and pollen counts have shown that the peak of the season occurred during the period of nasal therapy from June 22 to June 28 (H A Hyde, personal communication)

Both the symptoms of rhinitis and the itching and congestion of the conjunctivæ were relieved by the inhalation of prednisolone A similar observation was made by Herxheimer and McAllen (1956) using hydrocortisone snuff for hay-fever Cotes et al (1956) have shown that the inhalation of 45 mg of hydrocortisone powder through the mouth produces an increased urinary excretion of 17-hydroxycorticosteroids, suggesting that hydrocortisone is absorbed systemically when inhaled from a powder spray It seems unlikely, in view of the small quantity of prednisolone used in our trial, that sufficient of the drug had been absorbed to exert a general effect, but this point requires further investigation

The 5 patients treated with prednisolone who had bronchial asthma in addition to hay-fever are so few that it is impossible to draw any definite conclusion about the efficacy of prednisolone snuff in bronchial asthma

The relief of symptoms in the group treated by inhalation of prednisolone compares satisfactorily with the experience of the patients who had been desensitised to pollen The latter therapy, though usually effective, is somewhat undesirable because of its potential danger and the necessity of weekly injections for three months before the start of the hay-fever season We therefore consider that our results warrant a more extensive trial of prednisolone snuff, which may provide a simple, safe, and effective remedy for hay fever

Summary

The effect of the inhalation of prednisolone snuff was compared with that of placebo snuff in patients with hay fever

38 patients were studied 18 in the prednisolone group and 20 in the control group Treatment was given from June 1 to June 30 1956

The results suggest that the daily inhalation of 2 mg of prednisolone snuff is of considerable value in the control of symptoms due to hay fever

No side effects were observed after the inhalation of prednisolone, and this treatment is considered to be worthy of more extensive clinical trial

One of us (K M) has done part of this work with the assistance of a grant from the Geoffrey Duveen Trust

We are very grateful to Messrs Pfizer Ltd for providing the two sets of capsules and the nasal insufflators, and to Dr M J H. Smith for help with the statistics

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BILATERAL BRONCHIAL FOREIGN BODIES

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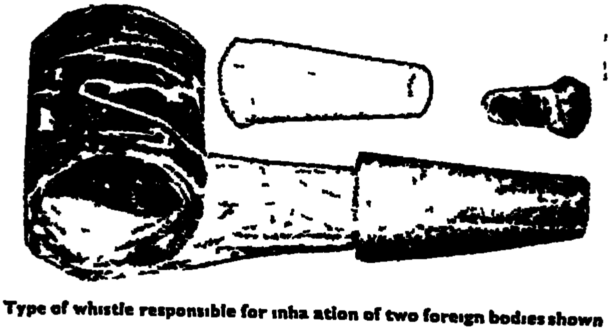
The rarity of such an occurrence, with the unusual and misleading bronchoscopic appearance produced, prompts us to report this case of simultaneous inhalation into the right and left lower lobe bronchi respectively of a metallic radio opaque and a plastic radiotranslucent foreign body The latter remained in situ unrecognised for ten months despite several bronchoscopic inspections

Case-report

A farmer, aged 35, was dancing at a Christmas Eve party when he inhaled part of a " blow out " whistle (see figure) Forceful exhalation produced a slight whistling sound from the right side of his chest On arrival at hospital about two hours later, radiography revealed the presence of a metallic reed in the lower lobe of his right lung At bronchoscopy the reed was easily found and removed without difficulty The left bronchus was not inspected The patient's statement that he had inhaled a plastic whistle was discounted because of his somewhat convivial state on admission and the absence of any abnormal clinical or radiological signs at the time of discharge from hospital three days later

About two months later he developed a wheeze and later a cough with occasional bloodstained sputum and slight left sided chest pain Further radiography during the ensuing months did not reveal any abnormality Nine months after the incident a chest physician reported excellent general health, a recurrent dry cough, and rhonchi on auscultation, chiefly on the left side, with good air entry to the left lung *The result of bronchoscopy by the chest physician at this* time was reported as follows "Marked fœtor In the left stem bronchus, below the left upper lobe orifice, there is gangrene The whole bronchus from this level down appears to be involved It is avascular and completely covered by white slough There is a sharp line of demarcation between this and the proximal part of the main bronchus, which is entirely healthy Basal orifices can just be seen, and there is no foreign body "



Type of whistle responsible for inhalation of two foreign bodies shown

Accordingly the patient was transferred to a chest surgery unit, where he was described as being in excellent general condition and apyrexial, with a wheeze present over both lungs but loudest at the left base Nothing abnormal was found on radiography Bronchoscopy was repeated, and a similar report was given of the appearances in the left lower lobe bronchus Coliform organisms were grown from the bronchus, and the patient was given a course of chloramphenicol Once more he was submitted to bronchoscopy (by a fourth bronchoscopist) and on this occasion palpation with forceps revealed the "gangrenous slough" to be a tubular piece of yellow plastic, the original mouth-piece of the whistle This was removed with some difficulty It had fitted the left lower lobe bronchus snugly between the apical and distal segmental bronchial orifices, thus producing no obstruction and allowing a clear view of all segmental orifices The patient's symptoms were relieved immediately, and the wheeze disappeared at once

Comment

The only previous report that we have been able to discover of bilateral bronchial foreign bodies is that of Orton (1924), who removed half a peanut from the right stem bronchus of a child and the other half two days later from the left side Here also the left bronchial tree was not inspected at the original bronchoscopy Orton states that Chevalier Jackson at that time had seen three cases in which peanuts acted as bilateral bronchial foreign bodies

Examining our patient's X-ray films in retrospect we could just make out the faint outline of the plastic tube It was very faintly radio opaque, whereas the metal reed was, of course, distinctly so It was unsuspected because of the rarity of simultaneous inhalation of dual foreign bodies and the very faint radio-opacity, it was undiscovered at the first examination because the examination was incomplete, the left bronchus not being inspected The appearances at two subsequent bronchoscopic examinations, some months after the original one, did not arouse suspicion of this second foreign body because of apparent disease within the left bronchus, the preservation of a clear lumen, and possibly because the bronchoscopists were less familiar with the details of the original incident and examination

The immediate disappearance of the generalised bronchospasm on the removal of the offending foreign body was very striking It brought to mind the reflex bronchospasm not infrequently found in patients with localised disease in the bronchus or in the lung In such patients, perhaps also having chronic tuberculosis, bullous emphysema, or bronchial adenoma, operation may be long delayed because of associated "generalised bronchitis," only to find that the rhonchi, which have failed to respond even partly to medical measures, have disappeared immediately after resection

It is worth remembering that generalised, as distinct from local, bronchospasm may have a reflex ætiology from a focal source of irritation

Summary

A man inhaled the proximal end of a toy whistle

The metallic radio opaque reed was removed from the right lower-lobe bronchus about four hours after the incident, but the plastic mouth-piece remained in the left lower-lobe bronchus for ten months and was recognised and removed at a fourth bronchoscopy

No localising radiological signs were produced by this tubular plastic foreign body, but reflex bronchospasm was relieved immediately by its removal

We are grateful to Mr Bruce Dick, of the Hairmyres Hospital thoracic unit, for his encouragement and permission to publish

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Preliminary Communication

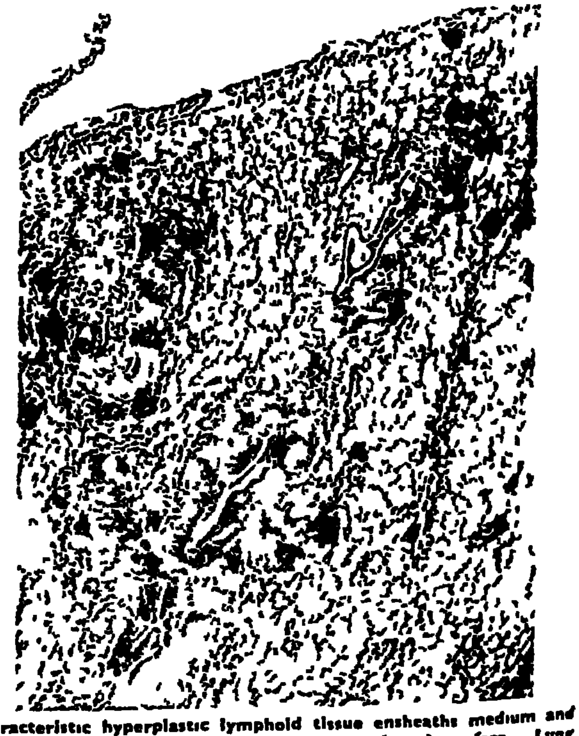
NON-TUBERCULOUS JUVENILE BRONCHIECTASIS A VIRUS DISEASE?

NON-TUBERCULOUS bronchiectasis in the child is usually ascribed to some ill-defined episode of pyogenic bronchitis, perhaps complicating a specific fever We suggest that, in a substantial number of such cases, the lesion is due to chronic infection of the bronchi with the adenovirus (A P C virus), and that some of the characteristics of the lesion are due to the persistent presence of virus

This suggestion arose from the demonstration to us by Dr W F H Jarrett, of the veterinary pathology department of Glasgow University, of the lesions of the common respiratory disease of cattle which he has described[1] under the name of "cuffing pneumonia" and has suggested might well be of virus ætiology Since this work was begun, the description by Innes et al[2] of similar lung changes in the rat, which they ascribe to infection by the Nelson rat lung pneumonia virus, adds further support

Jarrett[1] has shown that the cattle disease begins in the calf in an acute form with mild peribronchial lymphocytic infiltration, passes through a chronic stage in which lymphoid hyperplasia is the main feature, and ultimately develops into bronchiectasis with fibrosis

From early 1956 our morphological investigation of lobectomy specimens from patients with bronchiectasis indicated strongly the presence of a similar process in human lungs In brief, the dominant feature present in about three quarters of the cases was lymphoid hyperplasia affecting the hilar nodes and irregularly narrowing the lumen throughout the whole length of the bronchial ramifications in the affected segments or lobes (see figure) In 1948 Cruickshank[3] investigated bronchiectasis in rats and suggested that lymphoid hyperplasia might



Characteristic hyperplastic lymphoid tissue ensheaths medium and small bronchi and extends almost to pleural surface Lung parenchyma is not severely diseased (Hæmatoxylin and eosin ×10) play some part in the pathogenesis of bronchiectasis in children A comparison of healthy lungs and of lungs showing other types of chronic disease, with the bronchiectasis material, has confirmed the impression that lymphoid hyperplasia is the important feature in bronchiectasis

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[2] Innes J R M, Adams A J, Yevich P *Amer J Path* 1956 32 141

[3] Cruickshank A H *J Path Bact* 1948, 60, 520

INVESTIGATION AND RESULTS

These considerations led us to investigate the possibility of demonstrating a virus in such patients In 18 cases so far investigated serological tests were made before and after operation, and the resected specimen was used for bacteriological, virological, and histological investigation At first complement-fixation tests, as described by Grist,[4] were made with antigens from several possible viruses influenza viruses A, B, and C, newborn pneumonitis virus (type Sendai), and the adenovirus group After testing the first 8 sera, however, we saw that positive results were being obtained only with the adenovirus-group antigen, our attention was therefore concentrated on this group

8 of our cases showed a titre of 1/16 or over, 3 one of 1/8, and 7 one of less than 1/2 Our previous experience with complement-fixation tests in 600 cases of respiratory disease suggests that titres of 1/16 or more, in single or repeated specimens, indicate continuing adenovirus infection, whereas titres of 1/8 are doubtful and those below 1/8 are negative

In 1 case with positive serum more conclusive evidence of the rôle of the adenovirus in bronchiectasis was obtained with the isolation from the resected lung tissue and hilar lymph-nodes of an agent which produced the cytopathogenic changes in tissue culture and the complement fixation reaction characteristic of an adenovirus

DISCUSSION

Many of the pathological features of these cases can be attributed to the secondary effects of lymphoid hyperplasia, which is apparently the characteristic lesion causing irregular bronchial stenosis That the adenoviruses are responsible for this, at least in many cases, is less surprising when we consider their rôle in connection with lymphoid hyperplasia at other sites (tonsils and adenoids,[5] conjunctiva,[6] and mesenteric lymph-nodes [7])

In bronchiectasis pyogenic infection is important, of course, and it is not our purpose to minimise the rôle of *Hæmophilus influenzæ* [8 9], but we suggest that, as in influenza, the primary pathogen is a virus, and that pyogenic bacteria are secondary invaders

We are investigating the relation of the adenovirus group not only to the relatively well recognised acute respiratory diseases but also to chronic lung disease, which is considered to be an intermediate stage in the development of bronchiectasis, and already we have serological evidence of its association with some cases of "sinobronchitis"

SUMMARY

Lymphoid hyperplasia is an important element in most cases of juvenile bronchiectasis

Resemblance to animal diseases which are almost certainly of virus origin prompted search for a virus in such cases

Of 18 cases so far investigated serological evidence of adenovirus infection has been obtained in 11 and an adenovirus has been isolated in 1 case

We acknowledge with pleasure our indebtedness to the following physicians and surgeons whose willing coöperation provided us with the clinical cases Prof S G Graham and Dr J H Hutchison, Messrs R S Barclay, K. Fraser, T M Welch, R A McCluskie, and N McSwan, to Prof D F Cappell and Dr G B S Roberts, who made available histological material from their departments to Miss Helena S Adamson, B SC, for making the bacteriological tests to C McLean, F I M L T, for assistance with the serological tests and to the house surgeons at the thoracic units concerned for their help in obtaining specimens

P S M also gratefully acknowledges the constructive criticism given him by Dr W F H Jarrett of the veterinary pathology department of Glasgow University and the encouragement offered and facilities made available by Dr A M MacDonald

University Departments of Pathology at the Western Infirmary and Royal Hospital for Sick Children Glasgow, and the Virus Laboratory of the University Departments of Bacteriology and Infectious Diseases, Ruchill Hospital Glasgow

P S MACFARLANE
M B Glasg, M.R C.P E
R G SOMMERVILLE
M B Glasg

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[4] Grist N R Brit med J 1955 ii 994

[5] Rowe W P Huebner R J Gilmore L K Parrott R H Ward T G *Proc Soc exp Biol, N Y* 1953 84 570

[6] Rowe W P Huebner R J *Amer J trop Med* 1956 5 453

[7] Kjellén L *Arch ges Virusforsch* 1955 6 45

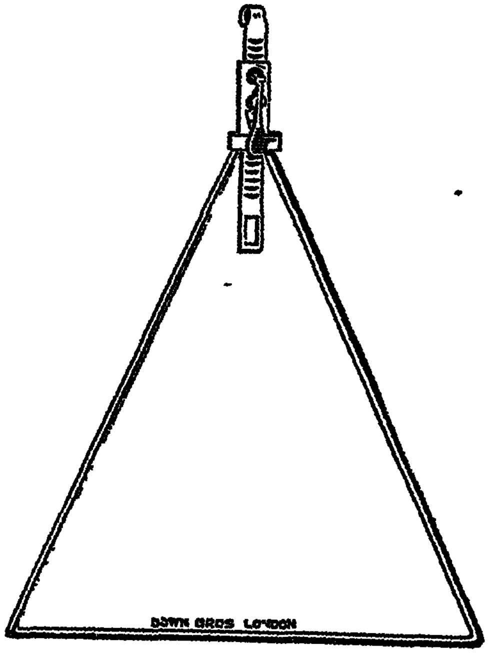
[8] Allison P R Gordon J Zinnemann K *J Path Bact* 1943 55 465

[9] Allibone E C Allison P R Zinnemann K *Brit med J* 1956 i 1457

New Inventions

INSTRUMENT FOR RATCHET SUSPENSION OF THE BOYLE-DAVIS GAG FOR TONSILLECTOMY

THE accompanying diagram illustrates a suspension instrument designed for this purpose It is a triangle, constructed of a steel rod, which carries a sliding bar with ratchet at the apex of the triangle, the bar has a large slot at the bottom to accommodate the hook of the Boyle-Davis gag



The triangle is slipped over the patient's head, the cross-bar base of the triangle prevents skidding and damage to the rubber cushion of the operating-table.

The ratchet mechanism is similar to that on the Boyle-Davis gag and allows easy, quick and accurate adjustment and release of the gag This is of advantage if it is found necessary to reposition the gag during operation, and it also enables the surgeon to get the necessary position of the head without raising it from the operating-table The degree of adjustment on the ratchet enables the suspension to be used for adults and children

This instrument incorporates the principle of suspension by the 'Draffin Bipods'

I wish to thank Mr Maurice Down, of Down Brothers & Mayer and Phelps Ltd, for his help in constructing the instrument

London

W H B MAGAURAN
M D, M CH N U I F R C S

Reviews of Books

Taylor's Principles and Practice of Medical Jurisprudence

11th ed Vol I Editors SIR SYDNEY SMITH, C B E, F R C I E, F R S F, emeritus professor of forensic medicine, University of Edinburgh, KEITH SIMPSON, M D, reader in forensic medicine, University of London London J & A Churchill 1956 Pp 626 70s

"Taylor" first appeared in 1865, but the 11th edition bears few marks of antiquity Dr Keith Simpson is now associated with Sir Sydney Smith, an editor since 1928, so this famous work has now, in part, returned to Guy's

From 1865 until 1905 it stayed in the Borough, for Stephenson took over from Taylor In that year, however, it journeyed across London Bridge to Whitechapel, where F J Smith of the London Hospital became its new author His chief alteration was to introduce "small print" for quoted cases and to discard not only the illustration of the "Waterloo Bridge body" but also that of Dr Parkman, who was, however, restored to favour in a later edition In 1928 it moved again, this time north of the Border to Edinburgh into the capable and experienced hands of Sydney Smith who introduced new material but retained the small print which still remains Now he is joint editor with Keith Simpson, who has obtained valuable assistance from Gerald Howard, Q C, M P

As Sir Sydney says in his preface, Dr Simpson's influence can be observed in most sections, for not only has he included many of his well-known cases but he brings his characteristic style The text has been thoroughly revised, and several sections have been largely rewritten Nearly three hundred new cases and some forty new illustrations have been introduced The legal aspect has been revised by Mr Gerald Howard, a section on psychiatry and the law contributed by Dr David Stafford-Clark, and the chemical aspect revised by Mr L C Nickolls, director of the Metropolitan Police laboratory at New Scotland Yard

In forensic medicine, as in so many other branches of medicine, the days are past when a single expert can pronounce authoritatively on all questions As the senior editor remarks

"The assistance of the chemist, the physicist, the biologist and of experts in other branches of science has given greater precision in our work with a corresponding increase in the value of evidence Over all, however, there must be someone who is able to advise on the procedure to be adopted, the particular scientist whose help should be sought, and who takes a final responsibility of advising the Crown Thus there would appear to be no lessening in the need for a general work such as this " The editors of such a work must try to be clear without being dogmatic, for counsel may cite them as the ultimate authority, and if they have expressed their views with insufficient reserve the court may give different opinions less than their due weight

This leading reference book is indispensable to medical jurists The second volume in the new edition is expected to appear in a few months

Cytologic Technics for Office and Clinic

H E NIEBURGS, M D director of the Cytology Laboratory, Bethel Hospital New York, London and New York Grune & Stratton 1956 Pp 233 $7 75 -

MAKING no pretence to teach the art of cytological diagnosis, this eminently practical manual ranges over all parts of the body to which the technique has been applied recently "Recently" is an important qualification "cytology" has a curiously limited meaning in this context for instance, in the urine it is applicable to the diagnosis of tumours by examination of the sediment, but not to the more old-fashioned method of diagnosing nephritis The main diagnostic possibilities are considered at each site and the method of obtaining suitable specimens is considered in detail The section on laboratory organisation, dealing as it does with the methods necessary in handling material in bulk, may well prove to be the most valuable part of the book

Tratamiento de la Meningitis Tuberculosa y de la Tuberculosis Pulmonar Aguda

DR JUAN TORRES GOST, Sanidad Nacional de la Lucha Antituberculosa oficial Madrid España Calpe, S A 1955 Pp 122

THIS monograph summarises Dr Torres Gost's experience in the treatment of meningeal and pulmonary tuberculosis. He pleads for the association of isoniazid and streptomycin in the management of meningeal tuberculosis and records an overall mortality of 6 7% in a series of 278 cases This is a very high proportion of successes, which cannot be matched in this country Since other Spanish workers have achieved similar or even better results—Ramos and Soriano for example—using isoniazid alone, it may be that tuberculous meningitis is less severe in Spain than it is in this country The treatment is set out in detail, and some guidance about the handling of complications adds interest The second part of the book is concerned with the role of antibiotics in pulmonary tuberculosis

Stress and Strain in Bones

Their Relation to Fractures and Osteogenesis F GAYNOR EVANS, PH D, associate professor of anatomy, Wayne State University College of Medicine, Detroit, Michigan Springfield, Ill Charles C Thomas Oxford Blackwell Scientific Publications 1957 Pp 245. 50s

MOST of the recent experimental work upon the effects of mechanical forces on the skeleton has here been collected and examined The book is introduced by an explanation of the techniques which can be used, and it contains a critical examination of the applications and importance of the photo-elastic, stress-coat, and strain gauge techniques A consideration of stress and strain in long bones occupies most of the space, though there are useful sections on the skull and on the effect of stress upon development and bone healing and growth In certain regions the relationship between bone architecture, deforming forces, and fractures is considered, and for the femoral neck the analysis is made in great detail Dr Evans's main interest, however, has been in experimental work, and many of the illustrations are derived from his own investigations The text is remarkable for a most critical and stimulating reappraisal of the classical contributions to this subject, and the extensive bibliography will help to make this a ready source of reference

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The Essentials of Modern Surgery (5th ed Edinburgh and London E & S Livingstone 1957 Pp 1276 75s)—This work is reputed to be amongst the most popular text books of surgery for medical students It was an immediate success when it first appeared eighteen years ago, and it continues so as it matures with each successive edition under the editorship of Mr R M Handfield Jones and Sir Arthur Porritt Inevitably the cost has increased, but it is still excellent value

The Diseases of Occupation (2nd ed *London* The English Universities Press 1957 Pp 1100 £3 5s)—The appearance of another edition of Dr Donald Hunter's book so soon after the first indicates its usefulness and "box office" appeal A few additions have been made to the chapters on the historical aspects, and there are 11 new illustration The descriptions of poisoning by vanadium manganese and cadmium have been brought up to date, and substantial new sections on thallium poisoning, iron and steel foundries and the risks of work in sewers have been added The new sections are as instructive and entertaining as the old one and the whole book is uncommonly readable A new comment on the dangers of sandblasting says "of course the men themselves are aware of the hazard" thus in 1934 in a works in Coventry they put up a notice "Join the Navy and see the world Become a sandblaster and see the next" The first edition was criticised because no attempt was made to deal with the "epidemiology" of industrial diseases Fortunately Dr Hunter has resisted the temptation to besprinkle his pages with curves, graphs, and correlation coefficients on which the general reader usually looks with a glassy eye He has remained faithful to his purpose—"to review on a broad basis and with emphasis on its clinical aspects the problem of disease in relation to occupation" The book is well on its way to becoming a classic

THE LANCET

LONDON SATURDAY, APRIL 13, 1957

Discussion First

ALMOST every doctor in the country must now feel that the Government have been treating the profession neither justly nor courteously In a group of experienced laymen the same feeling was evoked last week by Lord MORAN's moderate statement of the profession's case[1], and to onlookers it seemed that, on a division, the House of Lords would have registered its evident opinion that on the point at issue—the terms of reference of the Royal Commission—the Government should think again Unfortunately, in their present mood, that is exactly what the Government are not prepared to do Having announced their programme, they intend no concession that might be put down to the British Medical Association's threat of direct action Were they otherwise untroubled and secure, they might attach less importance to so small a matter of prestige, but in face of many perils their need of confidence makes them chary of reversing even small decisions In this dispute some of their decisions, taken without consultation, have been rightly described as dictation, and this way of dealing with complex issues is wholly unsuited to the National Health Service On the other hand, the B M A 's objection to dictation is invalid so long as it is itself proposing, by a form of strike, to dictate terms of settlement to the Government In using these methods both sides are at fault and in everybody's ultimate interest the need is to get away quickly from dictation and counter-dictation and return to the plane of civilised discussion

The profession is not responsible for the Government's actions, but it is entirely responsible for its own, and this responsibility will not be properly discharged unless it ensures that these actions are beyond reproach In discussions up and down the country the plan for "phased withdrawal" from the National Health Service has had an uneasy reception —partly because it is thought likely to be ineffective but partly because this means of exerting pressure on the Government is seen to be wrong The growing demand for complete rather than partial withdrawal is not wholly due to growing belligerence or to the natural preference for unanimous action it also springs from the knowledge that deliberate resignation from the service is professionally defensible, whereas any kind of temporary strike is not Fortunately, though the threat of action has been freely used, no decision on its nature can be taken by the B M A until the representative body meets on May 1, and perhaps the representatives will then come to the correct conclusion that withdrawal, if undertaken at all, must be final If that were their opinion, the next step must be for their leaders to produce a scheme whereby, with sufficient notice, the bulk of general practice could be removed from the National Health Service For our part we should profoundly regret such an outcome of the present disagreements, but this kind of withdrawal is feasible, and it would be justified if, after full consideration, a majority of practitioners felt that the service denied them satisfaction in their calling At the same time, such a decision is certainly not one to be made without examining the implications, or without devising alternative arrangements for practice which might protect the public from suffering by the change Since apparently no such plan has yet been worked out in detail, we may reasonably hope that, before practitioners are finally asked to decide on it, they will at least have heard what the Royal Commission recommends and what the Government propose to do

What, in the meantime, should be the profession's attitude towards the Royal Commission ? Its appointment without consultation was something not easily forgiven, the suitability of such a body for its task is questionable, and, by refusing to give evidence before it, doctors could make a dignified protest against the Government s arbitrary handling of their affairs The temptation to such a protest is great, but in so far as its origin is emotional it should be resisted—if only because a boycott would inconvenience the Government very little, and instead of arousing general sympathy might impress the public unfavourably Far more important than indignation as a reason for refusing to help the commission is the serious doubt whether its terms of reference will let it give proper consideration to the conditions on which doctors entered the service, and unless it can do this it will be wasting its time so far as the profession is concerned Lord JOWITT, as a lawyer, and others in the Lords' debate, clearly thought it rash to proceed unless the Government will remove this uncertainty by altering the commission's remit On the other hand the Government spokesman, Lord HOME, said

> " there is no reason to think that they [the Royal Commission] will not put a realistic interpretation upon their terms of reference, nor any doubt that they will listen to any evidence put before them which is relevant " They can " take into account all the circumstances that are relevant, and one of the factors which is clearly relevant is consideration of the Spens reports Clearly, the Royal Commission will take into account rewards for skill in other comparable professions and, equally, the special conditions of a doctor's life—the long and irregular hours, the load of responsibility, great in human terms and the financial factors, which affect recruiting to a profession which is of such vital importance to the community "

Doubtless it is true, as Lord MORAN pointed out, that a Royal Commission is closely restricted by its terms of reference, and that no Minister—indeed nobody except the chairman of the commission—can decide what is within its ambit But to boycott the commission at this stage because doctors have no guarantee that the Government spokesman is not misinformed would be to carry the legalistic approach altogether too far (Some of us think that legal advisers have already had too much influence in the negotiations) If the commission should in fact find itself legally debarred from taking into account " all the circumstances that are relevant," including the Spens reports, the Government would then be bound in honour to add another paragraph to its terms of reference—a recent precedent (Lord MORAN said) being provided by the Royal Commission on Taxation, whose remit was modified half-way through its proceedings Though the Government may feel unable to do this now at the demand of the profession, they might do it quite easily later at the request of the commission. Similarly if, as we expect, Sir **Harry Pilkington** comes to feel the need of one or two colleagues with a good background knowledge of the National Health Service or the profession, persons of this kind (guaranteed non-medical, of course) might presently be discovered and added to the membership. Possibly they could not actually be industrialists, but the balance of the commission need not be gravely disturbed.

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[1] See p 793

The State, remarked Lord **Home**, has "no inherent virtues as an employer." This "is the first time it has had to work out a relationship with one of the great skilled professions, and inevitably, I suggest, it must take time . . . before a satisfactory code of relationship and conditions of service can be finally established." We shall all agree with him that it has taken time. "It has been heartbreaking," as Lord **Moran** put it, "to see all this bungling and mishandling of the human element." But at the present juncture it would be foolish as well as unfair to treat the Royal Commission as though it too bears responsibility for past failures. Unless or until it proves itself otherwise, the commission should be regarded as a body of reasonable people anxious to do all it can to form a reasonable opinion on the evidence before it; and those who, in protest against the Government, would refuse the commission cooperation should ask themselves whether they would really like it to reach its conclusions without ever hearing the case for the profession put by the profession. Though neither side will be bound by its recommendations, these cannot fail to affect both public opinion and Government policy; and the chance of their being constructive and practicable will be much smaller if the commission has guidance in only one direction. Finally, if it had no other advantage, cooperation with the commission would be desirable because it will oblige all parties to state their case in reasonable and persuasive terms. The horrifying alternative is a period of unrelieved hostility in which the normal flora of discussion gives place to pathogenic propaganda.

Rectal Biopsy

The use of biopsy to confirm a clinical diagnosis of rectal cancer was first recommended by **Gabriel** in 1931,[1] and this was soon adopted at St Mark's Hospital as a routine aid in the diagnosis of neoplasms and obscure granulomatous lesions.[2] More recently rectal biopsy has been advocated for the control of cortisone treatment in ulcerative colitis;[3] but it was found that, in general, the mucosal changes appear much the same at the end of treatment as at the beginning, even when symptomatic relief is complete and sigmoidoscopic appearances are greatly improved.[4] In some cases the surface epithelium appears more gravely disturbed during treatment than before. **Lumb** and **Protheroe**[5] found that in ulcerative colitis the correlation between histological appearances and clinical and sigmoidoscopic findings was close, but that in quiescent cases microscopy might sometimes show the characteristic histological changes of ulcerative colitis even when the mucosa seemed normal by sigmoidoscopy. In the quiescent phase the change is always towards diminution in the numbers of crypts and a generalised thinning after destruction during the ulcerative phase; the regular arrangement of crypts which is so characteristic of the healthy mucosa is generally lost even when repair has taken place; but, although biopsy may thus reveal the existence or persistence of ulcerative colitis, it is not a reliable method of deciding the severity of the disease or of foretelling its future course.

On p. 763, Sir **Philip Manson-Bahr** and Mr **Muggleton** discuss rectal biopsy in the diagnosis of amœbic dysentery and other disorders. They obtain biopsy material by scraping the suspected area of the rectal mucosa with a long-handled Volkmann spoon, crushing the small fragment under a cover glass, and examining it immediately with a low-power objective of the microscope. (The more usual method of obtaining material is by means of a punch or special forceps; the fragment is then fixed, dehydrated, sectioned, and stained by conventional histological techniques.) Of 30 cases of amœbic dysentery, amœbæ or cysts were found in 23 by stool examination and in 15 by biopsy. But the active vegetative form of *Entamœba histolytica* was found in 7 cases by the proctoscopy scrape preparations when all the routine stool tests had been negative; 3 of these 7 had no previous history of amœbic infection. In the more acute phases of the disease diagnosis by examination of material obtained through the sigmoidoscope has been in common use for many years, and has been repeatedly recommended by Sir **Philip Manson-Bahr**.

Rectal biopsy for the diagnosis of schistosomiasis was first suggested in 1942 by **Ottolina** and **Atencio**,[6] who had noticed in necropsy material that the greatest number of *Schistosoma mansoni* ova was to be found in the upper half of the rectal ampulla. Since then this method has often been used when examination of the fæces has proved negative. The comparative value of stool examination and rectal biopsy has been investigated by **Spingarn** et al.,[7] who examined 187 patients with *S. mansoni* infections and found ova in 93% by biopsy and in 83% by stool examination. They attributed the superiority of biopsy both to the concentration of ova in the upper half of the rectal ampulla and to the fact that few ova escape from the colonic wall as the infection becomes chronic. In the acute stage, after deposition within venules by the adult female worms, the ova traverse the tissue spaces rapidly and many appear in the stool; but in the chronic stage a host-cell reaction impedes their progress and smaller numbers are evacuated. The ova which do not escape soon after deposition may die and become calcified. Necrotic ova are still recognisable by microscopic examination of biopsy fragments.

Before recommending the more general use of rectal biopsy we must be sure that it is indeed relatively harmless. **Truelove** et al.[3] found that small erosions caused by taking biopsy material healed without scarring within a few days. They decided that the risk of serious injury by their method was slight, but admitted that any break in the rectal or colonic mucosa might lead to ischiorectal abscess or perforation of the bowel At some hospitals, including St Mark's, rectal biopsy has been adopted, almost as a routine, to confirm a diagnosis of carcinoma and as an aid to the diagnosis of obscure lesions, and it has been found that material can be safely taken in the outpatient department without anæsthesia and without any preliminary preparation, provided that suitable instruments are used and that the operator is experienced in sigmoidoscopic technique

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[1] Gabriel, W. B. *Brit. med. J.* 1931, i, 52.
[2] Gabriel, W. B., Dukes, C. E., Bussey, H. J. R. *Brit. J. Surg.* 1951, 38, 401.
[3] Truelove, S. C., Horler, A. R., Richards, W. C. D. *Brit. med. J.* 1955, ii, 1590.
[4] Truelove, S. C. *Ibid*, 1956, ii, 1267.
[5] Lumb, G., Protheroe, R. H. B. *Lancet*, 1955, ii, 1208.
[6] Ottolina, C., Atencio, M. H. *Rev. Policlin. Caracas*, 1943, 12, 348.
[7] Spingarn, C. L., Edelman, M. H., Gold, T., Yarnis, H., Turell, R. *New Engl. J. Med.* 1957, 256, 290.

Annotations

ORAL PREPARATIONS FOR TREATMENT OF PERNICIOUS ANÆMIA

If our present ideas about the ætiology of pernicious anæmia are correct, it should be possible to treat patients successfully by giving them orally a preparation of intrinsic factor (hæmopoietin) together with a relatively small dose—say 30–45 µg —of vitamin B_{12} Preparations of vitamin B_{12} and intrinsic factor made from hog's pylorus or hog's duodenum have been marketed, but the results have been curiously disappointing Blackburn et al [1] used a preparation dispensed in tablets each of which contained 6 µg of vitamin B_{12} and 30 mg of an intrinsic factor concentrate They gave five tablets a day to 5 patients with pernicious anæmia in relapse, 4 responded reasonably, if slowly, but the 5th did not respond at all, though 30 µg of vitamin B_{12} given intramuscularly each day produced a satisfactory rise in red cells and hæmoglobin Maintenance with one tablet a day showed that after a time, usually about six months, the blood levels began to fall, and in 1 patient signs of neurological involvement developed Blackburn et al concluded that either they had not given big enough doses or the effectiveness of the intrinsic factor concentrate was falling off Dr Schwartz, Dr Lous, and Professor Meulengracht in Copenhagen have met with similar disappointing results, and on p 751 of this issue report investigations that suggest another explanation

They used the test devised by R F Schilling that utilises the urinary excretion of an orally administered test dose of vitamin B_{12} labelled with radioactive cobalt In a healthy person vitamin B_{12} is absorbed in the intestine and excreted in the urine, and the amount excreted gives a measure of the degree of intestinal absorption The patient with untreated pernicious anæmia absorbs hardly any vitamin B_{12}, so very little appears in the urine, but if an effective source of intrinsic factor is given with the vitamin B_{12}, absorption takes place and is reflected in the urinary excretion In health 10–38% of the orally administered vitamin B_{12} is excreted in the urine, whereas in untreated pernicious anæmia the figure is 0–8% The Copenhagen workers gave a combination of labelled vitamin B_{12} and intrinsic factor made from hog's pyloric mucosa to three groups of patients those with untreated pernicious anæmia, those whose pernicious anæmia had been treated with intramuscular vitamin B_{12} or liver extract, and those whose anæmia had been treated orally with a combination of vitamin B_{12} and hog's pyloric mucosa for periods ranging from six months to four years They found, as have others,[2] that up to a certain maximum the absorption of vitamin B_{12} increases with the amount of intrinsic factor given, with their preparation, the most effective dose was about 100 mg daily When this dose of intrinsic factor together with labelled vitamin B_{12} was given to patients with untreated pernicious anæmia the greatest proportion of the test dose excreted in the urine was 20–25%, patients whose pernicious anæmia had been treated with intramuscular vitamin B_{12} or liver gave a similar figure; but most of the patients treated orally showed remarkably low urinary excretion figures, varying from nil to 16% When a *human* source of intrinsic factor, in the form of 100 ml of normal gastric juice, was given with the labelled vitamin B_{12}, this was absorbed as fully by the third group of patients as by the other two groups

Dr Schwartz and his colleagues consider that long treatment with heterologous intrinsic factor must be connected with the long-term failure of these orally administered combinations of vitamin B_{12} and intrinsic factor, but they cannot suggest an explanation Wijmenga,[3] addressing the 1956 Hamburg conference on vitamin B_{12} and intrinsic factor, pointed out that there was evidence that intrinsic factor might be specific for each species, though it is known that activity is not limited to one species—for hog's intrinsic factor is active in man But he also cited some investigations suggesting that intrinsic factor concentrates prepared from one species might contain substances that inhibit the absorption of vitamin B_{12} in other species Williams et al [4] actually prepared intrinsic factor fractions some of which augmented and some inhibited the absorption of vitamin B_{12}, judged by the Schilling test Nevertheless physicians have had entirely satisfactory results from the treatment of pernicious anæmia over periods of many years by administration of relatively crude preparations of hog's stomach Thus Wilkinson [5] reported that of 441 patients treated for six or more years with preparations of desiccated hog's stomach, only 15 relapsed, these relapses occurred only because the patients neglected treatment and they responded promptly when given proper treatment again The cause of the failure of the present intrinsic factor concentrates may well lie in the method of preparation, and this needs to be fully explored as well as possible resistance, or inhibitors, arising because of the heterologous source of intrinsic factor Meanwhile practitioners can take the hint and avoid these relatively very expensive oral preparations for the treatment of pernicious anæmia

TRANQUILLISERS AND SOCIETY

Concern at the increasing abuse of tranquillisers has been expressed by the W H O Committee on Addiction-producing Drugs [6] In the U S A in the first ten months of last year some 30,000 million tablets of one particular tranquillising drug are said to have been sold to the public This figure is cited by Dickel and Dixon,[7] who report 328 instances of "physical dangers" arising from the treatment with tranquillisers of 8200 patients in the past eight years

The main thesis of Dickel and Dixon is that the dangers of abuse are altogether more subtle and pervasive than the occasional development of a skin rash or a blood dyscrasia [8] They consider that such abuse has caused emotional, moral, and philosophical dangers to the patient, dangers to medicine and the physician, and dangers to the whole structure of society In their experience, undesired emotional responses to tranquillising drugs occurred in 827 emotionally ill patients, whose condition was aggravated and distorted by these drugs Equally disturbing were 1700 instances in which serious problems were created in the minds of essentially normal people by the misuse of tranquillisers What very often

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[1] Blackburn E K Cohen H Wilson G M *Brit med J* 1955, ii 461

[2] Baker S J Mollin D L *Brit J Hæmatol* 1955 1 46

[3] Wijmenga H G *In* Vitamin B_{12} and Intrinsic Factor Edited by H C Heinrich *Stuttgart 1957, p 156*

[4] Williams W L Chow, B F Ellenbogen L, Okuda, K *Ibid* p 130

[5] Wilkinson J F *Lancet* 1949 i 291

[6] *Tech Rep W ld Hlth Org* no 116

[7] Dickel H A Dixon H H *J Amer med Ass* 1957 163, 422

[8] see *Lancet*, Feb 9 1957, p 308

Public Health

SOCIAL PATTERNS OF ANTIBODY TO POLIOVIRUS

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THE recent introduction of poliomyelitis vaccines is likely to upset for all time the natural poliovirus antibody patterns in Western communities If anything can be learnt from the distribution of antibody in these communities, it must be learnt now The social factors which are concerned with the spread of polioviruses through a population are not fully understood, and most of our knowledge comes from comparing the antibody patterns and vital statistics of countries with high and low standards of living In general, poliovirus infection has been found to be more common in the countries with a low standard of living, but paralytic poliomyelitis and poliomyelitis epidemics are more common in the countries with a high standard of living (World Health Organisation 1954, Paul 1955)

In this paper, antibody patterns have been related to a variety of social characteristics which reflect the standard of living of the children within a single community This has been done in an attempt to define in greater detail which social factors are associated with the spread of infection between groups in this community, and to see if they are the same as those which seem to operate between countries

As part of the preparation necessary for a field trial of poliomyelitis vaccines, the antibody patterns of a group of children in Northern Ireland were studied by Dane, Dick, Connolly, Briggs, and McLeod in 1956 295 of these were available for study Although the numbers were relatively small and the sample not necessarily representative, it was thought that a study of the social attributes of these children might contribute to the understanding of the mode of spread of the infection, and to the behaviour and health of the social groups concerned

It is suggested that, in communities with low standards of living, there is a widespread early subclinical infection which confers a lasting immunity to the disease, but this suggestion has not so far found general confirmation when groups with different standards are compared *within* the British Isles

In a study of these and other social factors and notified (i e , clinical) poliomyelitis between 1947 and 1950 in England and Wales, Benjamin and Logan (1953) found a pattern so complicated that they called for further inquiries into the distribution of the disease They were unable to find any correlation between the incidence of the disease and the proportion of persons in semi and unskilled occupations (social classes IV and V) or the density of housing After an intensive study in London they rejected the occupation of the principal wage earner in a family as being in any way associated with the notification rates Previously, occupational contact rather than social class had been suggested by Cowan (1950) and Logan (1953) as an important factor in the spread of clinical poliomyelitis Urbanisation (as opposed to housing density) had not been found to be associated with clinical poliomyelitis by Martin (1951)

Daley and Benjamin (1948) investigated the association of social class with notified poliomyelitis, and found no significant relationship Bradford Hill and Martin (1949) tested the association of social conditions and attack rates for poliomyelitis in 1947, using as indices infant mortality and general death rates They found no association, though there was a suggestion that crowding had played a part in the spread of the disease in London Support for the notion that social factors are important in the spread of the poliovirus, and that low standards of living (perhaps favouring early and subclinical infection) affect the pattern of the disease, comes from Daley and Benjamin (1948) who suggested that clinical poliomyelitis is less common in overcrowded conditions Several other writers have emphasised particularly the importance of standards of hygiene (e g , Benjamin and Logan 1953) Population density, economic status, and family size have also been shown by some to be associated with the spread of infection in other countries (e g , McFarlan, Dick, and Seddon 1946 Hammon, Sather, and Hollinger 1950)

Recent studies of the rate of movement of poliovirus in communities in America have emphasised the importance of the family as the site of most rapid spread (McCarroll et al 1955) , and Fox et al (1956) have shown that spread is faster in the families of Negroes than in the "lower Whites" and in the families of "lower Whites" than the "upper Whites" in the same neighbourhood That this difference in rate of spread is not only a question of family toilet hygiene has been shown by Eklund and Larsen (1956), who emphasised the importance of the oropharyngeal route of spread within the family

Further support comes from a recent study of three groups of enteric viruses (poliovirus, Coxsackie, and E C H O) where Honig et al (1956) were able to obtain relatively more positive cultures from children in poor socioeconomic groups than from children of the same age in more fortunate circumstances

The general hypothesis suggested by these studies may be stated as follows

More infection will be found in those families and social groups where there are poverty, overcrowding, many personal contacts between children, poor or inadequate sanitation and housing conditions, and many family occupational contacts More exactly, according to the hypothesis, for children of the same age, more neutralising antibody, and antibody to more of the virus types, would be expected among city-dwellers from large families of low social class, living in overcrowded unhygienic conditions or poor housing Those with many personal contacts would also be expected to have more neutralising antibody and antibody to more of the virus types

The study reported in this paper was designed to test this general hypothesis among 295 school children

Method

Results of the serological analyses of blood samples were obtained with the names and addresses of the 295 children from the university department of microbiology These analyses were available in eight categories, antibody being demonstrable for none, one, two, or all of the three types of virus From these detailed results a quantitative scale, representing the frequency or amount of infection, was derived (table I)

TABLE I—THE QUANTITATIVE SCALE POLIOVIRUS ANTIBODY PATTERNS OF 287 CHILDREN IN NORTHERN IRELAND IN 1955-56

—	Number of children with antibody pattern indicating				Total
	No infection (i e , no antibody demonstrated) (–)	Mild or infrequent infection (i e , antibody demonstrated for one type only) (+)	Moderate infection (i e , antibody demonstrated for two types only) (++)	Heavy or frequent infection (i e , antibody demonstrated for all three types) (+++)	
No of children	47	63	71	106	287
% of total	16	22	2[illegible]	37	100

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* Late lecturer in social and preventive medicine, the Queen's University of Belfast

It was realised that certain important assumptions are involved in using such a quantitative scale for example, frequent exposures are not necessarily to more than one type of virus Its use was considered justifiable, however, as the only available measure of quantity of infection It is used in the results presented below

The social variables investigated were suggested by the literature briefly reviewed above and by the fæcal and oropharyngeal routes of spread Information about them was recorded by health visitors who did not know the serological result and who visited the homes of 287 children and asked questions from a standard interview form 8 children had moved or for some other reason were not available when called upon The information sought was of the type which could be recorded in terms such as " present " or " absent," or which required the recording of a simple statement—e g , details of the occupation of each member of the family Duplicate visits were made to a sample of the homes to confirm the reliability of the data gathered All the coding was done without knowledge of the serology The following records were made for each child

(1) *Domicile* —Children were grouped as living either in the city, in small towns, or in rural areas

(2) *Hygiene, housing, and equipment of household* —Children were grouped according to whether the house in which they lived was supplied with mains or well water, and whether the supply was inside or outside the house They were also grouped according to the presence or absence of a bathroom and washing facilities in the toilet, and of a constant hot water supply in the house

(3) *Characteristics of the household of the child* —The size of the household was noted and the occupation of each member of the household recorded in detail, the social class of the household being coded according to the occupation of the principal wage earner The breadth of the occupational contacts of each member of the household was coded by reference to occupation Thus, the child was considered to come from a household with " many " occupational contacts if any member was a bus conductor, a general practitioner, a salesman, or a shop assistant, or had a job involving many contacts with others † All other occupations were coded as " normal " It was of course recognised that the extent of the occupational contacts of an individual gives only a crude indication of the breadth of his total contacts with persons outside the family group Work contacts must, however, contribute to this total, and it was not thought practicable or within the scope of the study to attempt to measure the contacts of each member of the family outside work

TABLE II—PERCENTAGE DISTRIBUTION OF CHILDREN BY SEROLOGICAL RESULT AND AGE (UNSTANDARDISED DATA)

Age (yr)	Serological result					Test of significance of difference of serological distribution (in absolute numbers) between subgroups
	–	+	+ +	+ + +	Total	
0–3	68·2	13·6	18·2	0·0	100 (22)	χ^2 = 23·84 D F = 3 P < 0·001 (combining columns – with +, and + + with + + +)
4–6	13·9	24·7	25·8	35·6	100 (194)	
7–9	5·9	17·6	23·5	52·9	100 (51)	
10 +	10·0	15·0	25·0	50·0	100 (20)	
Total	16·4	22·0	24·7	36·9	100 (287)	

(4) *The recreational contacts* of the child were coded as " many " if the child played in the street. All others were coded as having " normal " recreational contacts.

(5) *The crowding of the family* was the number of persons per bedroom Infants were excluded from this measure.

(6) In addition, the *age* and *sex* of the child were coded.

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† Occupations coded as involving " many " contacts were:

Bus conductors
Shop assistants
Hairdressers
Receptionists (Dentist)
Bookmakers
Customs officials
School teachers
Ward Orderlies

Receptionists (Doctor)
Usherettes
Physicians
Salesmen
Dentists
Solicitors
Messengers
Policemen

Clergymen
Counterhands in cafés
Bank clerks (counter)
General practitioners
Gas meter inspectors

Interviewers and Canvassers
Telephone engineers (domestic installation and repairs)

TABLE III—PERCENTAGE RATIOS OF THE NUMBER OF CHILDREN OBSERVED TO THE NUMBER EXPECTED ON THE NULL HYPOTHESIS, CLASSIFIED BY POLIOVIRUS SEROLOGICAL RESULT AND STATED SOCIAL FACTOR, AGE BEING HELD CONSTANT

Social factors		Serological result (%)				No of children	Test of significance of difference between observed and expected distributions
Description	Subgroup	–	+	+ +	+ + +		
Domicile	Rural	67·1	179·7	56·7	106·7	30	χ^2 = 31·[illegible] D F = [illegible] P < 0·0[illegible]
	Small town	157·2	133·4	94·5	40·0	81	
	City	67·0	70·8	109·5	120·1	176	
Toilet accommodation	Wash hand basin	119·1	126·0	107·2	68·4	126	χ^2 = 12·4[illegible] D F = 3 [illegible]
	No wash hand basin	79·4	80·5	94·5	122·3	161	
Household equipment	Constant hot water	130·1	120·2	110·5	64·3	159	[illegible]
	No constant hot water	47·0	76·2	87·3	140·0	128	
Bathroom	Yes	129·0	119·4	104·4	69·2	157	[illegible]
	No	47·7	78·0	94·8	133·2	130	
Housing type	Detached	153·3	167·0	87·0	43·2	47	[illegible]
	Semi detached	132·3	113·1	94·5	79·0	78	
	Terraced	59·5	77·7	106·3	124·3	162	
Social class of family	I and II	207·7	155·6	81·5	29·4	65	[illegible]
	III	84·7	110·8	88·0	109·2	129	
	IV and V	37·0	48·0	129·1	135·4	93	
Family occupational contacts	Normal	89·4	84·8	98·3	115·2	197	[illegible]
	Many	123·8	134·4	103·7	67·8	90	
Recreational contacts	Normal	150·2	129·4	102·2	39·4	104	[illegible]
	Many	48·8	82·9	98·8	127·4	183	
Crowding	< 1·5 persons per bedroom	138·5	152·2	92·8	47·8	79	[illegible]
	1·6–2·0	115·7	63·5	94·6	118·8	[illegible]	
	2·1–2·5	16·4	89·6	87·9	146·1	41	
	2·6 +	65·1	93·9	118·7	107·2	[illegible]	
No of children		47	63	71	106	2[illegible]7	

TABLE VI—THE POLIOVIRUS ANTIBODY PATTERN OF 287 CHILDREN DIVIDED ACCORDING TO AGE, SOCIAL CLASS, DOMICILE, BREADTH OF RECREATIONAL CONTACTS, AND HOUSEHOLD EQUIPMENT

Category	No. of children with antibody pattern indicating				Total
	No infection (–)	Mild or infrequent infection (+)	Moderate infection (++)	Heavy or frequent infection (+++)	
Social classes IV + V and/or city dwellers and/or 7 + yrs of age and/or many recreational contacts and/or poor household equipment	28	49	66	102	245
Other children	19	14	5	4	42
Total	47	63	71	106	287

$\chi^2 = 41.21$ D.F. = 3 P = < 0.001

Occupation and Family Infection

Table VI draws attention to a number of discrepancies —9 children who, on the general hypothesis, *should* have had little infection, but, when they were investigated, showed evidence of "moderate" or "frequent" infection. The records, however, showed that in these 9 families the occupations of the principal wage earner were general practitioner, furniture dealer and furniture-shop salesman, confectioner's shop owner and salesman, elementary school teacher, salesman in lime works, customs official, hairdresser, divisional medical officer, and electrician (house wiring). All but the last had been coded as having "many" occupational contacts. As there were only 90 families coded as having "many" occupational contacts among the 287 families represented, the probability of this happening by chance is very small (P = 0.001) and suggests that occupational contacts are important in infecting the family in certain cases.

Comment

It has long been known that countries where living conditions are poor and overcrowded, and sanitation and personal hygiene are bad, have more and earlier poliovirus infection. The present study confirms that the same pattern is found among groups with different standards within one community. Many factors may be implicated, and of those studied there is a strong suggestion that (apart from the age of the child) where he lives, the social class of his family, the extent of his recreational contacts, and the equipment of his household, all affect his chances of poliovirus infection. It has been assumed (Paul 1955) that infection by the polioviruses is through direct contact between individuals and by contamination of the environment due to poor hygiene. The importance of age, domicile, and recreational contact in the pattern of infection of the children studied could be explained in these terms by the relatively large chance of outside-the-home contacts likely to be experienced by older children, city dwellers, and children who play in the streets. Household equipment (in this case whether or not the family has constant hot water) may reflect an aspect of personal hygiene associated with the contamination of people and of surroundings. In turn, social class may cover other aspects of family hygiene as well as a variety of interacting variables such as crowding and the quality of housing. That this is not the whole story in the infection of the individual is suggested by some of the limited standardisations described above. It was found that the strength of the social class trend was almost unaffected by observing it under conditions of standard crowding or by holding constant the effect of the presence or absence of a bathroom, toilet accommodation, type and equipment of housing, or the extent of recreational contacts. This suggests that either none of these factors contributes much to the social class effect or that they are inadequate measures of contact and hygiene. Since the latter explanation appears unlikely the nature of other factors responsible for the social class trend remains problematical. We know that to measure the social class of a family is a crude way of measuring differences in environment and (perhaps more important in this context) behaviour, which are often crucial in health or mortality experience. For many other infections it is the children from the families of lower social classes which experience most disease (Registrar-General 1954). In their poliovirus infection the children in this study were no exception. But the effect on the child may not be quite the same as for other infections, for no actual illness was involved (of the 240 infected children, none had been suspected of having poliomyelitis) and all the infected children may be presumed to have some lasting immunity.

Because an infection early in life seems less likely to produce clinical disease than infection later on, one would expect that their early acquired immunity would protect the children of the lower social class families from the disease. The literature of the past hundred years and some current textbooks support this view. But the expected social class differential in mortality and morbidity was not found by Bradford Hill and Martin (1949), or by other workers reviewing notified poliomyelitis in post-war Britain. One reason for this apparent lack of social gradient could be that, though more vulnerable, the better off children were exposed less to infection. If so the expected social class gradient in the clinical disease would be apparent only after examination of the attack rates among children all of whom were known to have been exposed to infection. Such a gradient would not normally show itself in notification rates, except perhaps in the unusual situation where equal exposure of all classes of children became possible.

Summary

The pattern of neutralising antibodies to the polioviruses in 287 children in Northern Ireland has been related to the age, sex, home, social class, various measures of the type and equipment of housing, size of household, recreational, and occupational contacts, and crowding of the children and their families. None were thought to have had poliomyelitis, though 240 showed evidence of past infection.

After a series of standardisations five factors emerge as significantly and separately related to antibody pattern. Evidence of more frequent or heavier infection was associated with increasing age, life in the city rather than the small town, lower social class of family, an absence of hot-water equipment in the household, and the child having many recreational contacts. Children who showed unexpected evidence of infection came from families in which there were one or more persons from occupations (such as bus conductor or doctor) characterised by many contacts with others.

The social class of the family shows the clearest association with antibody pattern. This association does not disappear when variation due to differences in the extent of contact with others or household hygiene are held constant, and may therefore be due in part to other factors not yet investigated.

From these results it is suggested tentatively that a social class gradient in the occurrence of clinical poliomyelitis favouring the lower social class families of this group, would be expected only if all the children were to be exposed equally to infection.

This study would not have been possible without the full coöperation of Prof G W A. Dick and Dr David Dane of the department of microbiology of the Queen's University, and it is based on their investigations of poliovirus in Northern Ireland. Dr Dane was responsible for all the serology and has been a constant adviser

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The Minister and the Welfare Services

Addressing the local authorities' welfare conference, held in London on April 2, Mr Dennis Vosper, the Minister of Health, said that in 1957–58 57% of N.H.S. expenditure would go to the hospitals. about 30% to the general medical, pharmaceutical, dental, and ophthalmic services; and 8·3% to local-authority services. He believed that the amount allocated to the local-authority health service was not commensurate with their importance. The importance of preventive health measures and their welfare partners had been often stressed as a means of limiting the cost of the rest of the health service While he feared that the demands of the other partners in the health service would not diminish, he would try to encourage the local-authority health and welfare services, not only because it must be our general desire to keep people well and happy, but also because in the long run it should be to our financial advantage

There were, he suggested, four essentials to a successful welfare policy—that it should be local, that it should be unified that it should be centred on the family and individual, and that it should make full use of voluntary services A service which dealt with human problems must be administered by those in close contact with the people concerned It must always be not a national but a local-government service Welfare work could not be prescribed by statute and administered by regulation During the last two decades we had built up an enormous superstructure from the social services The superstructure needed so much effort and money that we might be precluded from reconsidering our social problems. With this background it was important to remember that we should concentrate more and more on the individual and the family. If at times, the superstructure or organisation did not fit the needs of the individual, then the organisation and not the individual must be changed.

Middlesbrough Award

An award (no 2646) by the Industrial Court asks the county borough of Middlesbrough to pay its medical officer of health Dr E C Downer, the salaries recommended by the regional appeals committee under the Whitley machinery

Middlesbrough has a population of about 148,000, and Dr Downer is school medical officer and port medical officer: but with successive rises in national salary scales since 1950 the corporation has always put him on the minimum salary for a local authority with a population of between 100 000 and 150 000, and it has twice ignored the strong recommendation of the regional appeals committee that, in view of his responsibilities, he should be paid at a higher rate Only under pressure from the British Medical Association did the corporation agree to arbitration by the Industrial Court It told the court that it had discretion to determine Dr. Downer's salary, within the prescribed limits, "having regard to local factors." and that, though he had given much shorter service to Middlesbrough than some other chief officers of the corporation, he received 'more cash salary' than any except the Town Clerk.

The Industrial Court's decision will perhaps restrain other authorities which may be tempted to pay no attention to what an appeals committee recommends

Mortality in 1956

Provisional figures for deaths from tuberculosis and cancer and for maternal mortality in England and Wales last year are announced by the Registrar-General [1]

Tuberculosis—The death rate for respiratory tuberculosis was 109 per million persons, compared with 131 per million in 1955 The death rate from other forms of tuberculosis was 12 per million persons, compared with 15 in 1955

Cancer—The provisional death-rate for all forms of cancer for men was 2274 per million population and for women 1891, the 1955 figures were 2252 and 1873 respectively The rise in the rate for men includes an increase from 693 to 726 per million population for deaths assigned to cancer of the lung and bronchus, the rate for cancer of the lung and bronchus for women increased from 106 per million in 1955 to 111 in 1956

Maternal mortality—The provisional rate for maternal mortality (including abortion) was 0·56 per 1000 live and still births—the lowest ever recorded

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[1] Registrar-General's weekly return no 13 1957 H M Stationery Office 1s 3d

Infectious Diseases in England and Wales

Disease	Week ended March				
	2	9	16	23	30*
Diphtheria	7	6	3	3	6
Dysentery	1291	1214	1416	1317	1222
Encephalitis					
Infective	3	4	2	4	1
Post-infectious	3	3	2	3	8
Food poisoning	174	131	164	298	210
Measles excluding rubella	23 060	24 844	24 832	27 179	25,185
Meningococcal infection	22	24	29	20	46
Ophthalmia neonatorum	28	37	37	35	36
Paratyphoid fever	10	7	4	3	3
Pneumonia primary or influenzal	664	755	770	695	545
Poliomyelitis					
Paralytic	21	27	23	26	18
Non paralytic	9	7	15	11	10
Puerperal pyrexia	222	206	230	216	240
Scarlet fever	833	838	935	822	512
Smallpox	-				
Tuberculosis					
Respiratory	608	583	676	593	683
Meninges and C.N.S.	6	7	15	11	9
Other	84	81	74	77	70
Typhoid fever		1	4	1	1
Whooping-cough	3000	2995	3180	2932	2549

* Not including late returns

TABLE I—AGE-DISTRIBUTION AT JUNE, 1950, OF CONSULTANTS AND S H M O s (GREAT BRITAIN)

Year of birth	General medicine		Diseases of the chest		Mental health		Neurology		Paediatrics		Radiology		Radiotherapy		Physical medicine		Pathology		Infectious diseases		Dermatology	
	Persons	Sessions	Persons	Sessions	Persons	Sessions	Persons	Sessions	Persons	Sessions	Persons	Sessions	Persons	Sessions	Persons	Sessions	Persons	Sessions	Persons	Sessions	Persons	Sessions
1886											1	10										
1887	1	6			1	7									1	3	2	2				
1888	1	4	1	11							1	4					2	12				
1889	2	1	1	9							3	8					2	11	1	1		
1890	5	35			4	33					1	4					3	18			1	9
1891	17	92	2	22	1	11			1	11	6	46	1		1	2	7	50	2	17	3	21
1892	11	58	7	63	9	54			7	41	8	67			3	22	6	35	3	26	3	14
1893	25	154	1	44	6	41	1	5	3	6	11	94	1	2			5	57	3	24	1	22
1894	15	80	7	60	11	77			1	5	7	57	1	7			11	95	6	50	7	37
1895	18	111	10	104	12	101	1	4	3	18	10	100			1	10	17	114	5	40	3	8
1896	20	142	9	82	17	127	1		5	31	11	99	2	22	1	6	16	147	1	36	5	42
1897	29	178	10	89	24	194	1	4	4	20	14	134	4	18	2	3	14	103	4	24	6	36
1898	30	195	11	108	28	259			7	38	16	113	3	30	1	11	12	106	7	67	8	40
1899	27	167	17	169	31	282	4	25	3	26	18	126	6	64	9	63	24	161	5	48	6	33
1900	52	302	22	217	37	335	2	5	9	35	14	120	3	33	2	11	18	160	9	49	10	48
1901	40	265	20	187	34	338			5	26	22	194	4	40	3	23	18	163	11	98	8	41
1902	29	186	32	343	33	312	5	36	11	53	12	113	3	29	3	16	11	87	4	21		
1903	37	247	29	300	28	240	5	42	6	31	13	96	3	32	3	14	21	180	5	31	7	38
1904	39	267	19	195	31	300	3	27	4	40	10	84	4	22	2	8	17	135	5	26	6	37
1905	35	299	25	236	40	369	2	10	6	50	13	115	3	28			27	247	1	1	4	30
1906	38	265	20	204	40	258	2	10	6	45	11	102	3	31	6	15	23	195	5	30	[illegible]	28
1907	61	468	26	258	38	366	5	31	11	74	10	105	2	22	3	31	20	192	5	29	7	37
1908	44	312	22	232	44	425	4	38	13	118	8	81	6	47	3	20	20	186	6	30	8	41
1909	52	363	22	207	32	313	6	52	12	80	15	126	3	22	3	22	20	223	4	41	4	20
1910	52	113	26	274	39	384	2	14	15	138	19	184	6	59	3	29	35	317	1	2	11	65
1911	51	301	43	438	41	397	3	15	8	66	16	161	9	87	4	28	34	267	4	25	8	56
1912	46	339	24	238	50	471	1		11	66	27	253	4	40	2	16	43	186	7	60	8	62
1913	50	444	43	458	38	348	7	57	9	85	24	248	11	119	5	34	37	333	3	33	7	49
1914	61	503	14	164	50	403	2	18	11	90	32	326	14	146	5	52	52	405	6	30	8	68
1915	68	518	45	462	52	521	5	47	14	110	27	240	4	40	8	55	50	478	3	19	9	57
1916	54	120	55	595	45	430	3	25	16	140	34	337	8	72	5	53	16	448	5	55	4	34
1917	42	331	37	395	41	391	6	45	14	128	21	205	11	116	4	28	49	449	1	2	3	26
1918	32	219	37	374	36	359			16	120	20	196	11	106	8	78	40	383	1	11	13	86
1919	32	216	26	276	36	342	2	4	8	60	23	211	10	94	6	58	37	331	2	17	6	41
1920	28	185	27	285	38	350	1	8	9	71	13	130	8	88	3	24	40	330	2	22	5	30
1921	16	85	25	273	23	231	1	11	3	29	20	208	8	88	2	22	34	284	2	22	2	16
1922	9	83	18	193	32	306	2	8	2	9	14	144	6	61			23	218	2	22	1	7
1923	3	26	13	143	16	162					10	96	4	36	2	11	11	86				
1924	4	27	7	77	8	83					1	11	2	22			11	99	1	11		
1925	2	22	4	41	12	126																
1926			2	22	3	33											3	22				
1927			1	11	1	11																
1928					1	11																
Totals	1178	8389	793	8162	1063	9967	76	550	253	1871	536	1948	167	1623	101	798	879	7582	130	1033	190	1182

Year of birth	Venereology		Ophthalmology		General surgery		Anaesthetics		Neurosurgery		Plastic surgery		Thoracic surgery		Orthopaedic surgery		Ear, nose and throat surgery		Obstetrics and gynaecology		Total	
	Persons	Sessions	Persons	Sessions	Persons	Sessions	Persons	Sessions	Persons	Sessions	Persons	Sessions	Persons	Sessions	Persons	Sessions	Persons	Sessions	Persons	Sessions	Persons	Sessions
1886					1	1									1	2					3	13
1887					2	7									1						8	25
1888	1	2	1	4	1	2	1	9									1	5	1	2	11	[illegible]
1889	2	9			3	7	2	10									2	8	2	16	20	40
1890			1	4	3	18	2	11			1				2	2	1	9			21	113
1891	1	2	7	28	14	91	1	2							3	10	3	20	7	43	77	465
1892	3	12	10	62	19	136	7	54							4	20	8	49	7	52	115	775
1893	4	18	15	83	23	172	11	83					3	11	1	10	6	31	6	39	132	904
1894	5	26	15	98	24	143	11	60							4	32	7	42	10	65	112	941
1895	2	11	9	62	21	142	16	112					1	3	2	11	7	[illegible]	11	88	147	1093
1896	7	40	13	90	25	206	23	134			1	2	1	11	4	11	11	84	10	75	189	[illegible]
1897	6	43	10	68	38	270	27	174	2	15			1	5	7	60	12	85	13	82	227	1611
1898	7	54	24	110	25	208	25	206							1	35	11	82	20	148	239	1840
1899	4	28	30	203	48	357	28	179	1	9					6	49	11	80	17	137	[illegible]	2206
1900	7	44	28	201	47	313	42	274	1	23	1	6	1	9	16	111	21	157	14	111	[illegible]	2591
1901	[illegible]	37	20	166	42	283	39	285			2	20	1	9	10	89	27	206	20	151	313	2618
1902	10	75	20	120	55	384	43	270	2	17	3	19	4	30	14	110	19	160	[illegible]	106	338	[illegible]
1903	5	35	19	129	48	365	34	266			2	21	4	34	11	79	10	73	22	175	312	2431
1904	6	32	14	87	58	481	28	212	1	9	1	9			11	86	11	110	21	155	293	2331
1905	11	72	21	132	37	253	36	270	1	9	1	9	3	26	8	58	11	95	18	110	303	2153
1906	5	39	11	85	48	403	37	305	3	29	1	9	3	22	12	116	13	107	18	151	310	2180
1907	6	52	16	93	36	270	[illegible]	198	1	9	4	24	3	17	25	216	11	90	25	183	349	2675
1908	7	53	19	[illegible]	47	380	11	301	1	9	3	27	3	22	20	178	12	103	18	163	318	2973
1909	4	25	24	144	38	335	32	278	4	41	2	18	3	28	21	195	16	137	28	243	354	2916
1910	9	50	25	167	69	[illegible]	32	251	3	31	1	4	4	31	21	197	13	100	25	193	411	[illegible]
1911	8	55	19	121	50	[illegible]	38	284	1	11	5	17	6	54	23	217	16	126	31	231	412	3115
1912	4	34	13	97	52	466	41	317	2	20	2	20	6	25	22	191	10	90	32	237	407	3176
1913	5	53	19	111	62	508	46	400	6	58	2	18	4	39	26	228	13	121	31	203	451	[illegible]
1914	10	53	22	156	49	398	45	406	2	18	2	18	6	16	23	216	11	100	31	255	485	[illegible]
1915	7	59	25	181	39	345	61	593	4	36	6	48	6	58	32	294	14	123	34	296	515	[illegible]
1916	3	17	25	170	51	410	50	462	4	28	5	12	6	[illegible]	27	255	15	132	22	189	483	4365
1917	4	36	24	154	47	274	61	506	6	62	3	27	9	81	18	181	13	107	19	142	423	3649
1918	2	18	12	84	27	226	43	385			2	20	7	60	13	120	12	91	16	127	349	[illegible]
1919	2	15	17	91	21	171	26	236	2	20			1	18	14	128	12	104	16	110	302	[illegible]
1920	[illegible]	[illegible]	11	55	18	[illegible]	17	[illegible]	2	20			4	34	11	95	[illegible]	42	9	47	256	2101
1921	2	22	11	56	8	47	32	301			1	9	4	35	7	73	11	98	7	19	219	[illegible]
1922	1	11	9	40	[illegible]	70	37	319	2	22			3	11	3	11	5	31			171	1379
1923	1	10	11	58	2	11	22	215									1	9	1	11	97	[illegible]
1924	1	3	7	35			18	171													60	[illegible]
1925			4	6	1		11	115													34	313
1926			1	1			4	44													13	122
1927	1	11	1	2				[illegible]													7	
1928																					1	11
Totals	172	1261	[illegible]	3736	1193	9180	1131	9190	51	496	[illegible]	117	[illegible]	[illegible]	[illegible]	3761	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

Consultants and S H M O s practising in more than one specialty have been included under each. Sessions of honoraries are excluded. Dentistry is excluded. Table includes honorary staff but

Special Articles

CONSULTANTS AND OTHER SPECIALIST STAFF IN HOSPITALS

THE accompanying tables have been issued by the Ministry of Health and Department of Health for Scotland as being of interest to the medical profession generally They may be of special interest to those who are intending to train as specialists All the figures relate to Great Britain

Table I shows the age distribution at June 30, 1956, of consultants and senior hospital medical officers practising in the various specialties It shows also the numbers of paid sessions undertaken by the consultants and S H M O s in each specialty for each year of birth

Table II shows the numbers of consultants in each of the specialties year by year from 1949 The corresponding figures for senior hospital medical officers are not available

Table III shows the number of senior registrars in each specialty on June 30, 1956, at the various stages of their training The column headed " Others " includes those holding " transitional " posts

TABLE III—SENIOR REGISTRARS IN GREAT BRITAIN ON JUNE 30, 1956

Specialties	Training plan					Others*	Grand total
	1st yr	2nd yr	3rd yr	4th yr	Total		
General medicine	39	40	30	27	136	68	204
Diseases of the chest	12	18	11	8	49	4	53
Mental health	49	32	20	9	110	12	122
Neurology	2	3	2	5	12	2	14
Pædiatrics	4	8	7	5	24	12	36
Radiology	25	15	16	8	64	3	67
Radiotherapy	4	5	4	3	16		16
Physical medicine	3	4	2	1	10		10
Pathology	16	17	14	16	63	40	103
Infectious diseases	2	1		1	4	2	6
Dermatology	2	3	4	7	16	13	29
Venereology	1	1	1	1	4	2	6
Ophthalmology	19	18	12	5	54	11	65
General surgery	47	41	31	26	145	66	211
Anæsthetics	39	19	11	4	73	6	79
Neurosurgery	2	6	2	2	12	3	15
Plastic surgery	1	4	2	2	9	8	17
Thoracic surgery	5	5	6	3	19	10	29
Orthopædic surgery	22	18	8	6	54	11	65
Ear nose, and throat surgery	17	9	9	5	40	7	47
Obstetrics and gynæcology	17	24	17	9	67	34	101
Totals	328	291	209	153	981	314	1295

* Includes 93 honorary and 26 part time senior registrars

TABLE II—NUMBER OF CONSULTANTS IN EACH SPECIALTY AT VARIOUS DATES SINCE DEC 31, 1949 (GREAT BRITAIN)

Date	General medicine	Diseases of the chest	Mental health	Neurology	Pædiatrics	Radiology	Radiotherapy	Physical medicine	Pathology	Infectious diseases	Dermatology	Venereology	Ophthalmology	General surgery	Anæsthetics	Neurosurgery	Plastic surgery	Thoracic surgery	Orthopædic surgery	Ear, nose, and throat surgery	Obstetrics and gynæcology	Totals
Dec 31 1949	755	216	449	53	166	327	85	49	495	50	127	89	331	927	496	37	30	49	252	312	424	5719
Dec 31 1950	831	250	504	53	202	278	93	57	526	52	136	101	341	942	602	39	32	57	269	328	439	6233
Dec 31 1951	857	266	532	59	208	400	101	61	541	48	135	99	342	948	655	42	33	66	293	341	449	6476
Dec 31 1952	904	310	566	61	214	414	108	70	581	51	142	97	351	986	714	44	36	81	320	339	473	6862
Dec 31 1953	905	340	595	67	222	436	112	75	631	60	145	94	342	982	748	46	43	89	328	346	473	7079
Dec 31 1954	924	344	616	68	226	447	116	74	646	59	146	93	340	987	782	48	48	91	335	350	485	7225
June 30 1955	932	346	633	69	228	455	120	73	659	58	146	93	341	988	797	49	50	93	339	353	493	7315
June 30 1956	946	347	640	70	229	468	127	77	689	56	150	92	339	988	815	52	50	97	353	347	495	7427

Consultants practising in more than one specialty have been included under each   Table includes honorary consultants

A SURGICAL RESIDENTIAL COLLEGE

Viscount Nuffield and Lord Webb Johnson have long had in mind a surgical counterpart in London to All Souls College, Oxford, and their thoughts have resulted in the foundation of the Nuffield College of Surgical Sciences Viscount Nuffield gave £250,000 for the building through his Charitable Trust and helped to make available a further £187,000 from King Edward's Hospital Fund for London It is a unique institution where postgraduate students training in surgery can gather for instruction and study The college is residential, and the students mix with their fellows and their seniors, the President will have a suite of rooms there It has been in use since the beginning of this year, and all 80 places are already filled, but the official opening was delayed to April 5, the anniversary of Lord Lister's birthday

The impressive ceremony in the great hall of the Royal College of Surgeons was attended by some 500 people

To the music of a contingent of the band of the Grenadier Guards several processions entered the hall and took their seats—the council of the Imperial Cancer Research Fund, the committee of management of the Institute of Basic Medical Sciences the boards of the Faculties of Anæsthetists and of Dental Surgery, the court of examiners, and the council, with the court of patrons and some honorary fellows Then the entry of the mace heralded the president (Sir Harry Platt), with the chairman of the building committee (Mr E W Riches), Lord Nuffield, Lord Freyberg, V C, and the Bishop of London

Sir Harry Platt, P R C S, welcomed the guests and read out a brief cable of good wishes from the Royal Australasian College of Surgeons Lord Nuffield asked him to accept the Nuffield College of Surgical Sciences on behalf of the Royal College of Surgeons, and he formally accepted the gift Mr Riches presented Lord Nuffield with a book to contain photographs of the new college and of the ceremony

Lord Freyberg, in a short address, spoke of his previous associations with Lord Nuffield in connection with London House—another educational institution particularly concerned with postgraduate study—and emphasised the value to the students of the collegiate life He then walked to the door of the new building, where he was introduced to Mr A W Hall, F R I B A, the architect, and declared the building open Visitors were then at liberty to inspect the lounge, with its portrait of Lord Nuffield, and the other common rooms The students' accommodation is comfortable and the provision for recreation excellent

All too often students of medicine are denied both a liberal education and a collegiate life Lord Nuffield's bounty will now give many postgraduates a taste of residence in college, where life with their fellows from several continents must enlarge their ideas and understanding

In England Now

A Running Commentary by Peripatetic Correspondents

THE DOCTOR'S WIFE WITHDRAWS

There is no time to write—
Interrupted always by the bells
(Yes, this is the doctor's house)
The door, the telephone, or the knell
For unfortunate patients predeceased
The church is inconveniently close

There is no time
To lie close, feeling creation's surge ,
No time
To carry carefully the embryo idea,
To know its certain growth, to brood for hours
Upon its pattern
There is no time to wonder,
Intrusion hammers always at the door,
Shrilling the bells

Serenity is marred, the embryo distorted ,
With dark pain
And long drawn labour it struggles to be born
(Interrupted by the bells, of course
Even *travailing I must answer them*)
What uneven monster now will wail
Its pitiful first cry, tuneless, harsh
Into a world uninterested in birth,
Being morbidly preoccupied with death,
Atomically gigantic, yet personally minute
Or should it be
Personally gigantic, atomically minute ?
The bells distract I cannot think
There is no time even to consider
Death in this house, the bells are rung so often
To outwit it

This moron child
Incapable of receiving or returning thought
Is all I can achieve, project or leave ,
So little worth !
Yet, since there must be death,
There must be also, first, some kind of birth
(The bells know that they ring so urgently
For the newborn Doctor, quick !)
So I ll take creation's side,
Withdraw (into myself)
And leave the bells to ring !

* * *

The other day chatting to a psoriatic old woodman who attends regularly for his "skin, doctor," I found that he came originally from the village where I was born, a hundred miles away There he had been treated by my father for the same complaint over 45 years ago He was very pleased at this discovery and seemed to bear no ill-will for two generations of unsuccessful doctoring

* * *

I see that the medical correspondent of a popular newspaper has been criticised for presuming to offer a spot diagnosis of a reader's illness, based only on a letter to the paper His troubles reminded me of the more exuberant days of the 18th century, when it was quite normal for the educated patient to submit his own written case-history to a consultant, together with the fee, and to receive by return a diagnosis and an appropriate prescription

The classical example is provided by that irascible and cantankerous hypochondriac, Tobias Smollett, who undertook the Grand Tour to France and Italy in 1763-64 His continued ill health during the southward journey across France (while at Boulogne he had even, he says, ventured on the 'desperate remedy" of plunging daily into the sea) constrained him to consult a prominent local physician at Montpellier—' one of the dearest places in the south of France "—since the many English who passed that way were regarded, and for their part were content to be regarded, as generous milords with inexhaustible resources

Smollett carefully wrote out a long description of his own case, in Latin and despatched it by messenger to the great man, accompanied by *a fee of one louis'dore* (= 12 *livres*) The reply, when it came, incensed him inordinately He did not object to the doctor's recommendation of a light diet, nor to the extremely odd concoctions he prescribed for the unseen patient's alleged fever and cough , but he disagreed with the consultant's general view of the case, and most of all he took strong exception to its being couched in the French language—then regarded by many intellectuals as a semi-barbarous tongue ill-suited to the exchange of educated views

Furious, Smollett sent the doctor another note, arguing with the diagnosis ("*tabes pituitaria*," he would call it, not "*tabes purulenta* ") and implying that the case history had not been read properly The French physician stood his ground, and intimated that he would be ready to resolve *Monsieur le Consultant*'s doubts in person if he cared to call At this, Smollett's anger at once subsided He sent a note of apology, with a supplementary fee of another *louis* , the physician courteously acknowledged both , and Smollett wrote a page and a half to a friend, proving to his own satisfaction how right he had been and what a costly charlatan the doctor was

* * *

Shirley came from a large but poor family As she had collapse of the lung with bronchiectasis she was advised to have postural drainage This involved sleeping at night with the foot of her bed raised This advice was readily accepted and it was only some months later that it transpired that the whole family had to sleep with their heads down as they only had one bed There were no complaints

* * *

Awake ! But it was not morning that had flung the stone into my Bowl of Night It was young Perkins from *The Golden Lion* flinging pebbles at my bedroom window Dad's face was cut something horrible, and would I come at once The urgency of heading off old Perkins from the Dawn of Nothing penetrated my veil of sleep Still befuddled, I pulled on my pants and jacket, picked up the emergency bag, and scurried along the street Sure enough, the landlord was not a pretty sight Apart from the till, that Saturday night extension had not been an *unqualified success The takings from a rather* wild party had included turning down an empty glass across old Perkin's refusal of yet another last round He was *sitting in the bar with a dish cloth clapped to* his cheek I reckoned it needed a fair few stitches to restore some sort of acceptable cosmetic effect Mark you, Mr Perkins is not a fussy man about appearances maybe twenty years of pub-keeping dulls the finer feelings Anyway, I gave him the benefit of the doubt and infiltrated the field of operation with a spot of local anæsthetic While it was having time to act, I wandered round admiring the murals behind the bar Gamecocks and race horses to the left, cheesecake and pin-up girls to the right Perkins was certainly a connoisseur of beauty Thinking it was time to get on with the job, I leaned over the patient and inserted the first stitch Perkins flinched I wondered if the anæsthetic was all right He said it was, so I pressed on As I approached once more he drew back with a look of horror before the needle even touched him

"What's the matter, Mr Perkins ? " I snapped testily, "Surely it doesn't hurt ? Why are you looking so scared ? "

"Well, doctor," replied the victim "Have you ever seen yourself without your teeth in ? "

I glanced in the mirror over the bar Indeed my dentures lay still in the *Bowl of Night*

* * *

The French government's campaign against alcoholism is gaining momentum, and in my *carriage* on the *Métro* in Paris last week I was surrounded by such notices as

Les prescriptions de l'Academie de Medecine
Jamais plus d un litre de vin par jour !
Sante Sobriete

In the next carriage I was glad to see the more usual *advertisements* for the many proprietary brands of *attractive alcoholic beverages* Paris, tu n'as pas change

* * *

Mother (on the telephone) *Johnny has cut his head* Doctor, what shall I do ? "

Doctor (about to go out) Take him to the chemist and if he thinks stitches are needed, take Johnny to the hospital !"

Letters to the Editor

SERUM-CHOLESTEROL RESPONSE TO DIETARY FAT

SIR,—Recently we reported in your columns (Jan. 12, p. 66) the results of controlled experiments showing that dietary fat has a powerful influence on the serum-cholesterol level in man but that this is not a simple inverse function of the amount of "essential" fatty acids in the diet. In due course we shall report the detailed findings in a systematic study, continuously in progress since 1950, of the relationship of serum-cholesterol concentration to the amount and kind of fats in the diet. In the meantime it may help to reduce confusion in this area of intense research interest to disclose a major feature of the findings in 20,000 man days of controlled experiments covering butterfat, lard, olive oil, cottonseed oil, corn (maize) oil, sunflower-seed oil, safflower-seed oil, and sardine oil, as well as mixed fats in the ordinary (high dairy and meat fat) diet.

The experiments dealt with groups of 12 to 27 men at a time subsisting in calorie equilibrium on a diet adequate and constant in proteins, vitamins, and minerals in which total fats provide 9.5 to 41.5% of total calories with one or another fat being the experimental variable, usually at the level of 90–100 g. daily, for periods of two to nine weeks, averaging four weeks on each diet. The responses of the serum cholesterol level of one group of men to several dietary changes, arranged so as to control time trends, constituted an experimental series. Pertinent to the present purpose are the data from 9 such series, providing 58 sets of comparisons of diets for which we have estimates of the fatty-acid composition in terms of glycerides of saturated (S), mono-ethenoid (M), and poly-ethenoid (P) fatty acids. Except in the case of the sardine oil diet, almost all of the poly-ethenoid was linoleic acid and the mono-ethenoid was oleic acid.

We formulated the hypothesis that each of these classes of fatty acids may make a different contribution to the serum-cholesterol so that, on a given diet, the serum cholesterol concentration (in mg. per 100 ml.) would be

$$\text{(1)}\qquad \widehat{\text{Chol}}_1 = a + bS_1 - cM_1 + dP_1$$

where S, M, and P are expressed as percentages of the total calories in the diet.

On a second diet, all other things being equal, the difference between the serum concentrations of the two diets would be given by subtraction

$$\text{(2)}\qquad \Delta\ \text{Chol} = b(\Delta S) - c(\Delta M) + d(\Delta P)$$

The least squares multiple regression solution for equation (2) was obtained with the data from 41 of the 58 dietary comparisons, excluding 12 corn oil comparisons because of evidence of the peculiarity of this oil, 4 comparisons involving sardine oil because the poly-ethenoids in fish oils are so different from those in the other food fats, and one comparison of corn oil v. sardine oil.

The result was

$$\text{(3)}\qquad \hat{\Delta}\ \text{Chol} = 2.73\,(\Delta S) + 0.01\,(\Delta M) - 1.31\,(\Delta P)$$

The coefficient of correlation between the averages of the predicted and observed Δ Chol. in these 41 comparisons was r = 0.97. The contribution of the term for ΔM is statistically non-significant and recomputation with this term omitted yielded the equation

$$\text{(4)}\qquad \hat{\Delta}\ \text{Chol} = 2.74\,(\Delta S) - 1.31\,(\Delta P)$$

Since the analysis with 41 comparisons involved pooling, we attempted to examine the propriety of this procedure by obtaining separate solutions for one major series (our JWX) which provided 10 comparisons, and the remaining series providing 31 comparisons. The results were

Series	*Comparisons*	*b*	*d*
JWX	10	2.57	−1.27
8 others	31	2.68	−1.31
9 series	41	2.74	−1.31

Equation (4) was applied to the 12 corn oil comparisons and proved, as expected, to over estimate the cholesterol values on corn-oil diets, the average discrepancy being 10 mg. per 100 ml. But the application of equation (4) to the sardine-oil comparisons yielded satisfactory predictions, the mean discrepancy being only 0.2 mg. per 100 ml. or, disregarding sign, 2.4 mg. per 100 ml., which is 10% of the average observed Δ Chol.

The good agreement between observed and predicted Δ Chol. obtained here refers to averages for groups of men. Much less close agreement can be expected for individuals because spontaneous, intra-individual variation is large, even on a constant diet. Further, the analysis here is in terms of absolute units of cholesterol concentration and this is suitable because the averages of the various groups of men studied here show little dispersion on a standard reference diet. But from analyses of results with the men classified according to their serum cholesterol level on a given diet, we find the magnitude of the response of serum-cholesterol concentration to a given dietary change is correlated with the intrinsic level of cholesterol.

Accordingly we conclude that the numerical values of equation (4) apply only to persons whose serum concentration is of the order of 225 mg. per 100 ml. on an average American diet (roughly S = 19, M = 17, P = 4% of calories). With men who are intrinsically more hypercholesterolemic, the coefficients in equation (4) would be increased.

Finally, these results refer to dietary changes maintained for a few weeks long enough to complete the first phase of rapid response in the serum cholesterol concentration. Smaller effects are obtained with shorter duration of dietary change and we suggest that the magnitude of the response is a function of time so that

$$\text{(5)}\qquad \Delta\ \text{Chol} = f(t)\,[b(\Delta S) - c(\Delta M) + d(\Delta P)]$$

From some short-period experiments and from observations on populations subsisting for many years on different diets, we hazard the crude estimate that f(t) is such a function that the resulting Δ Chol. after a week of dietary change is about half that observed after three weeks, while the three week Δ Chol., in turn, may be something like half of the eventual effect produced after some years.

The result of this analysis is the indication that saturated fatty acids have, per gramme, about twice as much effect on the serum cholesterol level as do the poly-ethenoids which, moreover, act in the opposite direction. Whether the mono ethenoids (essentially oleic acid here) have any effect is uncertain, but if there is an effect it is certainly small.

A practical consequence of these findings may be illustrated by an example. It is indicated that the *addition* to a diet, as an isocaloric exchange for carbohydrate, of one ounce of sunflower-seed oil (10% and 62% of the fatty acids being saturated and linoleic acids, respectively) would be expected to lower the serum-cholesterol by an average of about 5 or 6 mg. per 100 ml. in a few weeks. The corresponding *removal* of an ounce of butterfat (57% and 4% saturated and poly-ethenoid, respectively) should produce about 3 times as much cholesterol fall. The substitution of an ounce of sunflower seed oil for an ounce of butterfat might be expected to cause a fall of a little over 20 mg. per 100 ml. in a month, *three quarters of the effect* being attributable to the reduction in butterfat. These computations are for a man in equilibrium at about 2600 calories whose cholesterol level on an ordinary (high-fat) diet is "normal" —i.e., under 230 mg. per 100 ml. In hypercholesterolemic men considerably greater responses may be expected.

Acknowledgment of our numerous obligations to sponsors, collaborators, and assistants will be made in fuller publication elsewhere.

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ANCEL KEYS
JOSEPH T. ANDERSON
FRANCISCO GRANDE

INSULIN TREATMENT OF SCHIZOPHRENIA

SIR,—The impressive statistical results with insulin-coma treatment obtained by Dr Ackner and his colleagues (March 23) in a "controlled" trial will make heartening reading for some who still have doubts about the potential value of this method of treatment in properly selected schizophrenic patients. And I understand that the routine daily insulin-coma treatments in this particular series were often given by ever changing and sometimes quite inexperienced psychiatric registrars, or even by psychiatric nurses. Patients who might need it were also denied any further E.C.T. during the course of their insulin-coma treatment, and only 30–40 comas were given to patients; whereas we know from Polonio's ten-years statistical study of insulin coma treatment that such a low number of comas can markedly reduce the number of successful results obtained.[1]

The excellent results reported despite these drawbacks, therefore, suggest what can be achieved with insulin-coma treatment when given by highly trained and experienced therapists in properly selected patients, and when it is combined with all the other methods likely to be needed, including the new tranquillisers, psychotherapy, and E.C.T. given during the course of insulin treatment. It also makes more understandable why its use has grown in this country ever since it was introduced twenty years ago.

It is also not very surprising that the use of daily barbiturate comas followed by strong brain restimulation with dexamphetamine also produced almost equally good results as those obtained in this particular insulin group, though no less than four out of twenty-five patients may need to remain in hospital as chronic patients because a barbiturate induced coma was substituted for insulin comas.

Do many experienced therapists really believe, as Dr Ackner and his colleagues suggest they do, that insulin is the specific agent of recovery in insulin coma treatment? If so, why does not modified insulin treatment work just as well? Over the past twenty years, as one has continued to use this treatment, one has seen time and time again how really deep comas may help a patient when less deep comas have failed to do so, and "irreversible" comas can sometimes produce the most dramatic results of all. This is why really skilled insulin therapists are needed to get the best results with this particular treatment. It is probably the combined sedative and the stimulating effects of the coma itself that matters, and not the giving of insulin per se, just as in E.C.T. it is the convulsive brain fit that is really important and not the electricity that produces it. Gain in weight, helped by insulin, may however contribute to the stability of recovery, and this could possibly help to explain why four more patients were able to leave hospital even in this particular insulin group as opposed to the barbiturate coma group.

What these authors also did not tell us was that Russian workers have used methods resembling their so-called "control" method as an alternative and successful physical treatment of schizophrenia. They have, for instance, reported the value of repeated narcotic treatments with 'Sodium amytal' and other barbiturates combined with subsequent restimulation of the brain by caffeine, fever therapy, convulsion therapy, and therefore also, presumably, by dexamphetamine. Reports on the use of such methods in schizophrenia appear in Wortis's book.[2]

As long as I have known him, Dr Ackner has been suggesting in conversation and discussions that the beneficial effects of insulin coma may be due much more to the group psychotherapy of the total insulin regime than to the actual physical treatment used. I have no doubt that this supposed "control" group was meant to try and throw more light on this matter, and he refers to the possible psychotherapeutic effects of insulin coma treatment in discussing these results. But this paper really provides very little evidence either way on this point, for Dr Ackner and his colleagues have so unfortunately chosen for their "control" group a method which resembles successful Russian physical treatment methods in schizophrenia, based on carefully controlled pavlovian physiological research.

Having often suggested that it could be the psychotherapeutic aspects of the insulin régime that really mattered, why did not Dr Ackner have the genuine courage of his convictions and use sterile water instead of this powerful and very physiological barbiturate-amphetamine combination for the control group? Then we might have really learnt something on this important point. We do know that a good atmosphere in an insulin ward is very important, whatever depth of coma is given, but I doubt whether it is really as important or gets patients well as quickly and as easily, as the giving of really deep and skilled comas, combined with E.C.T., psychotherapy, and the tranquillisers when necessary. Certainly I hope we are not going to go back (unless the evidence becomes statistically and clinically absolutely overwhelming) to too much loose psychological theorising about the treatment of schizophrenia; for we have come so far in the past twenty years using all these new physical methods, compared to the days when all we used to have at our disposal were the many and varied types of psychotherapy which all proved so very disappointing, when used *alone*, both inside and outside mental hospitals.

London W.1. WILLIAM SARGANT

SIR,—We have read with interest the controlled study of Dr Ackner and his colleagues on insulin treatment of schizophrenia. We feel, however, that their criteria for the choice of case grouping, based as they are on clinical psychiatric data only, are open to question. Our own studies[1,2] point to wide physio-pathological differences among cases of schizophrenia with similar psychiatric symptomatology. It would therefore seem that giving insulin coma therapy to schizophrenics in groups selected only on a clinical psychiatric basis may in fact be treating cases of widely differing physio-pathological make-up. It would not be out of place to compare insulin treatment given in this way to prescribing, shall we say, a certain convex lens to all those who complained of some defect of vision.

In studying schizophrenics who apparently formed a homogeneous group from the clinical psychiatric aspect we found,[2] for instance, that in the group there were patients with high adrenocortical function who reacted well to deep insulin coma treatment, at least temporarily, and others with decreased adrenocortical function who usually failed to improve with insulin comas and sometimes deteriorated. We could quote other examples of groups apparently homogeneous on clinical assessment that were heterogeneous from the physio-pathological aspect. We should also infer that any homogeneity in the groups studied by Dr Ackner and his colleagues was related much more to the genetically conditioned personality-pattern of the patients than to their physio-pathological state which determines their response to treatment.

It seems to us that progress in the classification or treatment of the schizophrenias cannot be expected so long as the criteria used by clinicians fifty years ago are still accepted and applied without further investigation or revision. If it were possible to reasthe data in the paper by Dr Ackner and his co workers on a physio-pathological basis, we feel that conclusions would be reached that might be more valuable for both present use and future progress than those stated by the authors These new conclusions might also give some insight into the value of a therapy which has mainly been used empirically in the past, but should now be applied on a more rational basis In our view, their approach to the problem of insulin-coma therapy endangers the continued use of this treatment in at least one group of schizophrenics—viz, namely with high adrenocortical function—for whom it cannot yet be replaced

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[1] Polonio, P., Slater, E. *J. ment. Sci.* 1954, 100, 442.
[2] Soviet Psychiatry. Baltimore, 1950. p. 161.

[1] Reiss, M. *J. ment. Sci.* 195[illegible], 101, 6[illegible].
[2] Batt, J. C., Kay, W. W., Reiss, M., Sands, D. E. *Ibid.* 1957, 103, 240.

J C Batt
G H L Bullmore
W W Kay
M Reiss
D W Smith
H Stott

St Ebba s Hospital
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THE FLOPPY INFANT

Sir,—I look to your annotations to clarify my thoughts and your remarks of March 30 (p 678) very properly alert me against making a generalising diagnosis of amyotonia congenita to cover up a multitude of somewhat similar conditions Amongst the alternative diagnoses put forward, however, we come across mental defect side by side, of course, with cerebral palsy—its only chance of equality with it, alas, as things are at present

What is mental defect ? If it is a diagnosis it is certainly a much more nebulous one than amyotonia congenita wrongly applied There should be no such diagnosis as mental defect It is simply a symptom of an underlying physical disability and, until you, Sir, and all other doctors realise this, the "mentally defective" child will continue to be the most ignored, least investigated, and worst treated patient in the community

Twenty years ago the cerebrally palsied, the phenyl ketonurics, and the victims of maternal rubella were all merely "mentally defective" One might say many of them still are but, at least, we are looking scientifically at them the other way round !

Let us give the same attention to the still unknown causes of the end-result and never, when we are unable to find anything else except "mental defect," accept that as a specific diagnosis or as final evidence of an irremediable condition treatable only by inaction, sedation, or segregation

Chertsey J M Crawford

DEPOT TUBERCULIN

Sir,—In contrast to Dr Hall (March 2), we have found that the use of tuberculin in a depot vehicle increases its sensitivity considerably

Comparative testing in adults from 30 to 50 years of age, has shown that depot tuberculin gives positive reactions with doses as low as 1/250–1/20,000 of the threshold dose of aqueous tuberculin[1] This greatly increased potency of depot tuberculin has been confirmed by Citron,[2] who obtained positive reactions to 6 T U depot tuberculin in tuberculous patients who had been thoroughly desensitised to tuberculin and who did not react to Mantoux testing with 100 T U aqueous tuberculin

Two age extremes are represented by the predominantly newborn and infants reported on by Dr Hall, and the elderly subjects reported on by Dr Kolcan and Dr Beresford (March 16) Reactions to depot tuberculin may differ in these age groups from those in adults of young and middle life We have found that reactions to depot tuberculin develop more slowly in elderly and aged subjects taking 7 or more days to appear in contrast to the usual 2–3 days

Like ourselves, Dr Kolcan and Dr Beresford did not have difficulty in distinguishing between reactions elicited by the depot tuberculin as compared with the control vehicle We preferred the soft thin skin of the outer upper arm for our tests and found that control tests, carried out in all the cases, gave reactions which were negative or insignificant The long persistence of the oily vehicle leading to reactions which may last for three months or longer in more sensitive subjects is, of course, a disadvantage if considered for routine testing The principle, however, of a "depot" tuberculin stands to gain, from this long persistence, for the study of the development of hypersensitivity in previously negative subjects Alternative vehicles may be better suited for this purpose

D Geraint James
London N W 3 J Pepys

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[1] Pepys J James D G Atti del III Congresso Europeo di Allergologia 1956 p 391

[2] Citron K M Tubercle Lond 1957 38 33

ATHEROSCLEROSIS AND VITAMIN B_{12}

Sir,—Oliver and Boyd's[1] emphasis on the part played by the hormones in atherosclerosis, and the more recent address by Morris,[2] tending to discount dietary fat as the main cause, have prompted me to describe, perhaps prematurely, my own findings with vitamin B_{12} (cyanocobalamin)

It had already been noted that, after a variable lag period, both vitamin B_{12}[3] and liver[4] appear not only to desensitise the allergic, but also to cause, in the presence of secondary infection, an increase in membrane permeability[3] At about the same time, it was also observed that 8 of my patients, who were all suffering from obvious atherosclerosis, and who had all been given vitamin B_{12} as a tonic (50 µg orally thrice daily), were all significantly and obviously worse, again after a lag period of similar duration—4–21 days

As a control, a further group of 6 patients also suffering from obvious atherosclerosis, and of a similar age group, were then maintained on control tablets over a period of one month During this time, they were kept under close observation 2 appeared to improve, 3 showed no change, and 1 showed some deterioration—i e, increased dyspnœa There was no severe clinical deterioration, such as the onset of angina pectoris intermittent claudication or "rest" pain as occurred in the group treated with vitamin B_{12}

After due consideration of these findings, it was decided that all patients suffering from atherosclerosis, should be treated as follows

(1) A lactovegetarian diet was strongly advised, emphasis being placed upon the necessity for increasing the patient's intake of vegetable protein and upon the need for as large a variety of cereals, vegetables, and fruits as possible Milk intake was limited to one pint per day for all purposes and all other casein containing milk products especially cheese, were excluded Animal fats were permitted and a timely warning against possible weight gain was given If there was any risk of congestive failure egg albumin (the yolk being excluded) was recommended as an added source of animal protein

(2) The patient was given orally 50 mg of ascorbic acid four times daily

During the past three years, 33 patients have been treated by this method 29 have shown a significant improvement in symptoms and signs, thus after a period of three to four weeks, they could walk further and faster and their legs, if cold initially, regained their normal skin-temperature

During these three years 12 patients failed to maintain their diet and all 12 relapsed 7 resumed the diet and have since improved again, 1 refused to maintain the diet and has since died of congestive failure and the other 4 of this group have only recently resumed their diet

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[1] Oliver, M F, Boyd G S *Lancet* 1956 ii, 1273

[2] Morris J N See *Ibid* Feb 23 1957 p 410

[3] Annand, J C *Practitioner* 1955 175 725

[4] Moll H M *Brit med J* 1932 i 976

The remaining 4 patients maintained the diet for a short period only, 1 has died of coronary thrombosis, 2 have survived a second coronary thrombosis, and 1 has had a cerebral thrombosis

A patient, who had had a bilateral lumbar sympathectomy for endarteritis obliterans, and who also suffered from angina of effort, admitted only slight increase of painless walking distance, in spite of strict adherence to the diet Later he resumed normal diet and survived a coronary thrombosis three weeks later

A correlation between intake of animal protein and atherosclerosis does appear to exist Thus, the people of Italy[5] and the Bantu of South Africa,[6] who both consume a diet low in animal protein, and also vegetarians[7,8] per se, are all relatively free from atherosclerosis On the other hand, there is the apparent contradiction that the meat eating Eskimo does not develop atherosclerosis[9] The comparison is not a true one, however, since the uncivilised Eskimo eats no fruit or vegetables and little or no fat (used for heating or lighting purposes) and consumes his meat entirely raw, thereby obtaining the advantage of all of its vitamin content At the same time, he, unlike the European, is subjected to long spells of near or complete starvation, a condition which has been found to double the urinary excretion rate of vitamin B_{12}, but not that of folic acid or of the citrovorum factor[10] Moreover, unlike the civilised Eskimo, who cooks his meat, he never gets scurvy, in spite of the complete absence of fruit or vegetables[9]

The following points also appear to be significant

(*a*) The urinary excretion rate of vitamin B_{12} has been found to diminish with advancing years,[11] whilst the serum cholesterol level, which vitamin B_{12} appears to control,[12,13] seems to increase concurrently[14]

(*b*) Both vitamin B_{12}[3] and animal protein[15,16] (not devitaminised) have been found to increase membrane permeability

(c) Finally, both reduced glutathione[17,18] (which vitamin B_{12} *appears to maintain catalytically in the reduced state*[19]) and vitamin B_{12} block the action of the glucocorticoids in both the animal[20] and the human[21] thereby possibly permitting the opposing action of the mineralocorticoids

To summarise, some circumstantial evidence, derived *mainly from clinical observation and partly from published* work, suggests that, after a variable lag period, vitamin B_{12} makes the symptoms and signs of patients with atherosclerosis much worse The existence of this lag period has made it difficult to prove cause and effect and medical ethics forbids a deliberate trial But a diet low in vitamin B_{12}, again after a lag period of three to four weeks, did appear to be of significant value in this limited series

Dundee J C ANNAND

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8 Donath W F Fischer I A van der Meulen, van Eysbergen H C de Wijn J F *Voeding* 1953 14, 153
9 Thomas W A *J Amer med Ass* 1927, 88 1559
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13 Register U D *Ibid* p 705
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16 Wilhelmj C M Milani D P Racher F M, McCarthy H H *Ibid* 1954 43 858
17 Cornforth J W Long D A *Lancet* 1952 i 950
18 Anderson G F Wiesel L L Hillman R W, Stumpe, W M, *Proc Soc exp Biol* N Y 1951, 76 825
19 Dubnoff J W *Fed Proc*, N Y 1951 10 178
20 Venkataraman P R Dublin A Hedell M T *Metabolism*, 1954 3 402
21 Lövgren O Norman A Wingqvist G *Acta rheum scand* 1955 1 101

CHRONIC BRONCHITIS AND SMOKING

SIR,—I am inclined to agree with Dr J P Anderson (March 30) that it was surprising that more mention was not made of cigarette smoking in the course of the N A P T Symposium on Chronic Bronchitis held last December The N A P T invites speakers to give their personal opinions at such gatherings, and does not put words into their mouths

The N.A P T leaflet "Bronchitis" is designed to give advice, in a persuasive manner, to those who need it There is no need to urge the non smoker to abandon cigarettes Only those who enjoy smoking have to be persuaded that it is in the interests of their health to give up what is, to them, a source of pleasure We shall be more *successful* in our propaganda if we admit that, to those who smoke cigarettes, smoking is an enjoyable habit

The *N A.P T Bulletin* for December, 1956, contains a statement by the N A P T council on smoking and lung cancer, and a memorandum of scientific evidence in support of the views expressed with which I am sure Dr Anderson would fully agree This can leave no one in doubt about the attitude of the N A P T towards the dangers of cigarette smoking

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HARLEY WILLIAMS
Secretary General

ÆTIOLOGY OF PRE-ECLAMPSIA

SIR,—During recent years, Mr Sophian has written extensively about his theory of a uterorenal reflex as a cause of pre eclampsia He has claimed additional points, including our own studies,[1,2] which he believes confirm his theory The majority of these claims have passed completely unchallenged and hence it may have been assumed, particularly abroad, that many obstetricians accept Mr Sophian's views For this reason I should like to review briefly the essential arguments *that have been* advanced to support the theory of a uterorenal reflex It may then be clear why, to many, they appear unconvincing

A primary stimulus is presumed to arise from the myometrium as a result of the uterus adapting to its *contents* and producing thereby "increased myometrial tension," or alternatively "myometrial resistance to stretch" Proof of increased tension can be derived, according to Mr Sophian, from (*a*) biochemical studies and (*b*) tocometric tracings However, it is not yet finally established that such methods do provide an efficient index of myometrial tension Furthermore, results obtained by using such measures have not confirmed a *consistent* increase in myometrial tension in cases of pre eclampsia Surely this initial criterion must be satisfied before assuming that myometrial tension is even associated with, let alone is the cause of, pre eclampsia

Mr Sophian also claims that intra uterine pressure has little relationship to myometrial tension, but, once again this is open to serious dispute This further assumption allows him to explain away why there is no consistent association between raised intra uterine pressure, as in twins, acute hydramnios, pregnancy in a rudimentary horn, and pre eclampsia

The kidney is thought to respond *to this* uterine stimulus in a way closely resembling that described originally by Trueta et al[3] in animal experiments and it is this renal reaction that finally fires off the syndrome that is recognised as pre eclampsia The extent *of this* reaction is said to be governed by the "responsiveness" of the kidney This again conveniently allows Mr Sophian to postulate that the renal response is often not propor

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1 Morris N Osborn S B Payling Wright H *Lancet* 1955 i 323
2 Morris N Osborn S B Payling Wright H *Ibid* 1956 ii 481
3 Trueta J Barclay A E Daniel P M Franklin K J Prichard M M L Studies of the Renal Circulation *Oxford* 1947

tional to the uterine stimulus This kidney reaction is completely incapable of reliable assessment, at least by measures so far at our disposal

Essentially, therefore, Mr Sophian postulates a cause (increased myometrial tension) for which there is at present absolutely no reliable evidence and an effect (renal shunt) which cannot even be measured

Animal experiments [4] do suggest that experimentally a form of uterorenal reflex can be established. There is no evidence that this in turn establishes a *clinical* picture comparable to pre-eclampsia

Severe concealed accidental hæmorrhage is often associated with extensive renal damage This reaction would therefore suggest a clear-cut uterorenal association in this condition Furthermore the kidney changes bear some resemblance to those described by Trueta However it is not yet clear whether these are the result of a reflex or of the liberation of a toxic substance from the utero-placental site The suggestion by Page and Glendening [5] that there could be a sudden liberation of serotonin or a similar substance seems a distinct possibility Few clinicians will find it possible to accept that the pathological changes in pre eclampsia and concealed accidental hæmorrhage are the same, and only differ in matter of degree

Finally, Mr Sophian explains away pre-eclampsia occurring in association with a late extra-uterine pregnancy by claiming that "blood and certain other substances spilled on the peritoneum can provoke a renal shutdown" This is indeed a bitter pill to stomach Why then does not pre-eclampsia occur in association with a ruptured ectopic gestation or corpus luteum, hæmorrhage from an ovarian cyst, or any condition causing peritonitis or peritoneal irritation in pregnancy?

I am sure that Mr Sophian will conjure up a further hatful of ingenious explanations, but until he provides reliable direct evidence in support of all the claims he makes, I shall continue to regard his theory as compounded of a mixture of assumptions and exceptions

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Hammersmith Hospital
London, W 12

NORMAN MORRIS

BURNS AND SCALDS

SIR,—The time is surely overdue for Professor Wardill and his colleagues in Baghdad to publish a full description of their method of treating burns Baghdad is admittedly only a few hours distant by air, but few of us have the financial resources to accept their invitation to see for ourselves The meagre details so far available excite intense curiosity, and their curt dismissal (March 16, p 588) of Mr Watson and Mr McLaughlin's well-reasoned letter [6] with a hypothetical Shakespearean quotation heightens the mystery

Professor Wells [7] has attested that granulations of an unusual quality are produced But now we learn—and here is the hub of the mystery—that only 1 case in 80 has been grafted This immediately suggests that the remaining 79 were superficial burns Why then the emphasis on the production of granulations?

Granulations as we understand the term, form only after full-thickness destruction of skin If ungrafted, they can heal only by ingrowth of marginal epithelium a lengthy process accompanied by scarring and contracture It seems unthinkable that this should be what Professor Wardill advocates Perhaps the explanation lies in the word "granulations" Are those of Baghdad merely the surface appearance which results when superficial burns are treated by exposure in a tropical climate? Or is there an element of mid oriental magic involved?

Professor Wells's enthusiastic letter on this method of treatment and the recent visit of his colleague, Mr J H Johnston, to study the technique have provided excellent advance publicity, and we hope that Professor Wardill will not long delay a fully detailed exposition

Glasgow Royal Infirmary

THOMAS GIBSON
IAN A McGREGOR

THE Rh BLOOD-GROUPS

SIR,—The letters of Dr Nicholas (March 2) and Dr Sheppard (Jan 26) cannot be allowed to stand unchallenged

Dr Nicholas now writes "I did not say that the use of 'most likely genotypes' leads to paradoxes—far from it" But "most likely genotypes" does lead to paradoxes, as I have shown, because it sets an unnecessary trap, and when there is a trap somebody falls into it Why use "most likely genotypes" at all when you can use separate designations for phenotypes and genotypes? In fact, there is a tendency among C-D-E protagonists to drop the phrase "most likely" and to speak of "*genotyping*" when *all that is really done* is Rh-Hr *phenotyping* I have already pointed out how Buchanan fell into the trap, and now Renton and Hancock [1] provide another example

They have written an entire article describing what they consider to be a new variant of factor Rho, and which in contrast to factor Rho renders blood cells more agglutinable by anti-Rho sera What they may actually be dealing with is probably a gene dosage effect Thus, their findings are readily explained if one assumes that the highly reactive bloods which they designate as CDe/cde and cDE/cde are really CDe/cDe and cDE/cDe, respectively In Renton and Hancock's paper, significantly, the phrase "most likely" has been dropped, just as in Race and Sanger's book If separate phenotype and genotype symbols had been used, as in the Rh Hr nomenclature, this blunder would not have been made

Dr Sheppard accuses me of not understanding the C-D-E notations, while Dr Nicholas charges me with being inconsistent They are both probably correct In fact, how can anyone understand or be consistent when discussing a subject matter like the C-D-E notations, which are inherently illogical, inconsistent, and self-contradictory? For example, will Dr Nicholas kindly *resolve the following* contradictions which puzzle me

1 In place of the Rh-Hr symbol Rh_1rh, I have seen the following C-D-E symbols used C—D+E—c+, CDe/cde, CcDe, CcDee, CDe/c, DCe/c, CDeF/cdef, or as Ford has suggested, *C*(A—B+), D(A—), E(A—*B*+) Which of these is the "official" designation, or have I failed to include the "correct" one in this list?

2 Blood cells lacking both factors of the pairs rh′ hr′ and rh″ hr″ are attributed to gene deletions (–D–/–D–), but blood lacking both factors of the pair S–s are ascribed to a special allele S^u This raises the question, how does one decide when to postulate a "deletion"?

3 One argument raised by C-D E protagonists against using symbols like R^1R^2 is that such symbols are difficult to understand Yet R_1R_2 is used by them as a short symbol for CDe/cDE Please explain on what basis R_1R_2 becomes related to CDe/cDE, and why R_1R_2 is more intelligible than R^1R^2?

4 On pp 129–130 of the 2nd edition of Race and Sanger's book [2] appears "The finding of the remaining antibody, anti-*d* was first reported by Diamond in 1946 Two further examples were reported by Hill and Haberman Thus the theory of Fisher has been confirmed in all its predictions"—*But on p* 181 these authors write about the Hill and Haberman report "Now that anti *f* is commonly found in anti-c sera we feel doubtful about the identity *of these* two examples of anti-*d*" Please reconcile these two contradictory statements in Race and Sanger's book

5 The supposed gene arrangement DCE was based on the statistical test $R = r' - r'' - R^z$ Race and Sanger now admit

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[4] Franklin K J Winstone N E *J Obstet Gynæc Brit Emp* 1955 62 29

[5] Page E W Glendening M B *Obstet Gynec* 1955 5 781

[6] Watson J McLaughlin C P *Lancet* 1956 ii 685

[7] Wells C *Ibid* p 577

[1] Renton P H Hancock J A *Brit J Hæmat* 1956 2 295

[2] Race R R, Sanger, R Blood Groups in Man Oxford 1954

(p 170) that "it is possible to pick results strikingly in favour of the cross-over idea—*and strikingly against it*" [italics mine] How then can one justify the position of Race who continues to speak of the gene order DCE ?

6 Since, as Race and Sanger admit (p 171), "It does not seem unfair to say that anthropological results have been inconclusive," they have abandoned the cross over hypothesis and now postulate "completely linked genes" or "pseudoalleles" If there is no crossing over and no "deletions," how does one determine the order DCEF ? Also, what is the difference between a completely linked set of genes and a unit gene ? And what exactly is the difference between the concept of complete linkage and Wiener's theory of multiple alleles ?

7 When calculating gene frequencies, Fisher and Race use the complex maximum likelihood method in order to achieve an increase in accuracy affecting the third or fourth significant figure, but at the same time they use "most likely genotypes" which entail errors as high as 15% Please explain this inconsistency

8 Symbols like anti-D+D^u, anti C+C^w, and anti-A+B are used by C D E protagonists to designate antisera supposedly containing "linked" antibodies Please explain how one decides whether one is dealing with "linked" antibodies or a single cross reacting antibody Also please explain how one knows whether the symbol represents "linked" antibodies or a polyvalent serum like anti C+D and anti-D+E

In closing I should like to emphasise again that the basic fallacy in the C-D-E notations is the failure to recognise the distinction between a blood factor and an agglutinogen[3]—a concept as fundamental for blood-group serology as Newton's laws of motion are for mechanics Unless this concept is understood, no worker may expect to master completely the science of blood-grouping

It is time to stop teaching this C-D-E nonsense, and to teach the Rh-Hr nomenclature exclusively But, as shown by the letters of Dr Nicholas and Dr Sheppard, it is far more difficult and painful to unlearn something which is wrong than to learn a subject correctly in the first place

Brooklyn, New York, U S A A S WIENER

THE STAPHYLOCOCCUS PLAGUE

SIR,—In your leader last week you say that the heart of the problem is the presence of nasal carriers of antibiotic resistant staphylococci, and that this is due to uncritical use of antibiotics in hospitals

If this thesis was true, swabbing all personnel and treatment of proved carriers with effective anti staphylococcal agents would surely abate the plague In practice, these measures, though helpful, are not a cure

Antibiotic resistant staphylococci enter a hospital in the body and fomites of a patient Thence they are disseminated by handkerchiefs, discarded dressings, the fingers of attendants, discarded clothing and personal effects, and coughs, sneezes, and discharges Staphylococci are very hardy organisms, and can survive unharmed for long periods in room dust, in the interior of pillows and mattresses, in blankets, and in patients' personal belongings kept in bedside lockers Because the sensitive strains of staphylococci have succumbed to the treatment of the patients with antibiotics, only insensitive strains survive, and these insensitive strains populate the foci detailed above

The provision of an air-conditioned room is excellent advice would that it could be implemented ! The brutal realities of the situation, however, reveal that much less expensive improvements are cancelled merely on the grounds of cost

For instance, the provision of effective masks and sterile gowns for all nurses in the wards and the provision of thin rubber gloves for all nurses handling infective material (e g, bedpans, the bottoms of infants with gastro enteritis, soiled napkins, soiled dressings, soiled linen, and soiled handkerchiefs, to mention only a few examples) is too expensive

The provision of covered bins for the bedside disposal of dressings, the routine treatment of pillows with moist gaseous formalin in the hospital steriliser (or the use of a 'Sparkhall'), the routine treatment of mattresses with formalin in the hospital steriliser (or the use of a sparkhall), the treatment of blankets by washing in 'Lissapol' followed by soaking in 'Fixanol', and the anchoring of bacteria laden dust particles on the floors, &c, of wards, all these simple, effective and relatively inexpensive measures are neglected The reason given is that these measures add to the cost of hospital administration

Actually one of the most expensive items in a hospital budget is the drug bill Antibiotics are the expensive items A small sum spent on banishing resistant staphylococci from the bedding and dust of hospital wards would be more than repaid in the saving in antibiotics that would follow Administrators cannot see this

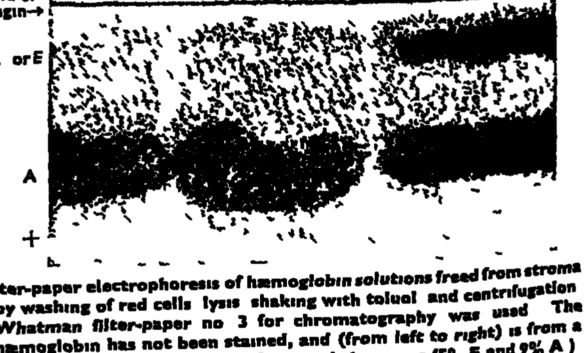
St Margaret s Hospital,
Epping FRANK MARSH

THE RECOGNITION OF HÆMOGLOBINS A_2 AND E

SIR,—There are now known two pairs of hæmoglobins with identical electrophoretic properties sickle cell hæmoglobin (hæmoglobin S) and hæmoglobin D, and hæmoglobins E and A_2 A survey of a population for the distribution of hæmoglobin variants merely by electrophoresis of blood specimens will therefore fail to differentiate between S and D and between E and A_2 respectively

In the case of S and D, differences in the solubility of the ferrohæmoglobin allow a separation Hæmoglobin D does not cause the sickling phenomenon when red cells are deoxygenated in vitro, and the routine test for solubility of reduced hæmoglobin in 2 24 M phosphate buffer devised by Itano[1] easily establishes whether S or D is present

Hæmoglobin A_2 is found in small amounts in normal people, but its proportion is raised in thalassæmia[2] Although the techniques usually used to demonstrate hæmoglobin A_2 are open boundary and zone electrophoresis, raised amounts can certainly be recognised by routine paper electrophoresis[3,4] (see accompanying figure) Even normal amounts can be demonstrated by paper electrophoresis when thick paper is used, and when large amounts of hæmoglobin are applied to the starting line If small amounts fail even then to be visible on the unstained paper, they can be made visible by staining



Filter-paper electrophoresis of hæmoglobin solutions freed from stroma by washing of red cells lysis shaking with toluol and centrifugation The Whatman filter-paper no 3 for chromatography was used The hæmoglobin has not been stained, and (from left to right) is from a normal individual (3 5 %A), from a thalassæmic (5% F and 9% A) and from an Eti Turk with hæmoglobins A and E (no F, 40% E) with a protein dye There is therefore a possibility of mistaking the electrophoretic pattern of the hæmoglobin from a thalassæmic for that of hæmoglobin AE heterozygote

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[3] Wiener, A. S , Wexler I B *Bact Rev* 1952, 16, 69

[1] Itano, H A *Arch Biochem* 1953, 47, 148

[2] Kunkle H G , Wallenius, G *Science* 1955 122 288

[3] White, J C Beavan G H , Ellis, M *In* Paper Electrophoresis Edited by G E W Wolstenholme and E C P Millar London 1956

[4] Crowley M F , McSorley, J G A Aksoy, M , Lehmann H *Vox Sanguinis* 1957, New Series 2, 53

We should like to point out that there seems to be a rule according to which the proportion of E in a heterozygote for hæmoglobins A and E does not fall below 20%, and that the proportion of A_2 in thalassæmia does not rise above 15% This rule is fairly general, though we have seen one exception If this differentiation is adhered to, serious errors will be avoided in mass surveys In individual cases other features characteristic for thalassæmia can of course be sought for to establish the diagnosis

Some of our surveys for hæmoglobin E were carried out before Kunkel's A_2 phenomenon had been fully appreciated We have therefore reviewed our previous surveys of populations in which the genes both for thalassæmia and for hæmoglobin E are found, and by taking due account of this rule we have come to the conclusion that we have no reason to correct former reports on the incidence of hæmoglobin E either in isolated instances in Turkey or in larger numbers in South-East Asia

We want to thank Dr H G Kunkel, of the Rockefeller Institute for Medical Research, New York, for advice and discussion and for confirming our results when we measured A_2 either directly following elution from starch after zone electrophoresis or indirectly following elution of protein dye from the stained paper after paper electrophoresis

Beyoğlu Ilk Yardim Hastahanesi,
Beyoğlu, Istanbul, Turkey
M AKSOY

St Bartholomew's Hospital,
London E C 1
H LEHMANN

University of Indonesia,
Djakarta Indonesia
LIE-INJO LUAN ENG

GASTRO-ENTERITIS IN UGANDA

SIR,—Your annotation on my paper[1] is quite correct in pointing out that simple clinical pathological tests can never be a complete substitute for more advanced bacteriology in this disease This particular study was, in fact, limited to ascertaining what information could be obtained from stool microscopy, and attempted to correlate this with the result of treatment and with such bacteriology as was then available to us It must be remembered, of course, that for a long time to come most tropical hospitals will not be able to carry out more than the simplest bacteriology and many can do none at all

Following on this, a further study was undertaken by Dr A M M Wilson and myself in which more detailed bacteriology was carried out and which does, in fact, set out to answer the points you raise concerning the efficiency of rectal swabs, the value of direct ward plating of swabs, and the use of carrier media in transportation to laboratories The results of this study, shortly to be published,[2] confirm the scarcity of *Escherichia coli* serotypes, which you suggest, and the preponderance of shigella infections

The Hospital for Sick Children
London W C 1
J LUDER

GOVERNMENT AND PROFESSION

SIR,—Your leading article of March 30 is by far the most important statement that has been made on the present regrettable state of British medical politics, it should be carefully studied by general practitioners, consultants, Ministry officials, Members of Parliament and, above all, by the leaders of the British Medical Association

You, Sir, expose clearly and objectively the absurdity of the threats of a doctor's strike (for temporary withdrawal is a strike) and you show how much we as a profession will lose by aping the methods of industrial trade unions

It is beyond doubt that a good case can be made for the improvement of doctors' working conditions in the Health Service We can best establish this case by a sensible and reasoned propaganda in the press and Parliament and by cooperation with the Government of the day—in other words, by the methods of an enlightened democracy

Leith Hospital,
Edinburgh 6
CHALMERS H DAVIDSON

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[1] Luder J J trop Pediat 1956 2 115
[2] Wilson A M M Luder J Ibid (in the press)

Parliament

THE ROYAL COMMISSION'S TERMS OF REFERENCE

ON April 4 Lord MORAN asked the Government whether they were satisfied that the terms of reference of the Royal Commission on the professional remuneration of doctors and dentists in the National Health Service would provide the necessary basis for a full examination of this problem

SPENS PAST AND FUTURE

He recalled that in the early days of the National Health Service the two Spens Committees were appointed by the Government to deal with the remuneration of general practitioners and consultants respectively Summarising Ministerial statements on the recommendations of these committees he reminded Noble Lords how in July, 1946, the permanent secretary to the Ministry of Health wrote to the British Medical Association "The Minister fully accepts the substance of the recommendations" Three years later, in January, 1949, the parliamentary secretary to the Ministry said in the House of Commons that the remuneration of general practitioners would be adjusted to give effect to the Spens recommendations In May, 1950, the permanent secretary to the Ministry wrote a letter saying "The Minister agrees that the Spens Report remains the basis of the remuneration of general medical practitioners until such time as after the usual consultations some other basis is substituted"

As a member of one of the Spens Committees Lord Moran could testify that the recommendations were then interpreted in the same way both by the Government and by the doctors Yet Lord Salisbury, in announcing the Royal Commission, said that the interpretation put upon the Spens reports by the profession could not be accepted by the Government The Government appeared to have first expressed doubts about the interpretation of Spens when a Judge of the High Court, Mr Justice Danckwerts, awarded the general practitioners £40 million in 1952 From that day until now the Government had been anxious to get rid of Spens Mr Attlee's Government, Lord Moran continued, might have been ill advised to accept these recommendations, but the fact remained that they did accept them, and that it was upon that acceptance that many doctors entered the health service In these circumstances he thought Noble Lords might feel that these recommendations could not be thrown on the dust heap because they had proved inconvenient

If the Royal Commission interpreted their terms of reference so that they were not required to pay regard to what had happened in the past, and dealt merely with future scales, then in his view they were wasting *their time*, they would not allay the discontent among the doctors, nor would they provide a lasting solution of this question of remuneration He pressed the Government to say whether the Royal *Commission* would or would not take into account the Spens reports

When the doctors went into the service they understood clearly that the cost of living would be taken into account when their pay was reviewed from time to time Nevertheless, Lord Moran trusted that the doctors would *not* try to bind the Government to a literal interpretation of Spens in perpetuity He admitted that this provision would excite the wrath of a section of the medical profession, but if there was to be a settlement satisfactory to the Government and to the doctors, there must be give and-take on both sides If the doctors were to give up the literal interpretation of Spens—namely, that every rise in the cost of living would be met by a rise in their salaries—then they were surely entitled to some quid pro quo What was needed even more than a rise in pay was some reformation of the arbitration machinery At present, a dispute between the consultants and the Government was referred to Whitley Council B This consisted of two halves, the doctors and the officials of the Ministry, and only if they agreed, could a dispute go to arbitration But in all matters of substance they never did agree The Government saw to that The result was that the consultants generally had lost confidence in this machinery What would they accept in its place? A special advisory committee lately appointed by the Prime Minister to supervise the pay of the higher ranks of the Civil Service was precisely what the specialists needed

AWARDS AND MERIT

Turning from the future and its possibilities to the present and the Royal Commission, Lord Moran suggested that it was inconsistent of the Government to press every section of the community to go to arbitration except the doctors Could Noble Lords imagine the Minister of Labour facing the shipping and engineering industries, when they are asking for a rise in wages, and fobbing them off with a Royal Commission? The doctors felt that they were being treated differently because they had no political power, and that produced bitterness Nor were the doctors better disposed to the idea of a Royal Commission when, on Feb 20, the Minister said to the representatives of the Negotiating Committee that if the Royal Commission found in the profession's favour, and if the economic situation of the country remained the same, it by no means followed that anything would happen Apparently, the findings of this Royal Commission were to be taken seriously only if they were in the Government's favour

But what really aggrieved the doctors were the terms of reference Royal Commissions were generally free to gather information wherever they could find it "All relevant factors" was almost a cliché in the circles that dealt with Royal Commissions But what had happened to this Royal Commission? It was the Government who directed what the Commission might and might not consider It was the Government, not the Commission, who decided the considerations that bore on the remuneration of doctors And these considerations boiled down to a specific comparison with other professions He had no doubt that the Royal Commission could compare the incomes of members of various professions But the hours of work differed completely the doctor was at the beck and call of the public at any minute in the twenty four hours The length of the training varied between one profession and another The responsibilities were not comparable But most important of all, these terms of reference had been so drawn up that they limited discussion, they excluded points which were greatly in the doctors' favour, and prevented them from bringing forward their case properly He was sure that that was not the intention of the Government, but that was how it was going to work

The doctors did not expect much good to come out of this Royal Commission Lord Moran himself was concerned that harm did not come from it He was thinking, in particular, of the "merit awards" These awards were brought in at the beginning of the service as an incentive, for it was seen that by going into a service the doctors would lose the competitive stimulus At first the idea met with some suspicion in the profession It was felt that the London medical schools might swallow them all up, and that the consultants in remote parts might be forgotten But there could be no doubt that at the moment the system enjoyed the confidence of the great majority of the consultants, and that they would be most aggrieved if anything happened to these merit awards Would the Royal Commission, he asked go into details of this kind?

CHANGING MINISTERS

But the dispute went deeper and was more fundamental than any question of finance It was a symptom of a good deal of unrest in the service When medicine was nationalised, it was carried over the heads of the doctors by the politicians The minority which supported the National Health Service Act and tried to work for its good had hoped that the doctors would be won over by an enlightened policy It had worked out otherwise It had been heartbreaking to see the bungling and mishandling of the human element Successive administrations had been more concerned with the cost of the service than with putting their minds to making it work While we boasted of our Welfare State, we banished the Ministry of Health from Whitehall and dropped the Minister of Health from the Cabinet In the past seven years, we had had six different Ministers, since Mr Neville Chamberlain's time, we had had sixteen The average life of a minister was twenty months, nine had served for less than a year Lord Moran had the impression that if they had stayed a little longer they might have caught a glimmering of what it was all about

The faults, he admitted, were not all on one side Some of the doctors were uncooperative Many had spent half a lifetime working as their own masters, and they were not likely to be reconciled in their lifetime completely and fully to the different conditions that obtained in a service Nor did it help that in some regions they were treated as employees, instead of being called in as partners in a great enterprise It was from the fringe of this section of disgruntled doctors that appeals came from time to time for a rise in remuneration—appeals which were in themselves just, but which were not always made at the most expedient time From the same section came threats of violent action But many doctors were completely out of sympathy with violent measures of that kind They felt, and Lord Moran shared their feeling, that they must look to public opinion for justice He advised the new Minister to leave his desk and go out into every part of the land, making friends everywhere with the doctors Then, and only then, would the country get some value for the immense sums it was spending on the health service

SUPPORT FROM THE PEERS

Viscount ALEXANDER OF HILLSBOROUGH believed that the service of the medical profession within the N H S had steadily expanded and improved at every point, and that the effect upon the health of the nation had been magnificent In these circumstances, it seemed to him that it was incumbent on the House to urge the Government to amend the terms of reference of the Royal Commission The Commission should not be hamstrung by the tags in the terms of reference which prevented them from looking at the matter with the wide, broad outlook that surely ought to be adopted if they were to deal with the grievance of the profession as it existed today Since the Danckwerts judgment in 1952, the medical profession as a whole had taken no real steps to ask for a steady annual review of their remuneration Only in the past two years had they drawn attention to rising costs, and they had had little sympathetic consideration of those claims

Now that the N H S had been running for almost ten years, Lord AMULREE considered that it would have been timely to set up a committee of inquiry, not because he thought the service fundamentally unsound or wrong but because when a great experiment had been running for ten years it was due to those engaged in it to take stock Instead the Government had set up a Royal Commission only on the payment of doctors That would leave a great deal undone But even under its present terms of reference he hoped that the Commission would deal with methods as well as rates of remuneration He would, for instance, like to see some change in the way of paying general practitioners Unlike the consultants they had no merit awards The only way for the G.P. to make more money was to take on more patients than he could properly cope with

Lord HADEN-GUEST pointed out that though a doctor wanted an adequate income he was not primarily concerned with making money He went into his profession because he wanted to do that work But the amount of money which he could earn in any form of practice or in any medical appointment might be much less than would be earned in ordinary business

Earl JOWITT hoped that the doctors would abandon any idea of what was called a "strike" On the other hand if there was to be arbitration, or its equivalent each side had a right to make its claim and put forward its case At present the doctors thought that the terms of reference did not give the arbitrators enough freedom They might be right or wrong but he felt that they had some reason for thinking so If one compared these terms of reference with those of the Spens Committee one could not but be impressed with the difference between the two If there was to be arbitration, we should start by having the doctors reasonably satisfied with the terms of reference. If they were not, then they were not really being given the benefit of arbitration Where the terms of a remit were found inadequate to embrace the whole dispute they might be enlarged. That should not be done by letters but regularly by enlarging the terms of the remit and putting the whole matter before the arbitration tribunal Lord CONESFORD believed that it was incorrect to describe a Royal Commission as an arbitration tribunal. Again and again the doctors had expressed their willingness that their claim should go to arbitration but that had been refused He could not conceive any lawyer advising the doctors that the terms of reference of this Commission were satisfactory How could they be satisfactory, if the terms on which doctors entered the National Health Service were to be excluded?

GOVERNMENT REPLY

The EARL OF HOME, Secretary of State for Commonwealth Relations and Lord President of the Council, agreed that, within the limits of reason and possibility, justice should be done to the medical profession, because no body of men gave more indispensable service to the people, and none had a greater sense of responsibility The National Health Service was a comparatively novel experiment The State had no inherent virtues as an employer It was the first time it had had to work out a relationship with one of the great skilled professions, and inevitably, it must take time to establish a satisfactory code of relationship and conditions of service The first eight years of the service had run concurrently with a time of intensifying inflation, and the doctors no doubt felt convinced that they had a case for increased remuneration, both actual and in relation to others But the taxpayers also were bearing record levels of taxation and they had an unanswerable case for relief The Government were responsible not only to the doctors but also to the taxpayers

The Spens Committees were set up to investigate the proper remuneration for doctors entering the National Health Service in 1948 But it had seemed to be argued since then that because the Spens Committees based their recommendation for remuneration on 1939 prices, subsequent settlements must always guarantee the doctors against the extra costs brought about by inflation He did not believe that that was really a tenable proposition So long as inflation persisted, it was impossible to insulate one profession against the effects of it or to guarantee that all professions should advance in their remuneration with proportional precision The remedy was to stop inflation, and that required the restraint of wage-earners and salary-earners Till then the best we could do was to try to ensure that no section of wage earners or salary-earners was put at a relative disadvantage to any other section of comparable skill and attainment

The Spens reports were accepted by the Government of the day and were expected to provide a basis for the entry of doctors into the National Health Service What, in the Government's opinion, was needed now, after eight years of experience of the workings of the National Health Service, was to determine the proper place of the medical profession in relation to other skilled professions, and, when that was done, to fix their scale of remuneration They believed that the Royal Commission could be the proper instrument for this It could take into account all the circumstances that were relevant, and one of the factors which was clearly relevant was consideration of the Spens reports If the doctors wished to put before the Royal Commission their interpretation of the Spens reports, there was no reason why the Commission should not listen to and consider their views upon them He had taken the advice of the Minister of Health and he was advised that what he had said fell within the terms of reference given to the Royal Commission

Other criticisms of the Commission included delay, but the Commission had already held a number of sittings and the chairman had every intention that it should act with speed. There had also been a criticism that there were no doctors or dentists on the Commission The Government took the view that on the whole, they would be more valuable as witnesses, and so long as the Commission had competent and able people on it, it was a good body, which would be seen to be impartial. It has also been asked why, if the terms of reference proposed comparison with the remuneration of other professional classes, they did not also include a direction to take into account remuneration in commerce and industry. The Government thought that, had there been a direction to that effect, it would have meant an immensely long inquiry, and there was a great field in industry and commerce in which conditions were not comparable at all He understood that the Royal Commission would normally be concerned with the levels of remuneration and not with the methods, as such Whether they would find it necessary to look at the question of merit awards in order fully to discharge their terms of reference would be for them to decide.

The Government hoped that the interim help which had been given to the profession, followed by a Royal Commission, armed, as they believed, with fair terms of reference, would enable them to move away from the atmosphere of distrust, of accusations of bad faith, of trials of strength and non-coöperation with the Royal Commission and with the health service, because that seemed out of character in a profession recognised everywhere for its sense of responsibility But it was equally true that the community, who were the new employers should not trade on the tradition of patience and good will of the doctors There must be understanding and sympathy on both sides The Commission were already pursuing their task, and he hoped that after they had reported, we should be able to arrive at a permanent settlement which would end for the doctors this rather unhappy chapter in their affairs

Lord Moran remained dissatisfied, for he pointed out that Royal Commissions were strictly bound by their terms of reference It was not the Minister of Health who would advise what those terms were, he had not the power It was for the chairman of the Commission If the Commission decided that this was outside their ambit nothing would happen "I go away," he said, "by the same door by which I came in, with no surety about the awards and nothing whatever on this matter of Spens"

QUESTION TIME

Cost of Prescriptions

Mr Blenkinsop asked the Minister of Health what had been the trend in the cost of prescribing under the National Health Service in January and February, 1957, as compared with previous months—Mr Dennis Vosper replied The average cost per prescription in January was about 5s 6½d This was almost the same as in December, and about 5d higher than in November An accurate figure for February is not yet available, but from a sample it is estimated that the average cost was about 1d more than in January Mr Godfrey Nicholson Is my right hon Friend aware that the medical training of doctors includes absolutely nothing to make them cost conscious? Does he not think that efforts should be made to inculcate in the medical profession some consideration of the cost of prescriptions? Mr Vosper Yes That is why my predecessor decided to set up a committee to examine the whole question of prescribing That committee will, I hope, start work very shortly

Nursing Recruitment

In 1956 20,000 girls began training as nurses or assistant nurses In the same year, 8000 withdrew

Medicine and the Law

Tetanus After Operation

At the inquest on two men who died of tetanus after operations at the North Staffordshire Royal Infirmary, Stoke on-Trent,[1] the jury returned a verdict that they "died from post operational tetanus accidentally contracted in a hospital operating theatre" The jury felt that there should be a thorough investigation as soon as possible,[2] and the coroner said that he understood that there would be inquiries by the Ministry of Health

Dr E M Mackay-Scollay, director of the Public Health Laboratory, Stafford, had given evidence that tetanus spores were found in samples of dust, débris, and wall plaster from the floor of the main theatre corridor, various sites in the annexe, on a naked light bulb, and in a surgeon's gloves No spores were found in any sample of catgut He said "It must be assumed that the process of sterilisation was incomplete The method of sterilising surgeons' gloves might be unreliable" He agreed that it is difficult to destroy tetanus spores, he could not trace the tetanus to any particular source It might have been infected animal hair used in the ceiling plaster in the operating-block A ceiling-light had been removed in the previous month, but its removal had not disturbed the plaster

131 operations had been done in the three main theatres in the week in which the 5 cases of tetanus arose These theatres have not been reopened, nor will they be Because of the tetanus outbreak, the regional board has approved plans for building a new theatre suite, with air-conditioning

We are happy to record that 3 of the 5 patients have now recovered

Obituary

CHARLES ERNEST SCOTT

M B Edn, F R C S.E

Mr Scott, who died on April 3 at the age of 61, was otolaryngologist to nine hospitals in Edinburgh and the Borders, and in all his parish he was recognised pre-eminently as the children's ear, nose, and throat surgeon

He was born at Selkirk, the son of Gideon Scott, and educated at Selkirk High School and Fochabers Academy His medical studies at Edinburgh University were interrupted by the 1914–18 war, during which he served with the Royal Navy, in Scapa Flow, as a surgeon probationer After qualifying in 1921 he held resident appointments at Edinburgh Royal Infirmary before becoming clinical assistant in the ear, nose, and throat department Later he became senior clinical assistant and clinical tutor to the department and in 1926 he took the F R C S E

The following year he received his first senior appointment when he became assistant E N T surgeon to the Royal Hospital for Sick Children In 1929 the hospital opened the first children's ward in the country to receive only E N T cases Mr Scott was given charge of wards in this hospital and in Leith Hospital in 1933 He also had beds at Western General Hospital, later transferred to Eastern General Hospital He was on the staff of the Edinburgh City Hospital for Infectious Diseases and the Princess Margaret Rose Hospital for Crippled Children

His service as secretary to the Scottish Otolaryngological Society from 1933 to 1946 was only broken by his year as president

J F B writes

Charles Scott had to the full the finest qualities of a Borderer—a natural reserve and modesty, a ready wit and a wide range of interests He shared the Borderer's love of rugby and, having played for Edinburgh University, he was a regular and welcome spectator at the seven a sides in his boyhood country He was an expert fisher and a keen curler In his sports cars he travelled widely in Scotland with his cine camera, and his colour films of Scottish scenery were greatly appreciated by his friends and the staffs of his many hospitals to whom they were shown Possibly his greatest hobby was the workshop which he had made in his house, where he turned out many examples of precision engineering He built numerous wireless sets, and constructed his own television set and high fidelity amplifier

Kind, gentle, thoughtful, and conservative he had an unequalled experience of his specialty as it affected children, an experience which could never have been expressed in print, depending as it did on a highly developed clinical judgment His clinical talents were communicated by precept and example to those who worked with him One could never wish for a more kindly or more helpful senior colleague, or one who could more persuasively train one's thoughts within the narrower confines of children's work, and teach the patient approach so necessary in handling the young Tens of thousands of parents have been grateful to him for the care and attention which he gave their children The same kindly manner, the diagnostic skill, and the meticulous operative technique were appreciated by the adults who sought his advice

The death of his wife was a heavy blow, for they were a devoted couple, but he found solace and companionship in his son, who shared so many of his hobbies and interests He faced his own illness with characteristic courage and humour Many friends will miss his counsel and his deep humanity as well as his wide interests which he was ever ready to share

FREDERICK DURAN-JORDA

M D Barcelona

During the Spanish civil war Dr Duran Jorda, a consultant pathologist of Barcelona, organised the blood-transfusion services of the Republican Army to such effect and with such originality that he was invited to advise other European countries on their services In 1939, with the help of the British Red Cross Society he came to this country, and he worked at first as a laboratory technician at Ancoats Hospital, Manchester In 1941, after being admitted to the Medical Register, he was appointed assistant pathologist to the hospital, later becoming pathologist Since 1949 he has been director of the department of pathology at Booth Hall Children's Hospital and Monsall Hospital.

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[1] See *Lancet* March 16 1957 p 575 March 23, p 634

[2] *Manchester Guardian* April 4

In these posts he was able to continue his studies on the blood, notably on the formation of the red cells His hypothesis that these are secreted by eosinophils was supported by exhaustive investigations, including studies of the blood of horses and camels After he was appointed to Booth Hall Hospital he reported a series of observations on the renal ducts of Bellini, whose interpretation was, like his views on blood-cells, regarded by most other workers as very certainly interesting but less certainly correct As lately as this year, he briefly described (with Mr A McDowall) a method of treating burns by the application of plasma

J T writes

All those who at one time or another of his hazardous life came into contact with Duran-Jorda will remember, as perhaps the most outstanding characteristic of his remarkable personality, his vitality which could not but impress by its almost torrential flow Even in the last phase of his illness—which an irony of Fate had made him, the creator of large scale blood-transfusion, diagnose in his own blood—his unabated energy did not desert him until the very end The name of Duran Jorda will be for ever linked with the organisation of the first blood bank for transfusion in war, a unique achievement which heralded the enormous revolution in life saving procedures which made the two world wars differ so much from each other As a surgeon in charge of a large hospital I witnessed the miracle which under his inspiration took place in Catalonia at the time of the Spanish war Severely wounded soldiers could be operated on with success in Barcelona eight or ten hours after the infliction of the injury, having been transfused at the front line and transported scores of miles while the pressurised citrated blood transfusion kept them alive By the end of the war over 25,000 donors had been organised by Duran-Jorda, and the experience then gathered was of inestimable benefit to us all when later, at the invitation of the British Red Cross, he came to this country to make it his home

An idealistic, patriotic, extroverted Catalan, he found himself surrounded here by a people whose values in life were very near to the ideal for which he had fought in Spain He told me on several occasions that in Lancashire he had found an industrial society loving freedom and music, two characteristics also of the Catalans A man of an extraordinarily impulsive nature, he was a meticulous recorder of observations and an accurate reviewer, and even critic, of his own achievements He was a happy man by nature and one could see him always surrounded either by his family or by his *microscopes*

It seems to me certain that time will enhance the value of most of his contributions His method for early treatment of burns and scalds merits more attention than that it has yet received, and several of his other works have brought him international recognition Above all he had the tacit recognition of all those who owe their life to a readily available blood-transfusion This was the highest prize for the simple and modest pathologist whose enthusiasm and organising ability contributed so much to the well being of so many people I hope that for this his name will not be forgotten

As an old friend who came to this country at the same time as he I express the sentiments of thousands in England—as in Catalonia—in waving a cordial farewell to a warrior whose only fear was to harm

Dr Duran-Jorda leaves a widow with two children He died on March 30 at the age of 51

Appointments

BETHELL, M F, M D Camb, D P M consultant psychiatrist and deputy medical superintendent, Tone Vale Hospital, near Taunton

BURROWS, H P, M B Lond, D I H district M O H, parts of Holland, Lincolnshire

MOORE, F W, M C, M B Brist, M R C P E, D M R D, D P H consultant radiologist, Bath clinical area

O DONNELL, [illegible], M CH, N U I, F R C S I county surgeon, Tipperary (N R), Ireland

ZEITLYN, B B, M D Lond, D P M part time consultant psychiatrist, Addenbrooke's and Fulbourn Hospitals, Cambridge

Notes and News

TOWARDS PREVENTING SUICIDE

A "psychotherapeutic" club has been provided by the public health department in Salford for the past few years, where mildly depressed and anxious patients may attend each afternoon from Monday to Friday The staff believe that several suicides have been prevented, and some withdrawn patients have made a striking recovery

Two afternoons each week are devoted to occupational therapy Patients are encouraged to bring handwork from home for instruction, and many have learned to use a sewing-machine One afternoon is devoted to drama therapy, play-reading, and acting as a group, and another afternoon to art therapy, free drawing, and painting Part of each afternoon is spent in music therapy, but that is one of the less popular subjects A psychiatrist attends weekly and gives private consultations and sometimes group therapy Half an hour of games has recently been introduced A mental-health social worker attends regularly Both the psychiatrist and the social worker have "time to listen" to the patients' anxieties, and the patients feel at the club there is someone who knows them, cares for them, and understands their difficulties

Although the club is a small one (at present about a dozen attend daily), it illustrates how much help can be given in this way Such clubs are comparatively simple and inexpensive to run, and in contrast to many of the schemes that have been described, they are in the community—to which the patient will have to return and in which he must learn to live—and not in hospital premises which are in several senses remote from the patient s home and social environment

A FILM FOR DIABETIC PATIENTS

A NEW film, *The Diabetic Diet* (16 mm, sound, black-and-white, 14 minutes) was lately completed with the coöperation of the medical advisory committee of the British Diabetic Association

In the opening sequence an analogy is drawn between a car engine and the human body, showing that fuel consumption in each case is related to energy expenditure Carbohydrates proteins and fats are described briefly and the storage of glycogen in the liver and its conversion to glucose with the aid of insulin are shown on an animated diagram Insulin deficiency can be made up by *injection* but the *dosage* must be accurately determined by a doctor The balance is then maintained by the patient having his meals at the right time and checking his urine regularly Reference *is made to the Diabetic Cookery Book* particularly to the section describing how, by interchanging foods of equivalent carbohydrate values, appetising meals may be prepared without altering the total allowed by the diet

The first part of the film, explaining the theory of diabetes, is valuable for patients and their relatives who prepare their meals But in the second part—which adds little to the information already available in the *Diabetic Cookery Book*—the scenes of a patient eating become monotonous, and shots of the sponsors' products are unduly extended The animated sequences are clear but rather long, and in places *the commentary is not well related to the action*

Copies of the film may be obtained, free of charge, from the Gaumont British Film Library, Aintree Road, Perivale, Greenford, Middlesex

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University of Cambridge

On March 23, the degree of M CHIR was conferred on *C H Talbot*

On June 13 the honorary degree of SC D will be conferred on Sir Geoffrey Jefferson, F R S

Royal College of Physicians of London

Dr F P Lee Lander will deliver the Mitchell lecture on Tuesday, May 28 at 5 P M at the college, Pall Mall East, S W 1 He will speak on rest and pulmonary tuberculosis

Royal Faculty of Physicians and Surgeons of Glasgow

At a meeting of the faculty held on April 1 with Prof Stanley Alstead, the president, in the chair, the *following* were admitted fellows of faculty qua physician

Goniamalimigie Herbert Allan Aponso Ashoke Kumar Dutta, Shanpur Janardhana G P McNicol

Heberden Society

A Heberden round will be held at the rheumatic unit of the Northern General Hospital Edinburgh, on Thursday May 16, at 11 A M

Scottish Medical Practices Committee

Dr John Baldwin, general practitioner of Penicuik, has been appointed chairman of this committee in succession to Dr A F Wilkie Millar

Institute of Diseases of the Chest, London

Clinical demonstrations, arranged by Dr F H Young, will be held at this institute (in the grounds of the Brompton Hospital, Fulham Road, S W 3) on Fridays, at 5 P M, from April 26 to July 5

Glasgow Medical Exhibition

Prof Stanley Alstead will open this exhibition at 11 30 A M on Monday, April 29, at the McLellan Galleries, Sauchiehall Street, Glasgow It will be open daily from 11 A M to 6 30 P M (8 P M on April 30) till May 3

South West Metropolitan Regional Hospital Board

The following have been awarded prizes in the board's 1956 competition

Consultants and S H M O s—Mr E H J Smyth Mr J H Mulvany, Dr A T Huston

Senior registrars, registrars, and J H M O s—Mr R A Denham, Dr J L Crammer Dr R S Jones

Senior house officers and house officers—Dr Ann Mullins

Notice of entry for this year's competition (with proposed subject) should be sent to the board's senior administrative medical officer (Gen /OST), 11A, Portland Place, London, W 1, by Sept 30, and reports must reach him not later than Dec 31

Broadcasts on Mental Health

The first of six weekly broadcasts on this subject is to be given on the Home Service on Wednesday, April 17 The programmes will include recordings made by patients, doctors, nurses, and welfare workers, and they will deal with the development of the child's mind, alcoholism, the rôle of the Churches in combating mental illness, and the problem of neuroses and everyday relations After the series, on Tuesday, June 4, at 7 45 P M, a panel of specialists will try to answer questions or criticisms arising from the programmes Listeners are invited to send their comments to Mental Health, Broadcasting House, Queen Margaret Drive, Glasgow, W 2

The B B C 's leaflet, *Mind Out of Balance*, published when this project was first announced, is still available and may be obtained by sending a stamped, addressed envelope (2*d*) to B B C Publications (Mental Health), 35, Marylebone High Street, London, W 1

British Association of Physical Medicine

Sir Cecil Wakeley, at the annual dinner held at the Royal College of Surgeons on April 5, said that from the first world war he had had reason to be grateful to those who practise physical medicine There was no branch of surgery that did not benefit from the work of the association The orthopædic surgeon relied on it, and " where would the thoracic surgeon or the geriatric surgeon be without your help ? " Even in the mundane treatment of varicose veins it was a necessity ' we strip the veins but you get rid of the ulcers ! " Dr P Bauwens, the president, recalled that since he took his first very junior post as a medical electrologist 30 years ago he had witnessed the birth, gestation, and formative years of physical medicine It defied definition yet had distinctive features, and he likened it to a painting with varying motifs which in course of time had come to form a well balanced pattern This picture, to which each generation added its contribution, he saw as a panel in a triptych whose other parts were medicine and surgery, and the themes of the three panels were sometimes different but often repeated and mutually complementary He hoped that, despite the continuous process of overpainting, the balance of the physical medicine panel and its main features would remain intact Group Captain C J S O'Malley, proposing The Guests, said that though young, the British Association of Physical Medicine, formed in 1943, was closely linked with old societies formed for mutual help, protection, good fellowship, and the protection of their crafts His kindly speech drew a response from Mr J C Butterwick, prime warden of the Goldsmiths' Company, which has been responsible for the presidential gold badge of the association, presented by the late Lord Horder He quoted Dryden's statement " the wise for cure on exercise depend,' and gave some account of his company s successful efforts in the past 8–9 years in training occupational therapists to teach the disabled how to make simple jewellery

Chronic Bronchitis

The National Association for the Prevention of Tuberculosis is holding a symposium on this subject on Wednesday, May 29, at 3 30 P M in the Clinical Science Building, York Place, Manchester, 13 Prof Fraser Brockington will be in the chair and the other speakers are to be Dr Lynne Reid, Dr Charles Fletcher, Dr D D Reid, Dr Thomas Lodge, Dr J L Burn, Mr Keith Roberts, Dr John Pemberton, and Dr William Robinson Further particulars may be had from the N A P T, Tavistock House North, London, W C 1

Society of Chiropodists

Speaking at the annual dinner in London on April 4, Sir Zachary Cope said that a book on the Feet, dated 1818, called on the Royal College of Surgeons to institute a sub diploma for chiropodists, but the first society was not formed until 40 years ago, and the union resulting in the now famous Society of Chiropodists took place only 10 years ago Chiropodists had been fortunate in having such good leaders, and he referred with pleasure to an award given earlier in the day to Mr J H Hanby Responding, Mr J R Hall, the president, said that in the past 8 or 10 years Sir Zachary had done more for medical auxiliaries " than anyone else we know of," and the conclusions of the Cope report were the first real basic recommendations ever put before the Ministry of Health and the public When agreement could not be reached, the protests of the Royal Colleges and the British Medical Association led to the setting up of a working party, and those who had gone in as " medical auxiliaries " came out, in the draft Bill, as " professions supplementary to medicine " A supplement was something that supplied a deficiency, and these professions supplied a deficiency in the Greater Medical Profession. Mr Hall hoped it would not be long before the Bill was passed and chiropodists were recognised with the new onus upon them they would try to maintain the same high principles as hitherto, recognising both in their private and in their professional life all that is involved by professional status Mr D Neale, proposing The Guests, thought that an empty chair might have been put at the table to symbolise an absent guest—the patient, " to whom we are all dedicated " In his reply Sir Heneage Ogilvie said he had been a guest in every continent except Antarctica, but his Swahili was inadequate and his English not as good as it should be Though he had often responded before, he still suffered from what those notable medical auxiliaries, the psychiatrists, would call the *Daniel complex* *Having* reviewed the development of numerous surgical specialties, culminating in the surgical biochemists whose talk is all of corticosteroids and milk equivalents, he expressed his belief that the really important people in the medical profession are the general practitioners —" because they don't think themselves important "

Baillière, Tindall, & Cox Ltd, have taken over the publication of *Public Health*, the official journal of the *Society of Medical Officers* of Health, for the society The journal has been redesigned and will first appear in its new format this month

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Diary of the Week

APRIL 14 TO 20

Tuesday, 16th

ROYAL COLLEGE OF SURGEONS OF ENGLAND Lincoln's Inn Fields, London, W C 2
3 45 P M Dr *H G H Richards* Parotid Gland Tumours (Erasmus Wilson demonstration)

ROYAL SOCIETY OF MEDICINE 1 Wimpole Street, W 1
5 P M *Experimental Medicine and Therapeutics* Dr William Lane Petter The Research Defence Society

WEST END HOSPITAL FOR NEUROLOGY AND NEUROSURGERY, 91, Dean Street, W 1
5 30 P M Mr Joseph Minton Ocular Manifestations in Clinical Neurology (Second of two lectures)

SOCIETY FOR THE STUDY OF ADDICTION
8 P M (11 Chandos Street W 1) Dr D J Parr Alcoholism in General Practice

Wednesday, 17th

ROYAL SOCIETY OF MEDICINE
5 P M *Comparative Medicine* Mr L E Rowson Dr Trevor Mann Dr Margaret Jackson Mr R H Boyd Artificial Insemination
8 15 P M *General Practice* Dr John Fry Dr Swithin Meadows Mr F A Williamson Noble, Mr Joseph Minton Eyes in General Practice

HARVEIAN SOCIETY 11, Chandos Street W 1
8 15 P M Dr Katharine Williams The Nuclear Age—Potentiality and Hazard

SOME PRINCIPLES OF PSYCHOTHERAPY IN GENERAL PRACTICE*

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SOME psychiatrists think that nothing is achieved by giving lectures or short courses on psychotherapy. I do not share this view. Psychotherapy is neither a purely intuitive art, which depends entirely on the personality of the doctor, nor something so esoteric that it can be undertaken only by trained psycho-analysts. Though long and specialised training is necessary for some types of analytic psychotherapy, many useful techniques can be acquired and used in general practice.

The bulk of straightforward psychotherapy is already done in general practice, and this is likely to continue to the betterment of general practice and psychiatry. Not every neurotic or "functional" disorder needs specialist attention. Many patients are frightened by being sent to a psychiatrist, and some refuse clinic appointments for this reason. Hence the general practitioner has to practise psychotherapy, in one form or another, whether he likes it or not. The problem is to make this form of treatment more effective and widely applied.

Psychotherapy remains an art, and has so far eluded study by accepted scientific methods; it contains no absolute truths. Nevertheless there is a body of principles that can be learnt and applied to its practice.

Before embarking on some of these principles I want to explode a few of the *misconceptions* that surround it. The first is that this treatment is too time consuming to be undertaken in general practice. This is true of analytical psychotherapy, but not of the many simpler methods. The second is the fable of the buried treasure—the idea fostered by films and books that a single traumatic episode buried in the patient's past caused the condition, and if the doctor can dig it up all will be well. One does not have to practise psychiatry and psychotherapy very long to know that this is true of very few patients. The third misconception is that an extensive knowledge of psychodynamics is needed. In point of fact much effective psychotherapy is done without recourse to the unconscious mind and without speculations about repressed conflicts and motivations. Indeed, too much sophistication in mental mechanisms, and too little common sense, may be a positive hindrance to success.

What is Psychotherapy?

Broadly speaking, any form of treatment designed to produce a response by its mental rather than its physical effects is psychotherapy. Such treatment falls into two groups. The first (which has been aptly called bedside manners or "prescribing the doctor") uses suggestion, persuasion, re-education, reassurance, and support. It includes managing the patient's problems and bringing about changes in circumstances which are noxious to him. This kind of psychotherapy is most suited to general practice.

The second group are the so-called deeper forms of psychotherapy, which often aim at uncovering psychological conflicts of which the patient is unaware and relating them to his problems. This group includes such special techniques as hypnosis, abreaction, and psycho-analysis, which are best left to those with special knowledge and experience.

History and Examination

History-taking

Unless the patient is already known to the doctor, history-taking constitutes the first interview, and first impressions are very important for both patient and doctor. Not infrequently the taking of a fairly detailed life-history is all that is needed to get the patient better. The opportunity to ventilate his problems with a sympathetic listener may previously have been denied him.

The important thing in history-taking is the *attitude of the doctor*. The key to a successful history is to be able to convey to the patient that one has plenty of time and is sympathetic and interested in his problem. One can learn to convey this impression to the patient even if one is short of time and not particularly interested. The technique I adopt is to allow the patient several minutes to say anything he wants, unprompted and uninterrupted, before proceeding to any special line of inquiry. Much of what the patient says may seem trivial and irrelevant but he must get the feeling that he has had a chance to say what he wants.

Besides the maxim "It's not what you ask but how you ask it," certain other points deserve mention. We all face the problem of being selectively deaf in history-taking: we hear only the things we want to hear. To approach every neurotic with a fixed idea that the problem must be sexual is as naïve as to suppose it never is.

One should avoid direct reassurance too early in the history even if the patient asks for it. Too quick reassurance is as unconvincing as that of the motor mechanic who says there is nothing wrong with the engine without so much as taking a look under the bonnet.

One can often see the key to the situation by watching the patient's expression of emotion during the examination. He may tremble with anxiety, burst into tears, or flush with anger when talking about people or situations which affect him closely. Likewise silence or evasion of a particular topic may be significant. It is unwise to press questions if the patient does not seem ready to answer them. Some neurotics have great difficulty in talking about their troubles; so the doctor should not be surprised or disappointed if the real problem does not emerge in the history. With tact and patience it will emerge later when the patient feels secure with the doctor. Be suspicious of the patient who produces intimate material on a plate at the first meeting—he may be near psychotic.

I have always found it a good plan to round off the history by asking the patient what he himself thinks is the trouble and how he thinks he may be helped to get better.

Physical Examination

The examination can be made an important adjunct to psychotherapy. The ideal time and place to reassure a patient is during and immediately after physical examination. If allowed to do so, a patient while being examined will often reveal information that he previously forgot or feared to mention.

An examination which is excessive is as dangerous as one which is cursory. An intelligent patient is not likely to be convinced there is nothing physically wrong if one only looks at the tongue and feels the pulse; but where neurosis is suspected, the greater danger is of too protracted an examination, too many special investigations, and indecisiveness about the results. It is highly important to get the physical side of the case cleared up right at the outset, and not to reopen it without definite indications: if one later yields to the patient's request for further physical investigation, his confidence is bound

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* Based on a paper read at a weekend course on Psychotherapy in General Practice organised by the Board of Graduate Studies, University of Birmingham, in conjunction with the Midland faculty of the College of General Practitioners and held in the Uffculme Clinic on Sept. 15–16, 1956.

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to be shaken. It is equally important to tell the anxious patient in very definite and simple terms the results of the physical examination.

Quite a number of emotional illnesses are precipitated or perpetuated by the doctor quite unwittingly. We are all guilty of contributing at times to these iatrogenic neuroses. Every psychiatrist sees patients who have been in the hands of three or four different specialists, all of whom are said to have told the patient something different. Such patients are hard to treat because they have lost faith.

If special investigations are pursued for several months the neurotic patient is bound to be influenced unfavourably. Moreover, laboratory studies are fallible and there is the oft quoted risk of placing too much weight on minor variations. The sooner one has the courage of one's conviction that there is nothing physically wrong, and tells the patient so, the better. Neurotics are very keen to have a definite cause for their symptoms and will fasten like leeches on to "fibrositis" or the like as the cause of their troubles. Once they are fixed in this sort of belief it is much harder to get them well.

If the patient is determined to have some special investigation, it is probably best to get it over and done with straight away—but on the understanding that it is to settle the issue and not be the prelude to a series of further tests. Our medical training makes us rightly afraid of missing hidden physical disease, but it makes us insufficiently aware of the danger of creating invalids by doubts and indecisiveness.

I must emphasise, too, that emotional disorders should not be diagnosed by the exclusion of a suspected physical cause. Their diagnosis must be based on the positive finding of an emotional disturbance in the patient.

The Therapeutic Interview

In most forms of psychotherapy an interview with the patient is the main vehicle of treatment. These methods have the common factor that they depend almost entirely on communication between patient and doctor. This communication may be spoken, or it may be implied by means of expression and gesture. There are no rigid rules, but some general principles of the therapeutic interview deserve consideration.

Number, frequency, and duration of interviews.—Many emotionally sick people can be adequately treated in half a dozen interviews or less. Some need many more, but I doubt the practicability of long-term psychotherapy (except of supportive type) in general practice. Weekly interviews are better than monthly, for long intervals make the treatment too diffuse to be effective. Forty minutes is long enough for most patients, though many will do very well with twenty. Some anxious patients cannot tolerate talking to the doctor for more than ten minutes or so.

Situation and flexibility.—Psychotherapy is traditionally depicted with the patient lying on a couch. Though this is regarded as essential for psycho-analysis, the face-to-face interview is better for less intensive treatment. Flexibility is a very important principle of psychotherapy, but it is not identical with vagueness. The standard method must be tailored to individual needs. The same technique will not fit both the managing director and the semi-literate man who sweeps the floor in his factory.

Objectives and errors.—Before embarking on treatment it is important to decide the objectives for each case; they should be kept in mind throughout treatment. The aim may be to get the patient symptom-free, to give him some relief, to get him back to work, to save his marriage, or to keep him going until circumstances take a turn for the better. The aims should be realistic. Many doctors get discouraged about their therapeutic ability by putting the sights too high. Our influence on the patient is considerable but not infinite.

Though there are plenty of mistakes to be made in psychotherapy, one should not be put off by fear of making them. Many of the errors can be corrected. Psychotherapy is not as dangerous as some make out. A common mistake is to use such clichés as "Don't worry," "Snap out of it," and "Pull yourself together." There is nothing a neurotic resents more than being told to pull himself together; he has been told this many times and has told it to himself before he saw the doctor. In most cases such admonitions convince the patient that the doctor does not understand him. Nor should one tell him that his troubles are purely imaginary; symptoms are always real to the patient.

Avoid giving advice unless you are confident your counsel is correct and will do no harm. This applies to patients who ask for advice as well as those who do not. It is generally a mistake to tell a patient to marry, to have a baby, or to change a job—in vague expectation that this is the solution of his difficulties. The new responsibilities often create additional problems. If the patient presses for advice, it is best to discuss the matter fully and help him to *reach his own decision*. If you give concrete advice be prepared to have it thrown back at you later.

Avoid prejudging the patient and his problems. Though one should try to feel with the patient, do not become so identified with his problems that you make him do what you would have done in his particular circumstances. Patients are individuals with their own aims and objects. The Pygmalion approach is almost always mistaken; the therapeutic subject is not clay to be moulded according to the doctor's ideals.

Timing, Minimal Activity, and Focus

The factors causing a patient's symptoms may be obvious after one interview; but, though very tempting, it is unwise to tell the patient all you know. Premature interpretation of the situation, even if it is correct, will be rejected. Unpleasant truths take time to be accepted. Correct timing here is as important as in glass blowing, where attempts to mould the material before it is at the right temperature may fracture it or cause it to run. The patient should be led by inference into seeing the situation for himself without being told directly. Self-made interpretations are more likely to be accepted than those made by others.

Patients will rarely benefit from a lecture or sermon. The aim should be to get the patient to do the talking. The less active the doctor the better. Keeping one's mouth shut is probably the hardest psychotherapeutic lesson to learn. One should not be afraid of saying little or nothing, or of pauses and silences. If we start to talk as soon as the patient dries up, the conversation will probably remain on a very superficial level. Half the art of psychotherapy is to be a good listener. Conversational grunts, and exclamations such as "uh huh" and "humm" which lack an air of finality, help to keep the patient talking without interrupting him. One's facial expression, intonation, and gestures can all help to keep the conversation going. If the patient comes to a halt, one can often get him talking again by repeating one of the last phrases or words he spoke. If he dries up completely one can discuss why he has difficulty in talking.

Some patients are evasive and become more so when discussing their real problems. They tend to be repetitive and to circle round and round the topic of their symptoms. By showing lack of interest when they talk of symptoms, and interest when they start to talk of something else, one can get them to focus on matters of importance. In short-term therapy it is quite legitimate to select important topics and ask the patient to talk about them, but leading questions, and those with the answer yes or no, should be avoided.

It may be a good plan to start treatment by a brief explanation of its aims, thus preventing the patient from expecting too much of the doctor and too little of himself. The patient must see the treatment as a cooperative effort.

Some patients have a fixed idea about the way in which they can be helped, and one can prevent blunders by finding out about this. They may have great faith in some particular nostrum, and if so one should be aware of it. It may, for instance, be good psychotherapy to prescribe a placebo. Many patients, particularly from the lower social strata, have so accepted the tradition of the "bottle of medicine" that if one resolutely refuses to prescribe any medicine with psychotherapy they will not come again. A small prescription may ensure the initial cooperation necessary for psychotherapy. This does not mean that the doctor should always heed a patient's wishes or become a pawn for him to manipulate. The doctor should remain in discreet control of the treatment situation throughout.

The Doctor-patient Relationship

Most psychiatrists agree about the fundamental importance of the doctor-patient relationship in psychotherapy of all types. This relationship can be defined as the mutual interaction between the personalities of the patient and of the doctor that pervades all treatment. The relationship is not one-sided and shows a large number of variations.

For convenience it is easier to consider the two sides of the relationship separately, though in reality they are indivisible.

The Patient's Attitude to the Doctor

To the sick person seeking help, the doctor is not just another person. Even today the patient not only thinks of him as an accomplished expert in medicine and accords him his traditional and cultural rôle; he also sees him as a symbolic figure. Many emotionally sick people do not go to a doctor for help. Those who decide to seek help from medical sources differ in their attitude to the doctor from those who go elsewhere or nowhere at all.

Patients may exhibit positive or negative feelings of great intensity towards the doctor. Such feelings may be of awe, distrust, anxiety, warmth, hostility, or subservience. The type of reaction a patient shows to the doctor is determined more by the patient's personality and previous experience than the doctor's.

Some examples may help to explain. At one end of the scale are the patients with a really positive relationship with the doctor. They often come along with their minds already made up that you are a good doctor with almost magical powers to help them. They sing the doctor's praises even before anything has been done for them. They take his advice and treatment without a murmur. They even, to please him, say they are better and are profusely grateful for the smallest attention. Such patients are good for the doctor's vanity and feeling of omnipotence; but they do not always persist in this attitude.

At the other end of the scale are the patients with strongly negative feelings about the doctor. They may be openly hostile, truculent, and aggressive, or more subtly they turn up late for appointments, fail to take the treatment prescribed, and do not discuss their problems openly. They are bad for the doctor's vanity and tax his patience to the utmost. The surprising thing is that they often continue to seek the doctor's help.

Between these two extremes we find the bulk of patients, who show mixed positive and negative feeling towards the doctor. Such patients' attitudes often fluctuate.

It is of fundamental importance to recognise that the patient's attitudes to the doctor are nearly always predetermined and *not personal* in any way. Some people may tend to repeat attitudes towards the doctor that have been laid down by previous life experience. In particular they tend to re-enact their childhood relationships with figures of authority such as parents and teachers.

The Doctor's Attitude to the Patient

An understanding of the doctor's part in the relationship is as vital as it is difficult. It is bound to be individual for each doctor and involves a certain amount of soul-searching and recognition of his own outlook and prejudice. Unfortunately, many a doctor cannot tolerate certain shortcomings in his patients—to the serious detriment of his ability to help them. Some doctors cannot tolerate stupidity; others cannot take the patient who is surly and hostile or one who is coy and flirtatious. Certain attitudes in our patients threaten us or annoy us, and we should recognise this. Each of us has his own emotional blind spots, and I do not think we can be all-round psychotherapists unless we are aware of these and how they affect our handling of patients.

It is relatively easy to be a good psychotherapist with certain types of patient suited to our own make-up; the difficulty is to be able to help more than an isolated group of emotionally sick people. A doctor who can learn to tolerate his patient's emotions, in the same way as he learned to tolerate pathological specimens without disgust, has gone a long way towards being an effective therapist.

If we are hostile and annoyed with our patients we cannot get their confidence and cooperation; through lack of empathy the therapeutic relationship does not develop. Doctors who regard all neurotic patients as weak and spineless are not likely to help them.

We all tend to develop defences against our patients, some open and some more hidden. We can of course dub them straight away as "another damn neurotic," or show our dislike more subtly by sending them at once to a specialist for protracted investigation, or abroad for a long holiday. Our letters about the patient often express our feelings well; the adjectives used often tell more of the doctor's feeling than the patient's condition.

Learning psychotherapy does not mean learning a new series of catch phrases; but the technique does involve an awareness of the importance of our own response to the patient and how this influences our ability to deal with his psychological problems.

Finally, I would emphasise again the importance of first impressions. If the doctor is sympathetically warm and accepting at the outset, he can build up the good relationship with the patient which is so important. If, later, the patient has to be dealt with in a more firm and positive manner, it can be done on the basis of the patient's confidence in the doctor and in a way he can more readily accept.

"A celebrated authority on Canon law and mediæval Universities, Dr Hastings Rashdall, was one of those who could ride but not understand a bicycle. One day, for example, having had a puncture in his front tyre, he was found vigorously pumping up the back one; when a passer-by pointed this out to him he remarked 'What? Do they not communicate?' I sometimes wonder whether, in our present-day eagerness to 'put people in the picture,' we do not behave rather like Dr Rashdall, strenuously pumping in information at one end of a firm in the hopeful expectation that it will find its way to the other. Perhaps we too ride but cannot understand."—T. M. HIGHAM, *Occupational Psychology*, January 1957, p. 1.

INTERMITTENT ALDOSTERONISM IN PERIODIC PARALYSIS

DEPENDENCE OF ATTACKS ON RETENTION OF SODIUM, AND FAILURE TO INDUCE ATTACKS BY RESTRICTION OF DIETARY SODIUM*

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D Phil Oxfd,
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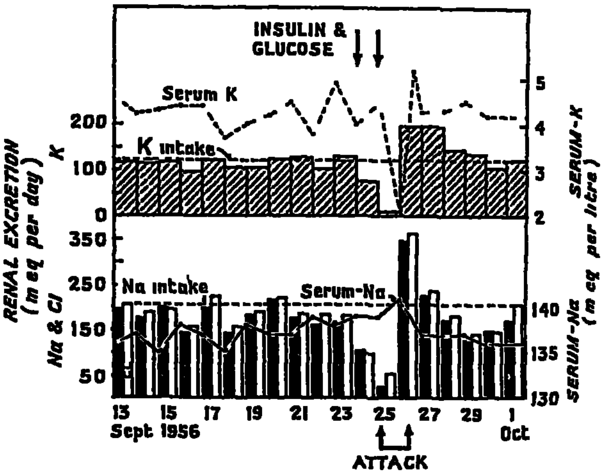
WE have reported that spontaneous attacks of periodic paralysis are preceded by large increases of urinary aldosterone and by intense retention of sodium (Conn et al 1956) This is followed shortly by sequestration of potassium within the body, both serum and urinary potassium falling abruptly and intensely Serum sodium often rises to abnormally high values as serum-potassium reaches its lowest ones As the attack subsides a great diuresis of sodium occurs together with a less intense increase of urinary potassium Serum-sodium and serum-potassium return to normal together By this time urinary aldosterone has returned to base line values

We have explored further the rôle of retention of sodium in setting off potassium sequestration—i e, acute hypokalæmia and hypokaluria Two young men with the familial type of periodic paralysis were the subjects of this study One of them, living in our laboratory, submitted cheerfully to 11 months of a rigid metabolic balance regime The other was studied for 30 days to test in a different person the applicability of the metabolic principles discovered in the first one The subjects are not related

The aim of this short communication is to disseminate quickly information which is of immediate practical value to patients with this disorder Extensive data will be published later At this time we wish merely to outline some of our results and conclusions



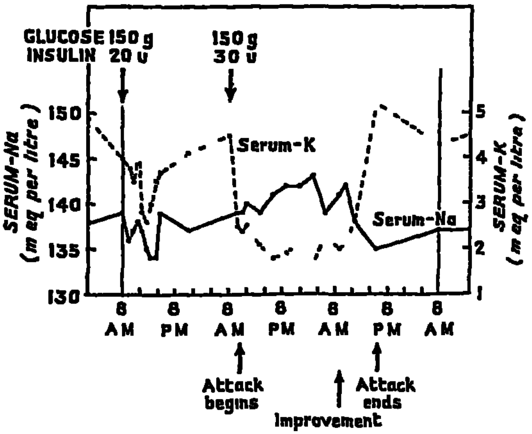


Fig 2—Changes in electrolyte metabolism during episode of periodic paralysis induced by administration of glucose and insulin

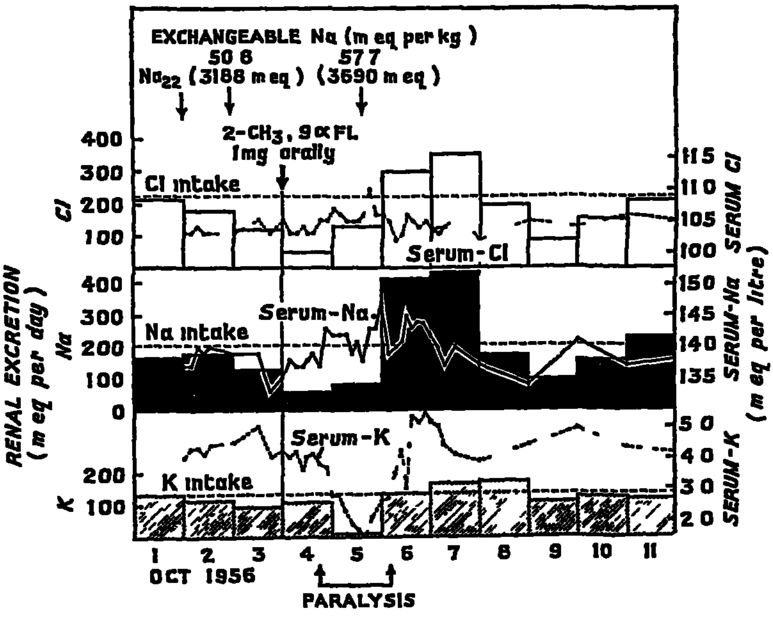


Fig 1—Induction of episode of periodic paralysis by 2 methyl 9-α-fluorohydrocortisone and high sodium intake

Method

Two levels of sodium intake were used—8 and 208 m eq per day The composition of the daily ration was otherwise the same, the high sodium régime differing from the low by addition of sodium chloride to the basic diet Chloride ion, the only other variable, was 27 m eq per day on the low, and 229 m eq per day on the high, sodium ration Potassium intake was constant at 132 m eq per day

Results

Under both of these dietary conditions a series of identical experiments were carried out, each designed to induce an episode of periodic paralysis The following facts were disclosed

(1) When the diet contained the larger quantity of sodium the administration of glucose and insulin, or of 2 methyl 9 α fluorohydrocortisone (an extremely potent mineralocorticoid) produced complete (from the neck down) and prolonged (24–48 hours) paralysis (figs 1 and 2)

(2) When glucose and insulin induce an episode of periodic paralysis the great

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* This study has been supported by a grant from the office of the Surgeon General, Medical Research and Development, U S Army

† Howard Hughes Foundation investigator

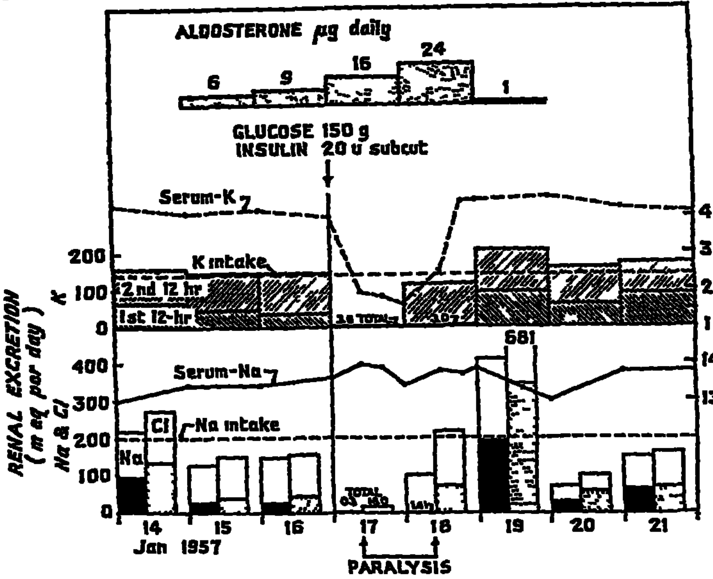

Fig 3—Changes in electrolyte metabolism and urinary excretion of aldosterone during episode of paralysis induced by glucose and insulin. Lower part of histogram first 12 hours, upper part, second 12 hours. Aldosterone estimated by method of Neher and Wettstein (1956).

retention of sodium which precedes the actual attack is accompanied by a sharp rise of urinary aldosterone (fig 3). During the intense diuresis of sodium which follows an attack urinary aldosterone falls below normal. By what means increased utilisation of carbohydrate produces increased secretion of aldosterone in this disease is now under investigation.

(3) In all of these paralytic episodes urinary and serum K fell sharply but the sequestration of K was always preceded and then accompanied by intense retention of sodium.

(4) The very earliest return of muscle function is related temporally to increasing amounts of urinary sodium, and in some attacks it can be demonstrated that serum potassium is still near its minimal value at the time that the ability to move muscles is returning. This is then followed by a rapid increase of urinary and serum potassium.

(5) Total body exchangeable sodium (Na^{22}) was found to be elevated before induction of attacks and this increased considerably during induction of an attack (fig 1).

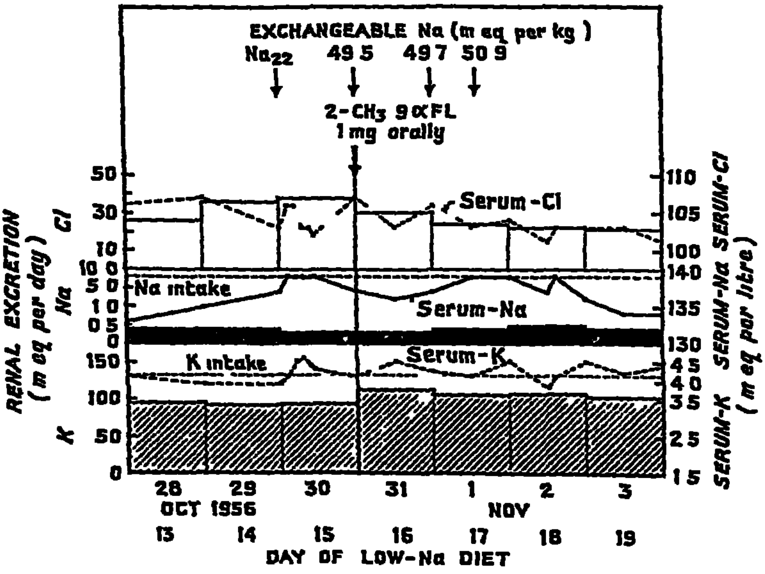

Fig 4—Data indicating failure of 2 methyl 9-α fluorohydrocortisone to induce attack when sodium retention is prevented by low-sodium diet.

(6) When retention of sodium was prevented by provision of the diet very low in sodium, *attacks of paralysis could not be produced* by the procedures which had provoked the severe ones previously mentioned, and sequestration of potassium did not occur (fig 4). This has been demonstrated in both of our cases of periodic paralysis.

(7) As in normal individuals, these subjects when taking the low sodium diet exhibited persistently raised levels of urinary aldosterone, yet there were no attacks. Thus, the sudden sequestration of potassium which accompanies an attack of periodic paralysis is not due per se to the presence of aldosterone. Sodium must be available and must be retained in the body before potassium begins to move to its site or sites of sequestration.

(8) Whereas 2 methyl-9 α-fluorohydrocortisone produced prolonged retention of sodium and diuresis of potassium in normal men (fig 5), it produced sodium retention followed by sequestration of potassium in both patients with periodic paralysis (fig 1). This would appear to rule out the possibility of production of an abnormal potassium retaining adrenal steroid in this disease. Instead it appears that when a sodium retaining corticoid is actively causing sodium retention in periodic paralysis the potassium response is a paradoxical one. This conclusion is strengthened by the fact that we have clearly identified as aldosterone the urinary sodium retaining corticoid found in excess in this disorder.

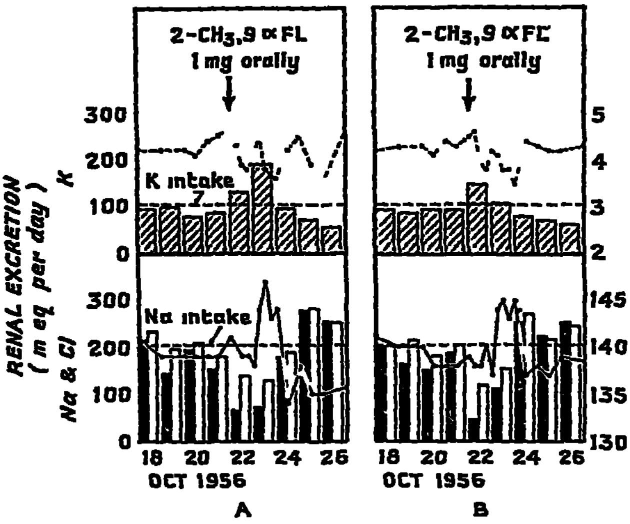

Fig 5—Effects of 2 methyl 9-α fluorohydrocortisone on electrolyte metabolism in two healthy young men aged 21 (A) and 19 (B).

(9) Skeletal muscle obtained during the period of high sodium intake contains much too much sodium and a normal or slightly subnormal concentration of potassium (see accompanying table). Microscopically, the lesion characteristic of this disease is observed—namely, numerous large and small glistening vacuoles within muscle fibres. The vacuoles do not stain as fat or glycogen (fig 6).

(10) In skeletal muscle obtained after 44 days on the low sodium diet this vacuolar change in the muscle fibres has disappeared (fig 6b). The accompanying table shows the values for concentration of Na and K in muscle at this time.

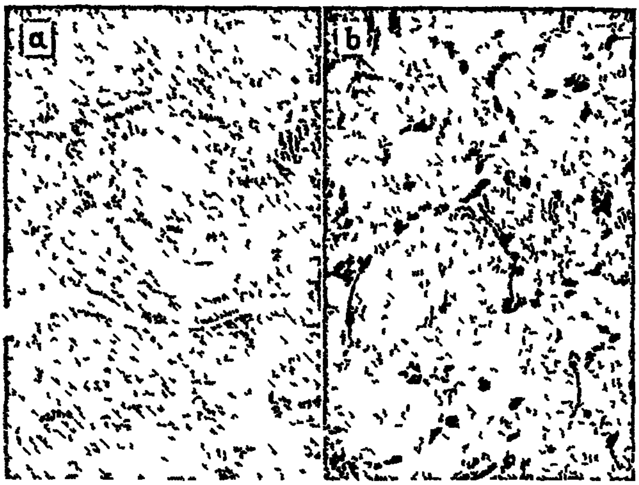

Fig 6—Skeletal muscle from patient with periodic paralysis (a) during high sodium intake, showing vacuoles (b) during low sodium intake, showing no vacuoles

Discussion

The dramatic decrease in the level of serum potassium at the beginning of a paralytic episode in the "familial type" of periodic paralysis has resulted in extensive studies of potassium metabolism in this disease Current therapy consists in administration of potassium salts daily by mouth as prophylaxis, and of potassium chloride intravenously for established attacks We are impressed with the facts that, although an incipient attack can be aborted or a severe one sometimes ended by administration of potassium, they still occur even when 10–12 g of potassium chloride is ingested daily

Studies of sodium metabolism in this disease are meagre In two studies sodium balance was found to be positive before and negative after the attack (Ferrebee et al 1940, Danowski et al 1948), but the significance of this finding was not appreciated It is clear from the present data that the sudden and profound sequestration of potassium is always preceded by an intense positive balance for sodium In normal individuals on very low levels of dietary sodium, urinary excretion of potassium is not increased by administration of 2 methyl-9-α fluorohydrocortisone (J W Conn, unpublished) Thus, it appears that even in normal people the effects of mineralocorticoids upon potassium metabolism are secondary to retention of the sodium ion

SODIUM AND POTASSIUM CONTENT OF MUSCLE AND SERUM IN PERIODIC PARALYSIS, HEALTH, AND PRIMARY ALDOSTERONISM

—	Date	Weakness	Paralysis	Muscle Sodium (m eq per kg *)	Muscle Potassium (m eq per kg *)	Serum Sodium (m eq per kg)	Serum Potassium (m eq per kg)
Periodic paralysis							
Case 1†	Oct 31, 1955	+	–	48	82	137	4 0
„ „	Jan 14 1956	+	+	52	85	146	3 0
„ „	Mar 10, 1956	–	–	46	75	139	4 5
„ „	Nov 29, 1956§	–	–	34	74	135	4 1
„ „	Feb 19 1957‖	+	+	46	81	137	3 7
Case 2‡	Feb 8, 1957	+	+	47	82	137	1 3
Healthy people							
Shohl 1939				31	93		
Farago et al 1951				21	100		
Baldwin et al 1952					95		
van Buchem et al 1956				26–36	91–107		
Primary aldosteronism							
Conn 1955 (preop)				49	62	144	3 1
Conn et al (unpubl) (18 mos postop)				32	76	141	4 1
van Buchem et al 1956 (preop)				52	68		

* Expressed in terms of fresh wet weight
† Male aged 19
‡ Male aged 24
§ After 44 days on low sodium intake plus initial desalting with acetazolamide (Diamox) and mercaptomerin (Thiomerin)
‖ After 38 days on high sodium intake

With respect to the *clinical* entity of periodic paralysis we call attention to several well-recognised discrepancies which make it difficult to correlate attacks of paralysis solely with an abnormality of potassium metabolism

(1) Attacks of total paralysis may occur at levels of serum potassium which when found in other conditions are not low enough to result in muscular paralysis (Darrow 1946, Danowski et al 1949, Elkinton et al 1951)

(2) The severity of different attacks in the same individual is not correlated closely with the degree of hypokalæmia

(3) When the serum potassium has been estimated frequently throughout attacks, we have often observed that muscular function begins to return while serum potassium values are close to the lowest value observed during the attack

(4) Sporadic cases (Watson 1946, Bull et al 1953) and families (Tyler et al 1951, McArdle 1956) exhibit the typical clinical syndrome without *any* decrease of serum potassium during attacks It seems very significant that in such cases Tyler et al (1951) have found the vacuolar myopathy (a lesion characteristic of familial periodic paralysis [Goldflam 1897, Schmidt 1919, Zabriskie and Franz 1932, Allott and McArdle 1938]) which is demonstrated in fig 6a and shown in fig 6b to have disappeared with reduction of intracellular sodium toward normal

All of these considerations viewed in the light of the experimental data described here, suggest that the common denominator is an excessive quantity of intracellular sodium This by no means excludes hypokalæmia, when it occurs, as a contributory factor, nor does it mean that a sudden increase of intracellular potassium does not influence the onset of a paralytic attack It does indicate, however, that retention of sodium is the primary factor which sets into motion the characteristic chain of events in an episode of periodic paralysis, and it provides a much more direct approach to the prevention of paralytic episodes

Comparison of the sodium and potassium content of muscle in periodic paralysis and in primary aldosteronism (see table) suggests that when intracellular sodium is too high the muscle cell must be able to extrude potassium if paralysis is to be avoided The sum of the *intracellular* cations may be a critical factor in the muscular paralysis The mechanism by which in most of these cases retention of sodium under the influence of aldosterone sets off the potassium-sequestration phenomenon requires *further* study Similarly, the mechanism by which *intermittent* aldosteronism exists in this disease is not yet clear

It seems likely, then, *that an abnormally high* concentration of sodium within the muscle cell is partly responsible for the disturbance of muscle function in periodic paralysis The histological lesion of this disease—i e, hydropic vacuolisation within the muscle fibre—is related *to the* high concentration of intracellular sodium, although total cationic concentration may be important Since the same pathological lesion has been observed in patients who, although suffering from typical periodic paralysis, exhibit no hypokalæmia or hypokaluria during attacks (Tyler et al 1951), it is probable that retention of abnormal amounts of sodium is the common *factor* in the various subgroups of periodic paralysis Balance studies for sodium are needed in such cases

From a practical point of view these studies indicate that a diet low in sodium prevents attacks of periodic paralysis A period of "desalting" with mercurial diuretics and/or carbonic anhydrase inhibitors, associated with a low sodium diet, may be required as an *initial step*

Apparently the stimulus for excessive secretion of aldosterone in periodic paralysis is extra adrenal in origin Although adrenalectomy would remove the source of aldosterone, we believe that this procedure is not indi cated because (1) episodes of paralysis become less frequent and finally disappear as the patient grows older, and (2) replacement therapy, unless grossly suboptimal, would probably be associated with periodic retention of sodium, especially under conditions of stress (Ingle 1952)

We wish to acknowledge the important technical assistance of the following members of our staff Mrs Frances M. Holcombe, research dietitian, and Dr Irving P Ackerman, Dr John A. Moorhouse Dr Abraham Rapoport, Dr Shafik Haddad, Dr Anita Franco, and Dr Lamont W Gaston

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THE EFFECT OF TOLAZOLINE HYDROCHLORIDE ON TIC DOULOUREUX

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It has long been recognised that attacks of tic douloureux may be suppressed by vasomotor agents such as choline derivatives, nicotinic acid, histamine, and amyl nitrite (Cooper 1938, Adams and Robinson 1941, Karl et al 1945, Wolff 1948) Such effects, even if temporary, provide a line of therapeutic investigation and are of interest in the study both of the disease and of the pharmacology of the agent used In this field the action of more recent and possibly more effective vasodilator agents appears little explored, and this report presents some experiences with tolazoline hydrochloride The aim has been to determine the existence and characteristics of any effects rather than to establish an optimal therapeutic régime

Material and Methods

Observations were made in 9 patients with tic 2 of whom had disseminated sclerosis and 1 an acoustic neuroma 3 had had alcohol injection years previously Only unequivocal cases of tic were accepted Patients with frequent daily pains and active trigger areas but without severe cardiovascular disease were selected Most of them were awaiting surgical treatment which was delayed only in some instances where the response seemed especially promising Tolazoline hydrochloride (Priscol Ciba) was usually given first orally (12 5 mg) as a test for idiosyncrasy and in 1 case this route alone was used However graduated intravenous administration (up to 50 mg in 10–15 minutes) was preferred so that observations could be made over a short period thereby minimising errors from fluctuations in clinical state Peripheral vascular responses were assessed by subjective flushing and by objective changes—e g, conjunctival suffusion and changes in skin colour and temperature (measured with Marks skin thermometers on the extremities) The patient was kept resting flat during intravenous tests, and the blood-pressure and pulse rate were noted at intervals

The effects on the tic were judged by the number of attacks and their ease of provocation, both with ordinary activity (talking, eating, &c) and with deliberate stimulation of the trigger area (touching, rubbing) before, during, and after administration of the drug It was, however, considered unjustifiable to activate deliberately trigger areas repeatedly during the course of an injection to determine the precise temporal relationship between the peripheral vascular effects and relief of pain, so this was not closely defined

Results

8 patients were given tolazoline intravenously, and in 6 there was a dramatic cessation of attacks and inactivation of trigger areas, persisting for some hours, but in 2 there was little definite change In 5 of these patients (3 responding and 2 resistant) further intravenous tests were possible (after at least 48 hours' interval) and gave similar results Of the 2 showing no remission with intravenous therapy one was subsequently found to have an acoustic neuroma and the other showed smaller peripheral vascular responses than usual The final case in the series was treated only orally and went into a remission for 4 months

Illustrative Case-reports

Case 1 —A woman aged 66, with tic affecting the second and third divisions of the right trigeminal nerve for 18 months She had had numerous increasingly severe attacks daily for many weeks when first seen, most of them coming on spontaneously, trigger areas being inconstantly active Her blood-pressure was 190/90 mm Hg Oral tolazoline 25 mg t d s produced subjective flushing and immediate reduction in the number and severity of her attacks, and at higher dosage (50 mg t d s) the attacks ceased entirely in 2 days, the patient remaining pain free under this régime for nearly a week At this point inert tablets were substituted and the pains promptly recurred though not to their usual extent before therapy Restoration of oral tolazoline did not control these pains as completely as before (nor was the flushing response so definite), but a single 50 mg intravenous dose produced marked vascular responses and immediate complete freedom lasting 3 days Over the next 2 weeks limited pains reappeared on three occasions, and on each 50 mg intravenously produced immediate relief lasting some days without further therapy The pains did not return after the final injection, and the patient has remained pain free for more than 2 years without further treatment

Case 2 —A woman, aged 52, with tic affecting the second and third divisions of her right trigeminal nerve for 16 years, treated 14 years previously by alcohol injection. She had had, for 3 weeks, numerous severe attacks daily, triggered consistently from gum and lip Blood-pressure 140/80 mm Hg Intravenous tolazoline 25 mg produced flushing and dramatic relief of both spontaneous and provoked pains Within 10 minutes food could be chewed on that side and dentures inserted for the first time in 3 weeks, the trigger areas being entirely inactive However, 3 hours later slight tingling and soreness could be provoked from the trigger areas and within 12 hours the pains had returned to some extent Surgical intervention prevented further observations

Case 3 —A woman aged 51, with tic affecting the third division of her right trigeminal nerve for 8 years, treated on three occasions by alcohol injection Numerous severe attacks had been occurring daily for 3 weeks and oral trigger areas were acutely active Blood pressure 105/85 mm Hg An oral test dose of tolazoline 12 5 mg was given but the pains were so distressing that an intravenous injection was started without awaiting the oral response 10 mg intravenously unfortunately produced "bumping" in the chest shivering and numerous extra systoles along with warming of the extremities However, the attacks ceased and within 25 minutes of the injection the trigger areas became inactive, and the face could be rubbed and food taken without incident for the first time in 2 weeks The cardiac abnormalities subsided within 2 hours of the injection Apart from one spontaneous attack several hours later, the patient remained pain free for 2 more days without further medication She had some tingling feelings of the type often heralding an attack, but they came to naught On the 4th day she had a moderate spontaneous attack, and oral therapy was cautiously instituted (12 5–25 0 mg t d s) Over the next 3 weeks the trigger areas remained inactive, but she had moderate spontaneous pains every few days These then increased, and occasional triggered pains reappeared Higher oral dosage was not tolerated A further intravenous injection again gave her 2 days of complete freedom with gradual return of first spontaneous and then triggered pains over the next week, whereupon root section was done

Case 4 —A man aged 47, with disseminated sclerosis for 11 years and mild left sided tic for 3 years When first seen he had been having pains daily for some weeks with numerous severe paroxysms for the past 3 days, trigger areas were well defined Blood pressure 155/100 mm Hg Intravenous tolazoline 50 mg inactivated the trigger areas, but limited spontaneous attacks recurred 1½ hours later, and therapy was continued orally (50 mg t d s) Under this régime the next 2 days were pain-free, but mild spontaneous pains returned again, and the trigger areas could not always be treated with complete indifference However, under continued oral therapy this again subsided, and the patient had weeks of freedom with only an occasional minor attack Therapy was stopped after 3 months, and inquiry 1 year later revealed no evidence of relapse

Discussion

These results indicate that tolazoline may, like nicotinic acid, histamine, &c , suppress the paroxysms of tic Such effects may be due to relief of nerve ischæmia and thus support the view that there is an ischæmic factor at some stage in the mechanism of some types of tic Triggered attacks seem more readily suppressed than spontaneous, and, even when the pain is abolished, the involuntary twitch of the facial muscles which often accompanies it may persist, as has been observed with other vasomotor drugs (Adams and Robinson 1941, Wolff 1948)

It is of interest that cases with disseminated sclerosis also respond, in view of possible vascular factors in its pathogenesis The variation in therapeutic response may derive from individual differences in drug susceptibility or capacity for local vascular reaction

The present series is too limited to show whether there is any significant difference between those cases responding and those that do not, but analysis of a larger series might prove of interest The fact that relief may long outlast the expected time course of the drug does not necessarily invalidate an anti-ischæmic explanation Factors determining the fluctuating course and long remissions so characteristic of tic are ill understood, and it might be that a vasodilator response over a short or long period favours those biochemical states existing in a remission Indeed the remissions following procaine nerve-block, incomplete alcohol injection, and surgical operation leaving nerve pathways intact might also derive from the beneficial effects of the period of vasodilation they provoke

Therapeutically the results in such a small series must be interpreted with great caution, as the history of tic shows, but it is evident that good temporary relief may be afforded Moreover a period of normal function with vigorous stimulation of the trigger areas may favour stabilisation in this state It remains to be seen whether prolonged oral or parenteral therapy with this or similar agents can induce more general and lasting results Its simplicity and immediacy commend it as one approach that should not be overlooked

Summary

The effect of tolazoline hydrochloride on tic douloureux was investigated in 9 severe cases, 2 associated with disseminated sclerosis

In most cases both spontaneous and triggered pains were suppressed for varying periods after parenteral administration

I am indebted to Dr W Ritchie Russell, Dr C W M Whitty, Mr J Pennybacker, F R C S , and Prof J E Caughey for permission to study patients under their care, Dr M Fischer Williams for assistance with case 1 , and Dr Whitty for advice and criticism Part of the work was done with financial assistance from the Medical Research Council of New Zealand

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BLOOD COAGULATION AFTER THE INGESTION OF SATURATED AND UNSATURATED FATS

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IT has been claimed that blood coagulation is accelerated by the feeding of fat (Waldron et al 1951, Fullerton et al 1953, O'Brien 1955, 1956) O'Brien (1956) has gone so far as to say "That a fatty meal accelerates blood coagulation is now established" On the other hand, there are contrary opinions (Tulloch et al 1953, Manning and Walford 1954, Hall 1956a)

Dietary fat has been said to be important in the genesis of atheroma (Keys 1952) It is also asserted that feeding of fats containing large amounts of unsaturated fatty acids reduces the serum cholesterol (Kinsell and Michaels 1955, Malmros and Wigand 1955, Bronte-Stewart et al 1956)

For these reasons it appeared to us to be important to re evaluate the effect of feeding different types of fat on blood coagulation

Material

All tests were done on patients in medical wards They were convalescing from a variety of diseases—chiefly peptic ulcer, uncomplicated hypertension, infective disease (e g , pneumonia, pyelitis, meningitis), skin disease, and cardiac and cerebral disease (*including* atheroma) Patients with uræmia, jaundice, or blood or bleeding diseases, and patients having anticoagulant or cortisone therapy or with cardiac failure of more than very mild degree were excluded Patients were asked whether they would be prepared to take either a high fat or a low-fat breakfast , those who consented were allocated to one or other group by random selection

Methods

The meals given were

(1) *Low fat* —This consisted of bread and jam, porridge tea, and fruit Sugar and skimmed milk were allowed The fat content of the meal was less than 5 g

(2) *Oil* —Salad oil was given as a draught together with the low fat breakfast In the experiment where consumption of prothrombin in silicone tubes was measured, 90 ml of a mixture of sunflower seed oil and pilchard oil (iodine number 137) was used In the remaining experiments, 120 ml of sunflower seed oil (iodine number 128) was given These oils were especially selected because of their high content of unsaturated fatty acids

(3) *High fat* —In the prothrombin consumption experiment, 4 patients received 180 ml and 3 received 210 ml of 40% cream, together with a low fat breakfast 7 additional patients received a breakfast containing 80 g of fat (bacon and eggs bread and butter, and cream) In all the remaining experiments the high fat diet contained at least 100 g of fat This consisted of fatty bacon fried with one or two eggs, bread and butter, 60 ml of 40% cream, and 180 ml milk Patients refusing bacon for religious reasons were given additional

butter and eggs Each patient was carefully observed to see that all the diet given was consumed A few baulked at the last pat or two of butter!

As far as possible an equal number of patients in each of the three dietary groups (usually two of each) were tested on the same day

Blood Collection

All patients were fasted from 8 30 P M, and "fasting" specimens of blood were collected between 8 A M and 9 A M the next day Breakfast was then given after which nothing was given by mouth until the final specimen of blood had been taken

In the prothrombin consumption experiment, 20 gauge needles and all glass dry autoclaved syringes were used In the remaining experiments syringes were not used 18 gauge needles were used alone, and the freely flowing or spurting blood was collected directly into the test tube Blood obtained by imperfect venepuncture was not used

Coagulation Tests

Lee and White coagulation time in silicone tubes—1 ml. of blood was placed in each of 6 (in some cases 20) test tubes (3 × $^3/_8$ in) in rapid succession. The tubes were left undisturbed for ten minutes and then each was gently tilted once a minute The end-point adopted was that which permitted complete inversion of the tube The coagulation time recorded for each patient was the mean for all tubes

Coagulation-time of recalcified citrated plasma (calcium time)—Decalcified plasma was obtained by the use of 3 8% sodium citrate (one part in ten of blood) and centrifuging the blood as follows

Slow-spun plasma 1500 revolutions per minute (r p.m.) for ten minutes
Fast spun plasma 3000 r p m. for forty five minutes
Super-spun plasma was obtained from slow spun plasma by centrifugation at 15,000 r p m for fifteen minutes

Plasma was recalcified with an equal volume of M/40 calcium chloride 4 tubes and in some cases 16 tubes were used for each test and the mean recorded

Prothrombin consumption—This was measured on serum from the siliconed Lee and White tubes and on recalcified citrated plasma as previously described (Mershey 1950) The result was expressed as an index as follows

$$\text{Prothrombin consumption index} = \frac{\text{prothrombin time of plasma} \times 100}{\text{prothrombin-time of serum}}$$

Thrombin generation in silicone tubes—This was tested on single specimens of fast spun plasma as described by O'Brien (1955) In this test the fibrinogen time is the shortest clotting time in any of the fibrinogen subsamples The thrombin generation time is the interval which elapses between the recalcification of the plasma and the fibrinogen time subsample tube

Blood thromboplastin generation—This test was performed as described by Biggs and Macfarlane (1953) Three components are required—(1) Platelets (2) Alumina treated plasma, and (3) Serum Samples of two components from fasting patients were tested with fasting and postprandial high fat meal samples of the third (1) 4 batches of platelets from fasting and 4 from postprandial blood were tested (2) A 1 in 5 and a 1 in 25 dilution of alumina-treated plasma derived from three specimens of fasting and postprandial blood, were tested (3) Serum was obtained from 18 fasting patients 9 were taking a low fat and 9 a high fat diet and serum was obtained four hours later This was stored at 37 C for twenty four hours, diluted 1/10 in saline and stored at − 20°C until tested

Factor V—This was measured by the corrective effect on the one-stage prothrombin time of a 1 in 10 and a 1 in 50 dilution of citrated plasma on aged human oxalate plasma Specimens of plasma were tested for factor V from patients fed low fat low fat plus oil and high fat diets

Factor VII—This was measured in plasma and serum by the method of Koller et al (1951) The same serum specimens were tested for factor VII as were tested in the thromboplastin generation test

Accelerated one stage prothrombin times (stypven time)—Russell viper venom ('Stypven') was used diluted 1 in 20,000 Equal volumes of fast spun plasma (or plasma diluted 1 in 4 with 0 85% saline) saline, stypven and M/40 calcium were incubated and the coagulation time recorded The calcium was added a minute after the stypven had been mixed with the plasma A separate bottle of stypven (with the same batch number) was diluted for the fasting and postprandial experiments because the diluted stypven appeared to lose potency even if stored at 4°C All tests were done in duplicate

All coagulation tests were carried out at 37°C Coagulation-times were recorded by technicians who were, as far as possible ignorant of the results which might be expected for any particular test For any test on any one patient, the fasting and later specimens were both tested by the same technician

Statistical Analysis

The significance of change in the coagulability of the blood was estimated with Student's t test and a level of probability assigned to the results for each experiment and each method of estimation of coagulability This significance was measured in two ways

(1) Each series was regarded as a single experiment of paired observations and a single value for each patient obtained for the difference between the fasting and postprandial blood samples t was then calculated from the formula

$$t = \bar{x}\sqrt{\frac{n(n-1)}{\Sigma x^2 - \frac{(\Sigma x)^2}{n}}}$$

where Σx is the sum of the values for the differences between fasting and postprandial blood in each patient, n the number of paired observations, and $\bar{x}$ the mean difference—$\bar{x} = \frac{1}{n}\Sigma x$

From this value for t a significance level was obtained (designated P_1) which indicates the probability that the mean of the differences is not significantly different from zero

(2) The mean differences between the paired observations for patients fed a high fat or oil meal were compared with the mean differences for patients fed a low-fat meal A value for t was calculated using the formula

$$t = \frac{\bar{x}_1 - \bar{x}_2}{\sqrt{\frac{(S_1)^2}{n} - \frac{(S_2)^2}{n_2}}}$$

where $\bar{x}_1$ is the mean difference in the high-fat or oil series and $\bar{x}_2$ the mean difference in the low fat-series, and S_1 and S_2 the respective variance of the series indicated by the subscript

From this value for t a significance level was obtained (designated P_2) which indicates the probability that the differences in the high-fat or oil series are drawn from the same population of differences encountered in the low-fat series This seemed a valid comparison to draw as there was no obvious sampling bias in allotting the type of meal to each patient

P_2 then takes into account any effects of a control meal and the variance of a controlled series of observations It is a more stringent test of significance and may allow for a large number of otherwise uncontrolled circumstances It may be argued that where the control series of preprandial and postprandial samples have not been shown to differ significantly they should be ignored This is a valid argument and for this reason we have quoted both P_1 and P_2

A value for P of less than 0 05 has been selected as a minimal significance level

TABLE I—LEE AND WHITE COAGULATION TIME OF WHOLE BLOOD IN SILICONE TUBES (MIN) IN 12 TESTS OF THE LOW FAT AND OIL SERIES AND IN 14 OF THE HIGH FAT SERIES THE MEAN OF 20 TUBES WAS TAKEN AS THE COAGULATION TIME IN ALL OTHER TESTS 6 TUBES WERE USED

Diet	Low fat		Oil		High fat	
No of patients	37		38		39	
	Fasting	4 hours	Fasting	4 hours	Fasting	4 hours
Mean	34 9	34 0	34 3	30 [illegible]	34 4	3[illegible]
P_1	> 0 4		< 0 01		> 0 4	
P_2			> 0 1		> 0 3	

TABLE II—COAGULATION-TIME OF RECALCIFIED PLASMA SLOW-SPUN IN GLASS TUBES (SEC)

Diet	Low fat		Oil		High fat	
No of patients	25		26		25	
	Fasting	4 hours	Fasting	4 hours	Fasting	4 hours
Mean	154 0	142 2	145 8	149 8	150 9	141 8
P_1	> 0 05		0 5		0 2	
P_2			>0 05 (increase)		> 0 7	

Results

Lee and White coagulation-time—The results of this test are shown in table I The changes produced by oil appear to be significant on their own (P_1), but P_2 for oil is not significant

Calcium-time of plasma (tables II–IV)—No significant changes are seen in the low-fat or high-fat series The oil seemed to cause a lengthening of the calcium-time when measured on plasma fast spun in silicone tubes This was in marked contrast to the apparent shortening caused by the oil in the Lee and White test

TABLE III—COAGULATION TIME OF RECALCIFIED PLASMA FAST SPUN IN SILICONE TUBES (SEC)

Diet	Low fat		Oil		High fat	
No of patients	21		20		21	
	Fasting	4 hours	Fasting	4 hours	Fasting	4 hours
Mean	302 0	280 1	315 2	363 2	287 3	302 9
P_1	0 3		0 02 (increase)		0 6	
P_2			< 0 02 (increase)		> 0 2	

Prothrombin consumption (tables V and VI)—The amount of residual prothrombin is high in all these tests Lipæmic plasma does not appear to consume more prothrombin during coagulation than the control specimens

Thrombin generation in silicone tubes (table VII)—The means of all tests have been combined in fig 1 No significant differences are to be seen in either of the series tested

TABLE IV—COAGULATION TIME OF RECALCIFIED PLASMA SUPER SPUN IN GLASS TUBES IN 12 TESTS OF THE LOW FAT AND OIL SERIES AND IN 14 OF THE HIGH FAT SERIES, THE MEAN OF 16 TUBES WAS TAKEN AS THE COAGULATION-TIME IN ALL OTHER TESTS 4 TUBES WERE USED

Diet	Low fat		Oil		High fat	
No of patients	37		38		39	
	Fasting	4 hours	Fasting	4 hours	Fasting	4 hours
Mean	247 6	257 7	253 2	232 2	259 4	247 9
P_1	0 4		> 0 05		> 0 9	
P			> 0 05		> 0 1	

Blood thromboplastin generation—No difference in activity in this test could be demonstrated between platelets, Al(OH)$_3$-treated plasma, or serum derived from either fasting or lipæmic blood

Factor V—No significant differences were found in factor-V activity in the three groups of patients tested

Factor VII—No significant differences were found in factor VII activity in the two groups of patients tested

Stypven times (table VIII)—P_1 was significant with the high fat diet, using both diluted and undiluted plasma, and with oil when using diluted plasma When P_2 was considered, both high fat and oil were significant in diluted plasma but not in undiluted plasma Not only were the final results significant but there was considerable consistency in the results, the lipæmic (fat or oil) plasma having almost invariably a shorter stypven time than the fasting plasma These consistent results were in marked contrast to the inconsistent and highly variable results obtained in all the other tests used in this series of investigations

Discussion

Our results do not confirm the claims that feeding of mixed animal and vegetable fats accelerates coagulation Inconsistent results were obtained with all the tests used except when the stypven-time was measured

TABLE V—PROTHROMBIN CONSUMPTION INDEX OF WHOLE BLOOD CLOTTED IN SILICONE TUBES

Diet	Low fat		Oil		High fat	
No of patients	7		7		14	
	Fasting	4 hours	Fasting	4 hours	Fasting	4 hours
Mean	60 0	75 9	67 6	78 0	50 1	77 3

Some authors assess the results of all these coagulation tests in percentage of normal and speak of "overall coagulability" This would presumably mean adding the effect of fat or oil in the stypven-time test (where the results appear to be significant), to all the others (where the results are generally not significant) This, in our view, would confuse the results and add nothing of value

Our choice of a "lipæmic" specimen four hours after the ingestion of fat may not have measured the greatest degree of the effect of fat and hourly specimens might have revealed a change in coagulation But a large number of four-hour plasma samples were grossly lipæmic, and the coagulation tests in these were little different from those which were not obviously grossly lipæmic (Both Fullerton et al. (1953) and O'Brien (1955) claimed to have shown acceleration of coagulation at this time after food) Choice of a four-hour specimen cannot, we think, account for our failure to demonstrate changes in blood coagulation after fat ingestion

TABLE VI—PROTHROMBIN CONSUMPTION INDEX OF RECALCIFIED PLASMA SUPER SPUN IN GLASS TUBES

Diet	Low fat		High fat	
No of patients	14		15	
	Fasting	4 hours	Fasting	4 hours
Mean	64 5	76 8	66 6	60 7
P_1	> 0 1		> 0·3	
P_2			> 0 05	

All our tests were done on patients in hospital Many other workers have used healthy people We cannot deny the possibility that this is the reason for our failure to demonstrate an effect on coagulation, but we think it very unlikely We took care to concentrate on con

TABLE VII—THROMBIN GENERATION TEST OF RECALCIFIED PLASMA FAST SPUN IN SILICONE TUBES

Diet	Thrombin generation time (min)				Fibrinogen time (sec)			
	Low fat		High fat		Low fat		High fat	
No of patients	11		12		11		12	
	Fasting	4 hours	Fasting	4 hours	Fasting	4 hours	Fasting	4 hours
Mean	12 4	14 1	13 8	13 8	55 0	50 8	51 8	47 4
P_1	0 3		> 0 9		0 4		0 2	
P_2			> 0 3				> 0 9	

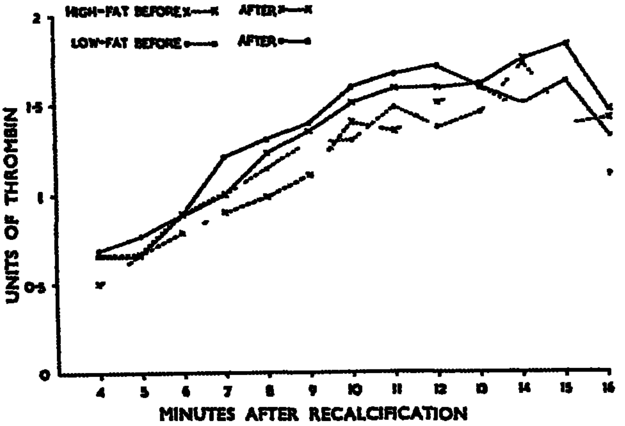

Fig 1—Thrombin generation in silicone tubes. This figure represents the means of all tests in each series The fibrinogen-time is represented by the amount of thrombin generated at the highest point of the curve The thrombin generation time is the time that has elapsed from recalcification to this point of the curve

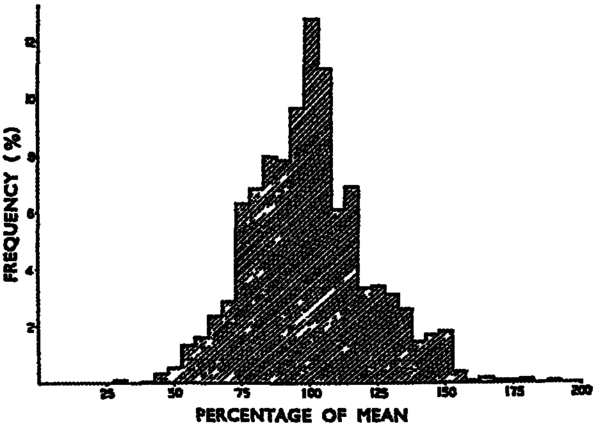

Fig 2—Lee and White coagulation-time in silicone tubes histogram of 1520 individual tube readings The 20 tubes used in each test have each been expressed as a percentage of the mean for that test The scatter is very wide

valescent patients and to avoid patients whose diseases were known to be associated with abnormal coagulation or a bleeding state It could even be argued that it is more important to know whether fat accelerates coagulation in people who are sick than whether it does so in those who are well.

TABLE VIII—ACCELERATED ONE STAGE PROTHROMBIN-TIMES (STYPVEN TIME) OF PLASMA FAST SPUN IN SILICONE TUBES

Plasma	Diet	Low fat		Oil		High fat	
	No of patients	21		22		22	
		Fasting	4 hours	Fasting	4 hours	Fasting	4 hours
Undiluted	Mean	28 5	27 9	29 5	29 6	28 8	25 9
	P₁	> 0 5		> 0 9		0 01	
	P₂			> 0 6		> 0 05	
Diluted	Mean	47 1	46 4	46 7	40 6	44 4	38 3
	P₁	> 0 6		< 0 01		< 0 01	
	P₂			0 02		0 05	

(Excluding table VIII for the moment, it will be seen that there are no significant changes after a low-fat or a high-fat meal) The oil appears to shorten the clotting-time in the Lee and White test (table I) and to lengthen it in a calcium-time test (table III), while another variant of the calcium-time test shows no significant alteration (Both fat and oil shorten the one stage prothrombin time with stypven (table VIII)

Very few authors emphasise the uncontrolled variables in these coagulation tests Even different tubes in the same test can give widely differing results Many authorities advocate the use of 3 or 4 tubes in the test and tilt the 3rd or 4th tube only when the 1st and 2nd tilted tubes have coagulated When this technique is used, blood in an untilted tube is occasionally found to have clotted by the time the tube is first tilted No acceptable end point would then be available The error due to differences in individual tubes can be minimised by the use of 20 tubes in the test The mean of these 20 tubes could then be taken as the best available estimate of the true coagulation-time The degree of scatter is shown in fig 2, where representative examples are shown of three types of result which have been encountered with about equal frequency

Fig 3 was derived from 76 such tests (1520 tubes), each tube reading being expressed as a percentage of the mean Only 26% of these tube readings fell with ± 5% of the apparent true mean Somewhat similar observations can be made for readings of calcium-time Thus it would appear at first glance that the insensitivity of the technique used would be the major obstacle in assessing the effects of food on the coagulation-time Through the kindness of Mr J N Darroch, of the department of mathematics of the University of Cape Town, we have been able to obtain a more detailed statistical analysis of the experiments where 20 tubes were used in the Lee and White test and 16 in the *calcium time test His conclusions can be summarised as follows* *

Analysis of variance shows that the random variation in clotting time between blood samples (by which is meant the residual variation when systematic changes from fasting to postprandial and from patient to patient have both been subtracted) is overwhelmingly larger than it would be if it arose simply from the variation within samples, that is from the insensitivity of the measuring technique For the Lee and White coagulation time it is 12 times larger and for the calcium time 23 times larger This completely contradicts one's first impression that the variation of readings within a sample is so large (coefficient of variation is 22% for the Lee and White coagulation time and 17% for the calcium time) as to destroy any possibility of detecting any systematic

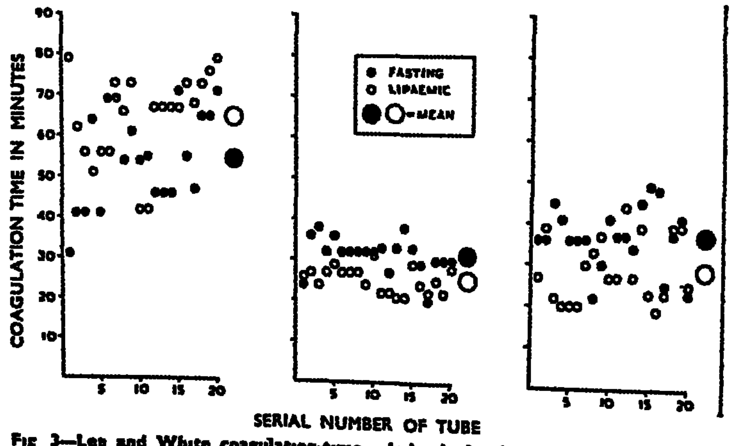

Fig 3—Lee and White coagulation-time Individual tube readings in 3 patients before and after a high-fat meal The three diagrams represent widest scatter, least scatter, and intermediate scatter The means are also shown

changes in clotting time It now appears that the spread of readings within samples is having far less effect on the experiment than the uncontrolled variability between samples

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* A full copy of the statistical analysis may be had in mimeographed form from the office of THE LANCET, 7, Adam Street, London, W C 2

It is suggested that this latter variability may be accounted for in one (or both) of two ways Firstly, that some artificial shortening of clotting time is introduced when the sample is taken from the patient, and that this randomly affects some samples more than others Secondly, that blood within a person has a clotting time which randomly alters at different times to such an extent as to overshadow any change resulting directly from the content of a meal

To us it seems that the most significant variable is the degree of perfection of the venepuncture Technically imperfect venepunctures were always discarded But there are unavoidable variations in what we regard as being acceptable for the purposes of the test The time of the day, the weather, the taking of a meal as distinct from its fat content, and other variables too numerous to mention might also be implicated Because of what has been said above and because of all these, we feel that we have been unable to show that fat materially alters blood coagulation when this is measured by the Lee and White or calcium time tests

Thrombin Generation Test

To obtain significant results with this test O'Brien (1955) found it essential to use platelet poor plasma collected in silicone tubes In this artificial system the generation of thrombin is slow, so it is not surprising that the plateau of thrombin generation is broad This has been clearly shown by Pitney and Dacie (1953) and is obvious from fig 1 It will be seen that very little thrombin is produced Differences of 5–10 seconds at these levels represent only infinitesimal amounts of thrombin Yet it is these differences that have to be used in this test to assess the effects of fat on coagulation

We have also obtained negative results with tests which measure prothrombin consumption and thromboplastin generation Our negative results with these tests confirm the findings of Manning and Walford (1954) and Hall (1956b) Only the results with stypven were consistent and reproducible

We feel that the results of tests where fat is added in vitro should be distinguished from those where fat is added in vivo

It is not difficult to show that fat added in vitro affects coagulation Poole (1955) showed that fat shortened the coagulation time It has been shown that cream can abolish the prothrombin consumption defect of recalcified platelet poor plasma (Merskey 1956) Macfarlane et al (1941) demonstrated that cream could shorten the stypven time But none of these in vitro tests should be regarded as proving an effect of alimentary lipæmia on coagulation

In our hands the shortening of the stypven time after a fatty meal is the only test which has given positive results We agree with Fullerton et al (1953) when they say that these findings "could not be interpreted as indicating that a real increase in coagulability occurs during lipæmia The inference that naturally occurring thromboplastin is influenced by lipæmia in a manner similar to viper venom is not justified" Hall (1956a) put the matter into a different perspective when he showed that the acceleration of the stypven-time was important only in the absence of platelets, and that fat merely returned the lengthened stypven-time to what it had been before the platelets were removed In other words no real additive effect has been demonstrated It is, of course, conceivable that areas of the circulation exist where platelets are filtered off in some way, and in such areas alimentary lipid might be important But this is pure speculation Our findings with stypven confirm the report of O'Brien (1956) and are opposed to the conclusions of Maclagan and Billimoria (1956) The latter showed, by in-vitro tests, that only a group of phospholipids found almost exclusively in milk products were important Mutton and beef fat, egg yolk, olive oil, and cod liver oil were inactive This once again demonstrates the differing conclusions which can be reached by the use of in-vivo and in-vitro tests and by varying the circumstances under which the tests are done

Recently fats containing large amounts of unsaturated fatty acids have been used to lower the serum cholesterol The stypven-time results mentioned above appear to be almost as applicable to fats containing small or large amounts of unsaturated fatty acids It could thus be claimed that unsaturated fatty acids are as dangerous as regards coagulation as saturated fatty acids In view of our negative results with all the other tests we have used, the evidence at present seems insufficient to indict either variety of fat as a cause of accelerated coagulation

Summary and Conclusions

An attempt was made to confirm the claim that feeding mixed animal fat shortens the coagulation-time of blood, and at the same time to determine the effect of feeding fat rich in unsaturated fatty acids

Patients were fed three types of meal—low fat, low fat plus salad oil, and high-fat Coagulation times were estimated in each series before the meal and four hours after

The tests which were done included coagulation time of whole blood in silicone tubes, calcium time of plasma with varying numbers of platelets, thrombin generation test, blood thromboplastin generation test, prothrombin consumption, and accelerated one stage prothrombin time (stypven time)

With the exception of the stypven-time, neither the high-fat nor the low-fat meal produced any significant change in coagulation The oil meal (when considered without comparison with the low fat meal) produced significant shortening of coagulation in the Lee and White test and inconsistent results with the calcium time test If these changes were considered together with those produced by the low fat meal, almost all these differences fell away

The stypven-time was significantly shorter in both the oil and high-fat series when diluted plasma was used, and in the high fat series when undiluted plasma was used Undiluted plasma was not significantly affected by oil

Variables have to be considered as arising in the patient and unrelated to the fat content of diet, during venepuncture, and during the measurement of coagulation time These are all very large but the first two are far more important than the third

The measurement of the stypven time is affected by the presence of fat in the plasma This is true of both saturated and unsaturated fat The importance of this in clinical medicine remains to be fully evaluated

We have to acknowledge the large amount of assistance we have received in this study To Prof J F Brock and Prof F Forman, in whose department this work was carried out To laboratory technicians Miss J Ethelston, B SC, Miss E Scholtz, B SC, Miss L Kaplan, Miss C Hoberman Miss S Tromp, Miss B Factor, and Mr M Boshof for much patient work To Dr E B Dowdle and Mr J N Darroch for considerable assistance with statistical analysis To Dr D McKenzie for laboratory facilities To the staff research fund of the University of Cape Town and to the South African Council for Scientific and Industrial Research for grants towards expenses To the many patients who volunteered for the feeding experiments To the Superintendent, Groote Schuur Hospital, for facilities

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GLUCOSE-6-PHOSPHATASE ACTIVITY IN HUMAN DIABETES

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THE activity of glucose-6-phosphatase, which catalyses the conversion of glucose-6-phosphate to free glucose in the liver, is affected by various physiological and pathological conditions

In certain types of glycogen storage disease there is a deficiency of this enzyme (Cori and Cori 1952)

Fasting increases its activity in rats (Weber and Cantero 1954)

Ashmore et al (1956b) have published an extensive account of the changes in its activity as a result of fasting and of treatment with various hormones

Langdon and Weakley (1955) demonstrated an increase in its activity in alloxan diabetic rats

In view of these reports the activity of this enzyme in human diabetes before and after therapy was investigated * Hitherto little work of this type had been done on man, partly because of the necessity of using micro techniques for assaying the enzyme in liver-biopsy material

Clinical Material

13 patients (10 males and 3 females) admitted to the University College Hospital of the West Indies with diabetes were investigated On admission all were placed on a diet, but further treatment was withheld until numerous investigations, including liver biopsy, had been made After stabilisation of the diabetes the investigations were repeated

2 female patients had "J"-type diabetes (Hugh-Jones 1955)—i e, they differed from the usual young acute diabetic mainly in that they were insulin-resistant They were aged 17 and 21 and had been diabetic for four and five years respectively Both were poorly controlled in spite of several hospital admissions and the outpatient administration of up to 160 and 260 units a day of insulin zinc suspension (I Z S) Hospital supervision during the admission under consideration led to the stabilisation of both patients on 120 units of I Z S a day while taking the type of diet that they would receive at home

3 patients (1 female aged 16 and 2 males aged 36 and 70) had diabetes of short duration—3 weeks, 5 months, and 5 days—and were insulin-sensitive 2 were moderately ketotic on admission These 3 patients could be grouped as type-I diabetes according to the classification of Bornstein and Lawrence (1951)

8 males were considered to have type-II diabetes The type-II patient of Bornstein and Lawrence (1951)—middle-aged, obese, insulin-resistant, and not liable to ketosis—is less common in Jamaica than the non-obese middle-aged diabetic Most of the middle-aged insulin-resistant patients admitted to hospital have never been overweight and when first seen are often well below their ideal weight (Tulloch et al 1956) All 8 patients in this series were underweight. only 2 had ever been obese, 2 had once been of average weight, and 4 had always been below their ideal weight Their ages ranged from 48 to 73, and the duration of their diabetic symptoms from 6 weeks to 5 years All were treated with diet 6 received insulin, and the daily dose at the time of their discharge ranged from 0 to 110 units of I Z S 2 patients were given carbutamide by mouth Both required large doses, 8 and 10 g a day respectively, to achieve adequate reduction of their blood-sugar levels and, after the liver biopsy and other investigations had been repeated, both were transferred to treatment with I Z S before their discharge

7 non-diabetic patients submitted to liver biopsy for other reasons were also investigated

Biochemical Methods

The liver biopsies were made in each case at about 9 A M while the patients were still fasting A Vim Silverman needle was used

The excised liver tissue was immediately placed in a small tube and frozen in solid carbon dioxide Experiments with rat liver had shown that this treatment had no significant effect on the enzyme activity (Patrick 1956) The method used for assay of the enzyme was a micro modification of that described by Langdon and Weakley (1955)

TABLE I—GLUCOSE-6 PHOSPHATASE ACTIVITY IN LIVER OF DIABETICS

Case no	Type of diabetes	Therapy	Glucose 6 phosphatase activity (units)*	
			Before therapy	After therapy
1	I	Insulin	0 397	0 141
2	I	Insulin	0 316	0 157
3	I	Insulin	0 286	0 191
4	J	Insulin	0 295	0 200
5	J	Insulin	0 221	0 157
6	II	Insulin	0 355	0 183
7	II	Insulin	0 175	0 146
8	II	Insulin	0 209	0 150
9	II	Insulin	0 354	0 214
10	II	Insulin	0 252	0 208
11	II	Insulin	0 201	0 172
12	II	Carbutamide	0 235	0 175
13	II	Carbutamide	0 233	0 178

* 1 unit of glucose 6 phosphatase is equivalent to 1 micromole of inorganic phosphate liberated per mg of liver nitrogen a minute

3–5 mg of the biopsy material was quickly weighed on a micro balance with a sensitivity of ±0 02 mg The liver was then homogenised in 120 µl of citrate buffer solution at pH 6 5 Several experiments had indicated that pH 6 5 is at or near the optimal pH for glucose 6 phosphatase activity as it occurs in the human liver Duplicate 20 µl amounts of the homogenate were removed for determination of nitrogen content, and duplicate 10 µl amounts of the homogenate were used for the enzyme assay The reagents were measured with micropipettes of the types described by Bessey et al. (1946)

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* Since the investigation was begun reduction of glucose 6 phosphatase activity by carbutamide has been demonstrated in liver homogenates in vitro and in laboratory animals (Ashmore et al 1956a Hawkins et al 1956) The dosage used however, far exceeded the therapeutic dosage in man

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The final concentrations of the reagents in the enzyme assay were

Liver	1–2%
Glucose 6 phosphate	0 02M
Citrate buffer pH 6 5	0 09M

The enzyme tubes were incubated for 30 minutes at 37°C, and the reaction was terminated by the addition of an equal volume of 10% trichloracetic acid

Inorganic phosphate was determined by a micro modification of the method of Taussky and Shorr (1953) which uses ammonium molybdate, ferrous ammonium sulphate as reducing agent, and a Beckman spectrophotometer fitted with the micro attachment described by Lowry et al (1945)

The amount of nitrogen in the homogenate was determined by Kjeldahl digestion followed by ammonia determination using micro Conway units as described by Kirk (1950)

Results

The results are expressed as micromoles of inorganic phosphate liberated each minute per mg of liver nitrogen Experiments with rat and human liver tissue had shown that the liberation of inorganic phosphate was proportional (within the limits of experimental error) to the concentration of enzyme and to time

Table I summarises the results obtained in the 13 diabetics The average enzyme activity in the whole group was 0 271 units before therapy and 0 175 units after therapy, whereas in 7 non-diabetic patients it was 0 155 units Results obtained for enzymic activity of duplicate amounts of the same homogenate showed consistent agreement to within ±1% It was impossible to compare enzyme activities in duplicate biopsy specimens obtained from different sites in the same human liver, but this was done in rat's liver, and it was found that the results were in agreement to within ±5% (table II)

TABLE II—GLUCOSE 6 PHOSPHATASE ACTIVITY IN BIOPSY SPECIMENS FROM DIFFERENT LOBES OF LIVER OF RATS ON NORMAL DIET

Rat no	Glucose 6 phosphatase activity (units)*	
	Left lateral lobe	Median lobe
1	0 200	0 202
2	0 215	0 228
3	0 190	0 214
4	0 216	0 228
5	0 224	0 227
6	0 292	0 307
7	0 341	0 323
8	0 370	0 370
Mean	0 256	0 262

* Units as in table I

Summary

There is increased activity of glucose 6 phosphatase in the liver of diabetics compared with non diabetics

Stabilisation of the diabetes was followed by decreased activity of the enzyme in 13 patients, whether the diabetes was type I, II, or J, and whether insulin or carbutamide had been administered

We are indebted to Dr R A Irvine for the liver biopsies

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PANCREATIC NECROSIS IN CORTISONE-TREATED CHILDREN

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NECROSIS of the pancreas and of peripancreatic fat tissue occurs only very rarely in childhood In the present two cases it was probably the result of cortisone therapy

Case-reports

Case 1 —A girl, aged 11 years, was admitted to the Children's Hospital, Birmingham, on May 24, 1955, under the care of Dr J W Gerrard From the age of 1 year she had had frequent severe attacks of asthma, which a course of cortisone, started in January, 1955, much improved Early in May, 1955, she came from Eire to Birmingham, and within a few days her supply of cortisone ran out During the next fortnight the attacks of asthma recurred, and on admission she was in a severe attack, cyanosed, wheezing, and dyspnœic

Treatment and Progress

This attack responded to aminophylline and ephedrine, but she had further attacks during the next few days Despite repeated injections of adrenaline and aminophylline and a course of aureomycin (chlortetracycline) the attacks became more severe On June 1 it was decided to start cortisone again, and at 3 P M she was given the first dose (25 mg by mouth) For the next five hours she appeared well, but at 8 30 P M she suddenly became deeply cyanosed and dyspnœic and died within five minutes This final episode differed from her attacks of asthma in that there was only very slight wheezing

Necropsy

A normally developed, well nourished girl with slight clubbing of fingers and toes, a pigeon chest deformity, and slight pitting œdema of feet and legs

The *lungs* were extremely emphysematous, particularly the upper lobes, and thick yellowish exudate was present in the small bronchi The tracheobronchial lymph nodes were swollen, dark red, and soft The *heart* (187 g) showed eccentric hypertrophy of the right ventricle The *liver* (990 g) was congested The *pancreas* was dark red, with darker blackish red spots, and extremely soft On the cut surfaces no lobular structure was discernible The spleen (95 g) was soft, with diffluent pulp The *suprarenal glands* were thin, the right depleted of lipids One *parathyroid gland* was enlarged (8 mm in longest diameter)

Histology

The *lungs* showed congestion and œdema , there was a very occasional small monocytic peribronchial infiltrate, but eosinophils were absent Some alveoli were lined by a pale eosinophil hyaline membrane The *liver* showed mild acute congestion The *kidneys* were congested, showing occasional cortical cysts (150 μ in diameter) and cloudy swelling of the proximal convoluted tubules

One *suprarenal* was 3 mm thick The zona glomerulosa showed œdema of interstitium , the zona fasciculata and zona reticularis were almost completely replaced by irregularly arranged spherical and polyhedric cells with a vesicular nucleus and an abundant cytoplasm filled partly with pale eosinophil granules, partly with vacuoles This zone resembled more the transient cortex or the hyperplastic cortex of adrenogenital syndrome than a normal permanent cortex The medulla was well developed and appeared normal The other suprarenal was 1 25 mm thick, with similar structure

Pancreas —Extensive areas of pancreatic tissue showed necrosis and necrobiosis In the most severely affected areas the secretory cells were anuclear, shrunk, pale, basophilic, and recognisable only by their outlines against distended capillaries, which were filled with clumped masses of red blood cells (fig 1) In other areas the cells were dissociated, without acinar arrangement, and they were shrunk, their cytoplasm

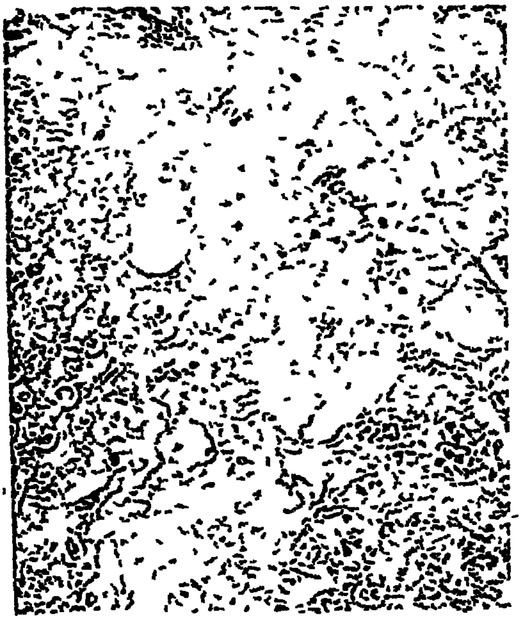

Fig 1—Case 1 pancreas (Hæmatoxylin and eosin ×150.)

homogenised and eosinophilic, and their nuclei pyknotic. The necrotic and necrobiotic process affected equally the secretory tissue, the islets of Langerhans, and the vascular system. The walls of arteries and arterioles were hyalinised or necrotic, and hæmorrhages were seen around necrotic arteries. Where the necrosis affected the periphery of a lobule, the whole interlobular tissue appeared as an anuclear mass of eosinophilic fibres and altered red blood cells, with many clefts and pseudocystic spaces; only the nerve bundles appeared resistant to the necrotising process. Hæmosiderotic pigment was absent. All intrapancreatic and immediate peri-pancreatic fat tissue was necrotic (fig. 2).

One *parathyroid* measured 4·00 × 1·75 mm.; another had a diameter of 1·2 mm.; their structure was normal. There were a few follicular cysts in the *ovaries*, and occasional cytomegalic inclusions in the *parotid gland*. The *pituitary* was unfortunately lost.

Case 2.—A boy was first seen by one of us (O. H. W.) in October, 1955, when he was aged 2 years and 10 months. He had developed normally until a month previously, when his parents noticed that his legs were becoming weak; he also had severe constipation. No definitely abnormal signs were discovered, but during the next three weeks the weakness increased so rapidly that he could not sit or stand without support; his voice became nasal, and food regurgitated down his nose. On Nov. 3, 1955, he was admitted to the Children's Hospital, Birmingham.

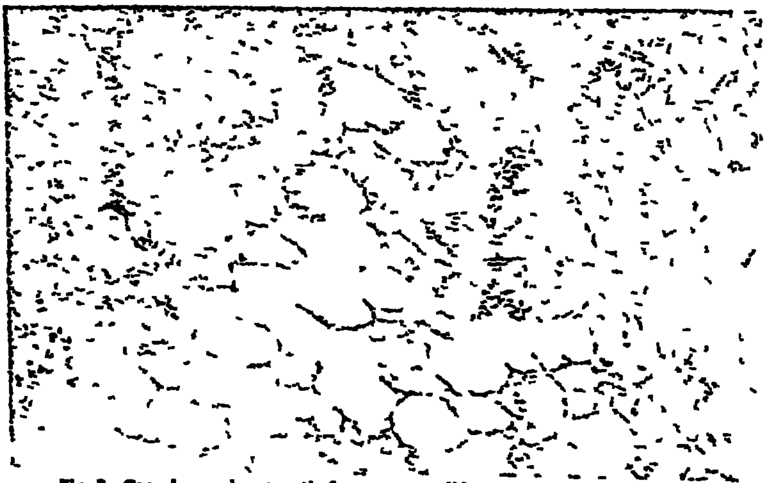

Fig 2—Case 1 peripancreatic fat-necrosis (Hæmatoxylin and eosin ×80.)

Examination

There was now definite weakness of all muscles of his limbs, trunk, face, and palate. The tendon reflexes were present but diminished, the plantar reflexes being flexor. Sensation was unimpaired. The skin was normal. The cerebrospinal fluid was normal. White cells in the blood numbered 14,500 per c.mm. (polymorphs 62%). Urinary excretion of creatine was high, with a creatine coefficient of 12·6 (normal for age 7·9). Radiographs of skull, abdomen, and chest, examination of urine for porphyrins, and electro-encephalography gave normal results.

Treatment and Progress

During the next fortnight the weakness progressed rapidly: the limb muscles became abnormally firm and passive movements of knees and hips became restricted. He developed great difficulty in swallowing and had to be tube fed; simultaneously his respiratory muscles became weaker, and he showed cyanosis. At this stage a diagnosis of polymyositis was made and on Nov. 17 treatment with cortisone 25 mg.

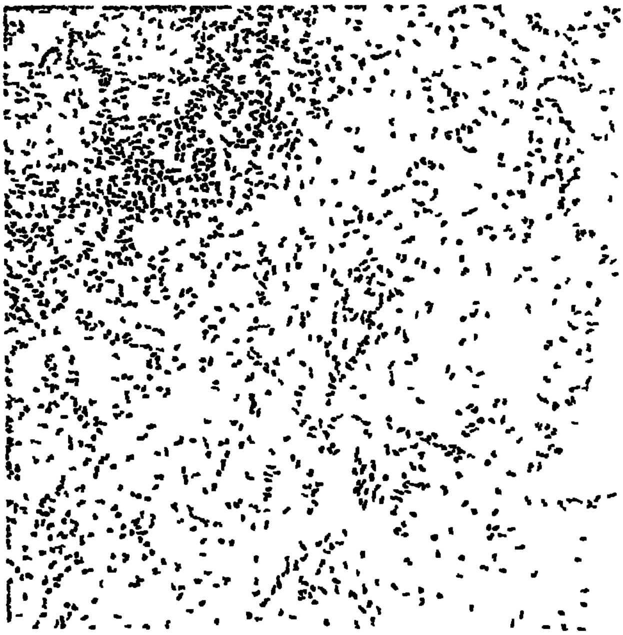

Fig 3—Case 2 pancreatic necrosis with cellular infiltration and deposits of calcium (Van Gieson and elastic-tissue stains ×80.)

thrice daily was started. During the next few days the improvement in respiration and swallowing was dramatic, but on Nov. 28 signs of congestive heart failure appeared. The electrocardiogram was normal. Treatment with digoxin, mersalyl, salt-free diet, and penicillin relieved the heart failure. From Dec. 12 prednisolone (5 mg. four times daily) was given instead of cortisone.

The initial spectacular improvement with corticoids was not maintained, despite physiotherapy; fibrous contractures of hips and knees and an equinus deformity of the ankles developed. Repeated severe infections of the respiratory tract necessitated several courses of antibiotics, and in March, 1956, he developed thrush stomatitis. At this stage skin changes were first noted: areas of brown pigmentation on the extensor aspects of the forearms; reddening of the skin on the cheeks; over the back and the dorsum of the feet the skin was shiny and tightly stretched; and several areas of alopecia developed. There was much skin irritation. A firm diagnosis of dermatomyositis was now made and on March 19 he was discharged home, where he continued to receive prednisolone (5 mg. thrice daily). During the next five months his condition remained almost stationary.

Readmission

On Aug 13 he was readmitted For twenty four hours he had had abdominal pain and vomiting His condition was very poor, temperature 102°F His abdomen was distended, and a round mass was palpable in the midline below the costal margin, it extended about four finger breadths below the xiphoid process The white cell count was 20,000 per c mm (polymorphs 74%) Radiography of the chest showed a small area of consolidation in the posterior basal segment of the left lower lobe After screening, Dr R Astley reported "Normal movements of the diaphragm The upper abdominal mass shows a rounded lower border on the right Its margin appears to run into that of the liver There is no indication of its nature" A blood culture was sterile The vomitus contained altered blood The urine contained sugar during the first twenty-four hours after admission His bad condition contra indicated laparotomy The pneumonia was treated with tetracycline, but the pyrexia continued Ten days later the dose of prednisolone was increased to 5 mg four times daily Within forty eight hours the pyrexia abated, the abdomen became less distended, and the mass decreased and became impalpable Radiography of the chest on Aug 28 showed resolution of the consolidation. The boy was discharged home on Aug 30

Further Readmission

On Sept 15, 1956, he was again admitted, having had abdominal pain and distension and vomiting for twenty four hours The physical findings were essentially the same as at the time of the previous admission Within a few hours he had another vomit, became deeply cyanosed, and died six hours after the last dose of prednisolone

Necropsy

An extremely wasted boy, normal in height for his age, with hips and knees fixed in half flexed position The *skin* was thin with pale brownish macules on the extensor surface of both arms The *lungs* were congested, the *heart* weighed 83 g and appeared normal The *abdominal cavity* contained about 20 ml of clear pale brown fluid The whole epigastrium was filled by a firm mass partly yellowish white and partly white, surrounding the pancreas and the spleen After separation from the liver a plum sized cavity was exposed within the mass which was filled with diffluent material The mass was attached to the stomach, but nowhere was there a communication with the lumen of the stomach, and the gastric mucosa was normal The *pancreas* was embedded in the main mass, it was in some parts hard, in others very soft, the cut surfaces, in which no lobular structure was discernible, had a variegated appearance, with pink, red, yellowish, and white areas The *liver* weighed 870 g and showed severe fatty changes The *spleen* was enlarged (70 g) The left *adrenal gland* was extremely atrophic, discernible as a thin leaf within pale yellow hard fat tissue On the right side a firm pale yellowish-white pad was seen which had the shape of the adrenal but within which only fat tissue was discernible There was œdema of the *brain*

Histology

The *liver* showed severe fatty changes and abundant glycogen granules in the liver cells, round-cell infiltration, and some fibroblastic proliferation in the periportal spaces In the *spleen* the red pulp was studded with numerous nests which consisted of 6–20 spherical or ovoid cells 14–26 µ in diameter The morphology of these cells, their staining properties, and histochemical reactions corresponded to Gaucher's disease, but in no other organ apart from the spleen were such cells seen (Their chemical analysis and histochemical study will be reported later)

Kidneys—Most of the parenchyma showed no significant changes but there were a few small foci consisting of hyaline casts in grossly distended tubules, calcium deposits, occasional hyalinisation of a glomerulus, with very occasional calcification, thickening of capillary basement membrane, and interstitial fibrosis

The left *suprarenal gland* was 1 0–1 5 mm thick its structure was normal There was extensive necrosis of the peri adrenal fat tissue The *right suprarenal* showed nothing abnormal apart from atrophy No necrosis of surrounding fat

Pancreas—The pancreatic tissue was reduced to a few small irregular lobules in which secretory cells were intact and contained zymogen granules Most of it was replaced by necrotic, fibrillary, or granular faintly eosinophilic masses, patches of polymorphs, nuclear debris, and granular calcium deposits (fig 3) Here the islets of Langerhans were affected by the necrotising process to the same extent as the secretory tissue Capillaries were not seen in the necrotic areas, and arterioles were often recognisable only by wavy rings of elastic tissue Intact red blood cells were not seen Hæmosiderin was scanty in the form of widely scattered extracellular granules Often the necrosis involved the whole arterial wall, including the elastic membrane In none of the recognisable arteries was fibrinoid demonstrable Occasionally a thrombus in organisation was seen in a not completely necrotic artery Sudanophil material was scanty, it was seen in patchy distribution in the form of extracellular drops In such areas a few anisotropic crystals with "Maltese crosses" were also seen

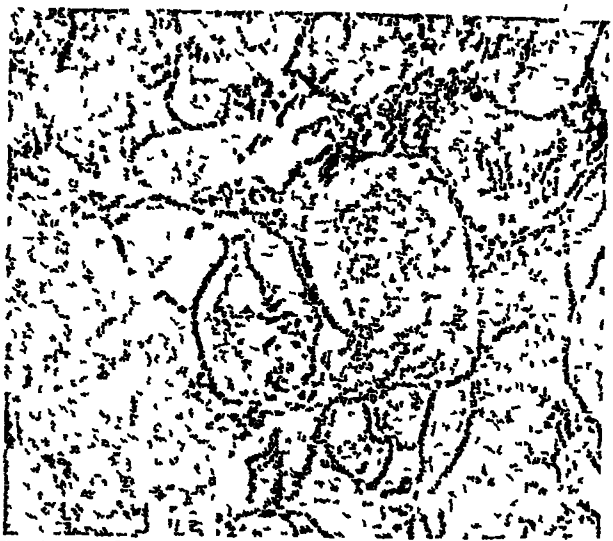

Fig 4—Case 2 necrosis of peripancreatic fat tissue (Hæmatoxylin and eosin ×80)

Peripancreatic fat tissue—All the fat cells were necrotic and replaced by irregularly outlined masses of pale eosinophilic anuclear material (fig 4) The fatty lump adherent to the left abdominal wall consisted of lobules of necrotic fat tissue with calcification, surrounded by a fibrous capsule and granulation tissue which was poor in capillaries An occasional patch of a mucoid (periodic acid Schiff positive) substance was seen within the necrotic fat tissue Cell membranes separating two or more cells were often ruptured or had disappeared, forming micro fat cysts

Pituitary—The number of basophil cells appeared to be increased, but sections from only one level were examined Those cells stained blue with azan and appeared to correspond to delta cells (Purves 1956) Some of these cells were hypertrophic and/or showed hyalinisation of the cytoplasm Such changes were best seen with the stain of Róna and Morvay (1956), and degranulation was evident in the performic acid aldehyde fuchsin stain of Russell (1956) when compared with normal controls

Muscles and skin—Further histological findings, illustrative of the effect of cortisone in dermatomyositis, will be published separately

Discussion

Pancreatic necrosis—often called acute hæmorrhagic pancreatitis—is extremely rare in childhood Gibson and Gibson (1956) collected 27 published cases of severe "hæmorrhagic pancreatitis" in childhood and added 1 of their own Most of these cases were secondary to mumps, scarlet fever, diphtheria, typhoid fever, influenza, otitis media, or trauma (Shallow and Wagner 1947, Végelhyi 1947, Shanks et al 1954), and the so called primary form, which is the common form in the adult and is often associated with gall stones, was seen only exceptionally in a child (Dobbs 1935)

The association of such an exceptional disease with corticoid therapy on two occasions already suggested a causal connection This belief was strengthened almost to certainty when, shortly after the necropsy of case 1, the reports of Stumpf and Wilens (1955) and of Stumpf et al (1956) were published

These workers found pancreatic lesions in 44 of 53 rabbits given intramuscular cortisone 3–8 mg daily for periods of twenty one to eighty one days They emphasised the similarity to early autolysis The earliest observed changes consisted of reduced basophilia of the basal portion of acinar cells This was followed by vacuolisation, shrinkage, disarrangement of acinar cells, and necrosis, with accumulation of polymorphs Peripancreatic fat necrosis was present in 13 of 44 cortisone treated rabbits with pancreatic lesions Pancreatic changes in cortisone treated rabbits have been described by Lazarus and Bencosme (1955, 1956), who consider them to be proliferating intercalated ducts, but Stumpf et al interpret them as proliferation of duct like cells within remnants of destroyed acini

If we compare the descriptions of experimental pancreatic necrosis produced by administration of cortisone with the findings in our two cases, it becomes clear that they differ only in severity, our cases being instances of acute and subacute diffuse hæmorrhagic necrosis of the pancreas associated with peripancreatic fat necrosis

In view of the wide use of cortisone therapy in a variety of diseases, and particularly the reports on beneficial effects of cortisone in "acute hæmorrhagic pancreatitis" (Brockis and Jones 1956), one is forced to assume the existence of a peculiar constitutional disposition, but its nature is obscure Although a link between our two cases is suggested by the reported association of asthma with diffuse collagen-disease (Gillespie and Potellakhoff 1951), hypersensitivity per se cannot be responsible, because allergic patients represent a considerable proportion of those treated with cortisone and no instance of association with pancreatic necrosis in man has yet been reported (One of us [H S B] tried to produce cortisone hyper sensitivity in guineapigs but with no success) In addition, only in case 1 had there been a break in cortisone treatment, with a fulminating illness when the therapy was started again, in case 2 the therapy was continuous No indication of the nature of the disposition can be found in case 1, but in case 2 the association with an isolated lipidosis of the spleen may possibly indicate the presence of an inborn metabolic error

Similarly the mechanism of cortisone-induced pancreatic necrosis can only be a matter of speculation The "reflux" mechanism described by Opie (1901) is usually considered to be the main factor in the development of pancreatic necrosis Closely related is the mechanism of stagnating secretion resulting from squamous metaplasia of duct epithelium, which Rich and Duff (1936) believe to be the principal cause Block et al (1954) produced necrosis of pancreatic tissue and peripancreatic fat-necrosis when obstruction of pancreatic ducts was combined with experimental ischæmia of the organ Thal and Brackney (1954) produced fulminating pancreatic necrosis in rabbits and goats as a local Shwartzman phenomenon when they injected endotoxins of meningococci or *Escherichia coli* into the pancreatic duct and subsequently the same endotoxin by the intravenous route Rapid diffusion of the toxin from the duct after preparatory injection led apparently to sensitisation of vascular endothelium It is not likely, however, that this mechanism operated in our two cases There was no evidence of recent infection in case 1, and, although in case 2 an abdominal mass and pneumonia were diagnosed simultaneously, the size of the mass suggested that the pancreatic disease was present already before the development of the febrile illness Equally, mechanical obstruction and epithelial metaplasia can be excluded on the basis of the necropsy findings Dietary imbalance, which is known to produce "pancreatitis," was not present

A direct toxic action exerted on the secretory tissue of the pancreas is possibly responsible for "pancreatitis" due to ethionine, carbon tetrachloride, and other compounds, but is not probable with corticoids We believe that cortisone has an effect on pancreatic secretion and that, in the presence of an unknown constitutional disposition, this causes stagnation of the secretion and pancreatic necrosis by a "reflux" mechanism

The renal changes observed in case 2 were probably related to the pancreatic necrosis They were almost identical with those described by Lynch (1954) in 4 cases of "acute hæmorrhagic pancreatitis" Unfortunately only paraffin embedded kidney tissue was examined and therefore nothing can be said about the presence or absence of fat-emboli

Both cases showed atrophy of the adrenal glands, particularly case 2, in which atrophy was associated with replacement lipomatosis The structure of the adrenal cortex was in this case normal, but the milder atrophy in case 1 was associated with gross alteration of the architecture and cellular morphology This atrophy can be attributed to the corticoid therapy From our rather limited experience with leukæmic children it appears that severe atrophy may be commoner with prednisolone The pituitary in case 2 showed changes similar to those described by Thornton (1956) in cortisone treated patients

Summary

In 2 children pancreatic necrosis followed corticoid therapy for asthma and dermatomyositis respectively

The pancreatic necrosis was apparently caused by the corticoid therapy

We wish to thank Prof J W Gerrard for the clinical notes of case 1, Mr A R Detheridge for technical assistance, and Mr J G Williamson for the photographs

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PANCREATIC NECROSIS

IN A CASE OF STILL'S DISEASE

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EXCEPT in mumps, acute disease of the pancreas is rare during childhood Dobbs (1935) collected 14 cases and added 1 of his own Jaeger (1943) summarised 10 more, including 1 that he had seen 4 further cases have since been reported (Shallow and Wagner 1947, Shanks et al 1954, Gibson and Gibson 1956 Pender 1957)

Case-record

A boy aged 5 years was admitted to our clinic in August 1955 with pain in his joints He had been well until the previous June, when he had fever with enlargement of lymph glands A month later there was pain and swelling of ankle, knee, elbow, and wrist joints

Examination

On admission, his temperature was 37 8°C, and he had pain in the legs, hands wrists, and elbows The skin and mucous membranes were pale yellow and many lymph glands were enlarged The spleen was felt at the costal margin, and the liver three finger-breadths below the ribs The knees were swollen, spindle shaped, and slightly contracted, and the ankles also spindle shaped and swollen

The erythrocyte sedimentation rate (Westergren) was 120 mm in one hour and 150 mm in two The red cell count was 2,990,000 per c mm The albumin/globulin ratio was reversed Radiography of the affected joints showed only slight decalcification The diagnosis of Still's disease was established

Treatment

Treatment started with corticotrophin (A C T H) in large doses (10 mg six hourly) because the disease was acute, and a low salt diet After two weeks, the child was much better, but lowering the dosage of corticotrophin led to deterioration

Two months after admission, the dose of corticotrophin was increased again to 40 mg daily, but the joint pains in the lower limbs increased Improvement followed intravenous infusion of corticotrophin in a 5% solution of glucose, beginning with 40 mg daily and diminishing gradually to 25 mg Later, intramuscular injections were resumed the dosage was 40 mg daily at first but was then adjusted to the boy's state

Final Illness

At the end of the fourth month he had a left sided pneumonia The temperature rose to 40°C, and the joint symptoms increased This was followed by an attack of smallpox, during which the corticotrophin was stopped for four days On the day before his death (six days after developing smallpox), his general condition was rather good and his temperature normal, but in the evening he began to complain of acute abdominal pain, and his abdomen became swollen, with rebound tenderness but no muscle resistance Next day the temperature rose to 39 8°C, he became very restless, and generalised convulsions preceded death

Post mortem Findings

Necropsy showed fat necrosis of the pancreas and greater omentum, and a subcapsular hæmorrhage in the tail of the pancreas Histologically, the pancreatic lobules were well conserved, the interlobular connective tissue contained mostly lymphocytes, but in some parts leucocytes and hæmorrhage, and necrosis of fat tissue was widespread

Comment

Pancreatic necrosis has been reported in association with lesions of the neighbouring organs (Connell 1941, Herfort 1951), acute infections (Dozzi 1946), and intoxications In childhood mumps and otitis are the commonest causes (Adams 1939) In our case the pancreatic necrosis may have been caused by Still's disease (which could produce obliterative changes in the pancreatic vessels leading to necrotic changes), by the pneumonia or smallpox, or possibly by the corticotrophin the child had been receiving

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"One of the reasons why popular discussions on psychological matters are so uninformed is perhaps the fact that psychology, being a science, uses methods and discussions of a highly technical nature In particular, it uses statistical methods, and most people have developed a strong avoidance reaction to statistics This reaction is both interesting and odd because it seems to be rather one sided A discussion of odds in horse racing, or permutations and combinations in football pools, is no less statistical for being popular and widespread, yet when the psychologist attempts to employ statistical methods in relation to serious subjects he encounters the usual obscurantist notion that you can prove anything with statistics In a sense, this is true You can 'prove' anything with statistics, but only to a person who is completely ignorant of elementary statistical notions"—H J EYSENCK, *Sense and Nonsense in Psychology* Harmondsworth, 1957, p 17

SARCOSPORES AND TOXOPLASM SEROLOGY

AN INVESTIGATION OF THEIR ALLEGED CROSS-REACTION

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EXPERIMENTAL evidence (Cathie 1957) contradicting various attacks on the specificity of the dye test and the complement fixation test for toxoplasmosis seems to show that complement fixing antigens made from animal tissues give non specific results, that much of the experimental work done on animals was not applicable to man, and that a substance contained in some sheep and other animal sera and capable of modifying toxoplasms was not the dye test antibody because it was heat labile This observation led to the recommendation that sera to be used in the dye test should be previously inactivated to avoid misleading results due to this toxoplasm hostile factor

The Sabin and Feldman (1948) dye test for toxoplasmosis consists in showing that an antibody can modify normal toxoplasms so that, on the addition of methylene blue, they do not stain For this interaction a heat-labile substance, known as accessory factor, present in normal human serum is essential

Awad (1954) claimed that sarcospores of *Sarcocystis tenella* could be used interchangeably with toxoplasms in the dye test He found that all of 6 sheep and each of 2 rabbits infected with sarcocystis gave a positive dye test with sarcospores, all of 3 guineapigs infected with toxoplasms gave a positive dye test with sarcospores, and 3 human, 3 sheep, and 2 rabbit "control" sera were negative He found further that human sera giving a positive dye test for toxoplasmosis gave the same reaction to similar titres when sarcospores were used instead of toxoplasms

The many technical considerations involved in setting up a dye test with sarcospores are not dealt with by Awad The bugbear of all dye tests, both in this country and abroad (J K Frenkel, personal communication), is the necessity for adequate supplies of antibody negative suspending serum, and the provision of this in a form suitable for using sarcospores was not discussed by Awad

We report here an attempt to repeat Awad's work

Material and Methods

Sarcospores were obtained by the kind cooperation of Mr H T Yelland, of the Islington Cattle Market, who provided us with fresh sheep gullets containing visible parasitic lesions Suspensions of sarcospores were prepared from these by the method described by Awad (1954) Since Awad did not indicate to what age sarcospores could be used, tests were made with them as soon as a suspension had been prepared from fresh gullets and up to a month later

Sarcocystis complement fixing antigen was kindly supplied by Prof P C C Garnham

Suspending serum known to be free from toxoplasm dye test antibody was obtained from the same donor who has supplied us with serum for routine dye tests for the past seven years Dye test techniques were those described by Cathie and Dudgeon (1953) and Cathie and Cecil (1954)

Human sera containing different antibody content for toxoplasms were chosen from those sent by other laboratories for routine testing

Results

Dye tests with 23 human sera of known toxoplasm-antibody content were set up with toxoplasms and sarcospores, the sarcospores being used on the day of receipt or as fresh as possible About a third of the sera contained toxoplasm antibody, but all 23 gave a positive dye test with the sarcospores (table I) 93 other human sera were therefore investigated as they came to hand, and all were found to have antibodies which modified the sarcospores used in this test

TABLE I—RESULTS OF TESTS WITH HUMAN SERA

Human sera nos	Results			
	Toxoplasm dye test with suspending serum in dilution			Sarcocystis dye test with no suspending serum in dilution 1/4
	1/4	1/8	1/16	
1	−	−	−	−
2–7	−	−	−	−
8	−	−	+	−
9	−	−	−	+
10–11	−	−	+	−
12	−	−	−	+
13–14	+	−	−	−
15	−	−	+	−
16–18	−	−	−	−
19–20	−	+	−	−
21–23	−	−	−	+

On repeating the test with sarcospores and the same 23 human sera after inactivation at 56°C for 30 minutes, all the tests had become negative, the sarcospores not being modified but staining readily with methylene-blue

Awad (1954) said he suspended the sarcospores in either saline solution or "normal human serum," and his dilutions were made in "normal human serum" All the 116 normal human sera that we have tested contained sarcospore-hostile substances which render the dye test impossible In table I, where human sera were put up with sarcospores, the sera provided their own accessory factor if such were necessary When these sera gave no modification after inactivation, it may have been either because the sarcospore-hostile factor had been removed or because accessory factor had been destroyed, but, since all the sera not inactivated contained this sarcospore-hostile factor, it was impossible to add a secondary source of accessory factor to show precisely what factor or factors, had been inactivated

TABLE II—RESULTS OF TESTS WITH GUINEAPIG SERA

Guineapig serum immunised with sarcocystis C F T antigen	Results of dye test made with sarcospores and toxoplasmosis negative suspending serum in dilution							
	1/4	1/8	1/16	1/32	1/64	1/128	1/256	1/512
1 Guineapig serum unheated all diluents saline	+	−	+	−	+	−	−	−
2 Guineapig serum unheated suspending serum unheated	−	−	−	−	−	−	−	+
3 Guineapig serum unheated suspending serum heated	+	+	+	−	−	−	−	−
4 Guineapig serum heated all diluents saline	−	−	−	−	−	−	−	−
5 Guineapig serum heated suspending serum unheated	+	+	−	−	−		−	−
6 Guineapig serum heated suspending serum heated	−	−	−	−	−	−	−	−

Sera which contained dye-test antibody for toxoplasms and, after inactivation, did not modify sarcospores any longer were shown to have their dye-test antibody for toxoplasms still complete, thus showing the essential difference between this antibody and whatever in the non-inactivated state can modify sarcospores

Any attempt to remove this sarcospore-hostile factor differentially by inactivation would defeat its own ends because, unfortunately, accessory factor is heat-labile, and a dye test cannot be made if all the sera taking part in the test have been inactivated

Table II illustrates experiments which confirm this point In experiment 1 a guineapig was immunised with sarcocystis complement-fixing antigen, and its complement-fixation test became positive A false dye test with sarcospores on this guineapig's serum was positive at a dilution of 1 128 but negative at 1 256, this must have been a false test because the doubling dilutions were made in saline solution, and at a dilution of 1 256 there cannot possibly have been enough accessory factor present for this to be a true dye test (we have to make all our dilutions in normal human sera to make the toxoplasm dye test work satisfactorily) The same guineapig serum, put up as a formal dye test using our toxoplasm accessory-factor serum was positive at all dilutions, showing once again that "normal human serum" cannot be used for a dye test with sarcospores

The guineapig serum after inactivation at 56°C for 30 minutes fell in titre with sarcospores in saline solution from 1 128 to 1 4 If this fall was due to the destruction of accessory factor in the guineapig serum, the test should have become negative The result is far more likely to be due to the destruction of most of some sarcospore hostile factor That a similar factor is present in the donor of our accessory-factor serum for toxoplasmosis is shown by experiment 3 in table II, in which the guineapig's titre was still 1 128 when our suspending serum after inactivation was used for the diluent Experiments 5 and 6 of table II confirm that our normal human suspending serum cannot be used for a dye test with sarcospores

Age of Sarcospores

As we had no information about the age to which a sarcospore suspension can be used, the experiment was repeated which showed that inactivated sera had lost the ability to modify fresh sarcospores The sarcospores, on the second occasion being 30 days old, were still all modified by human sera On this occasion, however, inactivation did not affect the sarcospore hostile factor, all of 22 sera modifying the sarcospores after heating in the same way as they all had done before heating

The meaning of this finding is not clear As far as can be seen, the only variable factor is the age of the sarco spore suspension, the sarcospores, at the age of 30 days, had altered so that they became modified with inactivated sera, a property they did not have when fresh We had thought, on possibly slender grounds, that the dye test with toxoplasms was a vital phenomenon, but it does not seem likely that this alteration in the capacity of sarcospores, after 30 days in the refrigerator, for being modified by human sera can be connected with any vital capacity of the sarcospores particularly as, when fresh, they do not have this property of modification by inactivated sera

Sheep Sera and Sarcosporidiosis

Of 10 sheep sera collected at random from the abattoir 6 contained complement fixing antibodies for sarco sporidiosis and 4 did not All the sera gave an apparent dye test with sarcospores in that the sera modified them, but after inactivation these 10 sheep sera no longer modified fresh sarcospores This result indicates that sheep sera contain a heat labile substance similar to that in human sera capable of modifying sarcospores, but this substance shows no conformity with the complement-fixing antibody, and, if the latter can be taken to indicate infection with sarcocystis, the sarcospore hostile factor, giving an apparent dye test in 100% of all the sera that we have tested, does not appear to diagnose anything

Comment

We feel that Awad's (1954) claim that sarcospores can be used interchangeably for the diagnosis of both toxoplasmosis and sarcosporidiosis is refuted, because all of 116 human sera and all of 10 sheep sera contained a sarcospore hostile factor That this can be removed by inactivation at 56°C for 30 minutes would not help in establishing a dye test with sarcospores, because accessory factor would inevitably be concurrently removed, and without this the dye test cannot be made Also the dye test antibody for toxoplasmosis is heat stable Secondly, we have encountered this perplexing finding that fresh sarcospores are not modified by inactivated sera, whereas old sarcospores are, unless and until this phenomenon can be explained rationally and perhaps exploited, there seems to be no point in further concern with sarcospores in the laboratory diagnosis of toxoplasmosis Even if this were to be worked out, there is still our total inability to find either a negative control or, indeed, a negative test

On repeating Awad's (1954) work we were unable to obtain results at all comparable with his Our technique of the dye test does not differ materially from that originally described by Sabin and Feldman (1948) and used by Awad and has given us consistent results over eight years The only difference between the two dye test techniques used in our experiments was the substitution of sarcospores for toxoplasms Although we have meticulously followed such technical details as are mentioned by Awad, we have not found it possible to use sarcospores in the diagnosis of anything, and it seems probable that Awad did not mention some point of technical detail our omission of which has led to these discordant results

The suggestion that there is some common antigenic relationship between sarcocystis and toxoplasms is not upheld by our findings, in fact, the ability to remove the sarcospore hostile factor and to retain the toxoplasm dye test antibody, together with the apparent specificity of the toxoplasm dye test antibody for toxoplasmosis, indicates that these are two different substances It is a pity that we could not make this test work, because, as Awad points out, sarcospores are much bigger and more readily visible than toxoplasms, and if we had been able to use them we would gladly have substituted sarcospores for toxoplasms in the dye test for toxoplasmosis

Summary

Evidence is presented that human and sheep sera contain a substance capable of modifying the spores of *Sarcocystis tenella* so that they do not stain with methylene blue

This substance was present in all of 116 human and all of 10 sheep sera

Sarcospores therefore cannot be used to demonstrate the presence of dye-test antibodies for toxoplasmosis or sarcosporidiosis

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RESULTS OF RADIOTHERAPY IN OSTEO-ARTHRITIS OF THE HIP

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OSTEO-ARTHRITIS has been treated by radiotherapy for over fifty years, but its mode of action and value are by no means agreed (Tillis 1944)

Langer (1933) attributed relief of pain to the effect of radiation on non myelinated nerve endings, with consequent hyperæmia and improved metabolism

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Kahlmeter (1938) found these tissues the most sensitive to irradiation in all forms of degenerative joint disease

The purpose of the present investigation was to determine the efficacy of radiotherapy in relieving the pain from osteo-arthritis of one large joint By far the most important symptom to the patient is pain, and this is notoriously difficult to assess The symptoms of osteo arthritis tend to fluctuate irrespective of treatment, and there are no objective criteria Moreover, patients, reluctant to disappoint those who have been trying hard to relieve their pain, often colour their replies accordingly

Joly and Hanoune (1952) reported that pain was at least partly relieved in 66 of 295 patients treated by radiotherapy Some of these patients had additional radiotherapy to the lumbar spine Joly and Hanoune regard the most effective hip dosage as *1000–2000r* in six doses in one week from a 150 kV apparatus

It was felt that a more accurate assessment would be achieved by eliminating the personal factor of an interview and by sending a simple questionnaire to patients at least a year after treatment

After an initial explanatory note, the following questions were asked

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> If the pain was altered, how long after treatment started did you first notice the alteration ?
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Results

Of 62 patients treated 59 were traced 29 men average age 59, and 33 women, average age 58, when treatment began 2 of these patients had later died, each about two years after treatment and of unrelated causes, both had moderate improvement, which was maintained until death Of the remaining 57 patients 11, with twelve treated hips, had subjective improvement, but this lasted for more than a year in only 5 patients Improvement was considerable in 3, moderate in 6, and slight in 2 The average duration of symptoms before treatment was six years

Ill effects of treatment were few 2 patients complained of malaise and abnormal tiredness, 1 woman, aged 46, had persistent amenorrhœa after treatment—she was the only patient who found the pain increased by treatment

43 patients could not detect any appreciable effect of radiotherapy

Conclusions

Radiotherapy may be given in a dose of 1200–1500r to a hip joint in 6–10 fractions in two weeks with few complications due to treatment

Less than a quarter of 57 patients with osteo-arthritis of the hip derived subjective benefit from irradiation of the hip joint In only 5 patients did benefit last longer than a year

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PSEUDOHÆMOPTYSIS DUE TO CHROMOBACTERIUM PRODIGIOSUM

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IT is common knowledge that a green or blue tinge to the sputum may be produced by *Pseudomonas pyocyanea* It is far from common knowledge, however, that a red sputum, indistinguishable from a bloodstained specimen, may be produced by *Chromobacterium prodigiosum* Ignorance of this fact, even among chest physicians, is easily explained, for up to 1955 it has been possible to trace only two cases of natural infection of the respiratory tract with this organism

The classification of the chromobacterium group of organisms has always been somewhat difficult They are small gram negative aerobic rods producing a pigment which may be yellow, violet, or red *C prodigiosum* may vary morphologically from a coccobacillus to a rod The group is usually found in water and soil and may contaminate food (Wilson and Miles 1955)

Most infections in man with *C prodigiosum* have involved the genito-urinary tract (Wheat et al 1951), but cases have been described of fatal septicæmia (Patterson et al 1952), bacterial endocarditis (Hawe and Hughes 1954), and meningitis (Aronson and Alderman 1943) The type of case described below has rarely been published

Case-report

On July 19 1956 a man aged 59 was admitted to hospital because of a chronic cough and copious purulent sputum, these symptoms had been present since an attack of pneumonia five years previously His temperature and pulse rate were normal and a general examination showed little of note except finger clubbing generalised emphysema and bilateral basal crepitations in the lungs Naked eye examination of the sputum however showed it to contain pus and it appeared to be frequently bloodstained A blood count showed red cells 4 620 000 per c mm., Hb 56% colour index 0 6, and white cells 5000 per c mm Bronchiectasis was diagnosed and confirmed by bronchography, which demonstrated "cystic" bronchiectasis of both lower lobes, the middle lobe and lingula, and the anterior segments of the upper lobes Bronchoscopy revealed pus in both lower-lobe bronchi which were also appreciably distorted Specimens of sputum did not supply any microscopical evidence of blood, and it was subsequently noted that the red colour of the sputum developed only on standing Cultures were reported consistently as growing *C prodigiosum* and *Proteus mirabilis*, the former organism produced luxuriant orange-red colonies In spite of treatment with penicillin, streptomycin, terramycin, aureomycin, and chloramphenicol, the patient continued to produce cultures of this organism These cultures were resistant to all in-vitro drug sensitivity tests except as regards chloramphenicol and neomycin However, the patient's general condition was much improved—possibly owing to effective physiotherapy—and he was discharged home on Aug 28, 1956

Bacteriology —The organism consisted of short gram negative rods (about 1 0–1 5×0 7 µ, with occasional rods up to 4 µ long), motile by a few peritrichate flagella It formed round convex colonies with a smooth shiny surface on agar, and grew better at 37°C than at 25°C It produced deep orange red pigment on agar at 25°C but little or no pigment at 37°C The pigment was insoluble in water but soluble in chloroform and in alcohol An alcoholic solution of pigment turned pink, then violet, on the addition of acid, and yellow on the addition of alkali The organism grew anaerobically without producing pigment It produced dense turbidity in broth at 25°C, with a pink ring growth and a reddish deposit It produced clot in litmus milk, followed by liquefaction Saccate liquefaction was caused by a gelatin stab It produced acid and a little gas from glucose, mannitol, maltose, sucrose, and salicin at 37°C, but none from dulcitol and lactose Glucose was attacked fermentatively (Hugh and Leifson 1953) Indole –, M.R –, V P +, Koser's citrate +, nitrates reduced, NH3 production +, catalase +, methylene blue reduced urea – at 24 hr (Christensen 1946), H_2S + The description of this organism closely resembles that given for *C prodigiosum* by Wilson and Miles (1955) A culture has been deposited with the National Collection of Type Cultures (no 9940)

Discussion

There seems to be little doubt, from a review of published reports, that this organism can produce either a mild chronic illness or a fulminating fatal one, usually a septicæmia It is, of course, very difficult to assess the pathogenicity of the organism in the present case It is of interest that the sputum remained persistently contaminated in spite of heavy and varied antibiotic therapy These findings are in keeping with the experience of most other workers Hawe and Hughes (1954) thought that either chloramphenicol or neomycin might offer the best chance of successful treatment The in-vitro sensitivity tests tend to bear out this view

Aitoff et al (1936) have described a case in which a pure culture of *C prodigiosum* was obtained from a patient with lobar pneumonia Woodward and Clarke (1913) described a case quite similar to the one described above, the patient, who apparently had bronchiectasis, complained repeatedly of bloodstained sputum, whereas it really contained no red corpuscles but grew profuse colonies of *C prodigiosum* Sometimes the red colour of the sputum occurs only on standing, the degree of pigmentation depending on the oxygen supply

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dye test with sarcospores in that the sera modified them, but after inactivation these 10 sheep sera no longer modified fresh sarcospores This result indicates that sheep sera contain a heat labile substance similar to that in human sera capable of modifying sarcospores, but this substance shows no conformity with the complement-fixing antibody, and, if the latter can be taken to indicate infection with sarcocystis, the sarcospore hostile factor, giving an apparent dye test in 100% of all the sera that we have tested, does not appear to diagnose anything

Comment

We feel that Awad's (1954) claim that sarcospores can be used interchangeably for the diagnosis of both toxoplasmosis and sarcosporidiosis is refuted, because all of 116 human sera and all of 10 sheep sera contained a sarcospore hostile factor That this can be removed by inactivation at 56°C for 30 minutes would not help in establishing a dye test with sarcospores, because accessory factor would inevitably be concurrently removed, and without this the dye test cannot be made Also, the dye test antibody for toxoplasmosis is heat-stable Secondly, we have encountered this perplexing finding that fresh sarcospores are not modified by inactivated sera, whereas old sarcospores are, unless and until this phenomenon can be explained rationally and perhaps exploited, there seems to be no point in further concern with sarcospores in the laboratory diagnosis of toxoplasmosis Even if this were to be worked out, there is still our total inability to find either a negative control or, indeed, a negative test

On repeating Awad's (1954) work we were unable to obtain results at all comparable with his Our technique of the dye test does not differ materially from that originally described by Sabin and Feldman (1948) and used by Awad and has given us consistent results over eight years The only difference between the two dye test techniques used in our experiments was the substitution of sarcospores for toxoplasms Although we have meticulously followed such technical details as are mentioned by Awad, we have not found it possible to use sarcospores in the diagnosis of anything, and it seems probable that Awad did not mention some point of technical detail our omission of which has led to these discordant results

The suggestion that there is some common antigenic relationship between sarcocystis and toxoplasms is not upheld by our findings, in fact, the ability to remove the sarcospore-hostile factor and to retain the toxoplasm dye test antibody, together with the apparent specificity of the toxoplasm dye test antibody for toxoplasmosis, indicates that these are two different substances It is a pity that we could not make this test work, because, as Awad points out, sarcospores are much bigger and more readily visible than toxoplasms, and if we had been able to use them we would gladly have substituted sarcospores for toxoplasms in the dye test for toxoplasmosis

Summary

Evidence is presented that human and sheep sera contain a substance capable of modifying the spores of *Sarcocystis tenella* so that they do not stain with methylene blue

This substance was present in all of 116 human and all of 10 sheep sera

Sarcospores therefore cannot be used to demonstrate the presence of dye test antibodies for toxoplasmosis or sarcosporidiosis

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HÆMOLYTIC TRANSFUSION REACTION DUE TO ANTI-KELL

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EMERGENCY blood-transfusions may later lead to "emergencies" of a different kind The following case illustrates one of the complications which may arise if the tests preceding this treatment are not carried out completely

Case-report

A married woman, aged 30, became pregnant for the second time in August, 1955 She had had no serious illnesses in the past and had certainly never received any blood transfusions or injections of blood Apart from one normal live birth there had been no other pregnancy On April 12, 1956, she attended the antenatal clinic for the first time, and intra uterine death was suspected A swelling in her neck was noted and diagnosed as tuberculous adenitis On April 15, in her 36th week of pregnancy, she was admitted to hospital with vaginal bleeding and abdominal pain Next morning a dead 20 week fœtus was born, and this was followed two hours later by a fairly severe postpartum hæmorrhage An urgent request for three pints of blood was received by the pathologist on duty The patient's blood-group was determined as group A rhesus negative Three pints of homologous blood was cross matched by the albumin method, being incubated for an hour at 37°C, and all three bottles were found to be compatible An indirect Coombs test was not done

Transfusion and Progress —Two pints was transfused immediately and given fairly quickly The third pint was given during the morning of April 16 The patient's general condition improved, but in the afternoon she was found to be jaundiced On April 17 she became anuric Since the usual Bull's regime was not tolerated, owing to constant vomiting, 5% glucose in water was given by mouth, followed by 40% glucose by intragastric drip When, by April 20, diuresis had not begun an intracaval drip (Russell et al 1954) was set up and 40% glucose administered Insulin was given in an attempt to stem the rising serum potassium level Diuresis started on April 24, when she passed 160 ml of urine, and the amount of urine increased during the following forty eight hours Infection of the surrounding skin made it necessary to remove the intracaval catheter on April 26 Next day the serum potassium level rose to 9 2 m eq per litre and reached 10 2 m eq per litre on April 28 By this time a massive diuresis had set in (4 litres in twenty four hours), and the serum-potassium level dropped to 5 0 m eq per litre on April 30 The blood urea level rose to 252 mg per 100 ml on the same day but declined rapidly thereafter Polyuria went on for another week, with the serum potassium dropping to 3 3 m eq per litre The patient's general condition improved, but persistent anæmia necessitated a further blood-transfusion She was well enough on May 23 to be discharged home, when her blood urea was normal and her hæmoglobin 9 3 g per 100 ml (63%)

Follow up —By June 11 her hæmoglobin had increased to 10 9 g per 100 ml (74%) and on Nov 15 it was 12 3 g per 100 ml (83%), and her blood urea was 19 mg per 100 ml

Biochemical and Serological Findings —The clinical diagnosis of hæmolytic transfusion reaction was confirmed by a positive Schumm's test and a bilirubin level of 14 mg per 100 ml on the evening of April 16 The patient's cells on this date gave a positive direct Coombs test Reinvestigation of the serology showed that her blood group had been correctly determined as group A rhesus negative, and the donors' blood groups were also found to be correct The cross match was now repeated with serum obtained from pre and post transfusion specimens, and again no incompatibility was found when the cells and the specimen were suspended in saline solution or in albumin, but two of the three pints of blood gave a strongly positive indirect Coombs test with the patient's serum A full investigation then showed that the antibody present in the patient's serum was anti Kell The two bottles which gave the positive indirect Coombs test with the patient's serum were Kell positive, whereas the third, which had given a negative indirect Coombs test, was Kell negative The blood group of the patient's husband was group O rhesus negative, Kell positive, and Fy (a)

Discussion

This patient was not regarded as a "dangerous recipient" (Tovey 1950), having had only one pregnancy in the past and no history of transfusion or injections of blood Nevertheless her serum contained a powerful anti-Kell antibody obviously produced by the stimulus of the pregnancies Whether the tuberculous adenitis enhanced antibody formation is a matter for conjecture Unfortunately the dead fœtus was not examined, and cord blood was not obtained Therefore it is unknown whether the Coombs test in the baby's cells was positive No doubt the severe transfusion reaction could have been avoided had a Coombs test been done when the blood was cross matched, but it was assumed that the case was too urgent to allow time for this test It is common experience that the albumin method will not show up all antibodies which may produce a severe transfusion reaction The performance of the indirect Coombs test therefore appears to be advisable in all women who have been pregnant or cannot give a precise history

This case again shows the value of the intracaval administration of hypertonic glucose in the treatment of anuria

Summary

A severe hæmolytic transfusion reaction was due to an anti-Kell and caused anuria An indirect Coombs test should be used more often than at present in cross matching blood for parous women

Our thanks are due to Mr H Burton for permission to publish this case

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New Inventions

A NEW RECOVERY-ROOM TROLLEY

IN a recovery-room, the use of a standard hospital bed has many disadvantages It is space consuming where the space is often limited, it is cumbersome to move and tilt, and a fixed head makes laryngoscopy or bronchoscopy extremely difficult Moreover, it entails too frequent movement of the patient who is shocked or has had regional or hypotensive anæsthesia, in that he has to be moved from operating-table to trolley, thence to a recovery bed and later back to a trolley, and finally back to a bed again in the surgical ward These manœuvres require the close attention of several nurses and porters

To eliminate such difficulties, a recovery-room trolley has been designed incorporating features which allow the patient to remain on it from the time he leaves the theatre table, throughout his stay in the recovery room, to the time he returns to the ward Thus he has to be moved only twice

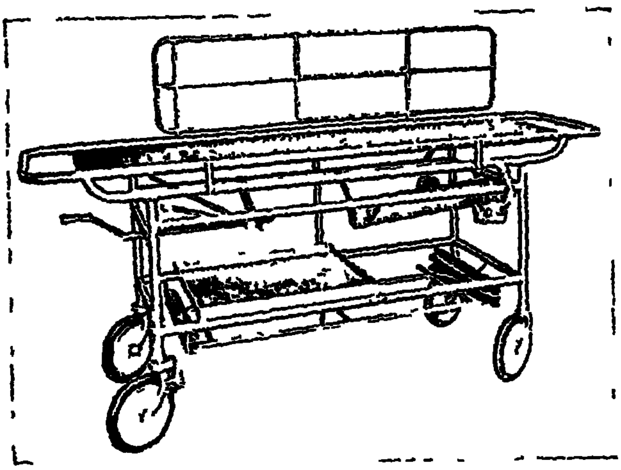
This trolley is basically similar to the standard hospital trolley It is, however, more sturdily built and has the following additional features

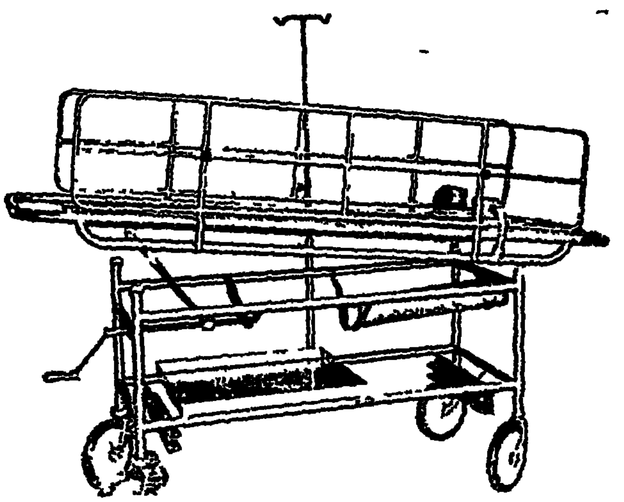
(1) Easily adjustable Trendelenburg tilt by means of a handle at the foot

(2) Adjustable self locking shoulder-rests.

(3) Detachable side rails with telescopic ends which stow away in a compartment beneath the trolley when not in use

(4) Adjustable drip stand attachment on either side of the trolley





(5) Container for oxygen cylinder beneath trolley

(6) Tray beneath trolley for case sheets, utensils, dressings, &c, brought from the ward

(7) Locking wheels (foot action)

(8) Thick 'Sorbo' rubber mattress

As the trolley stands just higher than a standard hospital bed, the patient who is on a draw-sheet can be lifted with a minimum of effort on to the ward bed when required Two of these trolleys have been in use in the recovery-room at the Royal Infirmary, Wigan, for some months and have proved so satisfactory that it is proposed to replace the remaining beds by more such trolleys soon

The trolley is manufactured by Messrs Siddall & Hilton, of Sowerby Bridge, Yorks, to whom considerable credit is due for their lively interest and cooperation in its production

Royal Albert Edward Infirmary
Wigan

G J C BRITTAIN
M D Lpool, F F A R C S

Reviews of Books

The Pathogenesis of Coronary Occlusion

A D MORGAN, M A, M D, head of the morbid anatomy department and reader in pathology, Westminster Medical School, and consultant pathologist, Westminster Hospital, London, Oxford Blackwell Scientific Publications 1957 Pp 171 42s

SINCE ischæmic heart-disease is now responsible for the deaths of one fifth of the nation, and coronary atherosclerosis is present to a greater or lesser extent in every adult irrespective of age, a new monograph on the pathogenesis of coronary atheroma commands immediate attention

In the first half of this monograph, which is based on his M D thesis, Dr Morgan recounts briefly the early history of coronary atherosclerosis and reviews some of the theories of atherogenesis The historical section is very interesting, but the review lacks continuity and does not analyse or summarise adequately the views of previous workers Many will take issue with Dr Morgan's acceptance of atherosclerosis as an inevitable result of advancing age, with metabolic and endocrine disturbances as merely aggravating factors

In the second half, he recapitulates Duguid's views concerning the formation of atherosclerotic lesions During the past ten years most pathologists have come to realise that there is much evidence to support Duguid's observations that wisps of fibrin and frank arterial thrombi can be overgrown by endothelium and incorporated into the arterial wall Duguid maintains that many atherosclerotic lesions result from fibrin deposition and thrombosis, and that much of the fatty material in the atherosclerotic plaque is the result of degenerative changes Dr Morgan supports these observations with a detailed histological study of the coronary arteries from 40 patients with advanced coronary atherosclerosis, there are 174 photomicrographs and many of these are admirable, though only the frontispiece is in colour In Dr Morgan's view, intimal vascularisation is entirely the result of retraction and organisation of mural thrombi He believes that most of the cholesterol in the atherosclerotic plaque comes from the breakdown of red cells after mural thrombosis or capillary hæmorrhage into any existing plaque, and that it is possible to account for the presence of cholesterol in an atherosclerotic abscess without necessarily invoking a disorder of lipid metabolism

It would have been better if this monograph had been confined either to the excellent histological studies or expanded into a more comprehensive account of other views of the pathogenesis of coronary atherosclerosis, the present title is misleading, since the monograph is really an exposition of one view of atherogenesis Dr Morgan contends that the increasing incidence of thrombotic arterial occlusion is largely responsible for the greater frequency of ischæmic heart-disease He offers no evidence to support this hypothesis which, if the thrombogenic theory is correct, is difficult to reconcile with the fact that coronary atheroma has not increased during the past half century—a distinction which Dr Morgan himself emphasises

Dr Morgan is an enthusiastic advocate of Duguid's thrombogenic theory of the origin of atheromatous lesions, and it is instructive to read a review of this important approach to atherogenesis

Clinical Use of Radioisotopes

WILLIAM H BEIERWALTES, M D, coordinator, clinical radio isotope unit, University Hospital, Ann Arbor, PHILIP C JOHNSON, M D, chief, radio isotope unit, Veterans Administration Hospital, University of Oklahoma, ARTHUR J SOLARI, M S, radiation physicist for clinical radio isotope unit and Kresge research isotope unit, University Hospital, Ann Arbor Philadelphia and London W B Saunders 1957 Pp 456 80s 6d

WRITTEN primarily for the doctor taking part in the development of a clinical radio isotope unit, this book gives a particularly clear account of the principles underlying the use and measurement of radioactive materials, which should be very valuable to the medical graduate, who may have only a very superficial knowledge of nuclear physics

Most attention on the clinical side is rightly devoted to thyroid disorders and radioactive iodine, since this is undoubtedly the most important and popular use of an isotope in hospital Practical therapeutic aspects are well covered and for the most part the advantages and limitations of the new methods are adequately presented Little is said about the more fundamental aspects of the nature of the action of radiation on the thyroid cells, and recent work on carcinoma of the thyroid in children resulting from irradiation of the neck is not included In the chapter on diagnostic procedures no mention is made of the possible use of the short half-life ^{132}I, which considerably reduces the exposure of the gland to radiation

After turning to the use of other radioactive isotopes in clinical investigation and treatment, the book deals with the biological effects of radiation It concludes with the practical details of measuring radioactivity, and it even goes into the costs of investigations and the charges to be made to patients In an American book the regulations regarding the supply of isotopes do not, of course, apply to laboratories in this country

Doctors beginning work in a department using radioactive materials in clinical investigation will certainly find much to help them in this book

Medical Negligence

LORD NATHAN, P C, solicitor of the Supreme Court, chairman of the board of governors of Westminster Hospital, with the collaboration of ANTHONY R BARROWCLOUGH, B A, of the Inner Temple, barrister at law London Butterworth 1957 Pp 218 35*s*

THIS book collects much material hitherto available only in scattered reports It should interest lawyers and doctors alike, and is intelligible to both It demonstrates the care taken by the courts to reach decisions which not only do justice to plaintiffs but also protect a doctor's reputation when it deserves protection The standard of care is decided by the judge after weighing evidence given by other doctors; it is not a subjective standard of his own The frequent reiteration of the words "reasonable care" should comfort those who think that the courts demand the highest possible degree of skill and experience In the words of Lord Justice Scott, "the standard of care which the law requires is not insurance against accidental slips, it is such a degree of care as a normally qualified member of the profession may reasonably be expected to exercise in the actual circumstances of the case in question" Many examples are given of the "actual circumstances," but non-legal readers should remember that there is little law in these cases Each has been decided on its own facts, and few can safely be treated as precedents

The author suggests that all that solicitors need do to secure immunity from actions for professional negligence is to act on the opinion of counsel of reasonable competence It is perhaps worth noting, therefore, that solicitors are sometimes sued for negligence where there has never been any question of referring the case to counsel They are in no better a position than many a doctor Doctors have been found guilty of negligence because they did not refer the case to another doctor with special skill or knowledge, and the inference is that, had they done so, they themselves would have been immune

The book contains just over 200 pages, some of which are not strictly concerned with medical negligence, and many of the cases are not English but are from the Dominions and the United States Does this suggest that doctors in this country are not, after all, forever hovering on the edge of a legal abyss?

Troubles mentaux au cours des tumeurs intracraniennes

H HECAEN, médecin des hôpitaux psychiatriques, J DE AJURIAGUERRA, maître de recherche à l'Institut National d'Hygiène Paris Masson 1956 Pp 152 Fr 1500

THE partnership of Hecaen and Ajuriaguerra is becoming well known in modern French neurological literature Their contributions are always of value, and though this monograph is slighter than some of their work it contains useful information and a full review of previous literature

This study is based on 449 cases of cerebral tumour, in 229 of which mental changes were present The findings show that, though raised intracranial pressure (as judged by papillœdema) plays a part in producing general mental changes, this is not the whole answer When both the type of mental change and the site of the tumour are considered, the most striking fact is the relatively high incidence of a Korsakoff syndrome in lesions of the diencephalon and this supports the histological evidence in cases of alcoholic Korsakoff psychosis A more generalised "confusion dementia" syndrome commonly arises in frontal and fronto temporal tumours, whether or not papillœdema is present, whereas in occipital or posterior fossa tumours this syndrome is usually associated with papillœdema

In general, the book confirms the experience of those who see a lot of cerebral tumours, and it will be of particular value to psychiatrists who wish to define the rather amorphous group of organic dementia syndromes that they see

Atlas der gastroenterologischen Cytodiagnostik

N HENNING, director, and S WITTE, scientific assistant, Med Univ Klinik, Erlangen English translation by R O K SCHADE, M R C S Stuttgart Georg Thieme 1957 Pp 104 D M 38

THIS unpretentious atlas includes German and English versions in one cover, and the sound English translation makes the book unusually valuable to students of scientific German The text, less than 20 pages in each version, is disappointingly brief it includes, for instance, no statistics on the reliability of the methods described Professor Henning has been using his *Zellitupfsonde* (a gastric-tube-enclosed swab) in the diagnosis of gastric carcinoma since 1948, and exact figures of his success with it would have been very informative The black-and-white figures are many and good The gut is one of the newer and more difficult fields of exfoliative cytodiagnosis, and this is a useful introduction to it

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Companion in Surgical Studies (2nd ed Edinburgh E & S Livingstone 1957 Pp 1302 84*s*)—A man seldom erects a monument to himself in his own time, but Prof Ian Aird has done so The first edition of his Companion had the quality of a "standard work" to which everyone turns for reference For the second edition he has an editorial committee of members of the staff of the Postgraduate Medical School of London and the Hammersmith Hospital to assist him, and together they have enlarged the book considerably Professor Aird has made no concession to those who deplored the absence of orthopædics from the first edition, he feels *he has been out of touch with the subject for too long* He should have stuck to his guns about illustrations too it seemed almost a merit of the first edition that it had none, now there is one plate and one diagram, neither of any importance, lost in the text, and they will hardly satisfy the critics who disliked a book without illustrations Nevertheless the second edition maintains the great reputation of its predecessor, and will indeed enhance it

Symptoms and Signs in Clinical Medicine (6th ed Bristol John Wright & Sons 1957 Pp 508 35*s*)—Dr E Noble Chamberlain's well known introduction to clinical medicine is now by way of becoming a minor classic In the new edition there have been changes, notably in the sections devoted to the cardiovascular and central nervous systems There are some new illustrations, including excellent coloured photographs Indeed, it seems a pity that any of the old coloured drawings were retained, for some of them now look very poor by comparison, and one or two are out of date and inaccurate We again commend this popular book to all students

Cleft Lip and Palate (2nd ed London Heinemann Medical Books 1957 Pp 187 42*s*)—The value of Mr W G Holdsworth's book has been much enhanced The chapters on operative repair include much new material and they now present a concise but comprehensive review of almost every surgical possibility A new chapter on embryology, contributed by Prof R J Harrison, is a masterly exposition of a complicated subject and goes far towards explaining some abnormalities which had hitherto been difficult to fit into the developmental pattern The second major addition, a chapter on orthodontic treatment by Mr M A Kettle, places in correct perspective the many claims made in this specialty, and enables the advantages of treatment to be properly evaluated Altogether, this new edition is vastly more informative than its predecessor

Shaw's Textbook of Gynæcology (7th ed London J & A Churchill 1956 Pp 704 32*s* 6*d*)—Wilfred Shaw's well known textbook was first published in 1936 Mr John Howkins has undertaken the revision for the new edition, and he is to be congratulated on maintaining the high standard and on preserving much of the original text while bringing the teaching up to date 116 new illustrations have been included and a number of important chapters have been largely rewritten

THE LANCET

LONDON SATURDAY, APRIL 20 1957

Vaccination and the Epidemiology of Poliomyelitis

RECENT studies have made clear the reasons for the striking differences in the incidence of paralytic poliomyelitis between countries with high and with low standards of living [1,2] In countries with a low standard of living people are usually infected by poliovirus in infancy or early childhood and thereafter they have a lifelong immunity to paralytic disease, whereas in countries with a higher standard of living and hygiene the first contact with poliovirus may be postponed to an age at which paralytic disease is more likely to result from infection. MELNICK et al [3] now report the results of a three-year study of selected populations in two American cities Specimens of sera and stools were collected repeatedly and were used to measure the infection-rates of different sections of the population in relation to their general socio-economic standards It was found that in each city members of the lower socio-economic group developed antibody early, and more than half of those aged 5–9 had antibody to any given type of poliovirus in higher socio-economic groups the same figures were not reached until early adult life These differences were clear on a gross district level, but, within each district, household size and state of sanitation were not important determinants of infection-rates The rates of virus isolation were more than three times greater in the lower socio-economic group and in certain cases it was possible to observe in retrospect silent subclinical epidemics in different districts There were no clinically apparent cases of poliomyelitis in the study-groups, but since clinical cases occurred elsewhere in both cities during the period of observation it was possible by assuming similar infection-rates to those of the study-groups to *compute crude* ratios of clinical to inapparent infections A rough calculation of this type suggested that the number of subclinical infections per clinical case varied from 32 to 406 clinical cases being associated most frequently with type-1 viruses Another interesting finding in this investigation [4] was that the presence of heterotypic antibodies did not reduce the incidence of subclinical infections among exposed persons On the other hand, the possession of homotypic antibody as a result of previous infection apparently prevented reinfection—a finding which falls in line with the work of others [5] A general conclusion from this work is that within relatively well-defined areas the age at which infection with polioviruses is acquired differs sharply and these differences can be clearly related to socio-economic rather than to climatic conditions A similar conclusion is reached by Dr BACKETT whose report we published last week.[6] BACKETT studied the poliovirus antibody pattern of nearly 300 children in Northern Ireland in relation to factors in their social background He found that there is more evidence of infection among children living in town than in country children, in lower than in upper social classes, in homes without constant hot water than those with and among children with many recreational contacts than those with few, and each of these factors seems to be independently associated with antibody patterns It is important that studies of this kind [7] should have been made now, since the picture may soon be greatly altered as the result of vaccination

What effects on the epidemiology of poliomyelitis may be expected to result from the continued use of formolised poliomyelitis vaccine ? A very thoughtful paper by Dr JOHN PAUL [8] raises important issues PAUL points out that so far the vaccine has produced acute immunity," which has reduced the incidence of paralytic poliomyelitis in children by 60–80% But we do not yet know whether vaccination of children by existing methods will protect them until they have reached the young adult age, at which infection is more likely to cause severe paralytic disease At the moment young adults in many populations are very vulnerable to paralytic disease In the U S A young parents are increasingly being infected by their children who have acquired virus at nursery-school and it will be remembered that many parents became infected when their children accidentally received live virus during the so-called Cutter incident in 1955 [9] Unlike natural infection vaccination does not prevent inapparent alimentary infections This has two implications When children are vaccinated first the young parents may for a time be more commonly exposed to the risk of paralytic infection as a result of inapparent infection by virulent virus in their children Secondly (as PAUL remarks) natural alimentary infection in a vaccinated child may still be necessary to maintain immunity throughout life Where and when these natural infections will occur may depend largely on the child s social circumstances Finally, PAUL raises the question whether reinfection should be left to pure chance or whether vaccination with live attenuated virus should be used as an adjunct to the vaccination with a killed virus Although the development of live virus vaccine has had a setback [10] this still seems a logical and hopeful line to pursue

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[1] World Health Organization. First Report of the Expert Committee on Poliomyelitis *Tech Rep Ser Wld Hlth Org* 1954 no 81

[2] Paul J R *Monogr Ser Wld Hlth Org* 1955 26 9

[3] Melnick J L Walton M Isacson P Cardwell W *Amer J Hyg* 1957 65 1

[4] Isacson P Melnick J L Walton M *Ibid* p 29

[5] Fox J P Gelfand H M LeBlanc D P Conwell D P *Amer J publ Hlth* 1956 46 283

[6] Backett E M *Lancet* April 13 1957, p 778

[7] Fallon R J *Ibid* 1956 i 65

[8] Paul J R *J Amer med Ass* 1956 162 1585

[9] See *Lancet* 1955 i 1207

[10] Dane D S Dick G W A Connolly J H Fisher O D, McKeown F *Brit med J* Jan 12 1957 p 59

Mechanisms of Periodic Paralysis

ONE of the things which makes medicine difficult (and interesting) is that apparently similar syndromes can be produced by several distinct mechanisms Familiar examples are megaloblastic anæmia and renal failure, and there is now a good deal of evidence that episodic paralysis, even in the absence of neurological disease, can be produced in different ways The first mechanism that was apparently established was the low plasma-potassium level giving rise to attacks of familial periodic paralysis, attacks can be terminated by giving potassium salts by mouth, and can be induced by giving adrenaline, or insulin and glucose, which lower the plasma-potassium[1] ALLOTT and MCARDLE[2] observed that the fall in plasma-potassium associated with the onset of an attack could not be accounted for by increased urinary excretion of potassium, and inferred that there must be a shift of potassium from the extracellular fluid into the cells Further balance studies have confirmed this finding[3] Last year ZIERLER and ANDRES[4] showed that there was a nocturnal shift of potassium into muscle-cells, which was five to ten times greater in patients with periodic paralysis than in healthy people The observed rate of entry into muscle of up to 1 m eq K per hr per kg of muscle would well account for the concurrent disappearance of potassium from the extracellular fluid (E C F), and it is tempting to relate the nocturnal entry of potassium into muscle to the tendency for attacks of periodic paralysis to start in the early hours

The association between hypokalæmia and paralytic attacks has now been observed not only in some patients with familial periodic paralysis but also in patients with abnormal losses of potassium, as in diabetic coma, the Fanconi syndrome,[5] and potassium-losing nephritis[6], yet evidence has also accumulated that hypokalæmia does not necessarily lead to paralysis and that familial episodic paralysis can occur without hypokalæmia Reviewing the relation between potassium and familial periodic paralysis, MCARDLE[7] draws attention to the common absence of paralysis at levels of plasma-potassium well below those associated with paralysis in the familial syndrome, and on the other hand to the remarkable family reported by TYLER et al[8] In this family episodic paralysis was inherited as a simple mendelian dominant, with 33 affected patients in seven generations, the paralytic episodes were not attended by any notable change in plasma-potassium, but biopsy showed vacuolation in the muscles The vacuoles did not contain fat or glycogen, and were presumed to contain "œdema fluid," although they lay within the muscle-fibres The relationship between potassium and paralysis is further complicated by the observations that hyperkalæmia may also be associated with paralysis,[9 10] and that hypokalæmia may at times be associated not with paralysis but with tetany[11] while in other patients the correction of hypokalæmia has unmasked hypocalcæmic tetany[12]

It is apparent from all this that no simple relationship exists between plasma-potassium and muscle paralysis, and speculative enterprise has tended to emigrate to the terra incognita within the cells A new lead in this direction is given by Professor CONN and his colleagues in their interesting observations set out in this issue on p 802 They outline their findings in two patients, unrelated to each other, who had "the familial type of periodic paralysis", one of them lived in the laboratory for eleven months of metabolic observation, and the other was studied for thirty days Both spontaneous and induced attacks of paralysis were preceded by massive retention of sodium and increased urinary excretion of aldosterone, recovery from the attack was attended by massive sodium diuresis Muscle biopsy during the attack showed a vacuolated lesion like that found in TYLER's family, but the two syndromes are not identical, for in CONN's 2 patients there was a profound fall in urinary and plasma potassium The sodium content of muscle was greatly increased, while the potassium content of muscle was normal, or a little diminished (The results now published do not indicate conclusively that the extra sodium in muscle is in fact intracellular, but a more detailed account is promised) When the patients were put on a low-sodium diet, it was no longer possible to induce attacks by glucose+insulin, or by fluorohydrocortisone On the basis of their findings, CONN et al suggest that "an abnormally high concentration of sodium within the muscle cell is partly responsible for the disturbance of muscle function" The cause of the observed intermittent aldosteronism is "not yet clear", and on the present results the possibility does not seem to be completely excluded that the increased aldosterone output is a secondary response to decreased E C F volume from a prior shift of fluid into cells along with potassium

This valuable new information raises further questions which can be readily studied Does artificial lowering of the plasma-potassium by insulin+glucose or by fluorohydrocortisone induce aldosteronism in healthy people, and if so how is this related to the stimulation of aldosterone output by a high potassium intake[? 13] If the aldosterone change is "primary," why is the sodium retention not accompanied by massive loss of potassium in the urine, as in sustained primary aldosteronism[? 14] If the intracellular vacuoles do contain sodium salts, by what mechanism are they sequestrated within the cell ? What part, if any, do the diurnal variations observed by ZIERLER and ANDRES play ? As MCARDLE[7] points out, quite a small primary change in extracellular potassium level may trigger off a chloride shift which will lead to further drastic lowering of external potassium, and it is notable that in 1 of the 2 patients studied by DANOWSKI et al[3] there was a negative external balance of potassium before the attack

From the practical point of view, perhaps the most interesting observation was that on a sodium intake

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1 Aitken R S Allott E N, Castleden, L I, Walker, N *Clin Sci* 1937 3 47
2 Allott, E N McArdle, B *Ibid* 1938, 3, 229
3 Danowski T S Elkinton, J R, Burrows B A, Winkler, A W *J clin Invest* 1948, 27, 65
4 Zierler, K L, Andres, R *Ibid* 1956 35, 747
5 Milne M D, Stanbury, S W, Thomson, A E *Quart J Med* 1952 21, 61
6 Mahler R F, Stanbury, S W *Ibid* 1956, 25, 21
7 McArdle B *Brit med Bull* 1956 12 226
8 Tyler F H Stephens, F E, Gunn F D Perkoff G T *J clin Invest* 1951 30 492
9 Finch C A., Marchand, J F *Amer J med Sci* 1943 206, 507
10 Bull, G M., Carter, A B, Lowe, K G *Lancet* 1953, ii 60
11 Fourman, P *Ibid*, 1954 ii 525
12 Engel F L Martin, S P, Taylor H *Bull Johns Hopk Hosp* 1949, 84, 285
13 Laragh J H Stoerk H C *J clin Invest* 1955 34 913
14 Conn J W Louis L H *Ann intern Med* 1956, 44, 1

of 8 m eq a day there were no spontaneous attacks, nor could attacks be induced The efficacy of a low-sodium diet may indeed be partly due to concurrent potassium retention, for BARTTER[15] has suggested that minimal excretion of sodium may depress potassium secretion through lack of sodium ion available for exchange The diet used by CONN et al in their studies is considerably more restricted than the conventional low-salt diet. it would therefore be of great interest to find out whether an ordinary low-salt diet would prevent spontaneous attacks, or whether this would have to be supplemented by mercurial or other diuretic agents In some patients such a regime might have advantages over regular potassium supplements, which are not very palatable We would certainly agree with CONN that adrenalectomy is not indicated in the management of periodic paralysis

Resistant Tubercle Bacilli

THE possibility that drug-resistant tubercle bacilli might spread among the population was recognised when streptomycin was first used more than ten years ago Instances of such spread have now been reported in the U S A[16–19] France,[20–22] and Great Britain[23–25] Studies in the U S A suggested that resistant bacilli might account for about 1–2% of newly diagnosed infectious cases in that country[26 27], but the information was incomplete Accordingly, warnings about the dangers to the public health of indiscriminate and irrational chemotherapy of tuberculosis have been based on a-priori arguments. The tuberculosis research unit of the Medical Research Council with the coöperation of many chest physicians, has now remedied this defect Fox et al[28] describe a survey of the drug-sensitivity of cultures of tubercle bacilli isolated from newly discovered patients in Great Britain between June 1955 and March, 1956

> The bacteriological and statistical methods were designed to detect all strains which were at all resistant and to distinguish these from strains that were actually sensitive but were apparently resistant as a result of experimental variations in the sensitivity tests MITCHISON and SELKON[29] in a separate report on the bacteriological aspects of the survey, show that their estimates of the prevalence of strains resistant to streptomycin and *p*-aminosalicylic acid (P A S), if incorrect, were likely to be too low and that their estimate of isoniazid resistance may have been too high

A representative sample of eighty chest clinics was selected by a random process 1404 sputum specimens from the same number of newly diagnosed and untreated patients were cultured at a central laboratory From these specimens 974 positive cultures were obtained and 50 (5 1%) were resistant to one or more of the three commonly used drugs 44 (4 5%) being cultures of *Mycobacterium tuberculosis* and 6 (0 6%) cultures of atypical mycobacteria Of the 44 resistant cultures of *M tuberculosis*, 22 (2 3%) were resistant to streptomycin, 21 (2 2%) to P A S, and 7 (0 7%) to isoniazid, 5 were resistant to more than one drug In many instances the cultures were only slightly resistant, 19 of the 22 strains resistant to streptomycin having resistance ratios of no more than 16 But 3 strains were highly resistant to streptomycin 11 to P A S, and 5 to isoniazid 3 of the 7 strains resistant to P A S were of bovine type and may therefore, have been naturally resistant[30]

At present probably 1 in every 20 newly diagnosed infectious patients in this country has resistant tubercle bacilli in the sputum The prevalence varies with the age of the patient The highest proportion of resistant cultures was obtained from young women nearly 10% of the women aged 15–34 were infected with resistant bacilli—an alarmingly high proportion On the other hand, only 3% of the men in this age-group had resistant cultures The reasons for this unexpected difference between the sexes is unknown In those older than 34 there was little difference—4 9% in women compared with 4 1% in men The prevalence also varied with the part of the country in which the patients lived, the rate being 8 3% in Scotland and 8 2% in the Liverpool area but only 2 5% in the Birmingham area and 1 6% in Wales But the numbers of resistant strains from each area were small, and these differences may only have been chance fluctuations

FOX and his colleagues also investigated the possible sources of infection of the 44 patients with primarily resistant cultures and compared their contact histories with those of 44 matched patients with sensitive strains 47 contacts of the patients with resistant bacilli had been diagnosed as tuberculous since 1945, compared with only 16 contacts of the group with sensitive bacilli Moreover for each drug separately more of the resistant than of the sensitive group were known to have been in contact with patients treated with that drug—13 against 6 for streptomycin, 12 against 3 for P A S, and 3 against 0 for isoniazid Definite evidence of contact with organisms known to be resistant was obtained from 10 of the 44 patients infected with resistant strains, but no such contact was found within the sensitive group In at least half the patients infected with drug-resistant organisms the searching inquiry for contacts revealed nothing to arouse the clinician s suspicion that he might be dealing with a patient infected with resistant bacilli

Some of the implications of this important piece of epidemiological research are clear For the sake of the patient and the community all chemotherapy should be planned so that the risk of resistance is kept as small as possible Probably many of the primarily resistant strains in this survey arose through treatment that would by present standards be judged inadequate and unsafe It should now be very rare for a patient to remain infectious after chemotherapy[31 32] It has been suggested that treatment is less effective in older people [33], but this is unproved and it seems improbable (The current M R C trial of long-continued chemotherapy should answer some of the questions about the response to treatment of this important group of patients) The fact that almost a quarter of the patients infected with primarily resistant tubercle bacilli had been in contact with others known to be expectorating resistant bacilli suggests that preventive measures are not applied as efficiently as they might be The well-known, but not always well applied, preventive measures that are necessary in all infectious cases should be imposed with particular vigour when a patient remains infectious after chemotherapy Sensitivity tests on all pre-treatment cultures are desirable, but not always practicable In most cases in this country it is still possible to give effective treatment without such tests, but if the tests can be done the treatment can be more rational, more patients can be effectively treated, and the occasional discovery of primary resistant cultures will remind the physician of this danger There is much to be said for starting treatment with all three drugs simultaneously in newly diagnosed patients if this is practicable and if the risk of vestibular disturbance after daily injections of streptomycin in the older patient is accepted, and if pre treatment sensitivity tests can be done the results will indicate the most suitable combination of two drugs for further treatment

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[15] Bartter F C *Metabolism* 1956 5 369

[16] Furtos N C Doane E A *J Amer med Ass* 1949 140 1274

[17] Brennan A J Wichelhausen R H *Ibid* p 1275

[18] Avery L S Lewis N G *Amer Rev Tuberc* 1950 61 851

[19] McCoy H I *Ibid*, 1950 62 227

[20] Brun J Kalb J C Viallier J Pommateau E *Lyon med* 1950 183 381

[21] Canetti G Saenz A Thibier R Chevassu Petigny J *Rev Tuberc Paris* 1951 15 125

[22] Meyer A Naveau P Naveau M *Ibid* p 238

[23] Harold J T *Lancet* 1951 ii 655

[24] Thomas O F Borthwick W M Horne N W Crofton J W *Ibid* 1954 i 1308

[25] Bruce L G Cuthbert J Ritchie J A *Scot med J* 1957 2 43

[26] Cummings M M Livings D G *Amer Rev Tuberc* 1954 70 637

[27] Chaves A D Robins A B Abeles H Peizer L P Dangler G Widelock D *Ibid* 1955 72 143 *Ibid* 1956 74 293

[28] Fox W Wiener A Mitchison D A Selkon J B Sutherland I *Tubercle Lond* 1957 38 71

[29] Mitchison D A Selkon J B *Ibid* p [illegible]

[30] Wallace A T Webber W J *Ibid* 1956 37, 358

[31] Crofton J W *Brit med J* 1956 i 345

[32] Middlebrook G *Bull int Un Tuberc* 1956, 26 179

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[33] Caplin M Griffiths, J J Silver, C P *Tubercle Lond* 1956, 37 233

Annotations

THE BUDGET AND MEDICAL REMUNERATION

IN his Budget speech last week the Chancellor of the Exchequer declared that one of his aims was to increase the incentive to further effort by those earning over £2000 a year, and his proposals provide substantial relief for many in this group Thus a man earning £3000 a year who is married and is educating three children aged 11–16 will have his tax reduced from £906 to £732 The difference of £174 represents a tax-free gain of about 6% of the gross income, which is almost comparable to the taxable 10% lately added to the salaries of junior hospital staff as an interim measure [1]

The *Economist* [2] suggests that, with a view to ending the dispute over doctor's pay, the Government should fix the maximum sum that they are at the moment prepared to offer by way of " interim adjustment " and offer to negotiate with the medical leaders on its distribution We should greatly welcome such arrangement If the profession's negotiators found themselves at such a meeting their first thought would no doubt be for those who have not shared in the 10% increase for junior hospital staff and will benefit little if at all by the Budget proposals We have in mind particularly senior hospital medical officers and family doctors with small practices

HAZARDS OF EPOXIDE RESINS

IN the past few years a new group of synthetic materials, the ethoxyline or epoxide resins, has come into extensive use in industry, chiefly in the manufacture of electrical equipment, car bodies, and aircraft Most of these resins are aliphatic aromatic polyethers containing hydroxyl and terminal epoxy groups When they are mixed with highly reactive hardeners, which are usually polyamines, they are transformed at room-temperature into solid infusible substances Manufacturers of resins and hardeners are well aware of the hazards involved, but the introduction of these substances into works unfamiliar with chemical processes has resulted in many instances of toxicity

Pletscher et al [3] reported that, of 20 workmen handling one of these resins, 6 had severe eczema and 8 temporary skin irritation On patch testing, 4 of the affected 14 were hypersensitive to the resin, 2 to the hardener, and 3 to both substances The 6 unaffected men were not hypersensitive According to Grandjean,[4] the eruption associated with these resins has an initial phase, lasting from a week to several months, during which itchy erythematous patches appear on the face and upper limbs In some people the reaction never proceeds beyond this stage, which may be due to primary irritation by the alkaline hardener or be an early manifestation of sensitisation to the resin In others, further contact leads to a very irritating papulovesicular eruption, and at this stage the patient has to stop work

Grandjean has formulated protective measures The worker should be taught to avoid spilling the resin or hardener or contaminating door-handles or pencils Good ventilation and local exhaust equipment are desirable Workers should wear gloves, plastic cuffs, and white overalls, and their faces may be protected by barrier creams

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[1] See *Lancet* April 6, 1957, p 746

[2] *Economist*, April 6, 1957, p 24

[3] Pletscher A Schuppli, R Riepert, R *Z Unfallmed Berufskr* 1954, 47, 163

[4] Grandjean, E *Brit J industr Med* 1957 14 1

VITAMIN A AND THE CEREBROSPINAL FLUID

DEFICIENCY of vitamin A is usually believed to give rise to nothing more severe than impairment of night vision This opinion springs largely from the observations of Hume and Krebs [1] on male conscientious objectors, and we have little information about the possible effects on pregnant women and their children Experimental studies suggest that slight deficiency of vitamin A early in pregnancy is very harmful to the fœtus Warkany [2] stated that gross maternal deficiency of this vitamin led to abortion, and minor degrees of deficiency resulted in the birth of deformed young, the nervous system was often involved, and hydrocephalus was common It was thought that abnormality of bone growth was primarily responsible for the hydrocephalus [3 4], but recent evidence runs counter to this opinion

Millen et al [5 6] found that young rabbits born to does deficient in vitamin A were constantly hydrocephalic Although stenosis of the aqueduct was found, these workers thought that the hydrocephalus was caused by over-production of cerebrospinal fluid (C S F) rather than obstruction of its circulation or reabsorption Vitamin A was known to cause a fall in the C S F pressure of hydrocephalic vitamin deficient calves [7]

Woollam and Millen [8] have now investigated the effects of vitamin-A deficiency on the C S F pressure in chicks In fifty normal chicks, the average pressure did not change between birth and the age of 150 days, but in thirty-five chicks hatched normally, and subsequently fed on a diet deficient in vitamin A, there was a progressive rise in pressure from an average of 108 mm of water at the age of 30 days to an average of 212 mm water at 125 days A third group of chicks were obtained from hens which had been deprived of vitamin A, after hatching, these chicks were fed on a diet deficient in vitamin A, their C S F pressures rose at the same rate as those of the second group, though the mean pressure was higher at a given age in this third group than in the second It was apparent that the pressure was related to the total (pre- and post-natal) time on a diet deficient in vitamin A rather than to the age of the chicks At necropsy no bony abnormality was found in any of these chicks, and clinically the vitamin deficient were indistinguishable from the normal controls Colloidal carbon was injected into the lateral ventricles of three vitamin-deficient chicks, and at necropsy it was found to have passed freely through to the ventricular system, and to be distributed around the meningeal cuffs of the spinal nerves The ventricles were not dilated in any of them, but Woollam and Millen point out that the choroid plexuses of birds, unlike those of higher animals extend out into the general subarachnoid space, and internal hydrocephalus would hardly be expected They still believe that the over-production of C S F is the cause of the increased pressure, but on the evidence this cannot be regarded as proven

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[1] Hume E M, Krebs H A *Spec Rep Ser med Res Coun, Lond* 1949, no 264

[2] Warkany, J *Advanc Pediat* 1947, 2 1

[3] Mellanby E *Proc Roy Soc* B 1941 132 28

[4] Wolbach S B Hegsted D M *Arch Path (Lab Med)*, 1952 54 12

[5] Millen J W, Woollam, D H M, Lamming, G E *Lancet*, 1953, ii 1234

[6] Millen J W Woollam D H M, Lamming G E *Ibid* 1954, ii 679

[7] Moore, L A Sykes, J F *Amer J Physiol* 1941 134 436

[8] Woollam D H M, Millen J W *Brit J Nutr* 1956, 10, 355

These observations raise important questions Hydrocephalus has occasionally been reported in infants born to mothers deficient in vitamin A[9] In this country it is unlikely that pregnant women will be deficient in this vitamin, but if the experimental findings are applicable to man, the hazards of such deficiency may rank with those of rubella Clearly this possibility must be considered in all cases of fœtal abnormality

EMMETROPIA AND AMETROPIA

THE impression that elongated eyes are myopic and short eyes hypermetropic is largely correct, but the mechanistic corollary—that all emmetropic eyes are of the same length and dioptric power—is far from correct The first breakdown of the concept of fixed optical components in the eye resulted from work by Schnabel and Herrnheiser,[10] who found a range of from 22 0 to 25 0 mm in the axes of 23 enucleated emmetropic eyes Studies by later workers on the other components of refraction—namely, corneal power, lens power, and anterior chamber depth—also showed a range of variation Before the advent of the modern concept of biological variation it must have been difficult to reconcile such variation with the accuracy of structure required in the emmetropic eye, but one by one the frequency-distribution curves of the components of refraction were shown to conform to a normal curve

At first the interpretation of such findings was that emmetropia and the refractive errors resulted from the chance association of the components of refraction[11] This, however was not quite true for the distribution of emmetropia and the refractive errors in the population does not fit a normal curve, there being an undue proportion of emmetropia and nearly emmetropic refractions[12,13] This departure from normal distribution denotes that, though each of the components of refraction shows a normal distribution, they cannot be freely variable, some correlating influence must organise them so that there is a tendency greater than chance to produce emmetropia

Prof Arnold Sorsby and his colleagues[14] have confirmed the normal distribution of the values of axial length, corneal power, lens power, and anterior-chamber depth They have also confirmed that there are more emmetropes and near-emmetropes in the population than can be accounted for by the free association of the optical components of the eye Their measurements of the optical components show that "a wide range of axial lengths, corneal powers, and lens powers is seen in emmetropia, the respective values being 21 to 26 mm, 38 to 48 D, and 17 to 26 D" They conclude therefore that "the emmetropic eye is not the end-result of a haphazard combination of variable components, but a coordinated organ The individual emmetropic eye, like the excess of emmetropes in the general population, is not accidental" They also show that the values of the optical components which occur in emmetropia also occur in ametropia up to ±4 0 D, but eyes with refractive errors greater than ±4 0 D show values of refraction components (especially axial length) greater than those which occur in emmetropia An important qualitative difference is thus shown between ametropias less than and greater than 4 0 D, the former being due to incoordination of optical components within the emmetropic range and the latter being due to components beyond the emmetropic range for which no coordination during growth could have compensated

Sorsby and his co-workers studied the correlations of the optical components and found that the correlation coefficient between axial length and corneal power in emmetropic eyes is as high as −0 877 but with increasing ametropia up to ±4 0 D the correlation becomes progressively poorer Thus in emmetropia the correlation makes it clear that longer eyes tend to have "flatter" corneæ and shorter eyes more "curved" corneæ, while in the refractive errors up to ±4 0 D corneal and axial length are less well adjusted to each other—facts acceptable to anyone with a knowledge of simple optics From these findings and from previous work on corneal refraction and axial length in the developing rabbit eye[15] it is postulated that a "simple mechanical and self-regulating process would appear to underlie the marked correlation between axial length and corneal power" The axial length of the eye in the newborn averages about 16 mm, whereas the full grown eye is about 24 mm long An increase of 8 mm in axial length demands a decrease of refractive power of some 20–30 D if the eye is not to become excessively myopic It is not clear yet how the exact adjustment to increased axial length is achieved, but clearly the simple mechanical effect of increasing the spherical size of the eye must automatically lessen the refraction of the cornea by flattening it The lens also must play a part in the adjustment and Sorsby's team have shown a correlation (−0 488) of lens power with axial length This correlation differs from that of cornea to axial length in that it applies equally in emmetropia and in the ametropias up to ±4 0 D It signifies that, irrespective of refractive error, there is a tendency for long eyes to carry "flattened" lenses and short eyes more "curved" lenses Probably the increasing pull on the zonule as the eye enlarges during growth provides a simple mechanical adjustment

Diminishing corneal and lens curvatures are the two main mechanisms by which the occular refraction is adjusted to the increasing axial length during normal growth It has been shown that each of these mechanisms can be accounted for mechanically by the increasing size of the eye during growth It is unlikely, however, that a mechanical process can be entirely responsible for the exactness of adjustment required Sorsby and his team put forward the interesting hypothesis that, just as the optic vesicle is the "organiser" of the overlying ectoderm into a lens and the overlying mesoderm into sclera and cornea, so the retina (derived from the optic vesicle) may well determine the scleral, lens, and corneal sizes A small retina will have a small overlying sclera, with, therefore, a small curved cornea and a highly curved lens A large retina will be covered by a large sclera, and the cornea therefore must be large and flattened and the lens of large diameter and flattened An emmetropic eye is thus conceived as the result of an orderly adjustment which takes place during growth and which is initiated by the optic vesicle and maintained by the retina

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[9] Cornfeld D Cooke R E *Pediatrics* 1952 10 33

[10] Schnabel I Herrnheiser I *Z Heilk* 1895 16 1

[11] Steiger A Die Entstehung der sphärischen Refraktionen des menschlichen Auges Berlin 1913

[12] Brown E V Kronfeld P C *Ophthal Congr* 1929 1 87

[13] Strömberg E *Acta ophthal Kbh* 1936 14 281

[14] Sorsby A Benjamin B Davey J B Sheridan M Tanner J M Emmetropia and its Aberrations *Spec Rep Ser med Res Coun Lond* 1957 no 293 H M Stationery Office Pp 69 7s 6d

[15] Sorsby A Sheridan M *Brit J Ophthal* 1953 37 551

Further understanding of the nature of the refractive errors, and especially of high myopia, depends on elucidation of the hereditary transmission of the optical components of the eye The manner of growth of the eye also requires investigation The valuable report by Sorsby and his team includes accounts of preliminary studies on both these questions

PANCREATITIS AND CORTISONE

ACUTE pancreatitis is usually a non-infective autolytic process precipitated by the release of activated enzymes into the interstitial tissue of the gland The extent and severity of the autolysis seems to determine whether hæmorrhagic necrosis or merely œdema ensues Normally pancreatic enzymes are detectable in the plasma—which suggests that a small amount of the acinar secretion is endocrine and enters the blood-stream direct, although by far the greater part is exocrine and flows into the small intestine What upsets this relationship and initiates pancreatitis remains a mystery Experimentally pancreatitis can be produced in several ways [1]—by rupture of the acini with injections under pressure down the duct, by blockage of the duct and stimulation of secretion, by damage to the pancreatic blood-supply and impairment of local nutrition, and by administration of ethionine (an analogue and anti-metabolite of the amino-acid, methionine) Clinically acute pancreatitis is usually associated with disease of the biliary tract or with acute alcoholism,[2] but in neither case is the mechanism clear Pancreatitis also arises in association with scarlet fever, otitis media, diphtheria, typhoid fever, influenza, trauma, and, of course, mumps [3]

If the diagnosis is sure, medical treatment is directed towards relieving pain, countering shock, correcting electrolyte abnormalities, preventing suppuration, and suppressing pancreatic secretion [4] The mortality varies from 5 to 30% and is highest in those with severe circulatory collapse Some patients have recently been treated with cortisone or other corticosteroids,[4–8] to combat the shock and suppress the inflammatory reaction The shock has been ascribed to adrenal exhaustion, and also to proximity of the pancreas to the adrenals causing adrenal involvement and hence adrenal insufficiency [9] There is no good support for these views, although one of Bockus's seventy-eight patients was found at necropsy to have adrenal atrophy [2] Whatever may be their action, cortisone by mouth or, when there is urgency, hydrocortisone intravenously seem to be of value, and several workers claim life saving results in severely shocked patients [4 7]

In papers which appear on earlier pages of this issue Dr Baar and Dr Wolff describe two cases, and Dr Marczynska Robowska describes a third case, of children in whom acute pancreatitis developed while they were having cortisone or corticotrophin, and the question arises what part, if any, these hormones played in its causation In a girl with asthma, the administration of 25 mg of cortisone was followed at once by pancreatitis, and she died within five and a half hours The other two patients had conditions which could well have been ætiologically significant—one had extensive dermatomyositis and the other had Still's disease, pneumonia, and smallpox Pancreatic lesions can be produced in rabbits by cortisone [10], but pancreatitis has not previously been described as a complication of cortisone therapy in man, and there seems at present to be insufficient reason for discontinuing the assessment of cortisone treatment in acute pancreatitis provided antibiotics are given concurrently

TONSILLECTOMY

IN the war against tonsillectomy the conservatives have so far made all the running [11] The surgeons have remained silent, even though, as Fry [12] points out, over 200,000 such operations are performed annually in the United Kingdom Crooks [13] has now written, with skill and ingenuity, in defence of the operation, and representing, as he does, the Great Ormond Street school, he deserves close attention

He has selected for evaluation a series of 50 doctors' children whose tonsils and adenoids he removed over a period of ten years In the follow-up, he says, a skilled observer—the doctor-parent—has been constantly present to assess the result (Skilled, certainly, but hardly unbiased or dispassionate) The results are presented under headings of the symptoms before operation and the effect on them of tonsillectomy Thus, of 42 children who previously had had tonsillitis and inflamed throat 20 were pronounced cured, 19 improved, and 3 unchanged For all cases and symptoms, 48% were judged cured, 42% improved, and 10% unchanged or aggravated These figures may seem encouraging, but there was no control series, and it is fairly well known that introduction of controls shows that the operation makes no impressive difference [14] Nor does Crooks say how many doctors' children he declined to operate on during the same decade

THE REFUGEES

ALTOGETHER £517 was made available to the fund for medical refugees from Hungary which we opened at the end of last year Nearly all this money was divided between thirty doctors for such expenses as clothes, journeys, and accommodation, but a small sum was devoted to the cost of dictionaries and of gramophone records giving elementary instruction in English In addition, temporary homes were found for several doctors and their families with readers who had offered such help Our Hungarian colleagues expressed warm thanks for this first aid, reaching them as it did before they had begun to find their feet in Britain

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ON April 15 Dr ROBERT PLATT, professor of medicine in the University of Manchester, was elected president of the Royal College of Physicians of London

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[1] Grossman M I *Arch intern Med* 1955, 96 298

[2] Bockus, H L Kaiser, M H Roth, J L A, Bogoch A L Stein G *Ibid* p 308

[3] Gibson, J M Gibson J M jun *J Pediat* 1956, 48 486

[4] Jones C A *Arch intern Med* 1955 96, 332

[5] Stephenson H E Pfeffer R B Saypol, G M *Arch Surg* 1952 65, 307

[6] Eskwith I S Cacace, V A, Sollosy, A *New Engl J Med* 1955 252 494

[7] Rogers N C, Wilson A O Meynell, M J, Cooke W T *Lancet*, 1956 ii, 651

[8] Brockis, J G Jones D T *Brit med J* 1956, ii 1524

[9] Jacobs A *Lancet* 1956 ii, 733

[10] Stumpf H H, Wilens, S L, Somora C *Lab Invest* 1956, 5, 224

[11] See *Lancet* 1954 i, 208

[12] Fry J *Brit med J* Jan 19, 1957 p 124

[13] Crooks J *Practitioner*, 1957 178, 215

[14] McCorkle L P, Hodges R G, Badger, G F Dingle, J H, Jordan, W S *New Engl J Med* 1955, 252, 1066, see *Lancet*, 1955, ii, 810

Special Articles

THE RESPONSE OF MALIGNANT TUMOURS TO RADIATION

A HYPOTHESIS

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THE only known agent which has any destructive effect on the growth of malignant tumours (apart from the metastases of carcinoma of the prostate) is radiation from radium or from an X-ray tube. Although this action has been known for upwards of fifty years we are still completely ignorant of the manner in which it acts. During all this time attention has been directed almost exclusively to working out appropriate dosage and methods of getting rays of the proper intensity at the site of the growth without damaging neighbouring tissues. Because, in tissue culture, X rays have been proved to kill malignant cells before normal cells, it has been accepted that all we have to aim at, to bring about a cure, is to get rays to the growth in sufficient intensity. For which reason the aid of physicists is regularly called in to calculate the correct dose and to give guidance as to how the rays should be directed to the desired spot. The surgeon, who has been instructed where he must put his radium needles to be effective is not likely, in the event, to get them near the sites recommended by the physicist. Nor is there such exactitude in the biological reactions as rules in the world of the physicist.

Clinical experience with radium needles has clearly demonstrated that the most important area in which to put the radium is in the healthy tissue round the growth. In the tongue the needles are placed as a palisade around the tumour. How strange this is if the greater intensity of the rays is required for the malignant cells. It is true that, if the tumour is at the centre of a sphere of radiating needles, it gets more radiation than the zone in which the needles lie. Since the less radiation the normal tissues get the better, it seems very odd that the needles are not confined to the region of the malignant cells where they are needed. Why is this other method, harmful to healthy tissue, universally used? For the very good reason that the clinical results are better. But it is possible that radiations do not work in this simple fashion. It is quite as sensible to believe that the radiation, acting on normal cells, alters their metabolism so that they produce substances which are antagonistic to the agent which causes cancer (in all probability a virus), or to the cells which have been altered by the cancer agent, and that these substances, being carried by the lymph stream to the area of the growth cause death of cancer cells. If such substances are produced they would seem to be destroyed before they reach the general circulation, because the irradiation of a tumour has no effect upon distant metastases.

EVIDENCE FOR CHEMICAL ACTION

Is there any evidence of such chemical action, apart from its being better to implant radiating foci outside the tumour in healthy tissue? In this connection an observation made by Geoffrey Keynes,[1] when he was carrying out his work on the treatment of carcinoma of the breast by the implantation of radium needles, is enlightening. Keynes's method was to implant radium needles in the breast tissue all round the tumour, but not actually into the growth itself. It was necessary in this pioneer work, to prove that the tumour treated was in fact a carcinoma, and to do this Keynes excised a small piece for histological examination. In the report of his cases he says he gave up this practice because he found that, although the primary tumour disappeared, carcinoma was apt to grow afterwards in the scar resulting from his biopsy. This is a very curious fact. The pieces of growth removed for examination were taken at the time of the removal of the needles—7–10 days after their insertion. The cells of the growth left behind in its original situation were alive at this time but subsequently died. The cells which were transplanted to the skin lived. Both sets of cells had been subjected to the same dose of radiation. And it does not seem that interference with the blood supply of the tumour by radiation could afford an explanation, for although, as is well known, some damage does occur it could not conceivably be as great as in a completely separated graft. The transplanted irradiated cells had so much vigour in them that they survived the period of formation of a new circulation and then grew rampantly.

Let us look at this matter a little closer. The breast is an organ which, as far as its lymphatic drainage is concerned, is quite free from the subcutaneous fat in which it lies. The lymphatics form a plexus round the alveoli of each of the 15–20 segments of which the breast is composed, and from this plexus the lymph collects into ducts which drain into the subareolar plexus from which two large lymphatic vessels run to the axillary glands. That some minor vessels run to the anterior mediastinal glands and to above the clavicle does not alter the fact that, if the lymphatics of the breast are injected with methylene-blue, none of the dye runs into the subcutaneous tissue in which the breast lies.

Now Keynes implanted his radium needles in normal breast tissue. Any chemical products formed as a result of this stimulation would be carried off by the lymphatics of the breast and necessarily bathe the tumour tissue. Let us assume that these chemical agents effect the destruction of the growth, not instantaneously but over some unknown period after withdrawal of the needles. If Keynes, by his biopsy, implanted malignant cells into the skin he would be carrying them away from the healing stream he created by his radium implantation, as none of the lymph of the breast passes through the skin. The cells, not having been killed by the direct impact of the rays, would be free to grow in their new situation.

This observation by Keynes (which he did not comment upon except to say that he abandoned biopsies because of it) would be explainable if cancer is cured by X rays as the result of a response of normal tissues to radiation. It is at least a possibility to which attention might be fruitfully turned.

Further support for this view would seem to be afforded by the frequent failure of a second dose of X rays when a recurrence has taken place at a site previously subjected to radiation. The normal tissues here have been damaged so that they are unable to respond to radiation, while the new vigorous cancer cells grow unaffected.

Little is known of the chemical effects upon the tissues of exposure to X rays, and it is most remarkable that intensive research has not been undertaken on this aspect of cancer treatment. There would be much to explain if we accept this chemical hypothesis. Why, for instance, is there no general action of the drug? There can be several explanations of this: it may, for instance, be produced in very small quantities and quickly diluted or destroyed in the blood stream. But the absence of distant action should not hinder us from a chemical investigation of what takes place at the irradiated site, and knowledge gained of this may point the way to the attack on metastases. That a local store is set up from which the substance is slowly released is indicated by the fact that the destructive process of the cancer goes on after the cessation of the radiation.

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[1] Keynes, G. *Brit. J. Surg.* 1932, 19, 415.

SUGGESTED RESEARCH

The testing of thousands of drugs has been without result Here there is something happening, here are tumours actually disappearing, in certain circumstances melting away before our eyes An investigation of what is taking place would surely be more likely to give results than the random testing of drugs or intensifying our efforts to get shorter and shorter waves in narrower and narrower areas—a line of research which has been singularly unproductive over many years

In planning such researches several considerations come to the fore Because of the element of time it is obviously best to work with implanted tumours in small laboratory animals, and it must be ascertained first whether the particular tumour we choose for experiment can be caused to disappear by exposure to X rays Then a tumour must be selected that will give as near as possible 100% positive results on transplantation No deductions could be depended upon with tumours showing great biological variations This is one of the difficulties hampering such work

The chemical extracts of tissue can be prepared by using lipid solvents in some cases and aqueous in others Heterologous extracts of this kind can be quite harmless on injection if protein be removed But by eliminating proteins we may be discarding the very agents we are looking for Then we are quite *ignorant as to whether the wanted* substance is thermo labile—another severe handicap to technique and the maintenance of sterility The particular tissue which should be extracted may be of great importance, so various tissues will have to be tested

The method of radiation needs much consideration, for the quantity of energy needed to produce chemical changes such as we want is quite unknown If a β radiator be used the problem of getting the whole volume of substance under the influence of the electrons must be solved

Such are the questions for which answers have been sought in some researches by Dr Arthur Compton and myself But the whole problem is a very large one, and I do not see, apart from the unlikely lucky hit, that an early solution can be arrived at unless such researches are undertaken on a considerable scale and by numerous experimenters To me it seems well worth pursuing any new path in the baffling enigma of cancer

PRICE OF PROPRIETARY PREPARATIONS

THE Government have accepted in principle a scheme for regulating the price of the 4000 proprietary preparations which the Joint Committee on Prescribing recommended should be available for National Health Service patients subject to satisfactory price arrangements with the manufacturers These drugs account for about 90% of the cost of all proprietaries prescribed under the health service—£23$^1/_2$ million out of a total of £25$^1/_2$ million The scheme has been negotiated by the Health Ministries and the Association of British Pharmaceutical Industry It will run for a trial period of three years

Under the scheme manufacturers will regulate their prices voluntarily according to the following principles

The price in the United Kingdom will not exceed that which the product commands in adequate volume in overseas markets in face of international competition

When a product is not exported in significant quantity, if an identical non proprietary standard drug is available in the U K the price of the proprietary shall not exceed the price of the standard drug

If it is impossible to apply either of the above provisions, a maximum price may be determined by using a detailed formula comprising (i) an ingredient allowance based on recognised trade prices and (ii) processing and packaging allowances according to a schedule covering different types of product

The prices determined by these principles will be maximum prices Immediate effect will be given to price reductions that result from the application of the scheme, but if the permitted maximum is higher than the existing price the existing price will not be increased on that account The scheme also provides that a manufacturer may instead negotiate "a fair and reasonable price" with the Health Departments

The scheme is not designed to reduce prices generally but to curb excesses where they exist While its effect on National Health Service costs is not expected to be large, a saving of up to £750,000 a year is thought possible To meet the industry's need to finance research and development no product will come under the scheme during the first three years of the product's life

THE ROYAL COMMISSION

Terms of Reference and Procedure

AT a special comitia of the Royal College of Physicians of London on April 11, Sir Russell Brain, the president read the answers he had received to questions he had asked the Prime Minister He also gave an account of his meetings with the Royal Commission and with its chairman, Sir Harry Pilkington After hearing his statement the college decided that they wished to cooperate with the Royal Commission

The Prime Minister's Answers

Question 1

In clause "A" of the *Royal Commission's terms of* reference the term "other professions" is a vague one, since today there is no agreed definition of a profession Apart from this it is difficult to see why the incomes of other callings should be treated as irrelevant to the economic and social status of the professions Will the Royal Commission be free to take into account incomes earned not *only* in the "professions," but also in commerce and industry, both as salaries and wages—a point of obvious importance in relation to recruitment to medicine?

Answer—It must be left to the commission to decide what interpretation should be put on the words "*other* professions," but I feel sure that they would not wish to adopt any narrow interpretation or refuse to consider any callings which might be cited in evidence *before* them

Question 2

Clause "B" begins "What, in the light of the foregoing, should be the proper current levels of remuneration?" This has been interpreted as meaning that the Royal Commission would have to limit itself to a consideration of the matters set out in clause "A" The fear has been expressed that this is unduly restrictive, and that the Royal Commission having heard evidence on other matters would find that its terms of reference precluded its consideration I have in mind the matters referred to the Spens Committees, namely, "the desirability of maintaining in the future the proper social and economic status" of general medical practice and consultant and specialist practice, and their "power to attract a suitable type of recruit to the profession" Hours of work and the responsibility of the work undertaken are also important considerations Would the Royal Commission be free to make recommendations "in the light" not only of clause "A" but also of any other evidence which the medical and dental professions might wish to present?

Answer—The medical profession would be free to bring points of *this kind to the notice of the* commission, and there is nothing in the terms of reference to prevent the commission from considering them Indeed, in order to satisfy their terms of reference they would have to consider some at any rate of them As in the case of other evidence it would be for the commission to decide what weight to attach to them

Question 3

It would seem that any recommendations about future remuneration should take into account how the present levels of remuneration have been arrived at, *and* this would include a discussion of the recommendations of the Spens *Committees and the Danckwerts* award Would the doctors and dentists be free to put before the commission their view that the remuneration of the professions, now and in future, should be determined on the basis of the Spens recommendations and the Danckwerts award?

Answer.—I feel sure that the commission will be prepared to receive and to take into consideration any expression of views which the medical and dental professions put before them as being in their opinion relevant to the commission's work.

Question 4

On March 11 in the House of Commons, Mrs Jeger asked the Minister of Health "whether it will be within the terms of reference of the Royal Commission on doctors and dentists remuneration to consider the abolition of merit awards." The Minister replied: "The Royal Commission will normally be concerned with levels of remuneration, not with methods as such. Whether or not questions such as that referred to by the honourable member are within its terms of reference must rest with the commission itself to decide." I should be glad to know whether the commission has reached a decision on this point, and, if not, when it will have done so.

Answer.—I cannot say what if anything the commission have decided; if it becomes possible for them to make any statement on the matter which you raise, they will no doubt do so themselves. But I imagine that they would wish to hear evidence and to make substantial progress with their work before arriving at a view as to whether and if so how far, their main task of recommending "proper current levels of remuneration" requires them to consider the particular matter which you mention.

Question 5

There is a strong feeling in the medical profession that our colleagues in the public-health service should not be excluded from the scope of any review of remuneration. Do the terms of reference of the Royal Commission include them?

Answer.—The remuneration of doctors employed by local authorities is excluded from the scope of the Royal Commission's recommendations but any claim on their behalf through the usual machinery would necessarily be considered in the knowledge of any recommendations of the commission.

Having begun his letter by saying that "interpretation of the terms of reference is a matter for the Royal Commission and I cannot in any way formally commit it," Mr Macmillan concludes with the statement that he has consulted Sir Harry Pilkington, who agrees with his replies.

Statement by the Royal Commission

On April 12 the Royal Commission issued a statement on how they have decided to proceed:

1. The Spens reports and the Danckwerts award will be studied by the commission, and also the reports of any other commissions and committees in so far as they are relevant to the circumstances of the medical and dental professions and to the relationship of those professions to the community as a whole.

2. The commission will bear in mind the need for maintaining a proper level of recruitment to the medical and dental professions in competition with other callings, and will consider evidence as to conditions imposed by the nature of the work.

3. The phrase "other professions" will be interpreted widely so as not to exclude, for example, science and other graduates in industry at all levels.

4. The commission are not asked to recommend remuneration for doctors and dentists employed by local authorities, but these doctors and dentists are among the "other members of the medical and dental professions" on whose remuneration evidence will be received for purposes of comparison.

5. "Other connected occupations" cover a wide range of persons, including on the one hand hospital administrators, and on the other nurses and medical auxiliaries whose remuneration will be considered with special reference to differentials.

6. The commission will in the light of all this and any other relevant evidence recommend such "current levels of remuneration" as appear to the commission to be justified.

7. The *commission's duty to recommend current levels* of remuneration calls for recommendations covering, for example, average incomes and the desirable spread between extremes; but it does not call for the construction of detailed schemes of distribution.

8. After consideration of the desirable current levels of remuneration for doctors and dentists, the commission will consider whether, and if so what, arrangements should be made to keep that remuneration under review.

In a separate notice the Royal Commission are asking all interested persons or organisations to offer evidence. "Preliminary inquiries have shown that the preparation of this evidence will take some of the bodies concerned considerable time. The commission are anxious to complete their task with the utmost speed consistent with thorough examination of all the relevant issues, and hope that all written evidence and submissions to the commission will be in their hands within the next three months."

Public Health

The Salford Radiography Survey

IN 1953, an intensive mass miniature radiography (M.M.R.) survey was made in Salford[1] and some of the new points made in a report on it by Hughes[2] will be useful in planning future surveys.

A feature of the survey was a special canvass of a random sample of the population, urging them to attend. The response was 29.5% (i.e., about the same as in the general population of adult Salford residents) when a commercial firm of canvassers was used, but 42.7% when the canvassing was done by health visitors, who more often elicited a family history of tuberculosis. The health visitors could not be spared for further canvassing from their other duties—one of the most important being to *supervise tuberculous patients* in their homes.

Persons in the random sample were asked various questions. Most preferred evening M.M.R. sessions, and thought that leaflets (which were sent to all householders) were the most effective form of publicity. But Dr Burn, the medical officer of health, was impressed rather by the value of personal interviews. Attendances for radiography were greatest in the early weeks of the campaign: enthusiasm fades after six weeks. When the numbers began to fall off, professional canvassers were used to rekindle it, but the response was slight. In general the response was regarded as disappointing, and this was thought to be due to the many previous selective surveys in the city.

As usual in mass radiography, the highest prevalence of tuberculosis was found in patients specially referred by the family doctor, and a substantial number of tumours was also detected. The group with the highest prevalence of tuberculosis was men of 45–59—in which the response was poor. In various surveys it has been found that the bigger the proportion of the population responding, the higher the number (per 1000 radiographed) found to have active disease. It is estimated that there may be 150–160 undetected cases in Salford, more than half of them with positive sputum.

As a result of the survey, there was a peak in the incidence of new cases found in Salford in 1953; since then the number has fallen sharply, and it is now below the average for the 21 largest towns of England and Wales. As in the country as a whole, about 21% of deaths from respiratory tuberculosis in Salford in 1955 were in cases not previously notified. The number on the clinic registers is rising by 2–3% a year, though the death-rate continues to fall. The record of patients recovered and erased from the register is said to be better than in most towns.

A list of priorities for the most efficient use of M.M.R. is given by Dr Burn.

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1. See *Lancet*, 1954, ii, 1172.
2. Hughes, H. F. The Salford Health Survey: Review of the Mass Radiography Survey in 1953 and the position to 1956. Obtainable from the Public Health Department, 143 Regent Road, Salford 5.

Medical Education

THE STUDENT AND SEX EDUCATION

BERNARD SANDLER
M D Manc , D M R , D Obst
MEDICAL OFFICER IN CHARGE, INFERTILITY CLINIC,
MANCHESTER JEWISH HOSPITAL

THE student and his problems are sometimes discussed as though he were a separate species of mankind created de novo, already 17 years old ! It seems to be forgotten that he is an adolescent, very recently a child, who often has just left the security of the parental home for the first time He is in fact especially likely to have emotional problems, since he commonly combines high intellectual equipment with inadequate emotional development, compared with the average adolescent in commerce or industry whose emotional adjustments are usually made earlier (Grant 1954, Logan 1954)

He is equally likely to have problems of sex The combination of emancipation from parental authority, a fevered romanticism, and an urge for erotic adventure may well throw his emotional stability out of gear In the case of medical students, the study of anatomy and physiology induce a mechanistic approach to matters which are primarily spiritual and psychological The student whose sex education has been inhibited or distorted by his home background can get into very considerable difficulties, for he may already have serious emotional tensions when he arrives at the university Parnell (1951) found that 1% of all undergraduates at Oxford were suffering from some mental disturbance, and of all those absent through illness for a full term over half were mentally ill Malleson (1954) said that 10% of all students in residence in any given year could be classified as "distressed students," and that the suicide rate was higher than in a similar age group in the general community Hence we cannot discuss sex education for the student without reference to the formative influences in his life before he reaches the university Sex education does not begin with the formal talk by father to son as pictured in Victorian times It starts at a very early age by unconscious absorption of the attitudes adopted by those handling the child, and it continues throughout life It is much more than a description of the genitalia and the sex act it includes the whole relationship of man and woman with each other Thus the student may enter medical school with only the vaguest idea of how to deal with manifest problems of sex and marriage which are so important to the welfare of so many patients , and of course he is still less likely to recognise these problems when they are concealed as symptoms to which his teaching has paid no attention

It is strange therefore that though every student during his training is expected to know how a gastrectomy and an arteriogram are done—operations which none will ever have to perform without further postgraduate training—sex and marriage are touched on only briefly as an incident in clinical teaching His instruction is still too often based on organ dysfunction rather than on the treatment of the patient as a whole , and where the two patients comprise the single entity of a marriage, such an approach is even more hopeless As a rule, the illness encountered in a clinic is seen from the viewpoint of the specific organs in which that clinic specialises rather than as a syndrome of the whole person The consequence is that most doctors who acquire any knowledge of sex by the time they graduate, do so, not by organised instruction in the subject but rather by personal enterprise Not all doctors may be suited temperamentally for giving advice on this subject , but at least they should receive sufficient basic training to enable them to recognise not only their patient's difficulties but also their own inhibitions

In an infertility clinic such as mine, where husbands and wives are seen together, and where an attempt is made to assess the marriage rather than one partner of it, many cases (which are referred apparently solely for sterility) are in fact found to have psychodynamic problems of marital disharmony which have unfortunately not been recognised either by the patient or the doctor Worse still, advice has been disastrous in certain cases when given by a doctor insensitive to, or untrained in, the recognition of these emotional problems This consideration led me to inquire whether medical education is adequate in these matters

Instruction at Medical Schools

To ascertain the present position of medical teaching I asked forty seven medical schools in Great Britain and abroad to tell me what instruction is given in the following subjects

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Thirty six schools sent replies—twenty-four in Britain and twelve abroad Of these, only two said that no instruction was given at all, one saying that it "was not desirable for students" But only five provided formal lectures on coitus and conception, though in a further six these topics were discussed in clinics In twelve, one formal lecture was given on contraception, and in another seven clinical instruction was arranged In seven, lectures were given on sexual maladjustment and in another five it was discussed in the clinics Finally, the psychological problems of the background to marriage were discussed by none in formal lectures, but in fourteen these were mentioned in a general way during the course of clinical teaching These figures suggest that probably less than half of the students at these schools have had anything like adequate instruction before they enter their professional life

To compare the opinions of the students with those of their teachers, inquiry was made of graduates from five universities who had qualified in 1951–53 The teachers at these particular universities had informed me that such instruction was included in general clinical teaching, though not in systematic lectures, and they were satisfied that enough was taught But at only one of the five was the training regarded as satisfactory by the graduates At the four others, all the graduates said that they were dissatisfied and had in fact very little or no instruction

We may compare this with the replies given to Ingleby (1952) on the teaching of teachers and clergy, who also have an influence on family life in the community

Teachers

Of fifty-one training-colleges and seven university education departments, all except three deal with sex education The courses of instruction were divided by Ingleby into three groups (1) Fifteen covered only anatomy and physiology and there were no other lectures (2) Twenty-one discussed the psychological implications and gave training for sex teaching in a broad sense Possibly this was done with an academic rather than a dynamic psychological approach, but at least an attempt was made to discuss emotional adjustments and sex relationships in terms of the students' own personal adjustments (3) In ten, attempts were made to give a broader approach to sex in the wider setting of marriage and the family , in some cases this included a completely separate course of lectures

Clergy

In sixteen out of twenty Church of England colleges, a course of 9–12 lectures with special references to the ethical and psychological aspects of sex and marriage was given Other denominations gave some training on marriage but none was as adequate as the Church of England training

From this it seems that doctors are the least equipped of the three professions dealing with these concerns of everyday life. If in fact the main obstacle (apart from inertia) is the overburdened curriculum, surely the time has come to discard some of the traditional items in favour of what is of increasing importance in the modern world.

This is not the place to outline all the psychosomatic syndromes likely to be encountered either in disguise or as diagnoses which the patients themselves make, such as impotence, frigidity, and vaginismus. Such cases should obviously be treated by those who specialise in them; but it is astonishing how many such patients are still treated with tonics, sedatives, or just "reassurance." Once rebuffed they will rarely return to the same doctor for advice on such a matter, and when their difficulties continue for years they eventually become hopelessly incurable.

My purpose is simply to state a case for the improvement of medical education on these topics, and to put forward suggestions for incorporation in the medical curriculum.

Recommendations

The student should receive instruction in sex education and be helped to solve his own personal problems. If he can understand himself, he is better able to understand others: an emotionally maladjusted student will be a bad student and a worse doctor. Each university should have an adviser for students, to whom they can bring their personal problems. He would combine knowledge with understanding based on experience. (An adviser whose advice is academic and who cannot perceive the unasked questions in the student's mind may be worse than no adviser at all. Equally, the other type of adviser who gives the student a slap on the back and the hearty advice to "go out and get a woman" may also do serious emotional damage.) Undoubtedly advisers with the right personal qualifications are scarce, but even so it seems that in many universities little attempt has ever been made to find them. Here the local marriage guidance councils could help.

Systematic lectures on the physiological and psychological background of normal coitus should be given to senior medical students. The relation of sex to the larger sphere of family life and human relations should be explained, and a sense of perspective given of its relation to right living. (At many schools such subjects as marriage guidance, premarital preparation, and marital dysharmonies do not seem to be covered.) Systematic lectures should also be given on sexual maladjustments, coital technique, impotence, vaginismus, &c., by someone experienced in these subjects. Each university library should contain a selection of books and pamphlets on all these subjects.

Instruction in contraception is indicated—both theoretical (with a film) and practical (by attendance at Family Planning Association centres).

Lectures on the spiritual and psychological background to marriage, with special emphasis on normal relationships, could well complete the course.

Lists of suitable books on sex and marriage problems may be had from the National Marriage Guidance Council, 78, Duke Street, London, W. 1, or the "Alliance," 238, Edgware Road, London, W. 2, free of charge.

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He is equally likely to have problems of sex. The combination of emancipation from parental authority, a fevered romanticism, and an urge for erotic adventure may well throw his emotional stability out of gear. In the case of medical students, the study of anatomy and physiology induce a mechanistic approach to matters which are primarily spiritual and psychological. The student whose sex education has been inhibited or distorted by his home background can get into very considerable difficulties, for he may already have serious emotional tensions when he arrives at the university. Parnell (1951) found that 1% of all undergraduates at Oxford were suffering from some mental disturbance, and of all those absent through illness for a full term over half were mentally ill. Malleson (1954) said that 10% of all students in residence in any given year could be classified as "distressed students," and that the suicide rate was higher than in a similar age group in the general community. Hence we cannot discuss sex education for the student without reference to the formative influences in his life before he reaches the university. Sex education does not begin with the formal talk by father to son as pictured in Victorian times. It starts at a very early age by unconscious absorption of the attitudes adopted by those handling the child, and it continues throughout life. It is much more than a description of the genitalia and the sex act: it includes the whole relationship of man and woman with each other. Thus the student may enter medical school with only the vaguest idea of how to deal with manifest problems of sex and marriage which are so important to the welfare of so many patients, and of course he is still less likely to recognise these problems when they are concealed as symptoms to which his teaching has paid no attention.

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* * *

The account of my peripatetic colleague's brush with the Law (March 30) reminded me of a similar occasion which, however, had a happier outcome

I was bidden to attend at ten of the clock in the forenoon precisely before London's senior metropolitan magistrate—no less The summons added ominously, wherein fail not The charge Unnecessary Obstruction ("What is necessary obstruction ?" a colleague of mine had asked the magistrate some weeks earlier and had promptly been fined double the usual amount) I was indignant because my car was proximal to the yellow-band notice which guarded the entry of a small tributary into the major artery of traffic I was even more indignant because I was parked next to a large delivery-van which the policeman told me he would not be prosecuting

On receiving the summons therefore I rang up the motoring organisation to which I belong "Leave it all to us," they reassuringly said "No need for you to attend the court you will plead guilty of course " They were shocked when I said I had no *intention* of so doing A barrister friend of mine was of the same spineless mind "Don't be an ass," he advised "I'll represent you if you insist, but it will cost you a lot of money and the old basket will fine you three times as much " I therefore conducted my own defence When I pleaded not guilty, a sigh compounded of disbelief mingled with pity wandered around the court The magistrate looked profoundly sad The atmosphere reminded me of the occasion when the Snark pronounced judgment "When it said the word *GUILTY* the jury all groaned and some of them fainted away"

The police gave their evidence I cross-examined Was I close to a hospital ? Yes Did I ask the constable if he was going to prosecute the delivery van ? Yes Did he do so ? No Why not ? It was here that he made his fatal error "Well, that's different That chap's delivering goods " "Sir," I said, turning to the magistrate, "I submit that when I go to a hospital I also deliver the goods " The magistrate could be seen wrestling with himself Hardened inspectors blanched a passing cloud obscured the sun Suddenly the Great Man beamed "Well, well," he observed genially, "I know you doctors have to do your job Case dismissed "

* * *

First rather senior registrar Are there any jobs in *The Lancet* today ?

Second R S R No But there is a rather promising obituary, from Newmanpool

* * *

News Release, New York (to be used on or after Feb 10, 1967)

After almost 5 years of intensive research by nearly 1000 company scientists in conjunction with hospital and university researchers the Pillum Ram Co today announced 'Multipanas,' an entirely new concept in medication In one pill it has been found possible to contain all the daily drug needs of the average American The 'Multipanas Magnatab' consists of an outer core containing 25 vitamins, 25 essential elements, aspirin, a tranquilliser, amphetamine, and bioflavinoids, whilst the delayed release' inner core contains barbiturates An ingenious label wrapping 3 times round the bottle makes it possible to list each ingredient so as to meet registration requirements In a companion product for those over 40 this balanced formula has been fortified by synthetic sex hormones with marked anabolic activity To devise and perfect this product researchers travelled over 600,000 miles Said the company's President "It is a pity circumstances did not permit them to travel further such products would never have been even thought of 10 years ago " The Pillum Ram Co has global branches and subsidiaries including The Pillum-Ram Co of England

Letters to the Editor

CÆSAREAN SECTION

SIR,—The picture painted by your leading articl (April 6) of maternal and fœtal risks of delivery by cæsarean section is black indeed, and some may fee that the dangers are exaggerated Crude morbidity figures are difficult to interpret and I have always found it hard to explain the high mortality-rate reported by Marshall and Cox,[1] whom you quote No practising obstetric surgeon could possibly accept a maternal death rate of 1% today In my personal series since 1943 of 1114 sections, 2 mothers have been lost

In one case a woman semiconscious after eclamptic convulsions died a few hours after delivery Necropsy showed a pontine hæmorrhage and a large subarachnoid hæmorrhage In the second case a primipara, exhausted by prolonged labour with an impacted breech presentation, died unexpectedly on the eighth day of the puerperium Necropsy showed a large pulmonary embolus, with extensive thrombosis of all pelvic veins, extending into the femorals In the first case, and perhaps also in the second, the operative delivery had little direct relation with the maternal death

I cannot believe that this experience is exceptional A similar criticism can be made of your quotation of a perinatal fœtal mortality-rate of 4 9% in Brooklyn I have not read Gordon's article[2] yet, but we may suppose that a high proportion of these infants were small prematures or otherwise prejudiced in some way Healthy mature infants should not be lost

It is easy to make further comments on controversial points in the operative technique you recommend Delivery of the fœtal head by the hand implies a uterine incision large enough to accommodate both hand and head at the same time It may be difficult to get the fingers below an impacted head and the uterine muscle is easily torn Some may feel that these are serious drawbacks, and that delivery by small Wrigley's forceps is more elegant and technically more sound Trendelenburg tilt of the table is permissible only if the patient is properly intubated with a cuffed tube Otherwise dangerous regurgitation of gastric contents may follow Ischæmic necrosis of the uterine muscle with continuous sutures is difficult to prove I have myself been well satisfied with continuous sutures On four occasions when I have been able to recover the uterus in later years, after a previous section, careful microscopic examination has failed to demonstrate any uterine scar It is necessary, however, to pay special attention to the strong fascia over the muscle, in order to obtain a perfect scar

Chobham Surrey L G HIGGINS

BENIGN MYALGIC ENCEPHALOMYELITIS

SIR,—The title of the paper by Dr Galpine and Dr Brady (April 13) and other reports[3] suggest that the term "benign myalgic encephalomyelitis" may find a place in medical terminology This name was first suggested in your leader last year[4] for a widespread epidemic disorder of presumed infective origin with the following clinical characteristics (1) symptoms and signs of damage to the brain and spinal cord in greater or lesser degree, (2) protracted muscle pain with paresis and cramp, (3) emotional disturbances in convalescence, (4) normal cerebrospinal fluid, (5) involvement, in some variants, of the reticuloendothelial system, (6) a protracted course, with relapses in severe cases, and (7) a relatively benign outcome

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1 Marshall, C M Cox L W Transactions of the 12th British Congress of Obstetrics and Gynæcology 1949, p 30
2 Gordon C A *Amer J Obstet Gynec* 1957 73 65
3 Crowley N, Nelson, M, Stovin, S *J Hyg, Camb* 1957, 55, 102
4 *Lancet*, 1956, i, 789

With the lapse of time and the publication of accounts of the Royal Free epidemic,[3 5 6] the clinical similarities of the various outbreaks classified in group II of your leader have been underlined, and there seems a prima-facie case that they are similar in cause and pathology

As Sigurdsson [7] pointed out, there are obvious dangers in naming a disorder in which the ætiology and pathology are unknown There is always the risk that the name will turn out to be inaccurate There appear to be two alternatives (1) the disorder should be named after the place where it first appeared, or (2) a purely descriptive term should be applied on the basis of the known clinical characteristics—"an epidemic disorder characterised by disturbance of the central nervous system, painful muscles, a normal cerebrospinal fluid and often enlargement of lymph-nodes" (or, to contract, "epidemic ameningitic lymphoreticular myalgic encephalomyelopathy")

The first suggestion has the disadvantage of all eponyms it conveys nothing to the uninformed There is also some doubt in this instance which place name to apply. The second, although informative and accurate, is obviously impracticable Clearly some compromise between accuracy and brevity must be found "Benign subacute encephalomyelitis" has been suggested [8] This name has the advantage of conveying that the active course of the disease is often long, but unfortunately it also suggests that the outset is insidious (as in subacute bacterial endocarditis and subacute combined degeneration), which is far from the truth Crowley et al.[3] have suggested "lymphoreticular encephalomyelopathy", whatever its other merits may be, this name defies pronunciation and defeats memory

"Benign myalgic encephalomyelitis" has been criticised because the disease is not always benign, nor invariably myalgic, and possibly never encephalomyelitic Benignity is relative, and it seems to me that "benign" is sufficiently justified by the fact that there is no other recorded infective disease of the central nervous system without mortality As various authors [5 9 10] have stressed, the pain in this disease, although not invariably present may be devastating and is perhaps the feature which impresses itself most forcefully on the observer As far as the final term is concerned, the clinical impression that the lesion is central rather than peripheral is supported by the electromyogram There appear therefore, to be the alternatives "encephalomyelitis," which suggests an inflammatory lesion, or 'encephalomyelopathy," which implies a toxic or degenerative lesion In our present state of ignorance "encephalomyelitis" seems preferable because it conveys the suggestion that the disease is almost certainly infective in origin As Sigurdsson points out however, a final decision must await the examination of pathological material, for even in infective conditions some of the lesions may be toxic (as in diphtheria) In the meantime the disorder needs a provisional name and "benign myalgic encephalomyelitis," although necessarily imperfect, has fewest disadvantages

To reiterate the main points, the following features appear early in the disease and should suggest this diagnosis

(1) Symptoms and signs of involvement of the brain and spinal cord

(2) Protracted muscular pain in chest abdomen or limbs, often with tenderness cramp, involuntary movements, spasm and paresis

(3) Normal cerebrospinal fluid

(4) A characteristic electromyogram

(5) Involvement, in some variants, of the reticuloendothelial system

Low or absent fever, protracted course, a tendency to relapse, and mental symptoms in convalescence are features of some cases A curious jerky response of the affected muscles to volition in convalescence may prove to be a further clinical characteristic of this fascinating disorder.

Middlesex Hospital
London, W 1

E D ACHESON

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[5] Compston N Communication to section of epidemiology Royal Society of Medicine Feb 9 1957

[6] Richardson A T Ann phys Med 1956 3 81

[7] Sigurdsson B Lancet 1956 ii 95

[8] Jellinek J E Ibid p 494

[9] Acheson E D Ibid 1954 ii 1044

[10] Bond J O Ibid 1956, ii 257

ÆTIOLOGY OF PRE-ECLAMPSIA

SIR,—An important point in considering Mr Sophian's views (March 9 and 16) is the question whether, in pregnancy (not necessarily the same conditions as those in Mr. Sophian's experiment when he demonstrated the uterorenal reflex) the growing volume of fœtus and membranes is in reality putting as high a pressure on the walls of the uterus as Mr Sophian assumes

Many obstetricians who have had to rupture the membranes of primiparæ who are not in labour have noted the fact that the bag of waters is very often not distended but shrivelled [1] The same thing has been found in twin pregnancy The intra uterine pressure in twin pregnancy is not increased.[1] In acute hydramnios a high intra-uterine pressure is obviously not primary but secondary to greater secretion of the amniotic fluid or to increased permeability of the vessels in the membranes

I find it hard to see how the intra-uterine pressure can be high during the whole of pregnancy The pregnant uterus is not distended by the growing fœtus (as for example, the finger of a rubber glove may be, by insufflating it and putting the contents under pressure), the muscle cells are multiplying continually, and in this way the walls of the uterus are trying to adapt themselves, by becoming longer, to the growing volume of fœtus and membranes, which are in no way exerting pressure upon the uterine walls

These walls are not overstretched and the lumina of their arteries not narrowed, the construction of these arteries (curling or corkscrew arteries of Hunter) is an extra safeguard against such events Hypertension in those arteries has never been demonstrated, but it is often said that, during pregnancy, conditions in them are the same as those under which Goldblatt demonstrated hypertension by applying a clamp to a renal artery Such assertions, however, are based on the assumption that in pregnancy the intra-uterine pressure is increased, but this assumption is not clearly proven

In adrenalectomised animals Goldblatt could not produce hypertension by applying a clamp Even admitting that in toxæmia of pregnancy (e g, in acute hydramnios) the contents of the uterus may now and then press upon its walls, in the way Mr Sophian does during his experiments obviously a situation of stress would be created and the adrenals might play an important part in producing the resulting symptoms—e g, by producing adrenaline and so constricting the renal cortical arteries The Trueta phenomenon is often observed after stress

Mr Sophian is obviously following Conn when he says that the hormones are playing only a secondary part during toxæmia of pregnancy But 2 of Conn's 5 patients were Negresses just recovered from severe toxæmia of pregnancy [2], and Conn's syndrome and aldosteronuria can be provoked in animals by implanting stilbœstrol crystals [2] or injecting growth hormone [3] For these reasons I am doubtful whether the distinction between primary and secondary aldosteronuria is a justifiable one

The study of Conn's syndrome, however, has made clear that

(1) The adrenal cortical hormones have a big influence on glomerular and tubular renal function, causing potassium loss, proteinuria, and sodium retention—symptoms which disappear when a cortical tumour is extirpated

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[1] De Snoo and Stroink Communication to a meeting of the Royal Netherlands Society of Obstetrics and Gynæcology 1953

[2] Franks L M, Chesterman, F C Lancet 1956 ii, 1193

[3] Moon, H D Koneff A A Li C H Simpson, M E Proc Soc exp Biol, N Y 1956, 93, 74

(2) These tumours often contain over 8000 µg of aldosterone[4] The quantity of aldosterone found in the urine daily in cases of primary and secondary aldosteronuria is of the order of 30–60 µg evidently the adrenal cortex is storing most of the aldosterone synthesised there, as the adrenal medulla stores most of the adrenaline and noradrenaline Only on special occasions is a little part of the store poured into the circulation Could this reaction be provoked by histamine, liberated after an antigen antibody reaction ?

The study of the urinary excretion of aldosterone, adrenaline, noradrenaline, and the so called catechol derivates, immediately before, during, or immediately after the eclamptic fits seems to me to be of prime interest for solving the question of the ætiology of toxæmia of pregnancy Recently Selye expressed the same view[5] The uterorenal reflex, curious as it may be, is to my opinion not an active factor in the pathogenesis of toxæmia of pregnancy

Amsterdam,
Holland

R SCHUURMANS

NEURONE SELECTION IN RELIEF OF PAIN

SIR,—Professor Lehoczky (Feb 16) refers to the use of 10 ml of 0 5% aqueous phenol injected into the first or second sacral foramen for sciatica and similar pain from other causes I have used this approach of Bonica[6] and endorse its value, and would in fact prefer it to intrathecal methods for non-malignant conditions

Pain from cancer, however, is a different proposition Here at the Pain Relief Centre we have to afford relief at any level ranging from the highest occipital to the lowest sacral segments To give some idea of how formidable this is, for cancer in the pelvis alone the segments which must be reached often extend from D11 to S3 or 4 Here, it is essential to eradicate systematically the small non medullated C fibres from some 11 to 12 roots for unilateral pain, and 15 or more for bilateral pain This number of roots can be influenced in bulk only by intrathecal injection using 1 ml phenol (1 in 20 in glycerin) at the D11–12 interspace, followed after five days by a similar 1 ml injection at the L4–5 interspace for one side Bonica's approach, though of value at the sacral sciatic site, could never be expected to cover this range of neurones often met in carcinoma After intrathecal injections, the rapidly acting phenol sometimes cannot penetrate at some of the roots and becomes inactivated, leaving pain residue at the corresponding sites This resistance is often due to sheltering of neurone cells by areas of carcinoma, as Dr Shrigley demonstrated for me

A slower acting agent, such as phenol and silver nitrate, allowed greater penetration before it was neutralised, and relieved half these resistant cases If such intrathecal methods were unsuccessful it was considered that the peripheral end of the ganglion might be reached For this purpose relief has often been completed by epidural injections at the resistant sites Bonica's method might be defined as epidural injection with the advantage of presenting a bulk of solution to the nerve-roots close to the ganglia This proximity to the ganglia is essential, otherwise gasserian-ganglion injection would not be required for 5th-nerve pain Ordinary epidural injections unfortunately tend to follow the diffuse outline shown in the first radiograph in my article (Jan 5) This has been partly overcome by collapsing the dural sac by puncture at a different level to drain the C S F, followed by an epidural injection further down, with the "draining" needle left in situ The patient lies on the pain affected side

I would therefore say that for pelvic carcinoma the neurone elements must be influenced in length—i e, from D11 to S1 or 2—and in depth, so that the ganglion cells are influenced throughout Recently I have added Bonica's method in some of my cases, and it has been of great value for providing penetration from the peripheral site in the locality where subarachnoid penetration was insufficient

Rochdale

R M MAHER

A STUDY OF WAKE

SIR,—Surely Dr Jacobides's definition of sleep (March 30) rests on the unwarranted assumption that the starting point for all thought about sleep wake is unquestionably and of necessity wake, not sleep It is this assumption that seems to me to be so wrong It is like a physiologist trying to study muscle action by assuming that the experiment begins with a contracted muscle, or like an educationist looking at a senior wrangler and wondering how such a person could ever have been in a state of not knowing his twice times table It is starting thought from the wrong end

One is surely justified in seeking an understanding of the problem from as far back in life as possible It is Barcroft himself who uses the words "asleep" and "wake" in describing fœtal behaviour

I quite agree with Dr Jacobides that the concept of "wake maintainers" may not appear convincing at first sight, and it is here that research is most necessary, especially in the earliest manifestations of wake maintenance in young babies Why does the reticular activating system sometimes "keep open" for a time after the original arousal stimulus has subsided, especially if the wake maintainer appears to be a simple, innocuous, and unvarying stimulus ?

Perfect sleep is certainly biological "well being," but this is not to deny that wake may be "better becoming" !

Hove 1

W. V CRUDEN

INSULIN TREATMENT OF SCHIZOPHRENIA

SIR,—Sacred cows are hardy animals, and the insulin coma treatment illustrates this too well It never was any good, but mental hospital doctors found relief in being high powered therapists of schizophrenia instead of the mere custodians they once were, so its legendary reputation thrived There were adverse studies, but they were lost amid an enthusiastic deluge and, for 20 years, the method lived on without a single comprehensive review in the language really to challenge it Ultimately, when I came to supply one in your columns,[1] the average psychiatrist was seldom any longer aware that strong doubts had always existed about insulin, and in some respectable quarters too

Heresies are not immediately popular, and the heated correspondence that ensued was largely as expected There has been no pause in expenditure on new insulin coma units, they have remained a priority, and even in poor, under developed countries, experts from Britain still have not hesitated to advise the immense investment they entail

However, there were signs of a turn in the tide Whereas only a bare dozen studies questioning, in one way or another, the value of insulin coma appeared over the whole 20 years preceding my review, at least seven have been published since[2–8] And now, surely, the report by Dr Ackner and his colleagues (March 23) must at last compel a change in prevailing policies Here we finally have the most carefully arranged trial on record, and it confirms that the treatment has no specific value, and none, moreover, in the very type of case where its use is particularly recommended

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[4] Lake, L, Linder, G C *Quart J Med* 1956 25 530
[5] Selye, H *Virchows Arch* 1956 329 420
[6] Bonica J J The Management of Pain London, 1953 p 352

[1] Bourne H *Lancet*, 1953, ii 961
[2] Boardman, R H Lomas, J Markowe, M *Ibid*, 1956, ii, 487
[3] David H P *Amer J Psychiat* 1954, 110, 771
[4] De Alarcon Trigueros, R *Act luso esp Neur* 1953 12 308
[5] Hoenig, J Leiberman, D M, Auerbach, I *J Neurol Psychiat* 1956, 19 130
[6] Kochn J D *J ment Sci* 1955 101, 871
[7] Lifschutz J E *Amer J Psychiat* 1954 111 166
[8] West F H Bond, E D, Shurley, J T, Meyers, C D *Ibid*, 1955, 111, 583

The purpose of this letter is to suggest that the continued use of insulin-coma therapy has not only become irrational but is an actual menace to the mentally sick Being wildly extravagant in the scarcest of mental-hospital commodities—namely, money, and medical and nursing time—it beggars other provision, it has a mortality which is not negligible, and, worst of all, it effectively screens doctor and patient from any other approach to the problems of schizophrenia The psychiatrist in training probably suffers most damage Juniors are usually posted in the insulin unit, thus, at its foundations, their knowledge of schizophrenia includes no subtle observation of its psychology and no experience of psychotherapy Insulin coma therapy even impedes the proper use of electroconvulsive therapy, which is learnt as a casual procedure, administered sporadically and without system, as an adjuvant to the insulin ritual

No doubt the insulin treatment will be defended to the death The "it can't do-any-harm-to-try" argument is not only destitute, it is false and dangerous

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HAROLD BOURNE

UTERINE ELECTROLYTES IN PREGNANCY AND LABOUR

SIR,—We were most interested to read the account of changes in uterine electrolytes in pregnancy and labour given by Dr Cort and Dr Cort (April 6), since we have been working on this and related problems for the past two years A preliminary note of certain of our findings has already appeared [1]

It is implied in the Corts' paper that hysterectomy specimens, from women under 46 years of age, represent normal uterus We feel that this assumption is probably unjustified To illustrate this point, table I shows a comparison between the electrolyte composition of normal myometrium (biopsies taken at mid-cycle during plastic and other operations on the uterus) and myometrium from uteri which contained fibromyomata The specimens from fibroid bearing uteri are divided into two groups—those in which one or more seedling fibroids were present and those in which a hysterectomy had been performed for multiple fibroids It will be noted that the changes in electrolyte pattern are more extreme in the second group We have some evidence that these changes are due to hyperœstrinism Electrolyte disturbance in the uterus appears to occur also in other disorders necessitating hysterectomy Further, Daniel and Boyes [2] have found some evidence of changes in uterine electrolyte pattern during prolonged bleeding necessitating hysterectomy

TABLE I—INTRACELLULAR IONS IN HUMAN MYOMETRIUM

—	Normal uterus	Fibromyomata present	
		Seedlings	Multiple fibroids
Intracellular K+ (m eq per 100 g dry)	28	31	27
Intracellular Na+ (m eq per 100 g dry)	1	4	6
K+ concentration (m eq per kg intracellular H_2O)	122	107	90
Na+ concentration (m eq per kg intracellular H_2O)	9	13	19

Dr Cort lays some stress on his finding of a progressive loss of potassium from the myometrial cells during normal pregnancy and labour Our figures do not entirely support this contention (table II) We were unable to detect statistically any actual loss of potassium from the cells as a consequence of pregnancy or normal labour, though the total intracellular potassium levels did fall in inert labour There was a fall in the calculated concentration of potassium in the intracellular fluid of the myometrial cells during normal pregnancy and labour (table II) This appeared to be due to increased hydration of the cells Our values for intracellular sodium, which is elevated in pregnancy, are probably comparable to those of the Corts though the actual figures differ because a slightly different assumption was used in determining extracellular space The values in pregnancy and labour in table II refer to the lower uterine segment, as do those of Dr Cort We have, in fact, found parallel changes in biopsies from the upper part of the uterus

TABLE II—INTRACELLULAR IONS IN HUMAN MYOMETRIUM IN PREGNANCY

—	Normal uterus	Early pregnancy	At term		Delay in labour	
			Not in labour	In labour	(a) Early	(b) Late
Intracellular K+ (m eq per 100 g dry)	28	32	34	30	27	25
Intracellular Na+ (m eq per 100 g dry)	1	6	12	10	9	10
K+ concentration (m eq per kg (intracellular H_2O)	122	99	95	103	87	79
Na+ concentration (m eq per kg intracellular H_2O)	9	18	35	25	27	31

The cases of uterine inertia we studied were divided into two groups (*a*) where there was delay in dilatation of the cervix in the first 24 hours of labour (cases of failed trial of labour), and (*b*) where labour was in fact prolonged for more than 48 hours, and cæsarean section had to be conducted for delay where the cervix was more than half dilated In both these groups there was evidence of depletion of intracellular potassium, the values being most markedly reduced in group (*b*)

We feel that while the potassium concentration in the myometrial cells is reduced during normal pregnancy and labour, this is probably a physiological phenomenon due to hormonal conditioning and water retention rather than to a process of depletion or deficiency When our values obtained from biopsies of myometrium at hysterotomy in early pregnancy are compared with those at term and in normal labour (table II) there is no evidence of progressive change in intracellular potassium The reason why Dr Cort and Dr Cort find potassium reduction in their group of "normal" labours may be the incorporation in this group of cases of failed trial of labour and failure of the head to engage, with their implication of uterine inertia Such cases (table II, delay in labour, early) do have much reduced intracellular potassium We could find no such depletion in our biopsy specimens from patients in normal labour—cases who had been scheduled for elective cæsarean section but had gone into labour, and cases of fœtal distress, where there was no evidence whatsoever of incoordinate uterine action

In conclusion, therefore, we feel that there is no clear evidence that the changes in uterine electrolytes occurring during normal pregnancy and labour are other than physiological, or that the reduction in intracellular potassium that occurs can be regarded as a deficiency These changes may well be the consequence of changed hormonal influence—Talbot et al,[3] and Horvath [4] have shown that hormonal changes can influence the uterine electrolyte balance We fully agree with Dr Cort and Dr Cort that in uterine inertia there is a deficiency of potassium in the myometrial cells We have shown, in fact, in another study,[5] that plasma-potassium also falls in long labour—an effect we attributed to prolonged hypersecretion by the adrenal cortex This intra- and extra cellular potassium depletion may well contribute to the uterine inertia

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[1] Nixon W C W, Smyth, C N *J Obstet Gynæc, Brit Emp* 1957 64 35

[2] Daniel, E E, Boyes D A *Amer J Obstet Gynec* 1957, 73, 395

[3] Talbot, N B Lowry, O H, Astwood, E B *J biol Chem* 1940, 132 1

[4] Horvath, B *Proc Nat Acad Sci* 1954, 40, 515

The use of rational intravenous electrolyte administration in uterine inertia might be very productive, and we await the introduction of such therapy with great interest

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D F HAWKINS
W C W NIXON

HEAD INJURIES

SIR —The letters of Mr Lowden (Jan 12) and Professor McConnell (March 2) prompt me, albeit with some diffidence, to offer yet another solution to the problem of acute extradural hæmorrhage occurring at a distance from a neurosurgical centre

Twice in the past three years I have been faced with this problem The first patient, a child of three years, was 150 miles distant and the second, a youth of 17, was over 200 miles away In each case the classical signs of extradural hæmorrhage, including coma, had supervened within three hours of an apparently trivial head injury Air-transport to this centre was arranged, but, because even this method of transfer was not likely to prove rapid enough in view of the early onset of coma, the referring physician was advised to make a burr-hole in the appropriate temporal fossa and pack the wound open while awaiting the arrival of the air ambulance (In the first case the burr-hole was actually made with an ordinary brace and bit obtained from the local ironmonger) Both patients arrived with somewhat bloody dressings but otherwise in sufficiently good condition to make excellent recoveries following evacuation of their extradural hæmatomas

Grey Nuns Hospital,
Regina, Saskatchewan

P B RYAN

CLEARANCE RESULTS IN OLIGURIA

SIR,—Phillips et al[6] stated that division of the clearance for any substance by the intrarenal plasma extraction of the same substance gives the value for renal plasma flow (R P F $= \frac{C}{E}$) Consequently the R P F multiplied by the E for any substance will give the clearance for that substance ($C =$ R P F $\times E$)

In the dog dehydrated by thirsting we determined R P F by measuring directly the blood flow from the renal vein and the inulin, creatinine, and P A H extraction by analysing arterial and renal venous blood The clearance of these substances was also determined We found, that, below a diuresis level of 0 35 ml per min per sq m (i e, in oliguria) the value of $\frac{C}{E}$ is but a fraction of the directly measured value As extraction (E) is normal in oliguria, the low $\frac{C}{E}$ value can be ascribed to a misleadingly low clearance value only On enhancing diuresis by mannitol or saline infusion the difference between the direct value and $\frac{C}{E}$ disappears inasmuch as R P F and F change very little, but the clearances increase to their true value

This finding has placed in a different light Chesley's statement[7] that in man the urinary concentration of different substances does not change below a diuresis value of 0 35 ml per min, and in that range the value of clearance is proportionate with that of urine output Our data indicate that in extreme oliguria the regulation of diuresis does not become a glomerular function, but the clearance values are unreliable We believe that in oliguria, even in clinical practice, one should be very cautious in evaluating clearance results

A detailed account of our data is to be published in *Acta physiologica hungarica*

Physiological Institute,
University of Budapest

P BALINT
E KISS
S SZALAY

RHEUMATOID ARTHRITIS WITH CHRONIC LEG ULCERATION

SIR,—In their courteous reply of March 30, Dr Allison and Dr Ray Bettley have paid but scant attention to what they themselves agree is the crux of their whole argument—namely, that in their cases they could apparently rule out any question of venous stasis because the ulcers failed to heal in bed

To say "we need hardly detail the bed rest and ancillary treatment" is to present statistics without figures, for if bed rest is not completely and accurately controlled in these patients it may quite well *appear* to be worse than useless

Many with stasis ulcers give a history of these failing to heal despite prolonged "bed rest" Fortunately most of them can be healed by elastic adhesive ambulatory compression, but in the very difficult cases that we are discussing, in which ambulation is reduced to a painful and pitiful minimum, bed rest will invariably do the trick provided the patient *lies down* (twenty four hours a day, except for meals and their excretion) *in a bed tilted nine inches at the foot*

My impression is that the Middlesex cases were *not* so treated, and I must emphasise once again that until this has been tried there is positively no evidence on which vascular stasis can be excluded as an ætiological factor

London, W 1

STANLEY RIVLIN

SIR,—Like Dr Rivlin, I fear that Dr Allison and Dr Ray Bettley's conclusions (Feb 9) are not quite justifiable I had the opportunity to treat 3 patients similar to those they cite, and I report here the history of 1 who is still under my care

Six years ago a housewife aged 50 first had symptoms of rheumatoid arthritis which steadily increased in severity and caused much deformity Three years ago many cutaneous nodules began to appear over the elbows and the backs of the thighs From time to time one or two nodules broke down and punched out ulcers were formed which healed rather easily She ran a fever for a long time, with spikes as high as 39°C (102°F) In the past skin eruptions had very often been controlled with anti histamine drugs

Fifteen months ago she was further crippled by a big ulcer on the outer surface of the lower third of the right leg The ulcer appeared on the fifth day of a course of treatment with cortisone, which was therefore stopped Previous treatment of the arthritis included courses of gold, salicylates, phenyl butazone, and iodides The ulcer healed very slowly, probably because she was not strictly confined to bed When bed rest was ordered with the leg raised above the level of the heart, after three months it was completely healed

Apparently the ulcer resulted from vascular stasis caused by the restricted muscular activity in the leg Interstitial œdema and decreased tissue resistance induced by cortisone may also have played a minor part

It is hard to accept the diagnosis of lupus erythematosus in the cases described by Dr Allison and Dr Ray Bettley Not only leg ulcers but also true allergic manifestations (skin eruption, drug sensitivity, and sometimes bronchial asthma) are quite common in rheumatoid arthritis Surely not all these patients have disseminated lupus erythematosus It would be better perhaps to put all these patients into the category of rheumatoid arthritis with collagenous manifestations

Athens

G E PAPAYANNOPOULOS.

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[5] Hawkins D F, Nixon W C W (In course of publication)

[6] Phillips R A, Dole, V P Hamilton P B, Emerson, J Archibald, R M, Van Slyke, D D *Amer J Physiol* 1946, 145, 311

[7] Chesley, L C *J clin Invest* 1938, 17, 119, 591

PHENYLBUTAZONE IN SUPERFICIAL PHLEBITIS

SIR,—Dr Gillhespy's observation (April 6) on the therapeutic effect of phenylbutazone in superficial phlebitis could be explained by its anticoagulant action, investigated and described by Humble.[1]

If in fact this is the correct explanation, phenylbutazone might not offer any advantage over the established anticoagulants, since its effect in this respect would appear to be variable and unpredictable.

Twickenham, Middlesex   DAVID WHEATLEY

EMULSIFIERS AND CORONARY THROMBOSIS

SIR,—Much has been published in the daily press lately on the increase in the number of cases of coronary thrombosis, the main suspicion being directed at the amount of animal fat consumed by the class of person most likely to be afflicted.

May I, just a layman, point a finger of suspicion at certain substances which are being used in ever-increasing quantities in many of the common items of food more than likely to be eaten by the same class of persons.

I refer to glyceryl monostearate and other emulsifiers which enable fats to be mixed easily with water, and I would suggest that when they are consumed in the diet in large quantities they may be absorbed and alter the state of the fat in the blood and so possibly be responsible for the damage to the arteries and cause thrombosis.

Taking this matter a step further, the use of detergents, which are also emulsifiers, for washing up crockery, and which are not properly rinsed off, can introduce into the digestive organs another substance which may alter the state of the fat in the blood.

Glyceryl monostearate is used as a crumb softener in much of today's bread, in ice-cream to increase the bulk or volume from a given weight of fat, in cake mixes to enable the house-wife to make quicker cakes, and in prepacked cakes which remain soft for many days.

I think investigations along these lines might prove very profitable, although I must confess I send this letter with trepidation.

Bristol 4   F. J. ROBERTS

FRACTURES OF THE FEMORAL NECK

SIR,—Mr Newman (March 30) paid a generous tribute to a factual review by Dr Murray and Mr Young (March 23) of fractures of the neck of the femur treated at the Southern General Hospital, Glasgow. He noted a high mortality rate and, while accepting the likelihood of error in any statistical comparison, suggested that this was evidence against delay in operation.

As an illustration that we are dealing here with a particularly poor-risk group, it should be said that some of our cases have been discharged home from other city hospitals as being unfit for surgery and thence admitted to our wards by the Beds Bureau. The high mortality quoted (33% overall, 26% for operative cases, and 48% for those treated conservatively) is also a measure of the difficulties of disposing of geriatric cases from acute surgical wards.

Mr Newman compared this with an average mortality of 16.8% among 564 patients treated surgically, collected from the literature. The mortality-rate for our 139 patients treated surgically *was 14% in the first twenty-eight days*.

This would surely provide a fairer figure for comparison, since as far as American publications are concerned at least, it is rare for a bed in an American hospital to be occupied by the same patient for twenty-eight days. Few of our patients went home within twelve weeks.

Certainly if we are to compare the results of immediate operation (within twenty-four hours) with those of elective operation (average time from fracture till operation, four days) surely the mortality-rate in the first month is the figure to take.

Southern General Hospital, Glasgow, S.W.1   W. SILLAR

CYTOLOGICAL DETECTION OF UTERINE CANCER

SIR,—Dr Anderson (April 6, p. 738) is quite correct when he states clearly that cytology is no longer an untried method in the research stage, but in the Birmingham study[1] of the value of cytology in gynæcological practice which we carried out at the request of the Royal College of Obstetricians and Gynæcologists, the establishment of the technique in the hands of technicians (none of whom is medically qualified) amounted to research.

First of all we had to show that in our hands the technique would confirm the presence of obvious cancer of the cervix, which was soon established. A lower efficiency, however, was inevitable in cancer of the corpus, for cells are not shed regularly or may be swamped with blood. The most important part of our research, however, was to find out for ourselves how many cases of cancer we were missing in routine investigation of outpatients. To keep our clinical practice up to a high standard we used a questionnaire and we inspected the cervix with great care. Since 1954 we have abandoned the detailed questionnaire and simply write down on our case sheets in the outpatient department that this patient has or has not carcinoma of the corpus or cervix. We are thus tied down as clinicians, leaving the cytologist a chance to claim a "pick-up" for the technique, should cancer cells be obtained from a clinically normal case.

How many cases were we missing, for obviously 1 per 10,000 would have made the technique valueless, whereas 2% would have made it almost obligatory for our or for any gynæcological clinic? We found that in 2250 patients (in two years) we had missed 1 case of early cancer of the cervix. We also missed 1 case of carcinoma of the corpus which escaped our exploratory curette, but the risk to her life was less in that postmenopausal bleeding would have made hysterectomy obligatory without positive smears.

Our conclusion was therefore that, in our practice, cytology was almost never required to reach a diagnosis of uterine carcinoma. But cytology led us to discover 8 examples of carcinoma-in situ which would have escaped our usual investigations. We have now screened over 5000 patients and the figure of 3 per 1000 is being maintained. With many hundreds of hours of microscopy was this a reasonable "harvest"? We concluded that it was, and in this came into line with many centres in the U.S.A. and elsewhere, including this country.

M. J. D. Noble and M. E. Attwood have applied this "search" technique to diabetics (Dr J. M. Malin's patients) and this study is ready for publication. Their "harvest" is greater than in our outpatients, not only for invasive but also for "in situ" lesions.

Studies are also continuing in the field of therapy; for instance, 13 of our cases of carcinoma-in situ have been "treated" simply by deep ring biopsies—i.e., we have the beginnings of information on therapy.

Dr Anderson suggests that although cytology per se is not research the technique can be used as part of research into the natural history of cancer. I suggest that the operative word "can" should be replaced by "must"; but in this my colleague, Dr C. W. Taylor, director of pathology, Birmingham Hospital for Women, does not entirely agree with me. My opinion is based not simply on the fact that it takes hundreds of hours of microscopy to discover 1 case of carcinoma-in situ but that each case should be a subject of study to offset the time-consuming work by the cytologist.

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[1] Humble, J. G. Empire Rheumatism Council Symposium on Butazolidin, Nov. 13, 1953.

[1] McLaren, H. C., Taylor, C. W., Attwood, M. E. J. Obstet. Gynæc., Brit. Emp. 1956, 63, 801.

In our own firm, ordinary clinical study involves the automatic admission of all patients with positive smears for ring biopsy and curettage, this is followed by long-term follow-up studies by the clinicians and cytologists and, of course, a complete study of the histology may require us to undertake radical surgery In other words, we are recording facts which may be of use to us when presented with therapeutic problems—e g, the woman of 28 with carcinoma-in situ who wishes to have a family

I believe further that the time has now come to carry out what Malcolm Donaldson proposed in 1951—namely, that our findings and our results should be centralised in a "British committee for the study of carcinoma-in-situ" The condition is rare so that individual centres in Worcester, Derby, Glasgow, Newcastle, Liverpool, Manchester, Oxford, and London, where cytologists are at work, are unlikely to find sufficient cases or to study them long enough to give us within a reasonable time some knowledge to guide us in therapeutic problems Therapy, of course, is based on a knowledge of the natural history of carcinoma in situ

To sum up, then, I agree with Dr Anderson that cytology is not per se research but offers a challenge to those who employ this most tedious and time consuming test not to be content with a "routine service" but to write up every case with care, and to include prolonged follow-up irrespective of the therapy employed An appeal is also made for an extension of the work at present centred in the Royal College of Obstetricians to include all centres willing to take part in a joint effort to increase our knowledge of what is a most interesting and ill-understood condition—carcinoma-in-situ

Queen Elizabeth Hospital,
Birmingham, 15 **H C McLAREN**

SIR,—Your leading article of March 23 surprised me by its arguments Some 15 years after the introduction of cytology into gynæcology, at a time when cytology has not only been fully recognised and established as a diagnostic method in the United States but is already represented by regional professors of the specialty, we are still asking in Britain, "is cytology really necessary?"

There should no longer be any doubt that cytology can detect cancer cells in vaginal secretions, that these cancer cells may come from the vagina, cervix, endocervix, body of the uterus, or, occasionally, from the ovaries, and that clinically unsuspected malignancies (be it that the lesion is microscopical or outside the reach of the inspecting eye) are recognised at a stage when other methods fail There is equally no doubt that cytology does not provide a 100% guarantee of a correct diagnosis No laboratory method is infallible there are as many pitfalls in biopsy techniques, and anyone who expects that the laboratory can replace clinical judgment lives in a fool's paradise

Is it really of paramount importance which figure of "pick up rate" (Anderson's 1 1% or McLaren's 0 44%) is more accurate, and do you really think the fate of cytology should depend on this assessment? "Pick up rates" vary according to the material screened, and depend also to a large extent on the clinical acumen of the gynæcologist as well as on the skill and experience of the cytologist All these points are variables and it is, therefore, not surprising that different figures are quoted in the literature It might be wise if, before discussing "the true value of cytology," we first found a definition of what constitutes a cytologist It appears that judgment on the value of cytological investigation is often passed by people who have been toying with the technique for a short while and, for lack of competition in this field, feel entitled to regard themselves as authorities

Early cancer detection is but one aspect of the method and there are others Vaginal cytology offers useful and reliable information on ovarian function during the reproductive period and provides important help in the decision as to what type of hormonal treatment should be used in menopausal disturbances Lastly, it plays a unique rôle in cancer follow-up examinations as a detector of early recurrence or failure of response to treatment

May I finally make a plea for cytology? Do not let us lose our sense of proportion when evaluating a new method by demanding the impossible Do not let us forget that the vaginal-smear technique is just one way of examining a patient, widening the field of diagnostic possibilities, and should be used in addition to but not instead of the other time-honoured methods We argue about a failure rate of approximately 10%, but do not let us forget that there are still 90% of patients who benefit by the method

Institute of Obstetrics and Gynæcology,
Hammersmith Hospital, London W 12 **ERICA WACHTEL**

HASHIMOTO'S THYROIDITIS

SIR,—Two recent papers[1] in which Hashimoto's thyroiditis or struma lymphomatosa are mentioned in the titles raise an important question When dealing with a condition which is not an everyday matter, it is, I think, necessary to define it beyond a perfunctory "histological sections showed the typical appearances of Hashimoto's thyroiditis," with or without the name of the doctor diagnosing the material It has been my own experience[2] that too often what is commonly referred to as "Hashimoto's struma" is not what Hashimoto[3] described, but what appears in textbooks, which, as I recall Gooch's remark about history texts that one is a copy of the other plus the spice of original error, is usually erroneous May I suggest that a brief summary of diagnostic criteria be included in any paper which seeks to discuss the less common pathological states

Los Angeles **S M RABSON**

GOVERNMENT AND PROFESSION

SIR,—I read with great interest Dr Fry's letter (March 30) and should like to support and reinforce much of what he says

If a Royal Commission is to sit on doctors' remuneration, then the terms of reference should be so wide that the whole system of remuneration of general practitioners will be brought under review, and for this purpose doctors should be added to the existing lay members

Is it not long past time to change a system which penalises the good doctor, which can pay to the experienced clinician the same emoluments as to his youngest colleague, and which offers as the only inducement to the keen and able doctor, if he wants a good reward, the compilation of a big list, with no hope of easing up until he retires?

What is the alternative? What method could be introduced which would encourage good practice only, which would offer incentive to the young, and some relief to those getting on in years? Here I break away from Dr Fry and put forward my own proposals

The general practitioner's income in future should be made up as follows

(a) An expense factor —This would very broadly cover his practice expenses as allowed for income tax purposes, thus giving the doctor every day as he starts the day's work a tranquil mind, without having to think "Have I got enough heads to live?"

(b) A length-of-service factor, as in other Government medical appointments

(c) Awards for special skills or a very high level of service

(d) Locality allowance, to be paid to doctors who practice in specially difficult areas or in resorts largely inhabited by old people

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[1] Luxton, R W *Lancet* March 2 1957 p 441 Morgans, M E Trotter W R *Ibid*, March 16, 1957, p 553
[2] Rabson S M Arata J E *Amer J clin Path* 1949, 19, 751
[3] Hashimoto H *Arch klin Chir* 1912, 97, 219

(c) A capitation fee, uniform throughout the country, to be paid for each patient

This method would encourage good practice, reward experience, and console those who work in difficult areas

Worthing HAROLD LEESON.

TRAINING IN ADMINISTRATION

SIR,—Your readers will notice in your advertisement columns this week that the Newcastle Regional Hospital Board are advertising for an administrative medical officer, that no administrative experience is called for, and that a clause is used saying that facilities for training will be offered. May I enlarge on this advertisement for what is essentially a trainee appointment ?

" No concerted action has, to the best of my knowledge, been taken in this country to train medical administrators, and the Newcastle board are hoping to do something of a pioneer nature It is hoped that applications will be forthcoming from those whose experience is solely clinical or solely in public health , if such a candidate is appointed to the post, a planned programme of training will be undertaken, including attendance at suitable courses and secondment to general, special, and mental hospitals for varying periods Very probably the doctor appointed will also be "lent out ' for periods of perhaps a week at a time to one or two hospital management committee group centres in order to see the work at this level Should the doctor appointed wish to take a higher qualification, full facilities for this will be offered , should he wish to take the D.P.H examination of the University of Durham suitable time off will be given in order to allow this

R H M STEWART
Senior Administrative
Medical Officer

Newcastle Regional Hospital Board
Benfield Road
Newcastle upon Tyne 6

SHERRINGTON CENTENARY

SIR,—This is the centenary year of the birth of Sir Charles Scott Sherrington. O M , a founder and main architect of the physiology of the nervous system The Royal Society of Medicine, wishing to pay tribute to his life and work, proposes to raise a fund towards a Sherrington lecture, for the furtherance of knowledge on the nervous system, to be delivered from time to time in the society's rooms in London It is felt that many will wish to contribute both those who were his friends pupils, and colleagues, and those, more numerous, who, as patients doctors, and scientists, have benefited indirectly from his work. We wish to take this opportunity to commend the endeavour of the Royal Society of Medicine to establish this memorial to a great pioneer in scientific medicine.

Donations should be made payable to the secretary, the Royal Society of Medicine, 1, Wimpole Street, London W 1, and cheques crossed " Sherrington Memorial.

RUSSELL BRAIN
President Royal College of Physicians

LINDOR BROWN
Foreign Secretary Physiological Society

JOHN FULTON
Sterling Professor of the History of Medicine Yale

W R HENDERSON
President Society of British Neurological Surgeons

CYRIL HINSHELWOOD
President of the Royal Society

E G T LIDDELL
Waynflete Professor of Physiology, Oxford

D W C NORTHFIELD
President Section of Neurology Royal Society of Medicine

CLEMENT PRICE THOMAS
President Royal Society of Medicine

CHARLES SYMONDS
President Association of British Neurologists

FRANCIS WALSHE
Chairman, Sherrington Memorial Committee Royal Society of Medicine

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Medicine and the Law

Shortening of Life

THE trial of Dr John Bodkin Adams on a charge of murdering a patient by administering drugs has been reported at great length in the national press, and there is no need to review here the course of the longest murder trial in English history and one which ended in the acquittal of the accused But the judge's summing-up, which lasted for four hours, contained some important remarks on the position of a doctor after health can no longer be restored to a patient

Mr Justice Devlin began by emphasising a point which is familiar enough to the medical profession—namely, that no one has the right deliberately to cut off life Murder, he said, was " an act or series of acts done by the prisoner which were intended to kill and did in fact kill." It did not matter for this purpose that death was inevitable If life were cut short by weeks or months, it was just as much murder as if it were cut short by years The jury, said his Lordship, had heard a good deal of discussion about the circumstances in which doctors might be justified in administering drugs which would shorten life—cases of severe pain had been suggested and also cases of helpless misery. "The law knows of no special defence of this category."

His Lordship went on to say, however that this did not mean that a doctor aiding the sick or dying had to calculate in minutes or hours or perhaps in days or weeks the effect on the patient s life of the medicines he administers " If the first purpose of medicine—the restoration of health—can no longer be achieved, there is much for the doctor to do, and he is entitled to do all that is proper and necessary to relieve pain and suffering, even if measures he takes may incidentally shorten life '

The judge was careful to explain what this last statement meant

It is not the case that there is any special defence for the medical man and it is not the case that doctors are put into any different category to other citizens What I have said rests merely upon this part of the offence of murder, that no act is murder which does not cause death—and ' cause ' means nothing technical or scientific it means what you twelve men and women sitting as a jury in the jury-box would regard in a common sense way as the cause

" Manifestly, there must be cases in the hospitals day after day in which a doctor is faced by whether giving certain treatment or omitting to give certain treatment prolongs or shortens life by hours and perhaps even longer

" The doctor who decides to administer a drug, or not to administer a drug is not of course thinking in terms of hours and minutes of life He could not do his job properly if he were

" If for example a doctor has done something or omitted to do something and death occurs say on the 11th or 12th or on the Monday instead of the Tuesday, no one with commonsense would say the doctor caused the death.

" They would say the cause of death was the injury or whatever it was that brought her to hospital It remains a fact and remains the law that no doctor, nor any man has the right to deliberately cut off life I say it to you so there can be no mistake

" It does not enter into the defence at all No defence has been put forward that has vested any right in Dr Adams to make this determination in this case or any other case

' Counsel for the defence is saying that treatment given by Dr Adams was treatment designed to promote comfort, and if it be the right and proper treatment the fact if it be that it shortens life does not convict him of murder ' [1]

In concluding this part of his summing up, Mr Justice Devlin referred to the use of the word " justify " in relation to a course of treatment It was, he said, a pity that the word had ever been brought into the case To the lawyer it suggested some legal justification

" In this case the word ' justify ' was used purely in the medical sense If a doctor is going to prescribe a course of drugs we have heard the sort of dangers that may result

' The patient may become comatose and the effect on the patient may be a complication, pulmonary congestion and so forth and it may lead to death. and therefore the doctor who is going to prescribe this treatment has to consider that and has to ask himself whether he is justified in a medical way in running that risk

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[1] *Evening Standard*, April 8 1957

"The word 'justify,' as I understand it, has been used purely in that way Dr Ashby has said there was no such dreadful discomfort as would justify the administration of those drugs, and he is saying simply the risks that were being run by administering those drugs were not justified"

Permanent and Pensionable

A woman clerical worker sought in the Chancery Division and the Court of Appeal of Northern Ireland a declaration that her engagement under the Northern Ireland General Health Services Board had not been validly terminated, and eventually appealed to the House of Lords against decisions in favour of the board The House of Lords by a majority (Lord **Tucker** and Lord **Keith** of **Avonholm** dissenting) allowed her appeal.

In June, 1948, when unmarried, she applied for a post as senior clerk under the board The post was advertised in a Belfast newspaper and the advertisement stated that "subject to a probationary period appointments will be permanent and pensionable" She was selected for appointment, resigned from her previous employment, and started work on a six-month probationary period in August, 1948 Shortly after starting work, she was handed a document containing the full conditions of service They included the following clause

> 'Dismissal and reduction in rank, and termination of employment otherwise The Board may dismiss any officer for gross misconduct and may dismiss any officer who is proved to their satisfaction to be inefficient and unfit to merit continued employment Except where an officer has been guilty of gross misconduct, the Board shall give at least one month's notice of their intention to exercise their powers of dismissal under this rule As an alternative to dismissal, the Board may order the reduction in rank of an officer who is found by them to be unfit to discharge the duties of the grade in which he has been employed One month's notice in writing shall be given by all permanent officers who wish to terminate their employment with the Board"

In February, 1949, having served her probationary period, she was confirmed in her post On Aug 14, 1950, the board inserted in the conditions of employment a condition that "female officers will on marriage be required to tender their resignations to the Board" After being advised that that condition did not apply to officers already on the staff, she got married in March, 1951 The board thereafter sought to determine her employment by notice expiring in August, 1954

In the House of Lords Lord **Oaksey** said that the question depended on the construction of the contract The board had contended that in the case of a general hiring for an indefinite time a master was entitled to give his servant reasonable notice and that the contract in question was one of master and servant for a general hiring In his Lordship's opinion this was not a simple contract of general hiring for an indefinite time It began by an offer of a permanent and pensionable post, and the contract incorporated provisions that the officer was entitled to an annual pension on a contributory basis on completing 10 years' service in circumstances of ill health or on attaining the age of 60, a short-service gratuity for 5 years, and other pension rights and allowances for sickness To offer an officer a permanent and pensionable post on such terms and then to claim the right to give him notice which would deprive him of all the pension and other rights offered by the express terms of the contract not only was not a right which the parties must have intended the master to have but one which no reasonable person could have contemplated he would claim The appeal should be allowed

Lord **Goddard**, concurring, said that, while he did not think that because a person was offered pensionable employment the employer thereby necessarily engaged to retain the employee in his service long enough to enable him to earn a pension, nevertheless when one considered the express condition here relating to dismissal the fact that the offer in the advertisement was for permanent and pensionable employment assisted in construing it On the true construction of clause 12 the board had debarred themselves from giving notice apart from the reasons specified therein

Lord **Tucker**, dissenting, said that the natural meaning of the words "permanent and pensionable" in their context in the advertisement indicated no more than that the posts available were on the regular established staff and were subject to the terms of a pension scheme The advertisement formed no part of the eventual contract The appellant could not reasonably have supposed that the final terms of her contract would give her the legal right to a life appointment

Lord **Keith** of **Avonholm**, also dissenting, said that the case might have repercussions on the powers of public bodies or authorities which did not rank as branches of the Civil Service to terminate the employment of their servants If the appellant succeeded the position would be the more remarkable in that it would be only the board that was bound, for the servant was entitled to terminate her employment at one month's notice

Lord **Evershed**, who concurred with the majority of the House, said that the result of the decision might be to saddle the board with contracts which they ought not reasonably to have undertaken, but to a servant, certainly one in the position of the appellant, the security of employment with the board for the period of working life was of immense value

McClelland v Northern Ireland General Health Services Board *House of Lords* (Lord Oaksey, Lord Goddard Lord Tucker Lord Keith of Avonholm, and Lord Evershed) April 4 1957 E W Jones Q C, and C B Shaw (Gouldens for J Morris McKee, Belfast), W F Patton, Q C, and John MacDermott (Hewlett & Co for Cleaver, Fulton & Rankin, Belfast)

M M **Hill**
Barrister at-Law

Allegations Withdrawn

Allegations of negligence against a casualty-officer were withdrawn after a hearing at Birmingham Assizes[1] A widow claimed damages for the death of her husband in Nuneaton Manor Hospital from the casualty officer and the Birmingham Regional Hospital Board

Her husband, who was 39, was taken to hospital by his family doctor because he was having difficulty in breathing The doctor told the casualty officer that, in her view, the patient had "an acute condition of the larynx" and would probably need a tracheotomy She impressed on him that it was a serious emergency and then left the hospital Counsel for the plaintiff said that though suing both defendants, from what the hospital had told him he was putting his case "fairly and squarely" against the casualty officer, and he spoke of a "deplorable state of inefficiency and panic" When the patient's wife arrived at the hospital, no one was able to tell her anything Later she was taken to the matron's office, where another doctor broke the news to her that her husband had died

In evidence the patient's family doctor said that when she heard the man had died she asked the casualty officer why "on earth" he had not attempted the tracheotomy He replied that there had not been time

Counsel for the casualty officer denied that his client had done "simply nothing" when the patient was brought in. He had done everything possible before he tried to get in touch with an ear, nose, and throat surgeon In his evidence, the casualty officer said that on the day in question his immediate superior and two other doctors were away When the patient was brought in he ordered an injection and telephoned a surgeon, who told him not to do the operation until told to do so by the surgeon on duty He was unable to contact the surgeon on-duty and while he was telephoning the first surgeon to say he intended to operate, he was told the patient had died

A consultant ear, nose, and throat surgeon gave evidence that a hurried tracheotomy was often very difficult "even to an expert" Counsel for the plaintiff announced that, in the light of this surgeon's evidence, it would not be right to proceed with the allegations of negligence The plaintiff recognised that the casualty officer had been faced with a most difficult dilemma

Counsel for the casualty-officer said that facts which had been clearly established at the hearing were not known to the plaintiff at the beginning of the case, and Mr Justice Pearce, agreeing to withdraw the record, said it was clear the patient was suffering from a rare disease which was very difficult to diagnose and treat

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[1] *Times*, April 9, 10, 11, and 12

Obituary

GEORGE RITCHIE MATHER CORDINER

C V O , M B St. And , D M R E

Dr Mather Cordiner, honorary radiologist to St George's Hospital, died at his home in London on April 8 at the age of 58

He graduated M B from the University of St Andrews in 1922, and after holding a house-appointment at Gravesend Hospital he served as a clinical assistant in the X-ray and electrical departments of the Prince of Wales's Hospital, Tottenham In 1924 he took the D M R E , and soon afterwards he became assistant radiologist to the Middlesex Hospital He also joined the staffs of the Evelina Hospital, St Paul s Hospital, the Royal Northern Hospital, and Oldchurch Hospital Romford In 1935 he was appointed assistant radiologist and later radiologist to St George's Hospital and after the introduction of the National Health Service he continued to serve the hospital as an honorary consultant He lectured in radiology at the London School of Hygiene and Tropical Medicine

Dr Cordiner was one of the consultants who attended the late King George VI, and for these services he was appointed C V O in 1951

A colleague writes

When George Mather Cordiner was appointed to St George's Hospital in 1935 he was already making a name for himself in the radiological study of gastro enterology, and before long he had a world-wide reputation in this field. His unassuming manner cloaked a high intelligence and an unflagging capacity for work Many of us were aware that he held decided opinions on the question whether the National Health Service was in the best interests of patients and of the medical profession, but this did not prevent him from carrying out with enthusiasm and devotion the work to which he had set his hand In this connection a great debt of gratitude was owed to him, especially by St George's Hospital To his unostentatious generosity I and many other of his younger colleagues, can bear witness

Dr Cordiner leaves a widow and a son and a daughter

ALBERT EDWARD MORTIMER WOOLF

M B Camb , F.R C.S

Mr Mortimer Woolf, consulting surgeon to Queen Mary's Hospital for the East End, a past president of the Hunterian Society and the present editor of its *Transactions*, died on April 6 at his home at Loughton, Essex

He was born in 1884, the son of the late Mortimer Woolf, O B E , and he was educated at Clifton College and Emmanuel College, Cambridge He completed his medical studies at the London Hospital and qualified in 1908 While holding house-appointments at the London he took his F.R C S in 1909 He was already finding his way in consultant practice when the war came, and he spent the next years serving as a surgical specialist with the R.A.M C in France, Mesopotamia, India, and Serbia After he returned to civilian life he joined the staffs of Queen Mary's Hospital for the East End, the British Red Cross Rheumatic Clinic, St. Margaret s Hospital Epping, the East End Maternity Hospital and the Lord Mayor Treloar s Home at Alton

Mr Woolf gave practical form to his admiration for John Hunter through his devoted service to the Hunterian Society For many years he was its honorary secretary and he was elected president from 1926 to 1928 and again in 1945 He was also for long the society s librarian and since the late war he had edited its *Transactions* His aptitude for this work was seen in his own papers many of which dealt with surgery of the gall-bladder and other aspects of abdominal surgery In one of his presidential addresses to the Hunterian Society in 1928 he examined pain from the surgeon's point of view, and in his Hunterian oration in 1931 he followed Hunter's example by turning to comparative anatomy for help in the elucidation of the problems of diverticulitis

D T D writes

There was something of Mr Pickwick in Mortimer Woolf Many of his friends called him Teddy and his presence in any company was always palpable as well as visible His joy in human company, his quick spontaneous laughter, his delight in jokes made him countless friends Like Mr Pickwick he was not unendowed with the goods of the world, and he was able to foster good causes and spend much of his time in making other people content

It mattered not whether it was exhorting the Hunterian Society to business, or whether it was discussing some topic at the dinner-table, or whether it was showing to friends the ancient trees in his delightful garden—it was done with great fun and with tremendous relish To Mortimer more than to anyone the Hunterian Society owes its present lively condition, and no council or committee or dinner of that society was ever complete without some quip or some words of wisdom from Mortimer Woolf Every institution that was fortunate to have him a member soon realised that every ounce of his enormous boundless energy would be used for that institution s welfare

He was a big man, big in physical frame and with a healthy florid complexion, his mind was also large tolerant, and honest and he was always ready to hear the troubles of those afflicted and to give all the help he could to ease them on their way

One sunny afternoon I watched him show with pride his garden to another great gardener, the late Lord Horder , and it was amusing to see the one examining the other in knowledge regarding the soil and regarding the health and the diseases of trees It was an examination conducted by one on the other, and I think that after some two hours both would have passed each other as being reasonably qualified in the knowledge they possessed of some of Nature's secrets

Mr Woolf married Miss Laura Nathan who survives him with their two daughters

THOMAS ARCHIBALD

M D Glasg

Dr Archibald who for 36 years, until his retirement in 1951, was physician-superintendent of Belvidere Hospital, Glasgow, died on March 26

A native of Greenock, he was educated at Allan Glen's School and Glasgow University, where he graduated in medicine in 1908 He joined the staff of Belvidere Hospital in 1911, and became its physician-superintendent in 1915, at a time when infectious disease was a much greater menace to life and health than it is today He found himself in charge of a busy hospital often full to overflowing, and often called to meet emergencies, such as the almost yearly outbreaks of typhus fever, or unusual incidents, such as outbreaks of cerebrospinal fever and encephalitis lethargica With the years he saw a decline in the incidence and a striking reduction in the severity of the commoner infectious diseases, and he played no small part in applying and assessing modern methods of treatment and prevention When he retired in 1951 tribute was paid to the administrative resourcefulness and clinical acumen which had enabled him to share so effectively in the work of reducing the death-rates and complications of infectious diseases " He did not seek the limelight, but went about his hospital work in a quietly efficient and admirable manner and could be regarded indeed as the ideal physician-superintendent, placing first the interests of his patients and his staff "

In his retirement Dr Archibald became a keen gardener and was justly proud of the results which he achieved by the same gifts of good husbandry and attention to detail that he had shown in former years in his professional work. He is survived by his widow.

GEORGE MITCHELL

M D Aberd., D.P H

Dr Mitchell, dermatologist to the Royal Hospital, Wolverhampton, from 1919 to 1945, died on April 6 at the age of 81 He graduated at the University of

Aberdeen in 1903, and took the D P H the following year, and the M D in 1905 After a short time in general practice he entered the public-health service, and from 1910 to 1912 he was chief school medical officer for Aberdeenshire He spent the next two years as assistant M O H and tuberculosis officer for Rochdale During the 1914–18 war he served with the R A M C After he was demobilised in 1919 he was appointed to take charge of the venereal-diseases services for Wolverhampton, which were centred in what is now the Royal Hospital, and he held this post until he retired in 1951 His interest in diseases of the skin grew steadily and in recognition of his work in this specialty a department of dermatology was set up and he became the first dermatologist to the hospital

J H S writes

George Mitchell was held in peculiar regard by all his colleagues in hospital, and by the practitioners of the district His personality evoked a mixture of the deepest affection and respect Respect for his intellectual abilities and intellectual honesty—two qualities by no means always synonymous—respect for his clinical judgment and integrity of life, qualities which to many of us seemed to typify the granite of his native country, but which by themselves could nevertheless suggest a personality essentially cold By contrast it was his warmth and sense of humour which seemed to enlarge and almost transfigure his mental equipment—so that in the course of time he became a central figure beloved by all.

Diary of the Week

APRIL 21 TO 27

Wednesday, 24th

INSTITUTE OF DISEASES OF THE CHEST, Brompton, S W 3
5 P M Dr J G Scadding Clinical Significance of Tuberculin Tests

BIRMINGHAM MEDICAL INSTITUTE, 154, Great Charles Street, Birmingham, 3
8 P M *Psychiatry* Dr J A Harrington, Mr K W Cross, PH D Survey of Chronic Patients in a Mental Hospital—Comparison With a Sample From a Different Culture

MIDLAND CENTRE FOR NEUROSURGERY, Holly Lane, Smethwick, near Birmingham
8 P M Dr J N Cumings Biochemical Abnormalities in Hepatolenticular Degeneration

Thursday, 25th

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, W C 2
3 45 P M Dr B D Wyke Surgical Considerations of the Temporal Lobes (Arnott demonstration)

ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W 1
4 45 P M *Dermatology* Dr J T Ingram Parapsoriasis
8 P.M *Urology* Mr John Howkins, Mr P H Newman, Mr R A Mogg Low Backache

Friday, 26th

ROYAL SOCIETY OF MEDICINE
5 P M *Pædiatrics* Dr R M Mavon White Outbreak of Infantile Gastro enteritis (*Esch coli* O, 128) in a Small Hospital Maternity Unit Dr Bruno Gans, Dr J C Thompson Neonatal Œstrogen Excretion and its Relation to Postnatal Weight loss Dr John Lorber Changing Ætiology of Erythema Nodosum

INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330, Gray's Inn Road, W C 1
3 30 P M Mr G H Howells Sinusitis

Appointments

COSH, J A, M D Camb, M R C P consultant physician, Bath clinical area
DAVIES, P D B, M D Camb, M R C P consultant chest physician, St Pancras chest clinic and Whittington Hospital London
GRAINGER R G, M D Leeds, M R C P F F R D M R D part time consultant radiologist, Hospitals for Diseases of the Chest, London
MCDONALD MARY G, M B Aberd, D P H M O, mobile clinic, North Riding of Yorkshire
MCNELIS F C M B assistant school M O, York
PINKERTON PHILLIP, M D Edin D P M consultant in child psychiatry United Liverpool Hospitals and Liverpool regional hospital board
SCOTT D P A L M B St And D I M consultant psychiatrist, Rainhill Hospital, Liverpool
STRICKLAND BASIL, M.B Lond, M R C P F F R, D M R T, D M R D D C H part time consultant radiologist, Hospitals for Diseases of the Chest, London
TAYLOR, IAN M R C S, D.P H assistant M O, Ealing and Acton area
TIMPERLEY MARY, M.B Manc school M O North Riding of Yorkshire

Notes and News

IMPERIAL CANCER RESEARCH FUND

IT is hoped that demolition will begin this year in preparation for the new laboratories in Lincoln's Inn Fields[1] In view of the expansion of research expected when the new buildings are complete, the clinicopathological research committee has been replaced by a research advisory committee to advise the council on the scientific aspect of all its activities The new committee, whose chairman is Prof G F Marrian, F R S, is actively considering what research will be done in the new buildings Dr A M Begg and Mr H G Crabtree of the scientific staff have both retired this year

The report includes some account by Dr James Craigie, F R S, director of the central laboratories, and Prof Geoffrey Hadfield, director of the clinicopathological research unit, of work in progress This includes study of a possibly increasing malignancy of cells in a growth, of the behaviour of cancer cells in the presence of various gases, of the changes (if any) in a tumour which has been frozen, and of methods of determining œstrogens Material from the " frozen tumour bank " has been provided to other research establishments The survival is reported of malignant cells for as long as seven years, without evident loss of viability

COLLECTION OF PRESCRIPTION CHARGES

IN his annual survey[2] of the National Health Service accounts for England and Wales for 1955–56, the Comptroller and Auditor General expresses concern about the collection of prescription charges by dispensing doctors In August, 1953, the Ministry informed a number of executive councils that the returns of charges collected by dispensing doctors had varied greatly between one area and another and, in general, charges collected were a good deal less than might have been expected Only 24 of the 47 councils concerned seemed to be satisfied with the rate of collections

Returns for later periods, the Comptroller says, have shown little improvement In 1954–55 remittances for all areas averaged about 1 8 statutory charges for the year for each patient on the dispensing lists, whereas collections averaged about 3 per patient for the year for patients whose prescriptions were dispensed by chemists For doctors who were paid for prescriptions actually dispensed, the Comptroller's auditors reported many cases where remittances from doctors appeared inadequate in relation to the number of prescriptions dispensed and, occasionally, no remittances at all had been made during the year

The report concludes " Consideration had been given to the possibility of some abatement of the payments to dispensing doctors to take account of the charges they were required to collect But it had not been found possible to negotiate a fixed abatement which, bearing in mind the conditions of rural dispensing practices, would be fair to all capitation doctors This did not apply with the same force to the minority of doctors paid at drug tariff rates, but it had been agreed to accept the British Medical Association contention that they had similar difficulties in collecting charges, and that the adequacy of their collection of charges should therefore be assessed under the same procedure " The Exchequer and Audit Department proposed to remind executive councils of the need to investigate cases in which the amount surrendered appeared to be inadequate

MENTAL FACETS OF MATERNITY CARE

THE latest memorandum submitted to the Maternity Services Committee deals with psychiatric matters[3] It points out that the mental health of mothers is one of the most important factors governing the well being of our children, and that pregnancy and parturition are responsible for a significant proportion of mental ill health It recommends that the psychology of sex, pregnancy, and infancy, and the psychological abnormalities of pregnancy, labour, and the puerperium should be included in the training of obstetricians, midwives, and health visitors Knowledge of the special emotional factors in illegitimacy is important Education for parenthood should begin in childhood, this demands further study

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[1] Imperial Cancer Research Fund annual report for 1955–56 Obtainable from the offices at 48 Lincoln's Inn Fields, London, W C 2

[2] H M Stationery Office Pp 41 3s

[3] Memorandum for submission to the Maternity Services Committee Royal Medico Psychological Association, 11, Chandos Street, London, W 1

The memorandum calls, as did previous ones,[4] [5] for coordination of the services, antenatal care and labour should be conducted by the same team Antenatal education should be given to both parents The pregnant woman must be given a proper explanation of what is coming, and she should never be left alone during labour Analgesia must always be provided in case antenatal training has not abolished pain Soon after birth, home help must be provided—by relatives, or otherwise if the relatives are unsuitable Finally, there must be provision for psychiatric care of those mothers who, during pregnancy or the puerperium, show psychiatric symptoms The commoner psychological upsets associated with pregnancy are set out

SCOTTISH REGIONAL HOSPITAL BOARDS

THE following doctors have been appointed to the hospital boards New appointments are indicated with an asterisk

Northern region—*James Ronald *M M Whittet
North eastern region—R J Duthie, *Prof John Craig
Eastern region—*Prof George Bell
South eastern region—Prof G H Percival and G C G Mercer
Western region—W W Galbraith, *J C J Ives and *Major General J M Macfie

SPEECH CORRECTION

A PUBLIC symposium was held in London on April 8 to demonstrate results achieved in the correction of speech defects by Mr H V Hemery, L R A M Those who spoke were all at present members of Mr Hemery's class, which has been held at Goldsmiths' College, New Cross, S E 14, for the past twelve years All read their speeches but all delivered them clearly and audibly, apart from a few failures by less experienced students The courage and self confidence of the speakers was particularly striking and illustrated how Mr Hemery's skill and personality had convinced them that they could overcome their disability All the speakers told of definite improvement achieved through recognition of basically faulty speech methods and progressive re education in proper use of the vocal apparatus Diagnosis of speech errors and early training are conducted individually, but speaking before others from the earliest possible stage of treatment is an essential part of the re education course The course has no set length but most stammerers with an established pattern of stammer are said to require up to two years' re education

There will be an informal demonstration of impromptu speaking by members of the class on May 18 at 6 P M, at Goldsmiths' College, and the next public symposium will be held on June 27 at 6 30 P M

TWO VALUABLE PAMPHLETS

Two pamphlets by Dr Edward Glover—one on homosexuality[6] and the other on prostitution[7]—deserve wide circulation That on homosexuality includes humane and intelligent comments on the present state of affairs, and also a good deal of original fact from the records of the Portman Clinic and from the results of circulating a questionary The Home Office committee to which this evidence was presented must have found it a refreshing spring of factual information in a wilderness of undocumented opinion. Dr Glover has the courage to stress the foundations of the current public estimate of homosexuality in ignorance and psychopathology, and to point out the origins of the persecution directed at supposed "perverts" by people over reacting to homosexual components in their own make up He refuses to compromise by acquiescing in the demand for "treatment instead of punishment" in cases where there is neither disease nor crime His careful though brief account of the persons and practices involved, from about 100 case-records, does much to explode the idea that there is any sharp division between "homosexuals" on the one hand and non homosexual individuals on the other

Dr Glover s discussion of prostitution here in its 2nd edition, is equally humane, though slightly harder to read. His account of the defects of personality which lead women to become prostitutes will meet few objectors if it is applied wholly to our own society and period, but the institution has wide roots, and its form and personnel have varied widely—it seems doubtful whether Dr Glover's conclusions would have applied to the colleagues of Rahab, to ancient India, or even to modern France or China This cultural aspect is important, for we are perhaps, on the evidence of history, more likely to be able to transform prostitution than to abolish it

RECRUITMENT OF NURSES AND MIDWIVES

FROM May 1, some of the functions of the Ministry of Labour and National Service for the recruitment of nurses and midwives will be transferred to the Ministry of Health and the Department of Health for Scotland The National Advisory Council on the Recruitment of Nurses and Midwives, which has hitherto advised the Minister of Labour and National Service, will be reconstituted and will henceforth advise the Health Ministers The Health Ministries will be responsible for the general oversight of recruitment activities and for controlling the use of the mobile nursing exhibitions and the mental health exhibitions By agreement with the ministries, regional hospital boards will organise these exhibitions and talks to schools

The nursing appointments service of the Ministry of Labour and National Service will continue and will provide, through its 166 nursing appointments offices, a placing and advisory service for those who wish to train or work as nurses or midwives The service will also be available to medical auxiliaries Regional hospital boards, hospital management committees, local health authorities, the Services and other employing authorities will, as before, notify their nursing and midwifery vacancies to the nursing appointments offices The Ministry of Labour will retain the services of their principal nursing officer and a small number of technical nursing officers

CLEAN BLANKETS

Dr Blowers and his colleagues[1] have drawn attention to three new types of blanket which may be boiled, and we may hope that such blankets will be introduced in hospitals But this will take a long time, and meanwhile any economically possible means of making the existing blankets safer will be of interest

Mr Leslie Bird, chairman of the laundry subcommittee of the Newcastle Regional Hospital Board, has done some controlled experiments to test an ordinary commercial shrink-resisting process in pure woollen blankets[2] 12 blankets were treated and 12 not, 6 in each group were washed in commercial and 6 in hospital laundries They were used normally in the wards between washings The shrink resisting process itself led to an inconsiderable loss of size After 17 washings the untreated blankets had become too short, and after 19 too narrow, to be used The treated blankets were still extensive enough for use after 60 washings, but had lost weight They could still be used as extra blankets and (unlike the untreated blankets) retained their fleecy handle and whiteness

These findings do not hold for boiling, which inevitably damages woollen blankets, but a low temperature sterilisation process[3] did not damage the treated blankets Another interesting finding is that untreated blankets which have shrunk not too badly can be restored to usefulness by stretching while wet, followed by the shrink resisting process Mr Bird estimates that the minimum annual economy if these processes were adopted would be £35 19*s* per hundred beds

BRITISH STANDARD FOR HEAVY-DUTY HELMETS

A STANDARD for heavy duty industrial safety helmets has now been published A standard for light duty helmets, chiefly for coalminers, was prepared three years ago The new standard provides for helmets which will be sufficiently strong to protect the wearer's head from more severe blows They are intended for use by workers in structural engineering—notably on building sites, at oil refineries, in shipbuilding, and in mining and quarrying While the light duty standard prescribes a shock absorption test of 28 ft lb the heavy-duty standard prescribes a test of 40 ft lb Helmets to the new standard will be heavier and will cost more than the light-duty variety Employers should consult helmet makers as to which kind their employees need to wear Copies of this standard (4*s* each) may be obtained from the British Standards Institution, sales branch, 2, Park Street, London, W 1

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[4] See *Lancet* 1956 ii 1056
[5] See *Ibid* p 1221
[6] The Problem of Homosexuality By EDWARD GLOVER M D LL D Published by the Institute for the Scientific Treatment of Delinquency, 8, Bourdon Street, Davies Street, London, W 1 Pp 40 3*s*
[7] The Psychopathology of Prostitution London Institute for the Scientific Treatment of Delinquency Pp 20 1*s* 6*d*

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[1] Blowers R, Potter, J, Wallace K R *Lancet*, March 23, 1957 p 629
[2] Report on Shrinkage of Woollen Blankets Newcastle Regional Hospital Board Benfield Road, Newcastle upon Tyne, 6 1957
[3] Blowers, R., Wallace, K R. *Lancet*, 1955, i, 1250

University of Liverpool

Dr Philip Pinkerton has been appointed lecturer in child psychiatry

Royal College of Surgeons of England

At a meeting of the council on April 11, with Sir Harry Platt, the president, in the chair, Sir Arthur Sims was admitted to the honorary fellowship of the college Mr A C McEachern (Adelaide) was admitted as a temporary member of the court of examiners The following were elected fellows of the college without examination as being medical practitioners of at least 20 years' standing

Mr G F Burnell (Truro) Prof P K Chanmugam (Colombo), Mr R F Guymer (London School of Hygiene and Tropical Medicine), Mr G G Lyttle (Belfast) Surgeon Vice Admiral R C May (medical director general of the Navy), Colonel J M Shah (Karachi)

Jacksonian prizes for 1956 were awarded to Mr A H Hunt (St Bartholomew's) and Mr J A McCredie (Belfast) for their essays on portal hypertension and Mr R E Horton (Bristol) was awarded a certificate of honourable mention The council selected as the subject for the Jacksonian prize for 1958 "Factors which influence the genesis and progression of cancer, and their bearing on the surgical treatment of the disease" The Hallett prize was presented to Dr S K Nair (Agra University)

The title of Bland Sutton lecturer was given to Dr Frank Stansfield, senior lecturer in anatomy, Royal College of Surgeons of England

Diplomas were granted, jointly with the Royal College of Physicians, to the following

D C H—I M Adamson, Bhisham Kumar Ahuja, Nimat Jabir Al Chokhachi, Patricia M Alexander Syed Mahmood Al Kudsy Ursula M Anderson, Kamar Jehan Ansari, Khwaja Mukhtar Mahmood Ansari, L P Balfour Lynn, Pinaki Bandyopadhyaya, J F X Bastiampillai Esther B Bevan, May Blythe, Shirley P A Borkowf N L S Bourchier, W H Brockett, C W Brookes Rusi Jehangir Buhariwalla, Alison G Carlisle, Nirmal Kumar Chanda Aileen P Cherry, Daphne G Chesshire, Sau Lan L Cheung, T A Daly, G J Davies T C Dennison, Gurtej Singh Dhaliwal Doreen J Dicks, Kali Prakash Dikshit, Jean E Drake, P G Drummond Smith, Ma Tin E, F P Frankel J D Frankish, H J Fredericks Puranmal Ganeriwala, Adi Jamshed Gazder, Grace M Gee, A G Giddins, Marianne A Glesinger, Elton Goldblatt, Vishnu Kumar Gupta R D Haigh Daphne J Hall, Hock Thye Heah, B E Heine, Margaret J Hicks, Siew Ting Hiew, F K M Hillenbrand, F T C Hu, M C J Hunt, Mohammed Farooq Husain, Cecile Ibrahim, Kathleen A Irvine, H J P Jayalath, E E Jones, Jaswant Singh Kalsi, Saroj Kapur Pensri Khanjanasthiti, G S T Khoo, Eleanor C Knox, J S Kothiwal, Joan M Leeming J F Leeton, R L Lindon Barbara Lobo, Derrick Lonsdale, Kathleen M Lumb, Jean Y MacDougall Agnes M Maclean, Pran Nath Mehrotra, Barbara P P Melhuish, Inez R Mendelson, Audrey Millar, C J Morgan, Kornkitch Mutirangura Elizabeth C Nelson, P G Newall Watson Pauline A Nock Nalinee V Odak Madhukar Manohar Pandit, Ranbir Singh Parmar, Margaret P Paterson, Monica B Pobl Bhoom Raj Pratap Krishna Rao Purohit C R Rainier Pope, Ian Ramage, Pratap Narain Rastogi, M J Ree, Kathleen M Robb D K Robinson, W G Roper Miro Albert Sasson, Narinder Singh Satija, Werner Heinrich Schutt Jane M Semmens, Bimal Chandra Sen Roop Kishore Seth, Leonard Sinclair, J J Slome, Mary N Smith, Mahalekshmi Thangam Sushila R N P Sutton Sara Syrop, I G Tait, Om Parkash Thaman, Ann Thompson, J A R Tibbles, S M Tucker Naomi Turner, Marian A Veitch, Lucy A Wagstaff, Alison S Wallace, I R Wallace Ravindra Gopaldas Wani G H Warrick, D T Weerawardene, Jean B Wickings Joan V Willcock, A R Williamson, R G B Willis, Mary B Woodfield, Joyce O Yates

D O—Premasingha Attygalle Abeyaratne James Abraham, J E Ball, C J Benson, Rusi Dinshaw Billimoria, T J A Casey, Ivan Cher, N J G Chouler B G Dias Mustafa El Sayed, R F Fisher, D C Gibbs, Abdel Gadir Ginawi, Vasudeo Laxmanrao Gokhale, Abdullahi Sid Ahmed Goreish P A Johnson, Theo Keldoulis, Tajuddin Hasan Kirmani, G M Krolman, H F Lake, V J Marmion H H Massie, Maung Maw F S Owen R A Owen, Irineos Papadopoulos, Ramachandra Pararajasegaram, C S L Peiris, Mohammed Hasan Rizvi, Leslie Rose, Om Prakash Sabharwal, Bhagwan Dayal Shrivastava, Keshmahinder Singh, S H Swift, S V Thambar, L J Topham, F L A Townshend, Dhara Venkateswarlu Vera M Vodden, Olga Voloshin, Jamshed Hormuzshaw Wania, Brian Waters William Wilson

D T M & H—Mirghani Yousif Ali, Thevapiriam Rajasekaram Arulambalam Sudhindra Nath Basu, Giorgio Battaglia, R C Braun Ponnuthury Brodie, Tarak Das Chatterjee Dorasamy Chetty, Arjan Chopra, Ram Karan Chopra, J A Cooney, Gourshankar Lal Das Sambhu Nath Dutta, Mohamad Ali Faghih, P D Farjo, R O J Fry, Paul Grech Manindra Nath Guha Majumder A B C Hotobah-During Valiyezhuth Krishnankutty Jayaram, Ko Ko, Hira Lal, Nigamuni Mervyn Piyasena Mendis Vinod Ratilal Mody Abdul Salam Mohamed P R H Molesworth Duraiswamy Aiyar Narasimhan Nur Ud Din G G Prinsell, Abdul Hafeez Qureshi Phyllida M M Roberts Yelahanka Patiamma Rudrappa, Nabendu Kumar Sarker M G Schmiedel, Venkatanarayana Balasa Setty, Mahendra Prasad Shaw Muthummah Sinnappu K G Somers-Dehaney, Tin U Francesco Vitanza Helena T von Schantz, Wan Yam Mow, D S P S V J Wijesekera, Yao Tsing Wu

D Phys Med—V C De Silva, Charlotte Feldman, S A James, B W Norington

D A—J E S Relton

D M R D—K M Nuttall

University of Dublin

Dr Frank B Walsh, associate professor of ophthalmology in Johns Hopkins University, Baltimore, will deliver the Montgomery lecture on Friday, May 17, at 5 P M He is to speak on ocular movements associated with regeneration of the third nerve Prof Adolph H Schultz, director of the anthropological institute of the University of Zürich, will deliver the John Mallet Purser lecture on Tuesday, May 21, at 4 30 P M His subject is to be Past and Present Views of Man's Specialisations Both lectures will be given at Trinity College

National University of Ireland

Mr Seaghan O'Beirn has been appointed to the professorship of surgery at University College, Galway

Prof Edward Keenan has been coopted a member of the senate in place of the late Prof John McGrath

Royal College of Physicians of Ireland

On April 5, the following were admitted to the licence of medicine and midwifery of the college

A S A Atchia, Beryl D Chalkley, S P J Halpin R W Kneafsey, M B Labode, G K Maghrajh, S V McAndrew, A G McInerney, H J O'Brien, C P Quinn, A C Walsh

British Association

This year the association will meet in Dublin from Sept 4 to 11 under the presidency of Prof P M S Blackett, F R S

International Congress of Group Psychotherapy

This congress will be held in Zürich from Aug 29 to 31 Further particulars may be had from Dr Adolf Guggenbuhl Craig, Lenggstrasse 28, Zürich 8, Switzerland

Assurance Medical Society

A meeting of this society will be held at 5 P M on Wednesday, May 1, at 11, Chandos Street, London, W 1, when Dr A H Douthwaite will speak on some dangers of therapeusis

Death Grant

The time allowed for claiming a death grant under the National Insurance scheme has been extended from three months to six months

Central Midwives Board

Mr Arnold Walker has been re elected chairman of the board, and Prof A A Moncrieff deputy chairman, for the coming year

Chalmers Medal

The council of the Royal Society for Tropical Medicine and Hygiene have awarded this medal for 1957 to Dr A J Haddow, director of the Virus Research Institute, Entebbe, Uganda

National Society of Children's Nurseries

The annual general meeting of this society will be held on Thursday, May 30, at 4 P M at 45, Russell Square, London, W C 1 At 4 30 P M Prof W S Walton will give an address on Mothers at Work

Indian Medical Service Dinner Club

The annual dinner of this club will be held at the East India and Sports Club Ltd, St James's Square, London, S W 1, on Friday, June 7 at 7 30 P M Tickets may be had from the secretary of the club, Medical Board Room, Commonwealth Relations Office, Matthew Parker Street, S W 1

Collegium Internationale Allergicologicum

The following officers have been elected for 1957–58

President Dr David Harley vice president, Dr J Duchaine, Brussels, hon secretary, Dr P Kallós Helsingborg, treasurer and executive secretary, Dr A Cerletti, Basle

Other members of council include Dr R R A Coombs and Dr W S Feldberg, F R S

Prof A C Frazer has been appointed a member of the food panel of the World Health Organisation

A travelling scholarship fund has been founded by Sir Edward and Lady Baron to enable junior members of the staff of the corneo plastic unit and regional eye bank Queen Victoria Hospital East Grinstead, to visit foreign clinics, and to continue their studies of the joint problems of plastic and ophthalmic surgery

COURSE AND MANAGEMENT OF HIRSCHSPRUNG'S DISEASE

G G WYLLIE
M B Adelaide, F R C S
LATE RESIDENT ASSISTANT SURGEON, THE HOSPITAL FOR SICK CHILDREN, GREAT ORMOND STREET, LONDON

Hirschsprung described the disease which bears his name in 1888 For the next sixty years there was no significant advance in its treatment, though one of the basic pathological lesions was observed on a number of occasions Dalla Valle (1924), Cameron (1928), Robertson and Kernohan (1938), Whitehouse and Kernohan (1948), and Zuelzer and Wilson (1948) all noted an absence of parasympathetic ganglia in part of the bowel, but the significance of this finding was not generally recognised Confusion undoubtedly occurred because of the tendency to group together under the common name of " megacolon " all cases of enlarged colon

Since 1948 advances in the treatment and understanding of Hirschsprung's disease have been notable The disease has been recognised in the neonatal period, its pathology has been understood, accurate diagnosis has become possible, and a rational treatment has been evolved A striking reduction in mortality has followed these advances

Swenson and Bill (1948) found that the obstruction could be attributed to inability of the distal narrow bowel to produce coördinated peristalsis and that resection of the rectum and rectosigmoid region, with preservation of the anal sphincter, led to dramatic clinical improvement

Bodian et al (1949) then showed how cases of Hirschsprung's disease could be distinguished from other cases of enlarged colon on clinical, radiological, and pathological grounds They demonstrated further a uniform pathology in Hirschsprung's disease, accounting for the lack of parasympathetic function, and they thus offered a scientific basis for Swenson's operation

The genetic study by Bodian et al (1951), the physiological studies of Hiatt (1951), and the investigation of newborn infants by Ehrenpreis (1946, 1955) have all helped to further our understanding of this disease

Diagnosis and treatment, however, need careful consideration and may be difficult in some atypical cases Delay in diagnosis may be as serious as mismanagement, for the disease is a severe one and critical episodes are relatively frequent

I describe here experience with 152 cases of Hirschsprung's disease treated in the Hospital for Sick Children, Great Ormond Street since 1948, and draw particular attention to the problem of management in infancy Hirschsprung's disease is a relatively common cause of intestinal obstruction in the neonatal period and in infancy, and the diagnosis often can be made early in life Correct treatment at this stage greatly simplifies the subsequent management

Clinical Features

Neonatal Period

Details of the immediate postnatal period have been ascertained in 127 cases Some abnormality occurred during this period in 119 of the infants

The abnormal signs vary considerably There may simply be some delay in the passage of meconium or, at the other extreme, the full clinical picture of low intestinal obstruction may develop

The passage of meconium characteristically is delayed for two or three days, and then it is passed only after a finger or tube has been inserted into the rectum, or meconium may be passed regularly but in small amounts It then tends to flow more freely towards the end of the first week, though it is usual for the change of the character of the stool, caused by digested milk to be delayed

Vomiting is common Vomiting of bile stained fluid was recorded in a quarter of our cases, the true figure may be higher, for some vomiting during the neonatal period is so often accepted as normal There is often reluctance to feed even if there is no vomiting Commonly the baby is taken from the breast or the feed changed in the mistaken belief that the difficulty is primarily one of feeding management

Abdominal distension is common In about half the cases in this series it occurred during the first week—usually about the third day

Typically, therefore, the baby on the second or third day is not feeding well, perhaps is regurgitating a little has slight abdominal distension, and has passed little or no meconium On rectal examination at this stage the anus looks small but dilates normally to admit a fifth finger The rectum is empty and above it the narrower rectosigmoid region can be appreciated On withdrawal meconium and gas usually are passed

In some cases the signs are less severe

Operations during the first week were performed on 16 babies in this series, in this or another hospital, but probably efforts to deflate the bowel were inadequate in some Hirschsprung's disease itself was responsible for the obstruction in 14, while Hirschsprung's disease was associated with small-bowel volvulus in 1 and with internal hernia in 1 The bowel was found dilated above the aganglionic segment, and usually a cone was recognisable The segment involved the rectum and rectosigmoid region in half the cases and was unusually long in the remainder, extending into the small intestine in 2 Colostomy or ileostomy were performed in 6 cases, appendicectomy for associated appendicitis with perforation in 1, and deflation by a tube passed into the rectum in 7

Infancy and Childhood

Constipation is the outstanding symptom It is severe and generally unabated But some patients pass stools regularly for weeks or even months, especially during infancy The baby may then seem healthy to both parents and doctor, though some abdominal distension may be present and the motions tend to be small

Most commonly the stools are small and hard, even during infancy Straining during defæcation is also common in infants The times of onset of constipation in 138 cases in this series are shown in table I In a few cases, whilst the constipation could be dated from early in life, it did not become troublesome until early childhood One boy had no constipation until he was 4, but his abdomen was distended by that time Thus there are exceptions to the rule that constipation begins at birth and is obstinate

TABLE I—TIMES OF ONSET OF CONSTIPATION IN 138 CASES

Onset of constipation	No of cases
At birth	114
2 weeks–3 mos	13
4–6 mos	5
7–12 mos	4
Over 1 yr	2

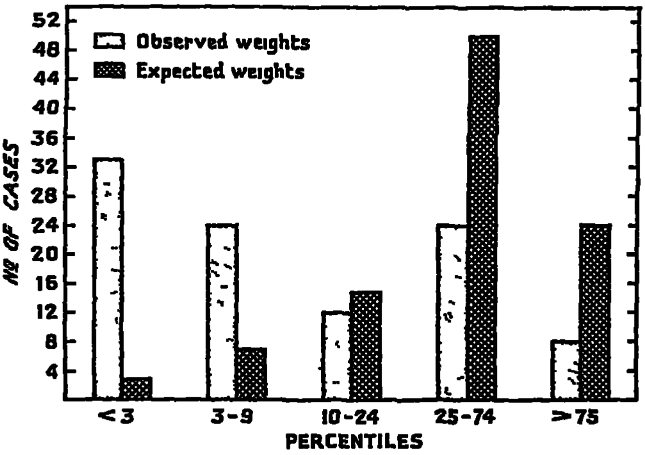
Episodes of more acute intestinal obstruction tend to occur, especially in infancy and early childhood Vomiting and abdominal distension result from retention of fæces and gas above the aganglionic segment Constipation is usual at these times, but " putrefactive " diarrhœa occurs in some cases and gastro enteritis may be superficially simulated These infants quickly become ill Toxic signs and dehydration are superimposed on malnutrition Abdominal distension may be extreme Findings on, and the response to, rectal examination are usually characteristic The rectum is empty, but the finger-tip may pass through the narrower rectosigmoid region into dilated colon On withdrawal, fluid fæces and gas are expelled under great pressure in a typically explosive way

Abdominal distension develops at or shortly after birth in the majority of cases Occasionally it is not noticed until the child is 2 or 3 years old Gas rather than fæcal masses is responsible, and loud borborygmi and visible peristalsis are common Quantities of foul smelling flatus are passed, particularly during the night, thus reducing the abdominal distension The distension is generally progressive, but it may vary from time to time It causes the characteristic flaring of the ribs and eversion and downward displacement of the umbilicus

Vomiting is not uncommon in infancy It is unusual after infancy except during obstructive crises

Growth is often retarded, especially in children with severe symptoms The weights of 109 children before treatment are shown in the accompanying figure Most were underweight, but 8% were above the average for their age Sexual development may be retarded, and puberty may be delayed in untreated children Hiatt (1951) and Kempton (1954) have described adults showing dwarfism and sexual infantilism

The findings on rectal examination in most cases are typical—i e, a narrow empty rectum with fæces at its upper limit or palpable in the sigmoid colon through the rectal wall But fæces filled the rectum at every examination in 4 of these cases, and in a further 22 there was usually some fæces extending down to just above the anal canal The initial diagnosis was wrong in 8 cases, chiefly because of the finding of a full rectum The abnormal segment was short and confined to the lower two-thirds of the rectum in most of these cases, but in some liquid fæces had probably trickled down to the rectum and solidified there A narrow empty rectum is of great value in diagnosis, but the absence of this sign does not exclude Hirschsprung's disease



Weight percentiles of 109 untreated cases of Hirschsprung's disease

Severity of Symptoms

The variation in the severity of symptoms between different cases is quite striking One child may not be seriously disturbed for some years, whereas another will have acute obstruction and be severely ill in the first days of life Yet the two have apparently identical lesions The length of the aganglionic segment is an important, though clearly not the only, factor In the present series several of the newborn infants with obstruction had affected segments of average length, whereas a boy with aganglionic bowel extending into the ileum did not come to hospital until he was $3^1/_2$ years old and was not operated on until he was 5 But usually the cases with long affected segments present early in life

TABLE II—CAUSES OF NEONATAL INTESTINAL OBSTRUCTIONS AMONG ADMISSIONS, 1949–53

Causes	No of cases
Jejuno ileal atresia	33
Duodenal atresia	18
Malrotation	15
Meconium ileus	14
Hirschsprung's disease	15

Hirschsprung's disease, unlike other forms of chronic obstruction associated with enlargement of the colon, carries a high mortality without treatment Formerly, many infants died of obstructive crises and few survived to adult life

Diagnosis

In most cases the diagnosis can be strongly presumed on clinical evidence Confirmation is first sought by radiology, the opaque enema is a most useful diagnostic aid in patients of any age, and it has established the diagnosis in babies a few days old Interpretation of the findings in young babies may be difficult, however, for at this age the contrast between the unexpanded segment and the colon above it may be slight and the examination may therefore have to be repeated

Rectal biopsy (Swenson et al 1955) has proved a most useful diagnostic measure In the present series specimens were obtained by submucous resection and the diagnosis was based on the state of the submucous parasympathetic plexus (Bodian 1956) Our experience has been similar to Swenson's, and the technique has been of most value in the following instances (1) with unusually long aganglionic segments, (2) with unusually short segments (part of the rectum), (3) where a colostomy has been established without confirming the diagnosis and the bowel below it has assumed a uniform calibre, (4) where doubts are raised by unusual symptoms or radiological appearances

Differential Diagnosis

During the Neonatal Period

Anal stenosis—The anus in Hirschsprung's disease often looks very small, as it does whenever gas and meconium have not passed through it It dilates without any sense of constriction on the passage of a fifth finger into the rectum, though the skin at the anal verge may split slightly and a little blood is seen after withdrawal This is a normal finding and does not represent anal stenosis The rectum normally narrows at the recto sigmoid junction and only the tip of the finger can be passed through it This finding is mistaken sometimes for a stenosis, but both stenosis and atresia at the site are extremely rare

Other types of intestinal obstruction—The clinical picture of Hirschsprung's disease may resemble very closely that of other forms of neonatal intestinal obstruction It is important to distinguish between them, however, for Hirschsprung's disease is often better treated conservatively at this stage whereas the other conditions mostly need urgent operation The incidence among admissions of newborn infants with intestinal obstruction during a five year period (1949–1953) is shown in table II

The signs of obstruction in atresia are usually established by the end of the first day, whereas a similar appearance in Hirschsprung's disease may not be seen until the second, third, or fourth day The findings on rectal examination tend to be similar—an undilated anus, an empty rectum, and narrower rectosigmoid region It is the response which is different In Hirschsprung's disease withdrawal of the finger is followed usually by the passage of enough meconium and gas to reduce the degree of distension In the presence of atresia some meconium may be passed, but it is drier than usual, a plug of white mucus may precede it, and it has no effect on the distension

Plain radiography is the most useful investigation If dilated large bowel can be identified, Hirschsprung's disease should be considered seriously, for it is much the most likely cause of colonic obstruction at this age But it may not always be recognisable, for the haustrations become taken up in the general distension of the colon above the aganglionic segment The type of Hirschsprung's disease with a long aganglionic segment extending into the ileum generally presents as a small-bowel obstruction and cannot be distinguished from the other forms

It may not be possible, then, to diagnose Hirschsprung's disease in the neonatal period until laparotomy is performed If, at operation, distension is found to extend into the large bowel and is succeeded by a cone-shaped narrowing, the diagnosis will be clear Where Hirschsprung's disease causes a small-bowel obstruction, dilatation and hypertrophy give way gradually to a narrow distal ileum The appearance may resemble that seen in meconium ileus In Hirschsprung's disease, however, the hypertrophy is less, and the meconium is above, rather than in, the narrow segment and is less viscous

During Infancy

Feeding problems—These may be suggested by vomiting and failure to thrive, but the history and physical signs should enable a distinction to be made

Constipation—This is usually much more severe and intractable in Hirschsprung's disease than constipation due to other causes in infants Hard fæcal masses may be felt in the colon above the narrow segment, this is uncommon in other forms of constipation in infants

Gastro enteritis—The acute episodes which tend to occur during infancy may simulate gastro enteritis Vomiting, abdominal distension, and frequent motions are seen in both states, but the stools are green in gastro-enteritis and usually yellow in Hirschsprung's disease The response to rectal examination may be similar except for the colour of the fluid ejected

Cœliac disease—This may be simulated by a failure to thrive and abdominal enlargement, but the history and the nature of the stools usually enable Hirschsprung's disease to be diagnosed clinically

During Childhood

Colonic inertia (idiopathic megacolon)—The diagnosis during childhood must be made primarily from colonic inertia (Bodian et al 1949) The history may be most useful, for it dates from shortly after birth in so many cases of Hirschsprung's disease whilst this is much less common in the other forms of constipation In colonic inertia, abdominal distension is slight or absent, fæcal masses, as opposed to accumulations of gas, are present, there are less borborygmi and flatus, and often there is overflow soiling, the rectum is always filled with fæces

Management

Incorrect early treatment may make subsequent management unnecessarily difficult It has been our aim to develop a standard programme for each circumstance until Swenson's operation can be performed

In the neonatal period if the signs are mild a finger or tube passed into the rectum will usually establish the flow of meconium This procedure should be repeated as necessary if meconium, and later stools and gas, tend to be retained At first many infants do not need any treatment other than this, which enables them to feed satisfactorily and to gain weight

If the signs are more severe, the abdomen should be X-rayed Hirschsprung's disease can be suspected if the small bowel gas shadows are uniform and large-bowel dilatation extends to the left side of the abdomen If rectal examination fails to produce a significant amount of meconium and gas colonic lavage should be carried out This must be done with great care, for the wall of the bowel may be thin and perforation is possible, either by the tube or from increased tension within the lumen Accordingly the surgeon himself should carry out this manœuvre, which, if it deflates the colon, will have averted the need for operation

If the diagnosis is not made until laparotomy, treatment will depend on the length of the aganglionic segment If the cone is at the rectosigmoid junction or in the lower part of the sigmoid colon, a rectal tube should be passed by an assistant and guided by the operator into the dilated bowel Deflation can be achieved in this way, and a colostomy avoided as subsequent bowel washouts can be expected to keep the colon empty

An enterostomy is necessary if the abnormal segment extends further along the bowel It should be sited just above the cone if this is in the descending colon or the left half of the transverse colon Full use is thus made of the normal colon, for the colostomy is brought down to the anus at the definitive operation When the aganglionic segment extends beyond the middle of the transverse colon, choosing the site may be difficult There have been instances of an apparent cone in the right half of the colon where the abnormal segment has in fact, extended into the ileum A colostomy then does not relieve the obstruction In these circumstances the small bowel should be examined carefully for hypertrophy and inequality in size Coning in the small intestine is much more gradual than in the rectosigmoid region and some gas, though very little meconium, may extend well down into the aganglionic ileum and even into the colon Frozen sections during operation are of great assistance in determining the correct site for enterostomy An ileostomy is the safest procedure if there is doubt and frozen sections cannot be examined, especially if part of the small bowel is hypertrophied

Meconium ileus must be considered when there is a hold-up of meconium in the small bowel and an unexpanded colon Usually the distinction is clear, for the abnormal meconium impacted in the lower ileum has a characteristic appearance and feel But there are occasions when it is more mobile and the dilatation and hypertrophy of the ileum above are less pronounced The appearance in long segment Hirschsprung's disease may be very similar Again, it is wise to perform an ileostomy if there is doubt

There are two essential points about an ileostomy in any of the above circumstances It should be sited carefully, and it should be accompanied by biopsy of the bowel wall It is easy to make the enterostomy in aganglionic bowel, for the coning is gradual, and ganglion cells may not be present except in the most dilated and hypertrophied intestine Apparent hypertrophy alone is a less reliable guide to normal innervation than it is in the colon Biopsies are also necessary to establish the diagnosis It is a simple matter to take a biopsy specimen from the ileostomy wall This will confirm that the ileostomy is in ganglionic intestine or provide a warning if it is not A biopsy specimen of the rectal mucosa should be taken at the end of the operation if the baby's condition is good enough This is preferable to sectioning the wall of the unexpanded colon at the time of the laparotomy

The majority of affected infants do not need operation in the immediate postnatal period If necessary their gut can be deflated by a tube or finger passed into the rectum as has been described Their progress should then be watched closely Gaseous abdominal distension may be controlled by the passage of a flatus tube or finger regularly before feeds Many babies feed well and thrive on this régime, but constipation may quickly become obstinate

If the baby becomes constipated, the diagnosis should be confirmed at once by barium enema Such confirmation depends on contrast between the bowel above and that below the transitional area, and this is seen best when the infant is constipated, the contrast may be lost after bowel washouts If the result is negative or doubtful, the examination should be repeated under similar circumstances after three or four weeks

After the diagnosis has been established, bowel washouts should be given regularly if constipation is at all troublesome They are not necessary in all cases, but a close watch must be kept on infants who are not having treatment, for an acute obstructive crisis may quickly develop and need treatment urgently Daily bowel washouts have proved satisfactory, saline is used and all fluid run in is recovered, the danger of water intoxication is thus greatly reduced In Hirschsprung's disease an ordinary enema is dangerous

Acute obstructive episodes usually can be overcome by bowel washouts, but an emergency colostomy is needed occasionally The aim of early recognition of Hirschsprung's disease is to avert severe constipation, recurrent crises, and the need for an emergency colostomy Instead, malnutrition can be avoided and the infant helped to thrive so well that Swenson's operation can be performed at an early age This is often possible from the age of about 6 weeks onwards

After ileostomy more strenuous efforts are needed to ensure a reasonable weight gain, and if the condition remains unsatisfactory colectomy and ileo anal anastomosis may be undertaken earlier than planned There is less urgency after a correctly placed colostomy, which is usually followed by weight gain and progress, though there is a tendency to hypochromic anæmia

Occasionally Hirschsprung's disease causes mild symptoms and the case may not present until later infancy or early childhood Some patients go through childhood with no more inconvenience than that of a slightly enlarged abdomen and moderate constipation which responds to aperients, but even these children may suffer from physical and sexual retardation, and their condition would be improved by Swenson's operation, which I regard as the treatment of choice in practically all cases

Summary

The signs of Hirschsprung's disease begin at birth in the majority of cases, and most cases can be recognised early in infancy

Before definitive surgical treatment by resection of the aganglionic bowel, management should be designed to prevent obstructive episodes and consequent retardation of growth

Ordinarily enterostomy is best avoided

I acknowledge most gratefully the cooperation of the consultant staff of the Hospital for Sick Children in allowing me to study their cases, and of the research committee which made possible the investigations I am particularly indebted to Mr Denis Browne, Dr Martin Bodian, and Mr H H Nixon for much personal help and for allowing me to draw on their great experience My thanks are also due to Mr Derek Martin and Mr G Lyth, of the department of medical illustration

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TREATMENT OF HIRSCHSPRUNG'S DISEASE BY SWENSON'S OPERATION

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IN 1948 Swenson and Bill showed that in "congenital megacolon" there was functional obstruction in the region of the rectum and rectosigmoid, and that resection of this normal looking bowel beyond the dilated colon, with preservation of the anal sphincter, was the rational treatment Shortly afterwards, Bodian et al (1949) demonstrated uniform changes in Hirschsprung's disease —absence of parasympathetic ganglion cells from the intramural plexuses, and presence of abnormal nerve fibrils in the undilated distal segment This was considered a congenital lesion Experience has confirmed the value of these contributions

Many series showing most satisfactory results from this operation have been published (Bodian et al 1951, Hiatt 1951, Ehrenpreis 1952, Swenson and Sugarman 1954), but none of these reports includes a detailed description of bowel function after operation, though they report a satisfactory degree of continence It is commonly accepted that some rectal mucosa is needed to provide an adequate sensory stimulus for defæcation Goligher and Hughes (1951) stated that in their experience of adults it was necessary to retain 5–7 cm to ensure continence The resection is carried lower than this limit in the Swenson procedure, however, and it seemed desirable to go more fully into the late results of operation The present report describes experience of 152 cases of Hirschsprung's disease treated in the hospital for Sick Children, Great Ormond Street, by excision of the aganglionic segment

The term "rectosigmoidectomy" has tended to focus attention on the rectosigmoid region rather than on the rectum itself, and it is inadequate in describing resection of an abnormal segment extending beyond the sigmoid colon I suggest, therefore, that the procedure be known as "Swenson's operation," consisting of complete excision of the aganglionic intestine This principle was used in the operations in this series, though in the majority the technique was altered, as suggested by Denis Browne (1949), to perform resection after intussusception of the mobilised bowel through the anus

Clinical Material

The series comprises 128 boys and 24 girls who have undergone operation for Hirschsprung's disease since 1948 The longest period of follow up is thus 8 years

The early cases were mostly in older children who had survived the disease for some years, but it was quickly found that younger children and infants withstood the operation well and much malnutrition and chronic ill health was thereby avoided Diagnosis has been made increasingly often early in life during the past few years, and early operation has become the rule The youngest age at operation was 5 weeks The ages at which the definitive operations were undertaken are shown in the accompanying table

AGES AT OPERATION

Age	No of cases
5 weeks–6 mos	15
6–12 mos	18
1–2 yr	11
2–5 yr	36
5–10 yr	28
Over 10 yr	11

6 children had other congenital anomalies Cleft palate, hypertrophic pyloric stenosis, congenital disloca

tion of the hip, bilateral ectopic testes, cataract, and mental retardation each occurred in 1 instance

Preliminary Colostomy

Initially transverse colostomy was performed routinely, making three stages—colostomy, excision of aganglionic bowel, and closure of colostomy Since 1952 single stage operations have been performed increasingly commonly, and this has become the standard practice The following circumstances are now regarded as indications for preliminary colostomy

1 Acute obstructive episodes in the neonatal period or infancy which cannot be relieved by bowel washouts Such babies may quickly become very ill

2 An unusually long narrow segment, revealed at laparotomy, causing an obstruction which cannot be relieved by guiding a rectal tube into the dilated bowel Such segments usually extend beyond the sigmoid colon, even into the ileum, and in this event ileostomy is necessary

3 Infants who do not thrive despite regular bowel washouts

4 Older children with advanced disease and gross colonic dilatation and hypertrophy Defunctioning colostomy then leads to improvement in general health and reduction in size of the dilated bowel, thereby reducing disproportion and facilitating the subsequent anastomosis

Site

In almost all cases submitted to preliminary colostomy, the site of this was the transverse colon This site has the advantage of leaving the lower abdomen free for the definitive operation Transverse colostomy is well withstood by infants, but hypochromic anæmia tends to develop, and, though they may look well, their hæmoglobin level should be checked regularly during the interval between operations Difficulty has been experienced in some cases with aganglionic segments extending to the proximal sigmoid colon and beyond There may then be insufficient normal colon beyond the colostomy to reach the bottom of the pelvis, and it may be necessary to perform left hemicolectomy and to bring down some part of the right colon This adds to the complexity and danger of the operation

An alternative site for the colostomy, used only twice in this series, is in the left hemicolon at the level of the transition between aganglionic and normal bowel (Swenson 1955) This level is determined, if necessary, by biopsy Subsequently the colostomy is resected along with the aganglionic bowel, and continuity is restored at the definitive operation, thereby reducing the number of operations from three to two Thus full use is made of the length of normal colon, and the procedure has the added advantage that at the subsequent operation the bowel to be brought down is predetermined However, it has the disadvantage of bringing the colostomy into the operation, and there may be difficulty in choosing the correct site in the neonatal period in cases with long segments, the apparent cone may then be in aganglionic bowel The surest way of correctly siteing the enterostomy in such cases is by rapid frozen sections

Technique

In Hirschsprung's disease the dilated sigmoid loop may extend well into the upper abdomen, and often it is the first segment of colon to present through an upper abdominal incision It has been mistaken for the transverse colon

The site of the cone should be marked with a black silk stitch which can be identified at the subsequent operation In some very ill young babies it may not always be expedient to perform the formal laparotomy which this manœuvre needs, but rather a small upper abdominal incision through which a loop of transverse colon can be brought out It is important then to attempt to identify the site of the cone by radiography as soon as the baby is fitter for the bowel beyond a colostomy may quickly assume a uniform calibre

Operation

Preparation

The essential measure is to empty the large bowel The general health usually improves remarkably as this is done

Daily colonic lavage has proved the most satisfactory method of emptying the colon In some long-standing cases many weeks of treatment may be necessary, but nutrition, which is poor in such cases, improves steadily during this period and the time is well spent In Hirschsprung's disease, enemas are generally ineffective and are potentially dangerous They should not be given

Fitness is so essential that if, as occasionally happens, these measures do not lead to a satisfactory gain in weight and improved nutrition, a colostomy should be established

Anæmia may require correction, especially in children who have colostomies Immediately before operation the bowel is prepared by an oral bacteriostatic or antibiotic agent Both succinylsulphathiazole for 5 days and streptomycin or oxytetracycline for 2 days have been used in this series and have proved effective

Technique

The Swenson technique (Swenson and Bill 1948), as modified by Dennis Browne (1949, 1955), has been used in the majority of the cases Single-stage operations were performed on 66 children, whilst 86 had preliminary colostomies

A simple small table maintaining the child in the semi-lithotomy position with a sheet barrier between the exposed abdominal and perineal fields has been found most useful (fig 1) Two surgical teams are needed, and, the patient being small, care in organisation around the table is important

An intravenous infusion is established so that blood may be given slowly from the start of the operation A urethral catheter is inserted and left draining It is a wise precaution to have a stomach tube in situ, for the small bowel has to be packed off for a considerable period and the colostomy closed temporarily

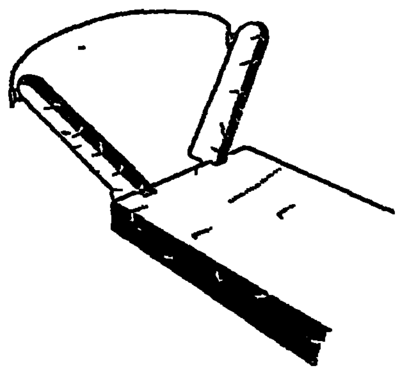

Fig 1—Operation table

On opening the peritoneal cavity, the large bowel may be distended with gas A useful measure then is to guide a sigmoidoscope, passed by an assistant, into the dilated colon

The operation consists in mobilisation of the aganglionic bowel right down to the anal canal, the dissection below the peritoneal floor being made on the rectal wall This dissection is time consuming, for there is no ready plane of cleavage, but it is facilitated by the use of divulsers (Browne 1955) These instruments enable the tissues to be split into strands suitable for ligation or diathermy coagulation

In selecting the site of proximal section, the most important factor is that it should be in normally ganglionic bowel Hypertrophy has been found a satisfactory guide in this regard, but recently, in cases of doubt, frozen sections during operation have been used They have been found particularly helpful in cases with long aganglionic segments where a colostomy has been established without a marking suture at the cone In experienced hands this method has proved wholly reliable

When the proximal bowel is widely dilated the upper section should be as high above the cone as is allowed by the vascular arrangement in the sigmoid mesentery and the length of available colon If very dilated bowel is anastomosed to the anus a terminal reservoir is created, and the risk of postoperative constipation increased It is important to mobilise sufficient colon to avoid any tension on the suture line low in the pelvis Mobilisation of the splenic flexure helps in this respect, and is particularly valuable in cases with rather long sigmoid segments

The rectal dissection has to be continued down to the anal canal Unless this is done the canal cannot be intussuscepted fully and the lower section will be made leaving behind a segment of rectum The distal transection should be made immediately above the anal canal and the anastomosis carried out 1–2 cm from the anocutaneous junction Even with such a low resection children achieve continence This low section is made in all cases, because Hirschsprung's disease may result from very short lengths of aganglionic intestine and because symptoms may recur if abnormal bowel remains below the anastomosis The anastomosis, made in the perineum after intussuscepting the mobilised bowel, is facilitated by preliminary dilatation of the anus, retraction of the buttocks, and the use of a suture plug (Browne 1955) If exposure is poor, or the dissection inadequate, the anastomosis tends to be too high

Recently at the finish of the operation a drainage tube has been placed in the pelvis in the space around the anastomosis and continuous suction applied in the postoperative period It is believed that this measure will reduce the incidence of pelvic infections

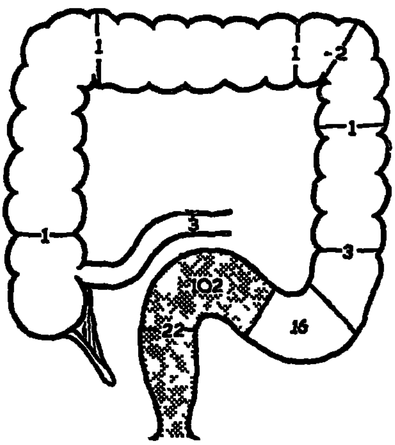

Fig 2—Proximal extents of aganglionic segments in 152 cases of Hirschsprung's disease

The aganglionic segment involves the rectum and lower sigmoid in the majority of cases In the remainder the segment may be shorter or longer The lengths in our series are shown in fig 2

The surgical approach in the long-segment cases may have to be modified to give access to the splenic flexure and even the whole colon

In cases with short segments, the bowel may be hypertrophied and dilated down to the pelvic floor and the cone not seen until dissection is carried out below the peritoneal reflection

Postoperative Management

Children withstand the operation well and usually are in good condition at its end as long as there has been adequate blood replacement The intravenous infusion generally is stopped after 24 hours, when fluid by mouth can be given Catheter drainage of the bladder is continued for 24 hours, but, should the catheter become dislodged before this time, replacement is seldom needed Chemotherapy is desirable, and we have given penicillin 10,000 units per lb body-weight 8-hourly and streptomycin 20 mg per lb per day for 5 days Some children, especially younger ones, develop gaseous colonic distension during the first few days after operation This should be relieved by a flatus tube passed carefully beyond the anastomosis—a measure which may be necessary every few hours Indwelling rectal tubes have been used in an attempt to prevent this distension and two small tubes, side by side so as to allow gas to escape between them, have proved satisfactory

The bowel acts usually after 48–72 hours Motions at first are loose and frequent, but become more normal in consistency and reduced in number by the time the child is ready to leave hospital The time taken for the bowel movements to become normal depends largely on the age of the child and the length of colon remaining

In general the uncomplicated postoperative course is quiet and free from restlessness Experience has shown that restlessness is often the first sign of some complication

Complications

The operative and postoperative periods were satisfactory in 117 of the 152 cases In 35 some complication, either early or late, occurred, and of these children 9 died 6 deaths were at, or shortly after, operation, while 3 occurred later This gives an operative mortality of 4% and an overall mortality for the series of 6%

Shock

Shock was responsible for 3 deaths 2 were early in the series when blood replacement tended to be inadequate and the 3rd was of a young infant who received insufficient blood in error Great importance is now attached to early and adequate blood replacement during operation

Ischæmic Necrosis of the Distal Colon

This caused 2 deaths In both, previous surgical procedures complicated the operations

The 1st case, a boy who had survived from the pre 1948 series, had had eight previous operations, including partial colectomy, and after resection of the aganglionic segment the colon passed under some tension directly from the transverse colostomy to the pelvis

In the 2nd case, a colostomy had been established in the middle of the transverse colon, but at the definitive operation the aganglionic segment was found to extend to the lower descending colon As there was insufficient colon beyond the colostomy to reach the anus the middle of the transverse colon was brought down on the right branch of the middle colic artery after mobilising the hepatic flexure

Extreme restlessness and shock characterised the postoperative period in both cases Death occurred after 36 hours and 55 hours respectively In each case at necropsy the colon was found under tension, and in the 2nd case the middle colic artery was in spasm

These cases illustrate the disadvantage of a colostomy in the transverse colon when the aganglionic segment is longer than usual Greater length of colon would be available by siteing the colostomy immediately above the cone, as has been described already Further experience has shown that the ascending colon, with the ileocolic artery, can be turned down into the pelvis without tension This procedure is now our standard practice when there is insufficient normal colon beyond a transverse colostomy

The ischæmic bowel is deeply situated in the pelvis and cannot be seen at laparotomy Proctoscopy may be useful if this complication is suspected

Pelvic Infection

This complicated 9 operations 1 child died after the development of peritonitis and septicæmia Infection has followed both single and staged procedures 6 followed one stage and 3 multiple stage operations This incidence is not high for this type of operation, and it should be reduced further by improvements in technique made during the series

The consequences of the infection were peritonitis in 6 cases, discharge of pus into the bowel through the suture line and subsequent stricture formation in 2, and ischiorectal abscess with fistula in 1

For peritonitis the procedure used was to remove all free fluid and establish a transverse colostomy

With the exception of the fatal case mentioned this led to remarkable recoveries

A single-layer anastomosis has been used in the great majority of the operations A small experience of a two-layer technique has shown that this does not eradicate the possibility of pelvic infection. It is believed that the pelvic drainage tube with suction, now being used, will lessen it

Infection is known to precede stricture formation in some cases, and whenever pus is discharged per rectum regular digital examinations of the suture line should be made

Disruption of the Wound

This occurred in 6 cases, following single-stage operations in 4 The ruptures occurred about the fifth postoperative day All the patients made uneventful recoveries

Intestinal Obstruction

This developed in 7 cases 2 children died and 5 recovered. In 4 cases the obstruction occurred early in the postoperative period and in 3 later The early cases were small-bowel obstructions due to peritoneal adhesions in 1 these dated from the colostomy operation. All recovered after laparotomy. The 3 later obstructions were each caused by a small-bowel volvulus—a month 6 weeks, and 8 months after operation Operation was delayed in 2 cases and both patients died

It should here be emphasised again that the normal postoperative course is smooth and that persistent restlessness should suggest the possibility of a strangulating or obstructive lesion Abdominal distension and vomiting early after operation might also result from a hold-up of gas in the colon above the anastomosis, but in this event the passage of a flatus tube will give relief The later obstructive episodes have to be distinguished from faecal impaction, which may lead to a somewhat similar clinical picture, but the child with faecal impaction does not become ill nearly so quickly, and the findings on rectal examination and the dramatic response to colonic washout are characteristic It has to be remembered, too, that the child with a small-bowel volvulus may continue to pass frequent loose stools

Anastomotic Stricture

This developed in 7 cases In some others the suture line felt tight temporarily but responded quickly to digital dilatation and healed without stenosis The majority of strictures were in young infants, and several had rather long segments with the likelihood of some tension on the anastomosis. Infection also was a significant factor in at least 2 cases

These cases emphasise the importance of full mobilisation of the left hemicolon whenever transection has to be in the upper sigmoid region and some tension would otherwise occur

The strictures generally developed within the first 3 weeks, but on two occasions were delayed for three months There is a need therefore for regular rectal examinations both early and later during the postoperative follow-up

Treatment by regular digital or instrumental dilatations is necessary. This may have to be continued for many months and even years in some cases 1 of the cases was cured only after dilatations had been continued for 3 years

The result in 4 cases has been correction of the stenosis and the development of normal bowel function while a further 2 are progressing favourably under this treatment 1 boy in whom an impassable stricture developed presumably after disruption of the anastomosis continues to have a colostomy; a further attempt to restore continuity is contemplated

Urinary Retention

Urinary retention, leading to chronic distension with overflow, occurred in 1 of the very early cases in the series Temporary cystostomy was followed by a return of detrusor function The boy now has full urinary control Since this case the rectum has been dissected against the muscle coat itself and there have been no similar urinary complications

Functional Colonic Distension

The 9th death was that of an infant aged 14 months 5 months after operation. He was admitted to another hospital in a collapsed state following an enema, given because of vomiting and abdominal distension He died within a few hours and at necropsy no organic obstruction was found Possibly his death was due to water intoxication

Functional Results of Operation

Children still less than 3 years old who could not be expected to be fully continent, and children operated on during the past 3 months have been excluded from this assessment. This leaves 102, whose ages range now from 3 to 22 years A recent survey shows that 55 are normal in every way The remainder still have some deficiency but in the majority this is slight and in many the result was regarded as imperfect only because it was desired to make a most critical survey of the operation.

The three most important aspects are general health, bowel regularity, and continence

General Health

This has been outstandingly improved by the operation Parents uniformly report improvement in appetite vigour, and general fitness For the first time in many cases schooling has been free from repeated interruptions Some of those early in the series are now carrying out National Service, and 1 has finished this Those at school can take a full part in games

The weights and heights were studied in a series of 40 cases (fig 3) In the majority these were at or above the average for the age and in some a considerable deficit had been made good

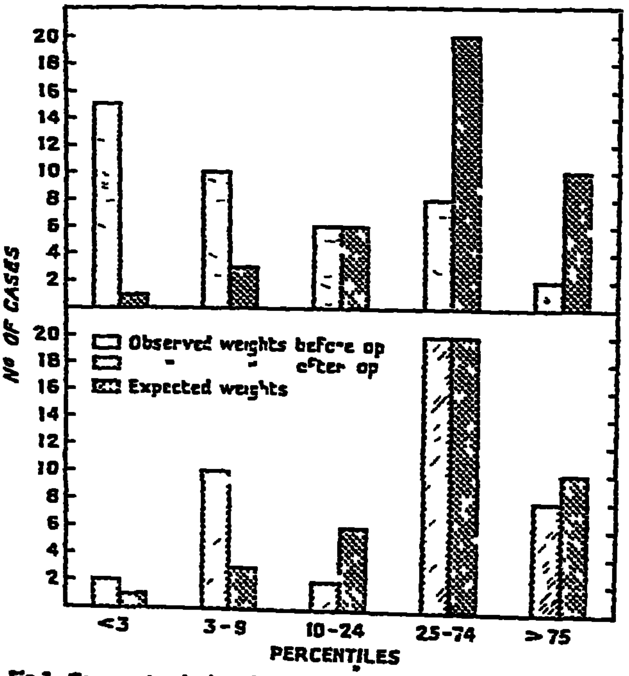

Fig 3—Comparative body-weights in 40 cases before and after operation

Bowel Regularity

There is considerable individual variation in the development of regular defæcation after operation. In most children this develops easily and at once, while others are prone to constipation and normal function is attained slowly.

Constipation is one of the most common problems in management. It required treatment in 34 cases in this series, of whom two-thirds were less than 3 years old at the time of operation. In most the trouble began within a few months of operation, but in 9 cases it was delayed for more than a year—even for as long as 3 years. 7 of them presented because of incontinence or frank soiling, and 10 with vomiting and abdominal distension.

The acute episodes with vomiting and distension were similar to the crises seen in the untreated disease. They occurred mostly in the under-2-year group, and there was a decided tendency to recurrence. Large quantities of soft fæces and gas under pressure were retained in the colon, though in some there was frequent overflow soiling. Vomiting soon became progressive, and several of these children were ill and dehydrated when admitted. The importance of the matter is emphasised by the death already mentioned. There was a dramatic response to rectal examination or intubation—fluid stool and gas were ejected with a great force—and the child's condition improved immediately, though active resuscitation might be necessary.

In other children fæcal accumulations, without much gas or distension, developed slowly. Often stools continued to be passed during this time; it might be recognised that these were smaller or less frequent than usual, or the parents might notice nothing abnormal until overflow incontinence occurred. Examination showed the rectum right down to the anus filled with fæces, which usually were soft.

The management of the two groups was essentially the same—the colon was emptied and kept empty until regular defæcation returned. It was often most satisfactory to readmit the child to hospital to begin the treatment. Later regular aperients and bowel washouts once or twice a week could be continued at home. Treatment was continued until complete evacuations occurred regularly. More than two years' treatment was necessary in 14 of our cases, but experience justified this conservative approach. Of the 34 cases in which constipation occurred, 24 are now passing motions regularly, while the remainder are still under treatment. As constipation was corrected, control improved.

There are probably two important factors in the production of this *postoperative constipation*. One is sensation, for until the sensation caused by a motion in the new "rectum" is appreciated by the child he may ignore it, and as a result fail to empty the terminal bowel; the higher incidence of constipation in young children is probably significant in this regard. The child must be sent regularly to the lavatory in the early stages, and it may be desirable to use aperients to ensure adequate evacuation.

The second important factor is the size of the colon proximal to the point of resection. Often the colon is considerably dilated and liable to empty incompletely, and treatment may be needed then to prevent the development of the "colonic inertia" syndrome.

The level of the distal section may be a further factor in the development of postoperative constipation. It is important to remove all the rectum and anastomose the colon directly to the proximal end of the anal canal.

Careful follow-up, including regular rectal examinations, is necessary as large fæcal accumulation may develop quite insidiously after a normal period as long as 3 years.

The long period of treatment needed in a few cases before regularity and control are gained has to be borne in mind when a revision operation for removal of a supposed small residual abnormal segment, is under consideration. Revision operations have been performed in 3 cases. In 1 case the gut resected at this further operation was ganglionic except for a small transitional area; while in another a further 2·5 cm. of aganglionic bowel was excised from below the suture line: good function resulted. Such limited resections have been accidental, but the fact that conservative treatment of many cases of postoperative constipation has ultimately led to a good functional result should be borne in mind when further surgery is being considered.

Continence

Of the 102 children now more than 3 years old, 61 have achieved full continence. In 41 there is lack of full control, but in most this lack is slight. Most of the children are still of an age when, in this respect, many normal children are not wholly reliable at times of excitement or loose motions, but in the follow-up survey continence was assessed in the strictest possible light. The individual variation in the time taken to gain full control after operation is considerable, but the reason for this is not always clear.

Most of the group with normal function became continent within a few weeks after operation, but a few children soiled for several years before acquiring perfect control.

Control is good in nearly two-thirds of the remaining 41 cases. The defect is now no more than occasional slight soiling of the perianal region, though in some cases this state has been reached only after a period of more heavy soiling. The tone of the anal canal is normal in practically every case.

The commonest time for soiling is before defæcation. Much less common times are after defæcation, at night, and when passing flatus. Urgency, especially early after operation, causes a few children to soil.

Attention to continence is one of the most important aspects of management after operation. In many cases constipation is an important cause of incontinence, and improvement in control usually follows correction of constipation.

Bowel training after operation is another important factor. Up to the time of operation many of these children have never experienced the normal sensations associated with defæcation and have not within memory had a bowel action without some aid. Afterwards they have to learn the sensations—and perhaps unusual ones at that—from the beginning. It is hardly surprising that some children are slow to achieve complete control. That soiling is commonest before defæcation suggests that they fail to realise, or realise too late, the need for defæcation. Bowel training after operation is therefore very important. Inevitably the social circumstances, the age and intelligence of the child, and the interest of the mother bear on the problem. Children should be trained to defæcate at regular times and aperients given as necessary. If they are left to their own devices there is a danger of sensations being ignored and of constipation developing insidiously.

A very satisfactory degree of control has been achieved by children who have had ileo-anal anastomosis because the whole colon was aganglionic. Soiling has been slight, and in the oldest case has almost stopped. About 3 stools are passed each day after the first 6 months.

Enuresis

15 children over the age of 4 years have nocturnal enuresis; all have perfect control by day. In 7 it is the only disability, for they have normal bowel function. Several parents have noted that bed-wetting is more frequent when the rectum is full.

This is a higher prevalence of enuresis than would be expected in normal children, but is probably not significantly higher than in those who have undergone any other embarrassing and uncomfortable illness and a major operation in childhood

Pyelograms have not been performed routinely, but during an earlier follow-up intravenous pyelography was carried out in 25 cases, none showed any significant abnormality Also, the ureters are always seen at operation, and no abnormal dilatations, such as those described by Swenson et al (1952), have been seen in this series

Summary

Swenson's operation has been undertaken in 152 cases of Hirschsprung's disease at the Hospital for Sick Children, Great Ormond Street

The operative mortality was 4% and the overall mortality 6%

The complications are described and their treatment discussed

Bowel training and prevention of constipation are necessary after operation

I acknowledge most gratefully the coöperation of the consultant staff of the Hospital for Sick Children in allowing me to study their cases and the research committee who made possible the investigation I am particularly indebted to Mr Denis Browne, Dr Martin Bodian, and Mr H H Nixon for much personal help and for allowing me to draw on their great experience My thanks are also due to Mr Derek Martin and Mr G Lyth, of the department of medical illustration

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XANTHOMATOSIS AND ESSENTIAL HYPERCHOLESTEROLÆMIA

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THE earliest descriptions of tendinous and tuberous xanthomas appear to be those of Addison and Gull (1857) and Fox (1879) Fagge (1873) observed the association of xanthomatosis and cardiovascular disease, and Müller (1938) noted the high incidence of angina of effort among his patients with xanthomatosis

Burns (1920) demonstrated the defective cholesterol metabolism present in this syndrome

The familial nature of the condition was mentioned by Torok (1893) and Gossage (1908), and many genetic studies of the syndrome have been made in America and Norway during the past twenty years, but no such studies have been published in this country We therefore report here the clinical and genetic investigation of five families with xanthomatosis and essential hypercholesterolæmia

Material and Methods

Members of these families were, except for a few in the first pedigree, seen by one of us, and wherever possible an electrocardiogram was obtained

Serum cholesterol was estimated by a modified Bloor method following extraction by the method described by Clarke and Marney (1945) or, as in the second pedigree, by the method of Zlatkis et al (1953) In some cases oxalated plasma was used, which tends to give a slightly lower reading

For the upper normal level of serum cholesterol we have used the figures published by Keys et al (1950), who investigated the range of serum cholesterol in healthy people and its variation with age The upper limit for 98% of their population in each age-group has been accepted Previous investigators have used various figures for the upper normal limit for serum cholesterol and, with one notable exception (Piper and Orrild 1956), have disregarded its variation with age

The accompanying pedigrees have been compiled to illustrate both the clinical features of xanthomatosis and the transmission of hypercholesterolæmia Because of the large numbers involved we have not included cholesterol values in pedigree no 1 except for the small branch derived from I 3 Unless the individual is deceased, the symbols □ ○ therefore imply, in almost all cases, that the individual is considered to be normal on clinical grounds and to have a normal blood cholesterol level

Clinical Features

The clinical features of these patients were typical of those described by Thannhauser (1950) The corneal arcus was observed frequently among those with xanthomatosis but may be the only clinical expression of hypercholesterolæmia and therefore merits investigation, particularly in younger age-groups

Tendon xanthomas were found over the tendo Achillis, the extensor tendons of hands and toes, and the extensor aspects of the knee and elbow Xanthelasma palpebrum usually accompanied these xanthomas but was occasionally found alone or in conjunction with the corneal arcus

Of the 10 patients with hypercholesterolæmic xanthomatosis 8 had had ischæmic heart disease, which had been the cause of death in 4

Hypercholesterolæmia was observed in 38 persons, of whom 15 had ischæmic heart disease

Pedigree no 1 (fig 1)

Attention was attracted to this family by the patient, II 18, a member of the branch derived from I 3 She was one of four siblings with hypercholesterolæmic xanthomatosis and ischæmic heart disease, which proved fatal in two (II 19, II 21) The father (I 3) was known to have had xanthomatosis and died at the age of 53, the sole representative of the third generation (III 35) has angina of effort and hypercholesterolæmia

No further example of the complete syndrome, hypercholesterolæmic xanthomatosis, was found in this family, but many members with the incomplete syndrome (xanthelasma palpebrum, corneal arcus, ischæmic heart disease, and hypercholesterolæmia) were discovered, particularly in the first branch, derived from I 1 The frequency of coronary disease, often proving fatal at an early age, is of particular interest and is illustrated by a girl (III 24) who died at the age of 27 and was found at necropsy to have extensive coronary atheroma

Pedigree no 2 (fig 2)

The first patient (III 6) had had xanthomatosis and angina of effort since the age of 16 and electrocardiographic evidence of coronary occlusion at the age of 21 Her sister (III 7), who presented an identical picture, died of ischæmic heart disease at the age of 21 In both there was clinical evidence of involvement of the aortic valve

This sibship (III 6–III 9) was derived from a consanguineous mating of two members of a family in which there was further evidence of the incomplete syndrome (xanthelasma palpebrum, corneal arcus, coronary disease, and hypercholesterolæmia)

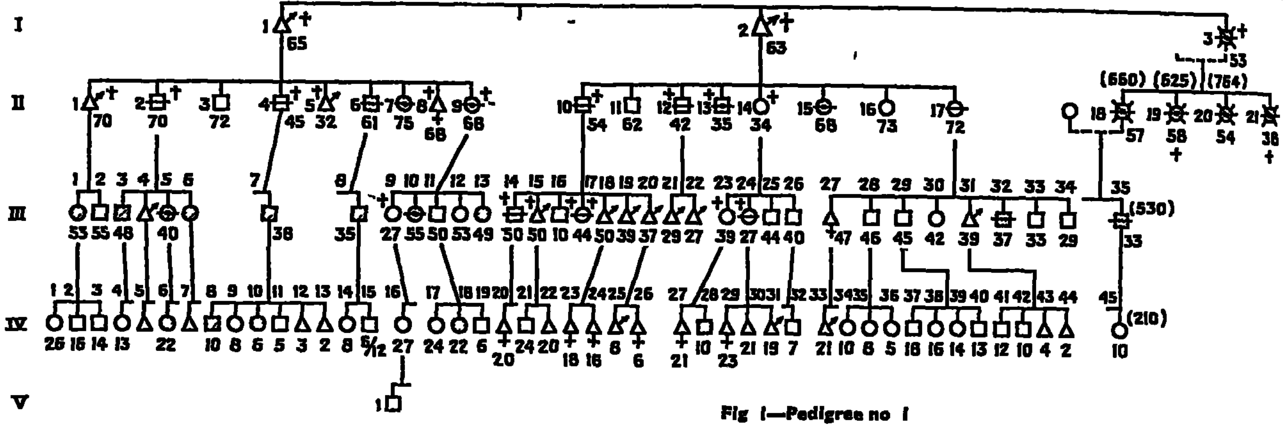
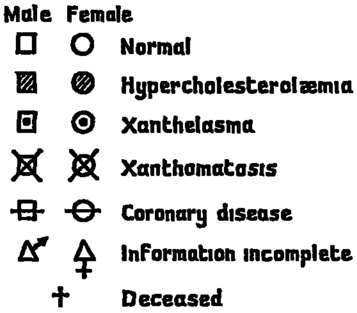


Fig 1—Pedigree no 1



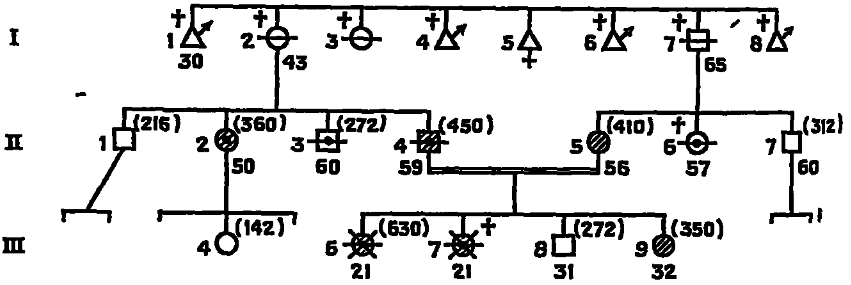


Fig. 2—Pedigree no 2 Symbols as in fig 1

Pedigree no 3 (fig 3)

The patient, II 2, was admitted after a coronary occlusion and found to have xanthomatosis There were examples of the incomplete syndrome in this small family, and her surviving siblings were shown to have hypercholesterolæmia

Pedigree no 4 (fig 4)

Clinical evidence of the syndrome in this family was confined to the patient, II 1, who had a well-developed corneal arcus and xanthomatosis, and his sister, II 3, who had a corneal arcus only, but familial essential hypercholesterolæmia was found later

Pedigree no 5 (fig 5)

Apart from the patient, II 3, who had xanthomatosis, there was no clinical evidence of the syndrome in this family, but hypercholesterolæmia was found in the siblings

Biochemistry

The basic abnormality in this syndrome is disordered metabolism of cholesterol, with xanthomatous infiltration of skin, tendon sheaths, and arterial intima as a secondary effect The relationship of some of these clinical features to the serum cholesterol level is shown in fig 6

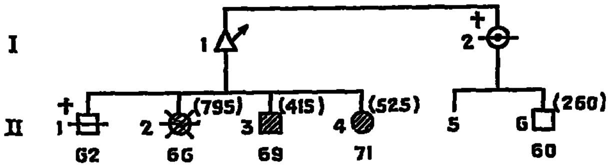


Fig 3—Pedigree no 3 Symbols as in fig 1

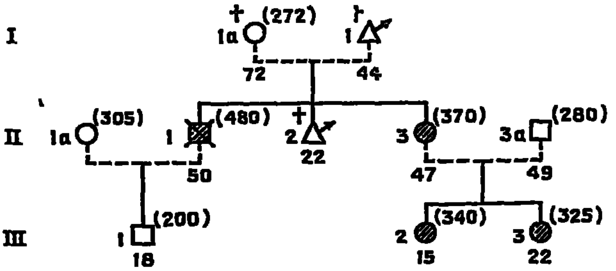


Fig 4—Pedigree no 4 Symbols as in fig 1

The concentration of fatty acids and phospholipids in the serum was estimated in a high proportion of the members of these families and usually found to be either high normal or slightly above normal The occurrence of a raised serum-uric-acid level in a significant proportion of individuals with hypercholesterolæmia, as reported by Adlersberg (1949), was confirmed

Paper electrophoresis was done on almost all the sera obtained from members of these families The increased density of the β-lipoprotein band characteristic of hypercholesterolæmic states was often seen

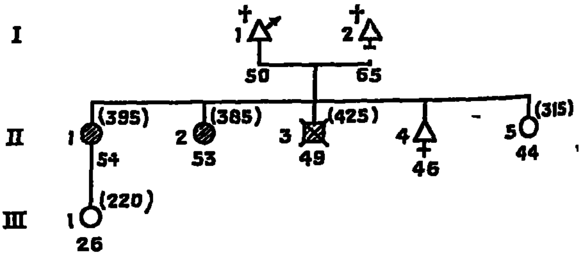


Fig 5—Pedigree no 5 Symbols as in fig 1

Genetics of Hypercholesterolæmia

This investigation was undertaken primarily to study the genetic pattern of essential hypercholesterolæmia At the start of this work the prevailing view was that essential hypercholesterolæmia was transmitted as an incomplete dominant trait (Wilkinson et al 1948, Adlersberg et al 1949, Alvord 1949, and Thannhauser 1950) Wilkinson et al (1948) considered that essential hypercholesterolæmia represented the heterozygous abnormal (Cc) and hypercholesterolæmic xanthomatosis the homozygous abnormal state (CC) for cholesterol On completion of the investigation of pedigrees 1–3 we considered that our results were compatible with this theory (Harris Jones et al 1956)

In tracing the genetic pattern in these pedigrees pedigree 1 (fig 1) is most conveniently considered in three sections

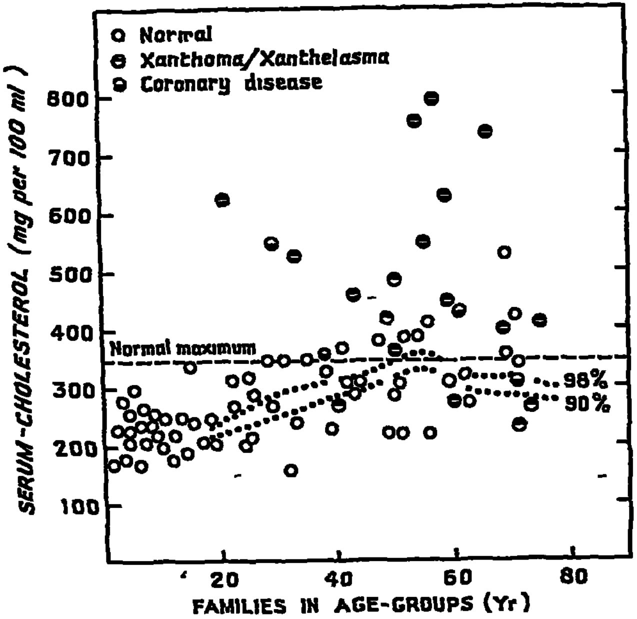


Fig 6—Incidence of xanthomatosis xanthelasma, and coronary disease and their relation to serum-cholesterol levels in pedigrees I–5 Dotted lines denote normal maxima of serum cholesterol levels in 98% and 90% of a population studied by Keys et al (1950)

In the first branch, derived from I 1, the transmission of hypercholesterolæmia follows a dominant pattern except for the kindred III 11 and IV 18, who require further investigation

In the second branch, derived from I 2, there was little clinical evidence of the syndrome, hypercholesterolæmia being found in only three persons Among the descendants of II 14, however, there is evidence of early death with coronary disease, xanthelasma, and hypercholesterolæmia (IV 28)

In the third branch, derived from I 3 there is a remarkable increase in both the frequency and severity of the condition. Here, according to the theory of Wilkinson et al (1948), we have a sibship of three, probably four, homozygotes (II 18–21) The undoubtedly rare mating of a homozygote (I 3) with a heterozygote has to be invoked to explain this The increased intensity of the syndrome in this branch might support this possibility The mating of a homozygote abnormal (II 18) with a normal person produced, as predicted, a heterozygote (III 35)

Pedigree no 2 appeared to provide evidence essential to the theory of homozygosis, according to which both parents of a person with hypercholesterolæmic xanthomatosis (CC) must be at least heterozygous abnormal (Cc) the sibship III 6–9, consisting of two homozygotes, one heterozygote, and one normal, was derived from the consanguineous marriage of two affected members (II. 4 and II 5) of a family with essential hypercholesterolæmia

Pedigree no 4, however, showed that the theory of homozygous heredity (Wilkinson et al 1948) was no longer tenable In this family (fig 4) both a parent I 1a) and a son (III 1) of the patient with hypercholesterolæmic xanthomatosis (II 1) had normal serum-cholesterol levels

Pedigree no 5 did not present an opportunity to clarify this point neither parents nor offspring of the patient with xanthomatosis (II 3) being available for study

The results of the investigation of these five families support the view expressed by Piper and Orrild (1956). who reviewed twelve families and confirmed that hypercholesterolæmia was transmitted as a dominant trait, but rejected the theory that xanthomatosis represented the homozygous abnormal state for cholesterol

Comment

The full syndrome of hypercholesterolæmic xanthomatosis is probably uncommon but its recognition should not be difficult The incomplete syndrome, which occurs much more commonly, appears to escape recognition more often

Essential hypercholesterolæmia should be considered when coronary disease, xanthelasma palpebrum, and corneal arcus are encountered, alone or in combination, in patients aged less than 50 The corneal arcus in particular appears to have received surprisingly little attention as a valuable clinical sign of hypercholesterolæmia The high incidence of coronary disease associated with essential hypercholesterolæmia and its alarming incidence in patients with xanthomatosis have been confirmed

Summary

Five families with familial xanthomatosis and essential hypercholesterolæmia are reported

Whereas essential hypercholesterolæmia is transmitted as a dominant trait, there is no evidence that xanthomatosis represents the homozygous abnormal state for cholesterol.

Essential hypercholesterolæmia and xanthomatosis is associated commonly with coronary disease of early onset

We are indebted to Dr C E Davies, Dr James Brown, and Dr J Carson for permission to study patients under their care, Dr A. Jordan, Dr T L Morris, and Dr F Young for their invaluable assistance, the many pathologists and practitioners who have helped us, and the Royal Society of Medicine for permission to reproduce fig 6 from their *Proceedings*

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HYPERURICÆMIA AND ESSENTIAL HYPERCHOLESTEROLÆMIA

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TOPHACEOUS gout is presumed to result from an inborn error of metabolism and is associated with a raised level of uric acid in the serum Essential hyperuricæmia may be detected in apparently healthy relations of a patient with gout

Xanthomatosis similarly results from an inborn error of metabolism and is accompanied by a rise in the serum cholesterol level Again a raised serum cholesterol level may be found in healthy near relations of patients with xanthomatosis

An interesting relationship between these two metabolic abnormalities was recorded by Adlersberg (1949) During an investigation of families of patients with xanthomatosis (Harris Jones et al 1956), the opportunity was taken to study this association

Methods and Material

The material for this investigation consisted of patients with xanthomatosis and their families In 85 people the serum

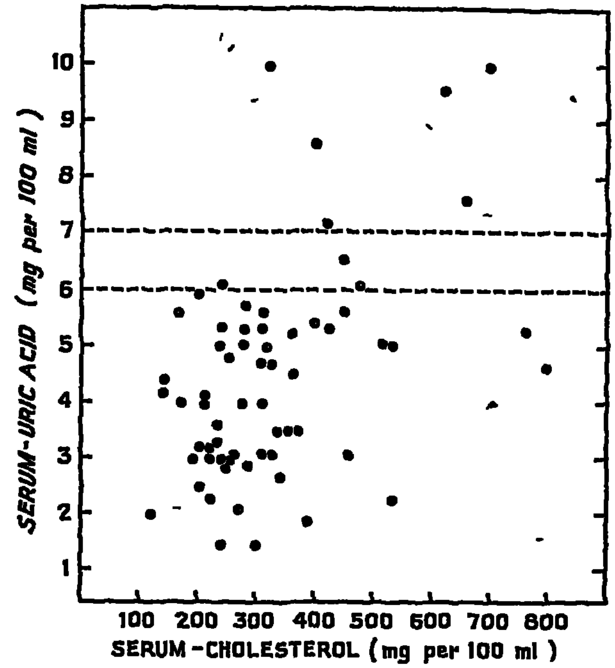

Fig 1—Relation of serum uric-acid levels to serum-cholesterol levels in patients with xanthomatosis and in their families

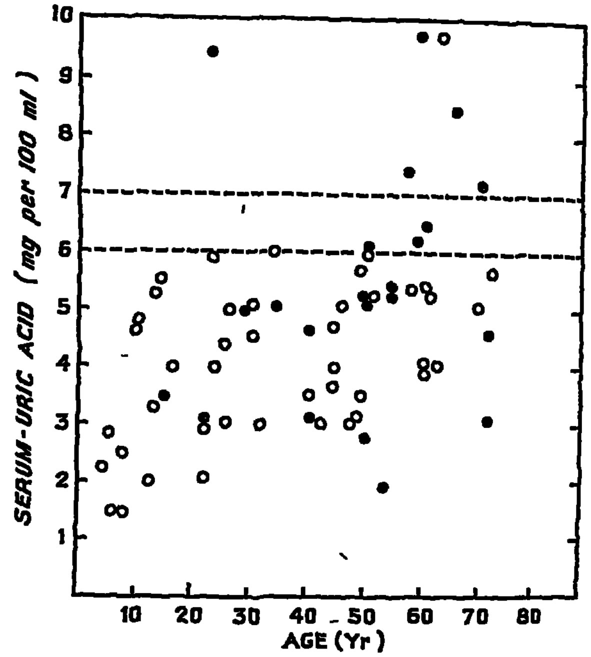

Fig 2—Serum uric-acid levels in relation to age and to hypercholesterolæmia in patients with xanthomatosis and in their families *open circles*, serum-cholesterol level normal, *solid circles*, hypercholesterolæmia

cholesterol level was estimated, and in 65 of these the level of uric acid in the serum was also estimated There were 32 women and 33 men in this group and the age range is shown in fig 2 7 members of this group had xanthomatosis, and there was a high incidence of ischæmic heart disease in their families (Harris-Jones et al 1957) No clinical evidence of gout was detected in these families The serum-cholesterol level was estimated by a modified Bloor technique after extraction by the method described by Clarke and Marney (1945), and in a few cases by the method of Zlatkis et al (1953) Oxalated plasma, known to give slightly lower results, was used on some occasions Because of the known tendency for the serum cholesterol level to rise with increasing age, its upper normal limit was based on the figures published by Keys et al (1950) The upper limit for 98% of their healthy population in each age group was taken, this ranged from 240 mg per 100 ml at 18 years to 364 mg per 100 ml at 55 years

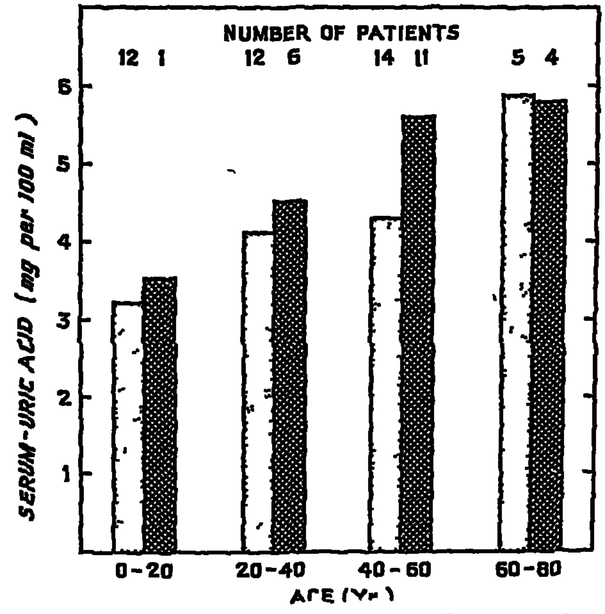

Fig 3—Mean serum-uric-acid levels in age groups of patients with and without hypercholesterolæmia *stippled*, serum cholesterol level normal, *hatched*, hypercholesterolæmia.

The serum uric acid level was estimated by the methods described by Kern and Stransky (1937) and Caraway (1955) The upper normal limit for serum uric acid was taken as 6 mg per 100 ml (Smyth et al 1948, Marson 1953) In a survey of serum uric acid levels in health and in coronary artery disease Gertler et al (1951) found that in only 6% of their controls and matched controls was the serum uric acid level above 6 mg per 100 ml, and that none were above 7 mg per 100 ml

RELATION OF SERUM-URIC ACID LEVEL TO SERUM CHOLESTEROL LEVEL

Serum cholesterol level (mg per 100 ml)	No of persons	Serum uric acid level (mean) (mg per 100 ml)
< 350	44	4
350 or more	21	5 5
< 400	49	3 9
400 or more	16	6

Results

Serum cholesterol and serum-uric acid levels of patients with xanthomatosis and their families are recorded in fig 1 Of these 65 people studied 22 were considered to have essential hypercholesterolæmia, 9 had a serum uric acid level above 6 mg per 100 ml, 6 of these having more than 7 mg per 100 ml All but 2 of those with a serum uric acid level above 6 mg per 100 ml and all but 1 of those with a serum-uric-acid level above 7 mg per 100 ml had a serum cholesterol level of 400 mg per 100 ml or higher

The relation of the serum uric acid level to age and hypercholesterolæmia is illustrated in fig 2, which shows the tendency for the serum-uric acid level to rise with age in both those with a normal serum cholesterol level and those with hypercholesterolæmia Of the 22 people deemed to have hypercholesterolæmia 8 had a serum uric acid level above 6 mg per 100 ml, 5 of these having more than 7 mg per 100 ml (Adlersberg [1949] reported that in a third of 37 patients with essential hypercholesterolæmia the serum-uric-acid level was 6 mg per 100 ml or higher) Of the 45 people with a normal serum-cholesterol level 3 had a serum uric acid level of 6 mg per 100 ml or higher, 1 of these having more than 7 mg per 100 ml, this finding is in keeping with values for healthy controls published by Gertler et al (1951)

The mean serum-uric-acid levels in those with hypercholesterolæmia and those with normal serum cholesterol levels in each age group is shown in fig 3 The mean serum-uric-acid level in relation to increasing serum-cholesterol level is shown in the accompanying table The striking rise in the mean serum-uric-acid level with the rising serum-cholesterol level recorded in the accompanying table is modified when this is studied in age-groups (fig 3) because the greatest number of people with essential hypercholesterolæmia will be found in the age group 40–60, a period in which the serum-uric-acid level usually reaches its highest values

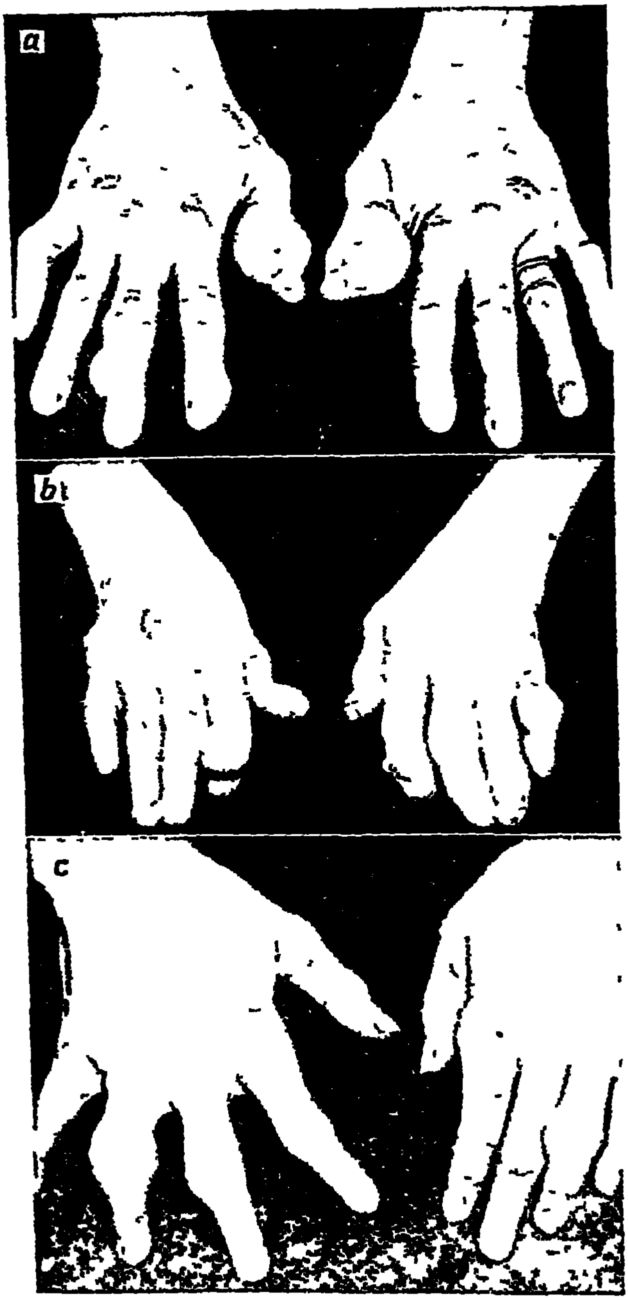

Fig 4—Hands of three women showing clinical similarities between gout and xanthomatosis tophaceous deposits on extensor tendons being indistinguishable from tumours of xanthomatosis *a* aged 58 with xanthomatosis serum-uric-acid level 9 7 mg per 100 ml., serum-cholesterol level 520 mg per 100 ml *b* aged 65 with gout, serum-uric-acid level 9 7 mg per 100 ml., serum-cholesterol level 260 mg per 100 ml *c* aged 22 with xanthomatosis serum-uric acid level 9 4 mg per 100 ml serum-cholesterol level 725 mg per 100 ml

Discussion

Essential or primary abnormalities of uric-acid and cholesterol metabolism are comparable in some of their genetic and clinical aspects Both result from an inborn error of metabolism which manifests itself clinically in only a small proportion of affected people It has been stated that hyperuricæmia, or the metabolic abnormality from which it arises, may be transmitted as a dominant autosomal gene (Smyth et al 1948), but Hauge and Harvald (1955) failed to confirm this It now appears established that the metabolic abnormality responsible for hypercholesterolæmia is transmitted as a dominant trait In some genetic studies it has appeared that the full clinical syndrome of both tophaceous gout and xanthomatosis multiplex represent the homozygous abnormal state for uric-acid and cholesterol metabolism respectively (Smyth et al. 1948, Wilkinson et al 1948)

Although tophaceous gout and xanthomatosis should easily be distinguishable clinically they have some features in common Both biurates and cholesterol esters tend to be deposited in sites of physical stress or trauma, such as the extensor aspects of joints, and in tendon sheaths This similarity of distribution of tophi and xanthomata is shown in fig 4 Estimation of the serum-uric-acid level alone might not differentiate these two conditions, but the serum-cholesterol level is almost invariably raised in xanthomatosis

Coronary-artery disease is reported to occur in about 40% of patients with essential hypercholesterolæmia (Piper and Orrild 1956) Clinical impressions of an association between gout and coronary-artery disease were supported by Gertler et al (1951), who found a positive correlation between hyperuricæmia and coronary-artery disease In attempting to relate ischæmic heart-disease to a biochemical index, these workers devised the "cup index," which is the product of

$$\frac{\text{serum cholesterol (mg per 100 ml)} \times \text{serum uric acid (mg per 100 ml)}}{\text{serum lipid phosphorus (mg per 100 ml)}}$$

Finally, although the metabolic abnormality in the form of hyperuricæmia or hypercholesterolæmia may be detected among the younger relations of patients with gout or with xanthomatosis, the emergence of the full clinical syndrome is uncommon in either before middle life

Although it is beyond the scope of this investigation to seek an explanation for this apparent association between hyperuricæmia and hypercholesterolæmia, some possible factors might be examined with interest. The possibility that tophaceous gout and xanthomatosis were both present in some patients was excluded by examination of the case-histories and the patients The chance inheritance of two inborn errors of metabolism for purines and for cholesterol, was rendered unlikely by the fact that three of the five families studied contributed members with hyperuricæmia

✓ The results of this investigation tend to direct attention to the effect of hypercholesterolæmia upon uric acid metabolism There is some evidence that high-fat diets inhibit uric acid excretion in man (Adlersberg and Ellenberg 1939), hyperlipæmia and hypercholesterolæmia have been reported in patients with gout (Albrieux et al 1953)

Before valid conclusions are possible, further and more detailed studies are desirable Such studies, which would include observations on the excretion of uric acid and the effect of cholesterol-lowering agents on the serum-uric acid level were impracticable because members of these families were so widely scattered Multiple blood sampling is also important in studying such variables as serum-uric-acid and serum cholesterol levels, and it is because this has been impossible that the results obtained have not been submitted to statistical analysis This report has aimed at attracting attention to the occurrence of hyperuricæmia among relations of patients with xanthomatosis, and to some of the genetic and clinical similarities between gout and xanthomatosis

Summary

Serum-uric-acid levels in patients with xanthomatosis and members of their families are reported

Abnormally high values were found among those with essential hypercholesterolæmia, the highest values being recorded in patients with xanthomatosis

There are clinical and genetic similarities between gout and xanthomatosis

There does not appear to be an obvious explanation for the association of these metabolic abnormalities

I am indebted to Dr A Jordan for biochemical estimations, and the Editor of the *Proceedings of the Royal Society of Medicine* for permission to publish fig 2

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CLINICAL COMPARISON OF DIAMORPHINE AND PHOLCODINE AS COUGH SUPPRESSANTS

BY A NEW METHOD OF SEQUENTIAL ANALYSIS

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In view of recent controversy over the value of heroin in the relief of symptoms it seemed desirable to test one action of the drug in man by a controlled clinical trial

Heroin has gained the reputation of being the most powerful drug in the suppression of cough and, since this action seemed to be more susceptible to measurement than the relief of pain, the trial was designed to study this effect The trial compared the effect on cough of three preparations—linctuses of diamorphine (heroin), pholcodine, and a placebo The original intention was to use the ranking method described by Rushbrooke et al (1956) Difficulties arose with the method, and it was decided instead to compare the treatments in pairs by a new method of sequential analysis, the theory of which has been described by Armitage (1957)

Materials and Methods

The patients all had cough of several months' duration 2 patients were uncooperative and had to be excluded from the trial, and there remained 45 patients No attempt was made to assess the degree of cough, but its severity in all cases was such as to lead the patients to ask for relief and, in some, to keep them awake for several hours during the night There were 14 outpatients who all had chronic bronchitis, and 31 inpatients with the following conditions chronic bronchitis 17, pulmonary new growth 6, bronchiectasis 3, mitral stenosis 3, and chronic pulmonary tuberculosis 2 Most of the inpatients with chronic bronchitis were convalescing from additional illness—e g, acute respiratory infection, spontaneous pneumothorax, and congestive cardiac failure—but by the time of study their cough had recovered to its usual state

The linctus of diamorphine was prepared according to the *British Pharmaceutical Codex 1954* and contained diamorphine gr $^1/_{30}$ in each 60 minims, with oxymel glycerin, and syrup The placebo was an identical mixture except that diamorphine was omitted The pholcodine linctus ('Lipect,' John Wyeth) contained in each dose

Antazoline hydrochloride	12 50 mg
Pholcodine	4 00 mg
Ext ipecac liq	0 03 ml
Sucrose	3 20 g

Each mixture was taken, for two days, in a dose of minims 120 at night before the patient went to sleep, the whole course lasting six days The use of linctus at night rather than during the day would probably make it easier for the patients to assess the severity of their cough An expectorant linctus was given to some in the day, but apart from this no drugs were given which might have suppressed cough

In advance the hospital dispensary had arranged for the patients to receive the three drugs in such a way that the six possible orders were distributed randomly among each succeeding group of six patients The patients were numbered consecutively, and the mixtures were prepared in three bottles labelled with the patient's number and a number showing the order of administration—i e, 1st, 2nd, and 3rd No other means of identification appeared on the bottles, and the patients nurses, and observer were unaware of their contents When the mixtures were required the patient's number was shown on the prescription sheet and the appropriate series of bottles was delivered by the dispensary

The patients were told that they were receiving three types of medicine and that we wished to find out which relieved their cough best They were asked to note the severity of their cough from the time of taking the medicine until going to sleep, so that later they would be able to rank the three treatments in order of preference After the six day trial period their preferences were recorded, as bottle numbers, and, after each batch of six patients had been treated, the bottle numbers were interpreted as names of the corresponding linctus mixtures by reference to the dispensary list

Early in the trial it became clear that the patients were rarely able to give a clear set of preferences, because they usually gave a tie for first or last place, or even for all three mixtures (table i) For this reason the statistical treatment for ranking methods used by Rushbrooke et al (1956) would have had to be modified We decided at this stage to compare the treatments in pairs, using for any one pair of treatments only those patients who gave a clear preference in favour of one or the other We decided, in addition, to use a new type of sequential analysis, called a "restricted sequential procedure," the theory of which has been described by Armitage (1957) Since this method has not been used previously in clinical trials, its main features are described here

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TABLE I—FREQUENCIES OF VARIOUS ORDERS OF PREFERENCE

Preference			No of patients
1st	2nd	3rd	
L P H			12
L	P H		11
L	H	P	4
H L	P		5
H	L P		5
H	P	L	2
H	L	P	2
P	L	H	2
P	H	L	1
P	L H		1

H, heroin. L, lipect P placebo

Sequential Analysis of Results

In sequential methods of statistical analysis observations are examined continuously as they become available, and the decision whether to stop at any stage or to make further observations depends on the results so far obtained Various sequential methods for use in clinical trials have been described by Armitage (1954) These methods had the useful feature that, for comparisons of two treatments, a trial could be ended relatively quickly if the treatments differed very considerably in efficacy, or if their effects were very similar. They had, however, the disadvantage that in intermediate situations the trial could last a very long time because there was no definite upper limit to the number of observations

Bross (1952) has given two sequential plans for medical trials, in which the number of observations is restricted to be less than some definite upper limit, and one of his plans has been used in a clinical trial by Newton and Tanner (1956) The "restricted sequential procedures" of Armitage (1957) are similar to those of Bross but provide a wider variety of plans suitable for different circumstances

The results are plotted on a chart (see figure)

Each of the three comparisons between pairs of treatments gives rise to a zigzag path starting at the origin (the point where the horizontal and vertical axes intersect) For each patient giving a preference in favour of one of the two treatments the path is continued one step in a "north-easterly" direction, for each patient giving the opposite preference the path moves one unit in a "south easterly" direction The area in which the paths develop is enclosed by three boundaries, shown by heavy lines in the accompanying figure These are chosen in such a way that, if two treatments are in fact equivalent (so that, in the long run, 50% of the patients' preferences will be in favour of one and 50% in favour of the other), there is a probability of about 0·95 that the zigzag path will end on the middle (V-shaped) boundary, and only 0·05 that it will reach one of the outer boundaries (the two divergent straight lines) In this sense we may say that a path ending on one of the outer boundaries indicates a difference between the treatments which is significant at the 5% level The probabilities stated above are only approximately correct, and exact calculations for the boundaries used here give values of 0·960 and 0·040

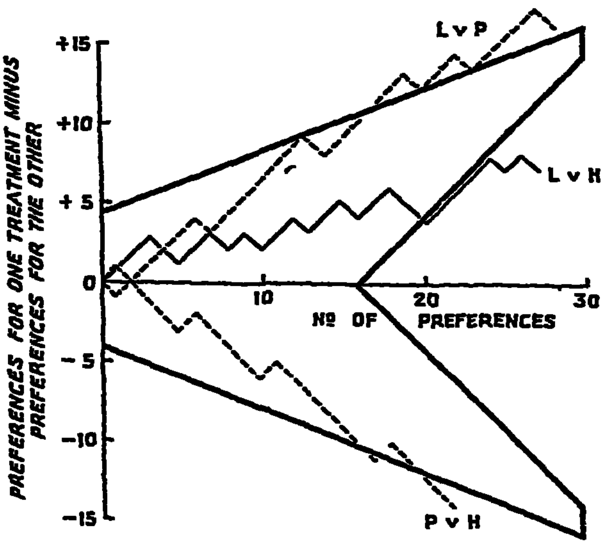

Chart for sequential analysis of results H heroin L, lipect P, placebo In each comparison the path is continued one unit "north-east for a preference for the first-named treatment and one unit south-east for a preference for the second named treatment.

Apart from the choice of the significance level to which the outer boundaries correspond, one is at liberty to choose the maximum of comparisons needed for any pair of treatments During the first few weeks of the present trial we were able to assess the rate at which patients became available for treatment and to make a rough estimate of the proportion of patients giving clear preferences The maximal duration of the trial was determined by other commitments, and we estimated that during this maximal period about 30–35 preferences would be obtained for each pair of treatments Accordingly a restricted sequential procedure, for which the maximum of preferences was 30, was chosen by reference to table v of Armitage (1957), which gives the equations to the boundaries shown in the accompanying figure. According to this table, if one treatment is such an improvement on another that 85% of preferences are in its favour, in a long run of patients, the zigzag path will hit the appropriate outer boundary about 95 times out of 100 Exact calculations confirm that the exact probability of doing this is 0·953 compared with the nominal figure of 0·95

TABLE II—FREQUENCIES OF CLEAR PREFERENCES BETWEEN EACH PAIR OF TREATMENTS ACCORDING TO ORDER OF ADMINISTRATION

Order of administration	Preference for	
	Lipect	Placebo
Lipect before placebo	11	4
Placebo before lipect	11	2
Total	22	6

	Lipect	Heroin
Lipect before heroin	11	2
Heroin before lipect	6	8
Total	17	10

(χ² with continuity correction = 3·41 P = 0·07)

	Placebo	Heroin
Placebo before heroin	2	10
Heroin before placebo	2	8
Total	4	18

The frequencies with which the treatments were placed in various orders of preference are shown in table I, and the sequential paths for each pair of treatments are drawn in the figure The two paths obtained by comparing the two drugs with the placebo both crossed the outer boundaries at the 17th preference, which means that both these comparisons are significant at the 5% level We can attach a rather more precise probability to these results by calculating the probability of reaching, by chance, the observed point on the boundary, or one indicating a more extreme contrast between the two treatments—i e, one further to the left on either outer boundary—if in the long run the two treatments were preferred equally frequently This probability is 0·033 for each comparison of a drug with the placebo

The path obtained by comparing lipect and heroin reached the middle boundary at the 20th preference Again we can calculate the probability of reaching the observed boundary point, or one indicating a sharper contrast between the drugs This probability is 0 36, showing that the slight excess of preferences in favour of lipect could easily be due to chance

If lipect and heroin had both been shown to be better than the placebo at a much earlier stage in the trial, it was intended to omit the placebo so as to concentrate on the comparison of the two drugs As it happened, all three paths approached the boundaries at about the same time A few extra cases were treated after the boundaries had been crossed, and it is clear from the figure that the general trend was confirmed by these additional results

A point of some interest is whether a patient's preference between two treatments depended on the order in which they were given The clear preferences between each pair of treatments are tabulated in table II according to the order in which the treatments were given There is clearly no evidence that order of administration had any effect on the comparison of either drug with the placebo, but there is a suggestion that, for the (presumably harder) choice between lipect and heroin, patients tended to prefer the treatment given first

Discussion

Where it is impossible to make objective measurements of a patient's progress the value of any drug is difficult to assess, but the likely response of patients to drugs will be gauged more reliably by a controlled comparison of the drugs with a placebo than by either experiments on animals or uncontrolled clinical impressions One objection to this type of trial is that the patients may prefer a drug for reasons other than the pharmacological action under test, diamorphine has hypnotic, analgesic, and euphoric properties in addition to relieving cough Possibly diamorphine was preferred to the placebo because of its other properties, but this is unlikely because it was, if anything, less popular than the pholcodine linctus

Another limitation to this, as to any other, type of trial is that the results strictly apply only to the conditions of the trial Thus, it may be said that a *B P C* linctus of diamorphine given in the largest recommended dose is not evidently superior to a pholcodine compound (lipect) when one dose is given at night to the types of patients tested We have no evidence on the effect of other dosages and forms of administration or on the response of different types of patients

The statistical method used in this trial offers certain advantages over previously used methods The boundaries may be drawn on the chart as soon as a decision has been taken on the maximum of patients to be studied, and the level of significance corresponding to the outer boundaries, for which fewer than the maximum are required From this stage, and without further statistical treatment, the results plotted on the chart provide a readily intelligible and graphic account of the trend of the results As soon as a significant difference is observed between one pair of drugs the trial may be stopped or modified so that attention is concentrated on the remaining comparisons

Summary

A controlled clinical trial was undertaken to compare the relative effectiveness in relief of cough of heroin linctus *B P C*, a pholcodine preparation (lipect), and a placebo in 45 patients with chronic cough Each patient received each mixture for two days and placed them in order of preference

A new method of sequential analysis was applied to the results and was found to have certain advantages over methods used previously

At the 5% level of significance there was no evidence of difference between the heroin and pholcodine preparations, but both were more effective than the placebo

We are grateful to Dr R D Green for allowing us to study his patients, and to Dr Gordon Fryers, of Messrs John Wyeth & Brother Ltd, for supplies of lipect

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LOCAL TREATMENT OF BURNS AND SCALDS

USING CHLORHEXIDINE

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ANTISEPTIC methods of treating burns and scalds are unfashionable, but aseptic and antibiotic methods are not free from complications nor are the results always good In one surgical unit of the Royal Hospital for Sick Children, Glasgow, burns and scalds have been nursed in a small "burns unit" since 1937 Until 1940, the lesions were gently cleansed under sedation or light general anæsthesia and the surface coagulated with tannic acid solutions, silver nitrate, or a mixture of antiseptic dyes "Open methods" of treatment were then adopted and bland dressings, pressure dressings Stannard envelopes, Bunyan bags, local sulphonamides, and local penicillin were all tried, and in the hands of the enthusiast all gave reasonably satisfactory results During this time there were great advances in the general treatment of the burned patient, and inevitably this led to improved results in the local lesion, irrespective of the local treatment adopted The "exposure method" of treatment was rediscovered and was used as a routine procedure for two years, at first with penicillin powder but later without any antibiotic or antiseptic To obviate the need for cleansing the damaged surfaces in the severely burned child dibromopropamidine isethionate cream ('Brulidine') was introduced and was the most popular form of treatment for almost three years Though it is an ideal first aid dressing, dibromopropamidine delays healing and is unsuitable for routine use

During 1955, chlorhexidine (bis *p* chlorophenyl diguanidohexane, 'Hibitane') was first used in the local treatment of burns and scalds The early results were so satisfactory that this antiseptic solution has now supplanted all our previous forms of local treatment

Method

The patients are nursed in three small wards, each with space for three or four cots, grouped round a central corridor which has glass walls The nurses can consequently observe the patients without entering the wards Masks are worn by the nurses and doctors when in the wards No visitors are allowed No woollen blankets, woollen clothing, or fluffy toys are allowed and no toys of any kind from the general ward are brought into the burns wards The furniture, walls, and floors are "damp dusted" twice daily with 1/20 carbolic-acid solution

The patient, after admission to hospital, is sedated and, if necessary, given intravenous fluid The initial dressing of the burn is done without anæsthesia, it is cleansed with 1% cetrimide ('Cetavlon'), rinsed with normal saline, and covered with gauze soaked in 0 5% chlorhexidine solution, a crêpe bandage holds the gauze in position When dressing the burns, the sister or nurse wears rubber gloves, and before attending to the next patient she washes the gloved hands with soap and water, rinses in 1/100 'Dettol' solution, rinses in sterile water, dries, and finally applies 1% chlorhexidine cream to the gloved hands (A no-touch technique is not used) The gauze dressings are resoaked with the chlorhexidine solution twice daily, and twice a week are removed to allow inspection of the lesion and removal of separating sloughs The areas are not left exposed until epithelial cover is complete It is usually possible by the end of the third week to decide where there is whole-skin loss, and these parts of course require grafting

Results

The method has been in use for fourteen months 108 patients have been treated with excellent results Infection is rare The superficial burns heal rapidly by regeneration of the surviving epithelium, and in the deep burns, after separation or removal of the sloughs, a clean granulating surface presents, which is eminently suitable for grafting In the previous twelve months 92 patients had been treated by a variety of methods, and of this group, clinical evidence of infection after admission to hospital had developed in 10 (11%) Of the 108 patients treated by chlorhexidine, clinical evidence of infection developed in only 2 (2%) There are so many variable factors that the two groups are unsuitable for statistical comparison, but the reduced incidence of infection in the second group suggests that chlorhexidine has reduced the incidence of cross-infection

Discussion

Prevention of infection is the fundamental principle in the local treatment of a burn, whether the lesion is superficial or deep If infection arises, it will delay healing and may so destroy the surviving epithelium that a superficial burn becomes a deep burn When a deep burn becomes infected, grafts do not readily take, the patient's stay in hospital is prolonged and he goes home with a poor cosmetic result The method used to prevent infection must not itself damage the tissues or delay healing

The methods used can be divided into three groups—an aseptic technique, an antibiotic technique, and an antiseptic technique

In practice we have found that a rigid *aseptic* technique is impossible The dressings and instruments can be sterilised but not so readily the patient, the patient's attendants, or the dust in the ward It is one thing to use an aseptic technique in an operating theatre for an hour or two with an unconscious patient who does not need a meal or a bowel movement, but quite another to maintain the same technique for three months with a patient who has lost half his skin

The second method using *antibiotics*, accepts that contamination is likely and relies on antibiotics to deal with the organisms before they gain a hold on their host But *Staphylococcus pyogenes* *Streptococcus pyogenes* *Pseudomonas pyocyanea*, and proteus organisms are all common contaminants of a burn, and there is no single antibiotic to which they are all sensitive Furthermore, the *Staph pyogenes* which breed in our hospitals today are seldom sensitive to penicillin or the other antibiotics commonly used, and as each new antibiotic comes into general use resistant strains rapidly appear Hence one cannot rely on local applications of antibiotics for prophylaxis against infection in a burn

Antiseptic methods have been criticised on the grounds that antiseptics, like infection, can destroy the surviving epithelium or inhibit its growth We are satisfied that chlorhexidine deals effectively with bacteria without damage to the surviving epithelium or appreciable delay in healing

Chlorhexidine is an antibacterial agent It is supplied by the manufacturers as 'Hibitane Concentrate 2%' which is a 2% aqueous solution of chlorhexidine diacetate together with a surface active agent This we dilute with three parts of water to produce a 0 5% aqueous solution Bacteriological investigations by Davies et al (1954) have shown that chlorhexidine has a high antibacterial action against a wide range of both gram-positive and gram-negative bacteria and that the activity is maintained in the presence of body-fluids They found no evidence of drug-resistance The manufacturers say that animal wounds heal quite readily when dressed with 1% chlorhexidine solution, they also say that repeated applications of 1% solution to fair skin may eventually give rise to erythema, and they recommend a 0 05% solution for wounds when used as a prophylaxis against infection Calman and Murray (1956) found that a 1% solution produced irritation of the nasal mucosa and conjunctiva, and they recommend that no solution stronger than 0 1% should be used on delicate mucous membranes They have also shown that a 1/40 solution of the 2% concentrate (i e, a 0 05% solution) was effective in killing *Ps pyocyanea* using a two-and-a-half minute contact test between organism and antiseptic in the presence of fresh blood (25% blood broth) *Staph pyogenes*, β-hæmolytic streptococcus, and *Escherichia coli* were killed by even weaker solutions They investigated the antiseptic properties of domiphen bromide ('Bradosol'), 'Dettol,' cetrimide, and benzalkonium chloride ('Roccal'), and found that none could be used in a concentration which gave this wide margin of safety and at the same time was harmless to the tissues We have not encountered irritation of the skin in our patients, though our 0 5% solution is ten times stronger than the solution used in the two-and-a-half minute contact tests It is possible that a weaker solution would be equally effective

We rely on the antibacterial properties of chlorhexidine as our first line of defence against infection, but at the same time take all practical precautions to prevent contamination of the burns

The patients, who are mostly under five years of age, are apprehensive of the twice-daily dressings, though these are not painful Also, the dressings are time-consuming for the nurses But those disadvantages are more than balanced by the absence of infection and the speed of healing

Summary

A method of treating burns using a 0 5% solution of chlorhexidine 'Hibitane' is described It has been used for fourteen months, and 108 patients have been treated

Infection has been rare and the chlorhexidine solution does not destroy the regenerating epithelium or appreciably delay healing

The practical advantages of the method over aseptic and antibiotic methods are discussed

We wish to thank Mr Wallace M Dennison in whose wards the patients were treated, for his encouragement and help

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ILEOSTOMY CHEMISTRY

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To provide a sound basis for protein and electrolyte therapy after the institution of a permanent ileostomy, the loss of fluid and the output of nitrogen, sodium, potassium, and calcium from the ileostomies of 7 patients are reported 6 with ulcerative colitis, and 1 with familial polyposis of the colon (the findings in this case are in keeping with the results of those with colitis)

Methods

Excreta were collected into Rutzen bags, which were emptied at intervals into enamel cans, collections being made in 24-hour lots The volume of each daily collection was measured and adjusted to a suitable quantity for homogenisation by the addition of distilled water Samples were thoroughly homogenised and analysed

For nitrogen two 2 0-ml samples were placed directly into flasks for estimation by a micro-Kjeldahl method For sodium, potassium, and calcium a 10-ml sample was placed in a conical flask, 2 ml of concentrated nitric acid was added, and the mixture was allowed to stand for at least 10 minutes It was then brought to the boil for a few seconds, cooled, made up to 50 ml with distilled water, and filtered (Whatman 544) After the filtrate had been suitably diluted with distilled water, sodium and potassium were estimated with the Eel flame photometer The instrument was graduated over the range 0 2–0 8 mg of sodium or of potassium For calcium 20 ml of the filtrate of the nitric acid digest was neutralised with ammonia and acidified with concentrated hydrochloric acid, and the calcium was precipitated with 2 5% oxalic acid and 20% sodium acetate, overnight standing ensured complete precipitation The precipitate was centrifuged and washed thrice to remove sodium oxalate The calcium content of the precipitate was then determined by titration in acid solution with 0 01 *N* potassium permanganate

The patients had necessarily to be treated according to their needs in respect of fluid and electrolyte restoration since their serious general condition allowed little latitude as regards treatment It was therefore impracticable to maintain an identical fluid and electrolyte intake in all the patients after operation and to follow a strict schedule Usually, however, intravenous fluids alone were administered until the ileostomy began to function, usually about 24–48 hours after operation Fluids by mouth were then permitted 30 ml hourly for the first twelve hours, increasing to 60 ml and then

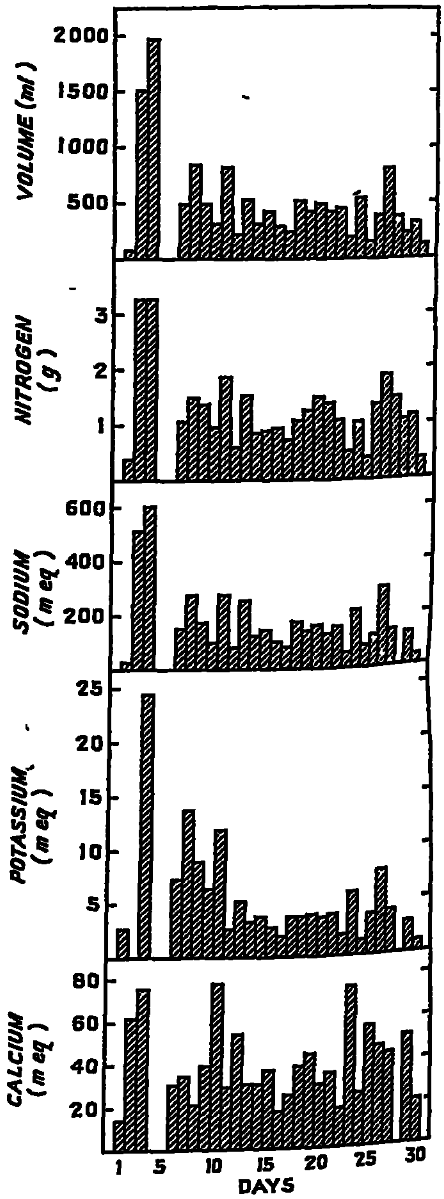

Fig 2—Output four days after primary panproctocolectomy

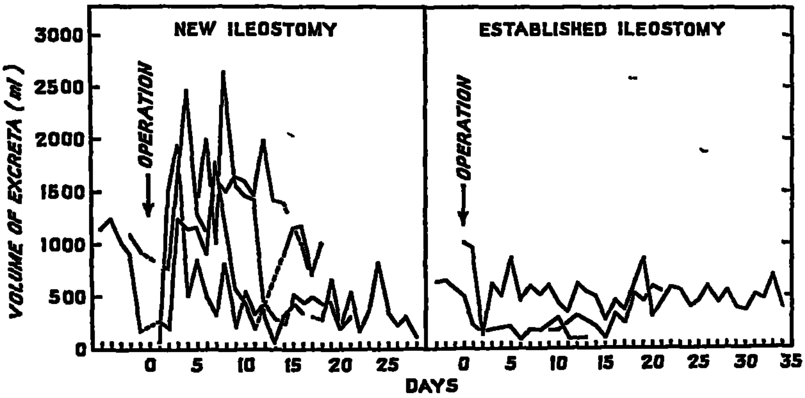

Fig 1—Volume of fluid excreted after institution of ileostomy *new ileostomy*, operation involving the institution of an ileostomy , *established ileostomy*, operation incidental being the removal of the rectum in 3 patients after primary colectomy with establishment of ileostomy 10, 18, and 30 months previously

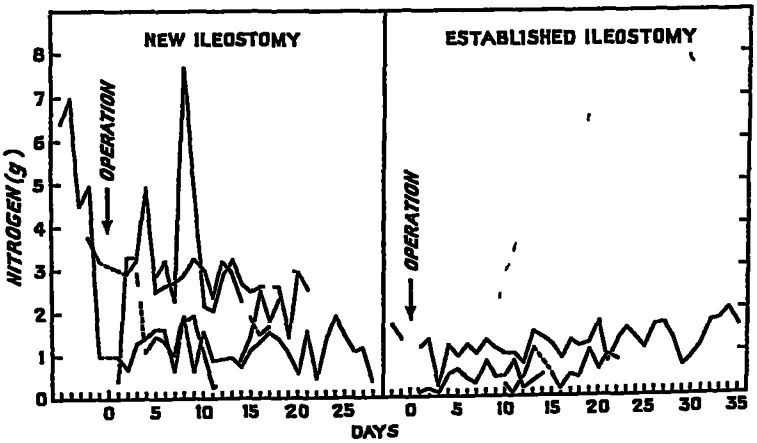

Fig 3—Output of nitrogen

120 ml at 12-hour intervals From about the 5th postoperative day a light diet was taken, increasing to a full diet within 7–10 days It is therefore impossible to present standardised figures from these investigations, we can only report what happened under routine postoperative conditions None of the patients had received corticosteroids

Results

Volume of Fluid

A characteristic feature of most ileostomies was the considerable volume of fluid excreted immediately after the institution of the stoma (fig 1) This averaged 2 litres or more a day during the first postoperative week Occasionally the immediate postoperative output was greater and sometimes considerably less Next it decreased to about 500 ml a day as the excreta thickened The average daily output remained at 500 ml in the established ileostomy, though this sometimes increased after subsequent operations Seldom, however, did it increase to more than 1 litre daily, provided that complications at the stoma—e g, partial obstruction—did not arise The mechanism causing this diminution in output is not clear, alterations in the activity and absorptive capacity of the small bowel are possible factors

During the initial postoperative period a direct correlation existed between the volume of fluid excreted and the quantity of some of the materials measured in the excreta, this relationship being clearest in the case of nitrogen and sodium (fig 2) This cannot be explained by considering the ileum as capable of excreting the various electrolytes only at a constant concentration, because the concentration of sodium became less in the established ileostomy, and that of calcium varied with its intake, as might be expected

Nitrogen

Losses of about 4 g of nitrogen a day were observed immediately after ileostomy, excluding complications, decreasing to 1–2 g in the established case, equivalent to an average daily excretion by normal persons Nitrogen loss was therefore insignificant from the therapeutic aspect Chromatography of exudates from 2 patients indicated that the following amino acids were excreted glycine, alanine, valine, leucine, and arginine Since the total daily nitrogen loss was so small, it seems improbable that the loss of these specific amino acids is significant

A general picture of the nitrogen loss immediately after operation in 4 patients and from ileostomies established for 10, 18, and 30 months is given in fig 3 The operation referred to in the established cases indicates a subsequent procedure in staged excision of the colon and is incidental The high peak of excretion at 8 g on the 8th day after ileostomy in one patient (figs 3 and 4) was associated with severe ileostomy diarrhœa due to pseudomembranous enteritis, which responded rapidly to erythromycin The continued excretion of 3 g daily by one patient (figs 3 and 5) was associated with ileitis secondary to ulcerative colitis (colo ileitis)

In ulcerative colitis more nitrogen may be lost preoperatively per anum than is subsequently lost from the ileostomy In one male patient 7 g of nitrogen (equivalent to 44 g of protein) was lost daily in this way, whereas after operation his nitrogen loss was only 1–2 g daily

Nitrogen-balance studies in 3 patients (fig 6) showed that they were in negative balance for a short period after operation but no longer than patients submitted to operations not involving intestinal fistula After this period they remained in positive balance

Sodium

At first the loss of sodium was considerable (fig 7), being about 200–400 m eq per litre, with no clear evidence of urinary conservation of sodium The total quantities lost at this stage might be greater than the

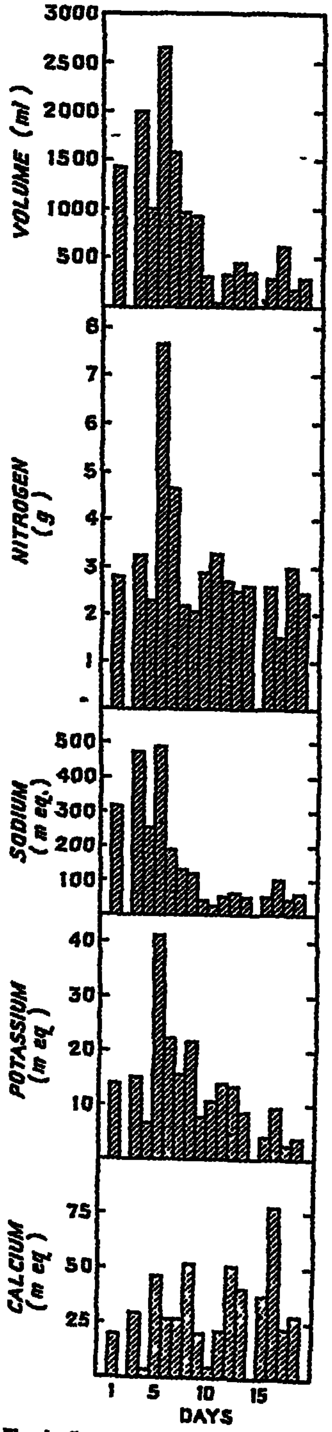

Fig 4—Output from fourth day after primary colectomy

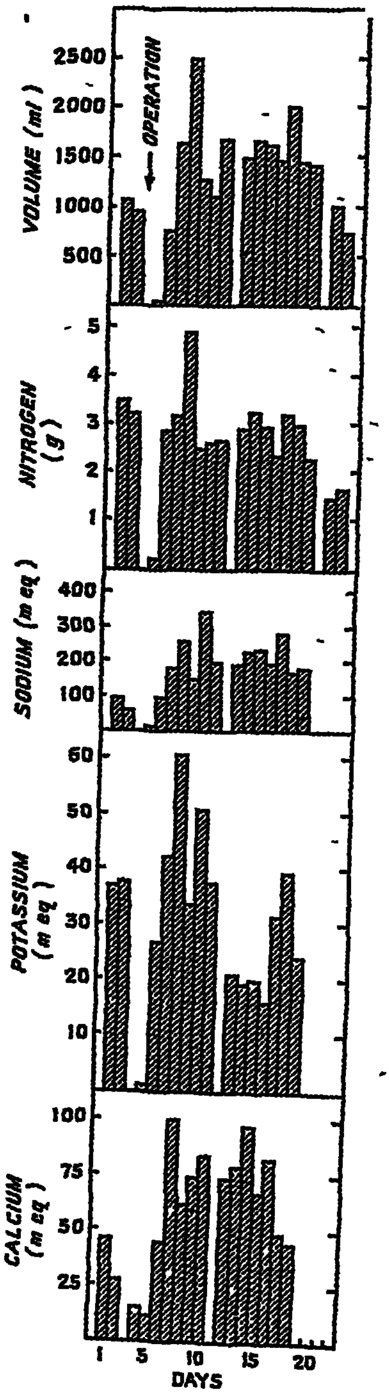

Fig 5—Output from two days before primary colectomy

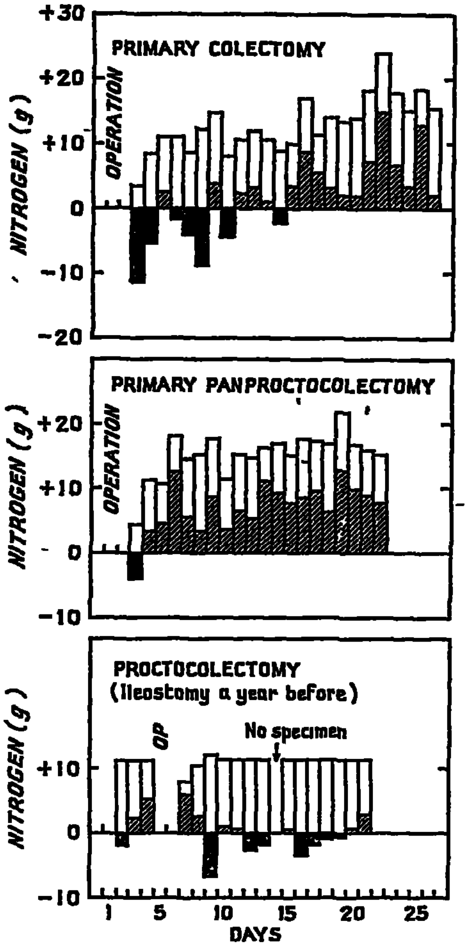

Fig 6—Nitrogen balance in two patients at the establishment of an ileostomy and in one at an operation undertaken a year after establishment of ileostomy

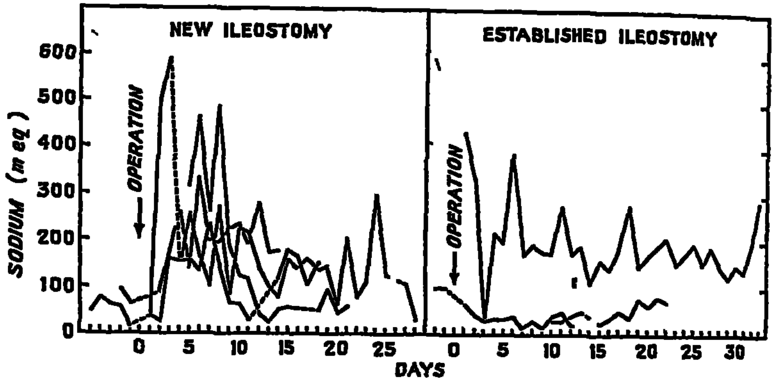

Fig 7—Output of sodium

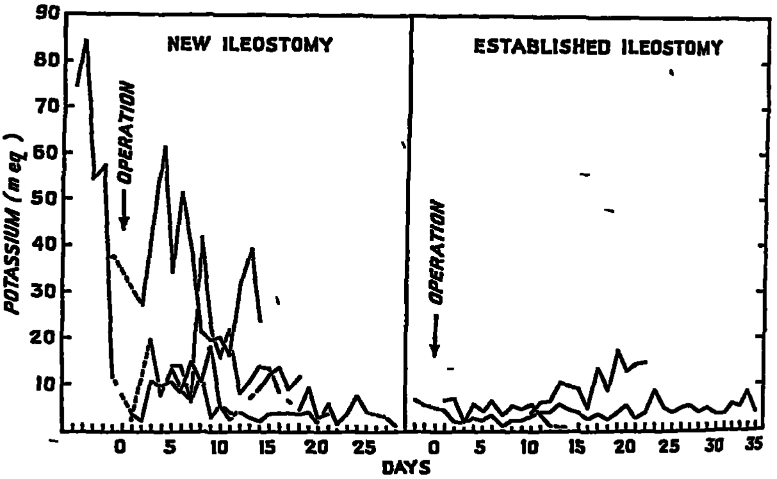

Fig 8—Output of potassium

previous loss in stools resulting from diarrhœa before ileostomy was established. As the excreta from the ileostomy thickened, the rate of loss fell to about 150 m eq per litre. The absolute loss of sodium was therefore great in the immediate postoperative period not only because of a larger volume of excretion but also because of a higher concentration of sodium in the excreta at that stage.

Potassium

In normal circumstances the excretion of potassium hardly exceeds 20 m eq daily—i e, about 10 m eq per litre—a rate which was continued in the established case (fig 8). One patient, who developed severe ileostomy diarrhœa due to pseudomembranous enteritis, had a large loss of sodium and potassium (fig 4); another had a large loss of potassium (fig 5) apparently due to ileal inflammation from persisting colo ileitis. In contrast with the patient with ileostomy diarrhœa, this patient's loss of sodium was less than usual (about 100 m eq per litre), suggesting a reciprocal relationship between sodium and potassium. It seems unlikely that potassium was being excreted in combination with fatty acids as soaps, because excretion was copious immediately after operation, when the intake of fat was nil.

Two preoperative estimations recorded in fig 8 show large losses of potassium (35 and 85 m eq daily) in the stools, these losses being considerably greater than from the subsequent ileostomy.

Calcium

The excretion of calcium was copious (40–100 m eq daily) immediately after ileostomy (figs 2, 4, 5, and 9). There was no associated decrease in excretion when the volume of fluid diminished, presumably because of an increased intake of calcium with more comprehensive diet. The last part of the graph for an established ileostomy (fig 9) indicates that the loss observed with an average normal diet was 30–50 m eq daily (0.5–1.0 g). Daily analysis of the fat in the excreta of 3 patients revealed no direct relationship between the outputs of calcium and fat.

Therapeutic Application

An ileostomy imposes no serious loss of nitrogen and does not disturb the state of balance usually seen after operations. As the ileostomy becomes established, the loss of nitrogen decreases to levels which are average for healthy people who have not undergone operation. Since

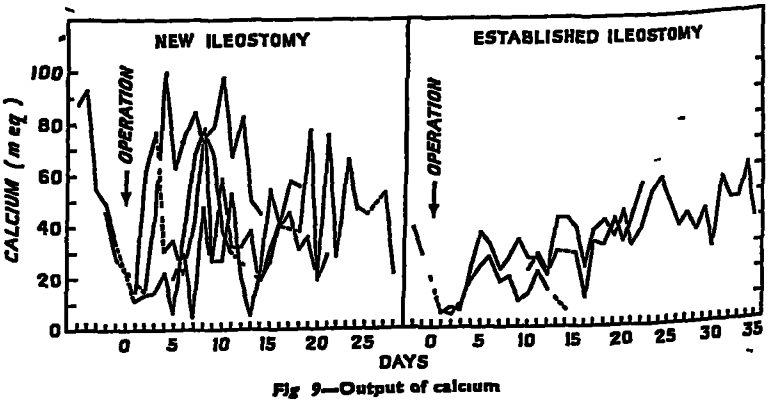

Fig 9—Output of calcium

CHEMISTRY OF ILEOSTOMY EXCRETA

—	Output from ileostomy			
	Recent		Established	
	Per 24 hr	M eq per litre	Per 24 hr	M eq per litre
Volume	1000–3000 ml		200–500 ml	
Nitrogen	2–4 g		1–2 g	
Sodium	200–600 m eq (4–14 g)	200–400	50–200 m eq (1–5 g)	100–200
Potassium	10–20 m eq (0 4–0 8 g)	5–10	5–10 m eq (0 2–0 4 g)	10–20
Calcium	40–100 m eq (1–2 g)	20–50	30–50 m eq (0 5–1 g)	50–100

the total daily loss of nitrogen does not exceed 1–2 g, it seems improbable that the quantity of each specific amino-acid excreted is significant, even though several may be essential for growth The rapid increases in weight seen after ileostomy for ulcerative colitis support this conclusion

The increased volume and the high concentration of sodium in the ileostomy fluid immediately after operation combine to produce a deficit of sodium which may, if not foreseen, induce sudden clinical collapse This is best treated prophylactically by routine intravenous therapy within the first 4 or 5 postoperative days For rule-of-thumb calculation of requirements of sodium it is only necessary to know the daily volume of ileostomy output (a simple ward procedure) and to assume that 300 m eq of salt has been lost with each litre of fluid If the patient suddenly collapses without any obvious surgical complication, especially if the excretion-rate has been persistently high, there is probably salt depletion, which should be treated as an emergency Intravenous double strength saline solution should be given rapidly, when the condition will quickly be overcome, often within half an hour It should also be borne in mind that an increase in the output of fluid from the ileostomy at a later stage from any cause will be accompanied by an increased loss of salt Patients should therefore be advised to take extra salt if ever they have an attack of ileostomy diarrhœa

Whereas loss of sodium is aggravated by ileostomy, loss of potassium is usually corrected thereby (figs 7 and 8) Therefore loss of potassium is mainly a preoperative problem Ileostomy may even have to be expedited for patients in whom it proves impossible otherwise to correct gross loss of potassium from continued diarrhœa Since it is impossible to undertake routine analyses of the potassium in the excreta of all the patients, some loss of potassium may be inferred in patients with ileostomy diarrhœa and in those found at operation to have ileitis In the case complicated by pseudomembranous enteritis the serum potassium level fell from a normal figure of 4 6 to 3 5 m eq per litre in two days In both patients with an excessive output of potassium the loss was about 30 m eq per litre, this figure should be borne in mind when calculating replacement in such patients

The body's reserve of calcium is such that loss immediately after operation causes no immediate concern The continued loss of about 1 g daily from an established ileostomy raises two points, one physiological and one clinical Such a loss is more than a healthy person on an average diet loses in the stools daily (0 4–0 8 g) Is the large bowel in man "inert" as regards calcium metabolism or does it play some part in absorption? It is difficult to believe that the loss of the last 2–3 inches of ileum removed for technical reasons when an ileostomy is undertaken, could explain this difference The clinical significance of this constant loss of calcium can only be judged when balance studies (now being undertaken) are completed Four studies now undertaken including one late in pregnancy, show positive balance

In the accompanying table these observations on the chemistry of ileostomy excreta are presented to facilitate assessment of therapeutic needs It must be emphasised that these figures represent only generalisations because in no two cases were they exactly similar

Summary

The effect of the operation of ileostomy on loss of fluid, nitrogen, sodium, potassium, and calcium in the ileostomy fluid was observed, mostly in patients who had ulcerative colitis

The loss of nitrogen in this disease was reduced by ileostomy

The average daily loss from an established ileostomy had no therapeutic significance for patients on a normal diet

Potassium replacement is therapeutically more important before ileostomy, sodium replacement afterwards About 300 m eq of sodium was lost per litre of excreta from a recently established stoma, and 150 m eq per litre from an established stoma The amount of sodium required for restoration may be calculated from the volume-output on this average

From the established ileostomy calcium was excreted at a rate of about 1 g (50 m eq) daily by patients on a normal average diet

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Preliminary Communication

RELEASE OF HISTAMINE IN URTICARIA PIGMENTOSA

THE idea that urticaria pigmentosa is a systemic disease with manifestations from different organs, has received considerable support in recent years It has been shown that tissue mast cells may be present in very large numbers in many organs, thus causing a "mastocytosis" Several workers have studied the mastocytomas occurring in dogs

Riley[1] reviewed the question of histamine, heparin, and hyaluronic acid in mast cells

Pernow and Waldenström[2] described a patient with widespread sclerotic foci in the skeleton and a flush resembling that seen after an injection of histamine This patient's urine contained large amounts not only of histamine but also of 5-hydroxytryptamine and *5-hydroxyindole acetic acid* Waldenström et al[3] later gave a detailed description of this case and reported finding increased amounts of histamine in the urine of a patient with typical urticaria pigmentosa

Some months ago I examined a young woman who complained of idiosyncrasy to acetylsalicylic acid

She said that she "nearly died" after taking 0 5 g of acetylsalicylic acid, but "her doctors would not believe" this statement Careful examination showed a few small skin lesions resembling urticaria pigmentosa Dr N Brogren, of the dermatological department, confirmed this clinical diagnosis which was verified on biopsy (Dr G Björkman) Radiographic examination of the skeleton showed definite signs of sclerosis, especially in the vertebræ and pelvis The picture resembled that described by Schorr et al[4] in urticaria pigmentosa Sternal puncture, however, did not reveal any increase in mast cells

The patient was interested in knowing if she could use acetylsalicylic acid, and therefore volunteered to take a test dose Accordingly on Jan 17 she was given 0 25 g of this substance by mouth Her blood pressure remained constant at 120/70 mm Hg for 20 minutes but in the next 20 minutes her systolic pressure fell to 60, her diastolic pressure was not measurable, and her pulse rate rose from about 90 to 150 The systolic blood-pressure was lowest an hour after administration, when it was 30 mm Hg Just before the severe drop in blood pressure the patient felt nauseated and the skin of her face became red She began vomiting intensely Unfortunately the vomitus was not measured until an hour had elapsed The total amount vomited between then and 15 hours later, when vomiting ceased, was 2150 ml The vomitus was strongly acid (pH 2) The patient's temperature, which had been 98 6°F before the test dose, fell to 96 1°F 1½ hours after the tablet was taken After a further hour it rose to 99 6°F, and 3 hours after the tablet was taken it was 101°F The blood pressure slowly rose after intravenous administration of a glucose drip, and after 2 hours was 100/50 mm Hg The pulse rate fell to 80 only after more than 2 days had elapsed After 3 days she was afebrile

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[1] Riley J F *Lancet* 1951 i 841

[2] Pernow B Waldenström J *Ibid* 1951, ii, 951

[3] Waldenström J Pernow B Silwer H *Acta med scand* 1956 156 73

[4] Schorr S Sagher F Liban E *Acta radiol, Stockh* 1956 46 [illegible]

Obviously this patient is very severely hypersensitive to acetylsalicylic acid Many data seem to indicate that the symptoms may have been caused by liberation of histamine The pronounced circulatory shock with low blood-pressure, high pulse rate, flushed face, and vomiting of enormous amounts of strongly acid gastric contents, and the demonstration of continuous histaminuria all support the diagnosis of histamine liberation by the action of acetylsalicylic acid This substance is not a commonly recognised histamine liberator, but on the other hand the conditions in this case were peculiar the amount of histamine stored in the patient's body may be very large, for the osteosclerotic process is obviously intimately linked with the presence of mast cells I therefore asked three other patients with widespread urticaria pigmentosa whether they had ever observed intolerance of salicylic acid Their answer was No

It therefore seems probable that the supposed action of acetylsalicylic acid as a histamine liberator may be particular to this patient The question of intolerance to acetylsalicylic acid being caused by histamine release and not by a true allergic (antigen antibody) reaction will be discussed in a forthcoming paper B Pernow and H Dunér (personal communication) have demonstrated considerable histaminuria in five further cases of urticaria pigmentosa We are therefore of the opinion that histaminæmia in mastocytosis is a counterpart to hyperhydroxytryptaminæmia in carcinoidosis

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Medical Societies

OPHTHALMOLOGICAL SOCIETY OF THE UNITED KINGDOM

THE 77th annual congress of the Ophthalmological Society of the United Kingdom was held in London on April 11–13, with the president, Mr J J HEALY, in the chair Visitors included members of the International Council of Ophthalmology, which met in London on April 10

Intra-ocular Circulation and Hypertension

In his presidential address Mr HEALY described the intra-ocular circulation in arteriosclerosis and hypertension He discussed the ætiological and pathogenic theories of hypertension, which were largely based on the evidence of experimentally produced and secondary hypertension, and he noted that although physiopathological research had made some progress, no definite results had yet emerged Arteriosclerosis might be present as a senile regression in the retinal and choroidal vessels, and essential hypertension might supervene or arise as a separate entity Mr Healy analysed the changes in 200 outpatients' fundi and assessed them with special reference to angiospasm, arteriolosclerosis, and arteriolonecrosis, and he made a plea for greater liaison between physician, ophthalmologist, and pathologist

Simple Glaucoma

The Bowman lecture was instituted by the council of the society in 1883, in recognition of Sir William Bowman's distinguished work in ophthalmology and other branches of medicine and in commemoration of his valuable services to the society, of which he was the first president The 35th lecture was given by Sir STEWART DUKE-ELDER, who spoke on the ætiology of simple glaucoma

Sir Stewart discussed the mechanism of the formation of the aqueous humour in the light of recent biochemical and pathological research, with particular reference to the extensive work carried out under his direction at the Institute of Ophthalmology He then turned to the variations in intra ocular pressure produced especially by peripheral and central nervous stimulation, and he indicated the factors responsible for the instability and range of variation of the intra-ocular pressure characteristic of the glaucomatous eye He traced the development of the initial functional and consequent organic changes with their terminal ischæmic effects upon the structures of the anterior and posterior segments of the eye and the optic nerve, and he examined their respective rôles in the development of clinical simple glaucoma Glaucoma should not be regarded purely as an ocular disease, but rather as a local manifestation of a more general disorder Advances in the scientific aspects had not been accompanied by similar advances in either medical or surgical treatment, which had made little progress during the past twenty years

Congenital Cataract

A symposium on this subject was introduced by Mr J H DOGGART, who said that although some slight opacity was visible in most human lenses, even among the newborn, most of those partial cataracts were harmless and stationary Nevertheless, they could not be dismissed as insignificant because (*a*) they might be misinterpreted and (*b*) they had supplied clues for embryological investigation Differentiation of the various congenital cataracts from other kinds of opacity was impossible without careful study of the living lens

Mr A B NUTT emphasised that the results of surgery for congenital cataract were disappointing and that the prognosis must therefore be guarded Having classified the cases requiring surgical treatment, he gave a brief resume of the operations commonly employed, their complications, and the methods adopted to avoid them He thought that the poor functional results were in many cases due to associated congenital anomalies

Ocular Aspects of Diabetes

Prof G I SCOTT classified the retinal changes of diabetes and discussed their possible ætiology This form of retinopathy could occur in the absence of any evidence of hypertension or arteriosclerosis and its incidence seemed to depend primarily upon the length of time that the patient had suffered from the disease

Dr J D N NABARRO expressed some alarm at the increasing incidence of serious visual defects due to diabetic ocular disease The speed with which vision deteriorated in patients with established retinitis was extremely variable and it was uncertain whether it could be influenced by treatment Strict diabetic control was essential, but there was no evidence that vitamins or sex hormones had any effect Hypophysectomy and pituitary destruction were being undertaken in a few centres, but their value was still uncertain

Dr NORMAN ASHTON dealt with the experimental side of diabetic vascular disease, with special reference to its ocular and renal manifestations He attempted to assess the bearing of experimental findings on the relationship between diabetic retinopathy and glomerulosclerosis

Retinal Detachment

Discussing the rôle of intravitreal vitreous injection in retinal detachment, Mr P McG MOFFATT and Mr C DEE SHAPLAND described the technique for obtaining the donor vitreous and its subsequent injection under pressure into the recipient eye Mr Shapland analysed the results obtained in a small series of his own cases and those of Mr Moffatt

Mr **GEORGE BLACK** criticised present day operations in regard to their effect upon the sclera, such as local necrosis, injury to nerves and blood vessels, and upon anterior structures The effects of diathermy treatment were variable when given through the full thickness of the sclera, and Mr Black described his own method of scleral trap door access to the choroid and its application

Ptosis Operation

Mr H B **STALLARD** advocated the anterior surgical approach to the levator palpebræ superioris, which exposes it in its normal relationship to other structures, reveals any unusual attachment of this muscle to the orbital fascia, allows the separation of any fascial connection with the superior oblique tendon sheath, and permits a greater length of the muscle to be resected and more accurate suturing of the resected muscle to the tarsal plate than other methods of exposure He described a new lidguard for use in this operation and illustrated the technique with a coloured film

Phacolytic Glaucoma

Dr P **SCHOFIELD** gave an account of the association of glaucoma with hypermature cataract Although recognised since 1900, this condition had only recently been defined as a clear cut pathological entity and named "phacolytic glaucoma" From the histological examination of 3 cases Dr Schofield described the pathology and pathogenesis of the condition

Venous Obstruction at the Disc in Chronic Glaucoma

Mr J H **DOBREE** described macroscopic lesions on glaucomatous optic discs, including central vein thrombosis, venous coils, anastomotic vessels, and hæmorrhages at the disc margin These lesions had been seen in a series of 200 cases of chronic glaucoma He discussed the relationship of these vascular changes to other signs of glaucoma such as the prevailing level of tension, cupping, atrophy, and field defects In a control series without tension but with gross arteriosclerotic changes in the vessels, the disc appearances were quite different The main factor determining the onset of the venous lesion was probably the glaucomatous cupping

Foreign-body Detector

Mr M J **ROPER-HALL** described a new electronic instrument which could detect small metallic particles, both magnetic and non magnetic, and assess their chemical and physical properties Two sizes of probe had been made, one $^1/_4$ in and the other $^1/_2$ in, the latter being sensitive to very small metallic fragments at a distance of 15 mm The prototype instrument had already been used to confirm the presence of intra ocular foreign bodies originally detected by X ray examination and localisation, and it had also been used to identify metallic fragments seen on radiographs as magnetic or non magnetic The instrument was insensitive to other metal bodies such as dental fillings and the operating table at distances greater than 3 cm The sensitivity of the probes increased with their size, but so did the range within which other metal bodies affected them (the $^1/_2$ in probe was unaffected by metal bodies at a distance greater than 4 5 cm) Mr Roper Hall said that the instrument was still being developed and that its uses were being extended from ocular to general surgery

Uveitis in Childhood

Mr **JOSEPH MINTON** gave an account of 3 children with severe uveitis, in 1 of whom the full clinical picture of Still s disease developed some time after the original uveitis Cortisone and corticotrophin, and more particularly the new derivatives prednisone and prednisolone, were valuable in treatment A child who had responded indifferently to cortisone was much improved by prednisolone

Ocular Onchocerciasis

Dr F C **RODGER** described an extensive field survey and clinical and experimental work undertaken to determine the types of onchocerciasis in which ocular lesions were most likely To estimate the density of infection he calculated an index which related the degree of infestation and its anatomical distribution over the body with the likelihood of ocular onchocerciasis He found cases in which infectivity was maximum by this standard of examination, and the eyes had actually been invaded, yet there were no ocular lesions This he attributed to an immunity which developed because of infestation in other parts of the body Experimental work with animals has shown conclusively that it was the dead parasite which led to an inflammatory reaction, and nearly all the manifestations of human onchocerciasis were reproduced in the rabbit Dr Rodger found in some cases with posterior-segment lesions, particularly choroidoretinal degeneration, that there was a low individual density figure, and the damage to the tissues might be due to a toxin secreted by the adult worms

Conjunctivitis at Moorfields in 1956

Mr **BARRIE R JONES** had investigated a proportion of the cases presenting at Moorfields Hospital with conjunctivitis during 1956, in order to establish the ætiology of the condition The particular aim was to evaluate the rôle of various viruses in the production of conjunctivitis and keratoconjunctivitis A few infections were due to some of the well-recognised bacterial infections, several cases were associated with infection by adenoviruses, and in others there was evidence of infection by the herpes simplex virus Among other infections seen in association with conjunctivitis were molluscum contagiosum, vaccinia, influenza, and cat scratch fever

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Reviews of Books

Injuries of the Hand

RONALD FURLONG, F.R C S, assistant orthopædic surgeon, St Thomas's Hospital, London London J & A Churchill 1957 Pp 215 36*s*

Mr Furlong set out to write a manual of practical instruction, and he has written a classic of its kind His style is direct, simple, and vigorous, and if at times his down-to-earth approach is reminiscent of a "do-it-yourself" pamphlet, it is distinguished by the uncommon assumption that those instructed will carry the movement far enough to include thinking One of its unusual feature is that the introductory chapter on anatomy illuminates important relations from clinical experience, rather than condenses them from standard tomes, and a masterly review of general technique answers all the questions that are likely to puzzle the young surgeon (Or almost all what is he to do if, on releasing the tourniquet, circulation does not return ?)

In the sections dealing with injuries to various structures, the perfectionists, the traditionalists, and those whom Mr Furlong calls the "activists" may find much to criticise, but the rest of his readers will readily submit to a guide of such experience and commonsense In the chapter on rehabilitation after tendon injuries he implements his thesis that, whereas the anatomy of the *manus* has changed little from reptilia to man, there has been much specialisation in its cortical control Emphasis is rightly laid not on the crude mechanism of movements (the whole book is happily free from engineering jargon) but on the obliteration of faulty cerebral patterns, and simple but ingenious procedures are described to achieve this

But the masterful "no nonsense" attitude has its perils "If the patient has just eaten a meal, and especially if he has been given a sedative, anæsthetists will make a fuss about giving an anæsthetic to the patient," Mr Furlong remarks drily, and ' take a great deal of convincing that a lacerated hand should be sewn up soon after a meal has been taken " We hope so even Mr Furlong's *haute couture* would be squandered on a dead body

Elaborate attempts at remodelling the thumb also receive abrupt dismissal "In these days of generous compensation for injury patients will not consider reconstructive surgery for loss of a thumb until the sum is awarded then they have no need to" Such pawkiness should perhaps be reserved for morning coffee in sister's office in a book of this kind there is much to be said for giving compensation claims the detailed, serious and practical consideration they deserve

These are but the growing pains of an infant prodigy So much practical wisdom has rarely been packed into the first edition of a book of some 200 pages The 99 illustrations are excellent and few authors have expressed their thanks to the photographic department of their hospital with such good reason In style, presentation, and price we hope this book will set a new fashion for surgical monographs

Battle for the Mind

A Physiology of Conversion and Brain washing WILLIAM SARGANT, M A, M B Camb, F R C P, consultant psychiatrist, St Thomas's Hospital, London London Heinemann 1957 Pp 248 25s

SURPRISING confessions of guilt have been elicited in some countries from political prisoners who seemed to have retained their sanity and who bore no obvious signs of torture Often these have been accompanied by a change of political faith which has outlasted the convert's release from prison These changes in personality have puzzled both doctors and laymen, and the descriptive term "brain-washing" has come to be applied Techniques change, but, as Mr Robert Graves shows in his chapter in Dr Sargant's book, brain-washing was used in ancient times

Dr Sargant was struck by a common thread running through sudden political and religious conversion, war neuroses, possession by Voodoo loa, abreactive techniques and shock treatments in psychiatry, the fantastic confessions of women accused of witchcraft, some of the changes in patients receiving psychoanalytic treatment, and certain confessions obtained by police after intensive questioning (even with the best intentions) He believes that all these changes can be described in terms of pavlovian psychology "Much human behaviour is the result of the conditioned behaviour patterns implanted in the brain, especially in childhood" In humans, as in Pavlov's dogs, these patterns can be destroyed or even reversed by intense nervous stimulation, especially when the resistance has been lowered—for example, by fatigue, fasting, illness, drugs, or endocrine changes The hellfire sermons of Wesley, the inquisitor's threats of torture, the psychoanalyst's insistence on dragging up painful images, the steady drumming and energetic dancing of Voodoo rites, the denial of sleep in a Communist prison, and constant questioning by police, all predispose to a breakdown in resistance If treatment is sufficiently sustained and protracted, nobody but a psychotic can survive unchanged Recent work in North America, not quoted by Dr Sargant, indicates that men starved of stimuli (by being kept in total darkness at a steady temperature and lightly restrained) can be made similarly suggestible their minds create fantasies which they cannot test against reality

This fascinating book is addressed mainly to laymen, but doctors will find it instructive Some will be upset by the mechanistic approach and some will disagree with certain by-the-way conclusions, but they will find it hard to refute Dr Sargant's facts and main conclusions Our legislators would do well to consider the evidence he presents that, even in this country, the confession of a prisoner may have been largely suggested by the examiners It seems questionable whether a prisoner's confession should be allowed as evidence of guilt

A particular merit of the book is that it will provoke a critical approach to evidence of every kind, including that of science

Novant'anni delle Leggi Mendeliane

Edited by Professore LUIGI GEDDA Rome Instituto Gregorio Mendel 1956 Pp 494 £6 5s

IT has been written that in the ten years that Gregory Mendel worked on his peas in the garden of a monastery, he made the greatest discovery in biology that has been made in the past five hundred years This lavishly produced and superbly illustrated book, written in many languages, recalls and honours the discovery of the laws of heredity ninety years ago

It is divided into three parts The first contains a facsimile reproduction of the original manuscript, Mendel's fundamental paper *Versuche uber Pflanzen Hybriden*, which few people have really read and digested, together with a translation into Italian There is also a short biography in Italian, an account of the Mendelian laws in German, and a history of Mendelism in later years in Japanese, with an English summary The second part contains original papers on *general and human* genetics written in honour of Mendel The third consists of fifteen studies of medical genetics

Of the twenty six papers in these parts, written by experts from all over the world, eleven are in English, and summaries in English are appended to the others Harry Harris writes on genes and enzymes in man and W G Lennox on transmission of the cerebral dysrhythmias and seizures in epilepsy An article on the colour of the iris in certain families is especially notable for its illustrations

This, then, is *not* a book of purely historic interest It points to the practical development of the studies to which Mendel gave so great an impetus by launching *them from the start* in the right direction, thanks to his genius and to his modern approach to scientific research Anyone interested in genetics will find this an exciting book

The Organisation of the Cerebral Cortex

D A SHOLL, reader in anatomy in the University of London London Methuen 1956 Pp 125 18s

THE keynote of this monograph is reason, and there is an impressive modesty about the way in which Dr Sholl puts forward his own hypothesis and attempts to evaluate those of others

The book begins with an account of the histological techniques which have been used in analysing the structure of the cerebral cortex, and refers to the work of histologists in assessing the effects of artificially produced lesions in the brain There is a short account of the results of electrical stimulation, but attention is then drawn to the limitation of the cyto architectonic approach to the interpretation of cerebral structure and its function Dr Sholl believes that mathematical and statistical methods are likely to be much more valuable and he gives a clear and concise account of the quantitative analysis of certain aspects of cortical organisation He then goes on to describe the technique of the quantification of neuronal connectivity, which he thinks is most important His work relates very largely to the visual cortex of the cat, but serves to illustrate the relevance and validity of mathematical analysis in human cortical structure

After this outline of structure, Dr Sholl turns to function He is dubious about the views of the cyberneticists and of those who construct machines in the hope of explaining cerebral function Later he states the value of mathematical theories in the interpretation of cortical organisation, and expounds very *clearly* the validity, of the mathematical approach

Even those who disagree with Dr Sholl's views will own that his ideas on cortical structure and function are well worthy of consideration by all interested in neurology, neuro-anatomy, and neurophysiology The main point which he makes is that it is the interconnections of the various types of cells within the cerebral cortex which are important, and it is probable that these interconnections constitute the real clue to the understanding of *cerebral function*

The Labyrinth

Physiology and Functional Tests JOSEPH J FISCHER, M D, clinical professor in otolaryngology, School of Medicine, Tufts University New York and London Grune & Stratton 1956 Pp 206 $6 00

The Inner Ear, written by Fischer and Wolfson, appeared in 1943, and it very soon became a standard work of reference for otologists Dr Fischer has now re-written and modernised it The labyrinth, as here described, includes only that part of the ear which was described by his late chief, Gustav Alexander, as the "*non-acoustic ear*" Dr Fischer describes in great detail the general and applied anatomy and physiology of the equilibrial labyrinth, and the functional tests of vestibular function The newer techniques of caloric testing are included, and such recent rotational tests as the method of cupulometry, described by Egmond and his colleagues in Utrecht, are evaluated Emphasis is also laid on the importance of electrical investigations in the study of labyrinthine function

This classical monograph will remain an invaluable guide to all otologists and neurologists

THE LANCET

LONDON SATURDAY, APRIL 27 1957

Hospital Infection

THE term ' hospital infection ' brings to mind surgery of the pre-Listerian era, with massive gangrene and laudable pus. Yet even now we cannot send a patient to hospital with the confidence that he will suffer no serious infection as a result of being there. Staphylococcal cross-infection is the most usual hazard[1,2], and staphylococcal enteritis is a common and serious complication of antibiotic therapy[3]. In maternity hospitals streptococcal puerperal sepsis is certainly less common than it was, but staphylococcal breast abscesses afflict mothers, and pemphigus and *Escherichia coli* diarrhœa their babies. Hospital tetanus, usually reported as single cases, has just occurred in an outbreak.[4] In a timely review WILLIAMS[5] makes clear two important facts. The first is that as the general frequency of these infections has never been known, progress in their prevention has never been accurately measured; and the second is that ideas on their cause and prevention have fluctuated rather than progressed—belief in airborne infection has been in fashion and out of fashion, and now is in fashion again.

The frequency of hospital infection has often been reported from particular units, but perhaps these reports were prompted by an unusually great amount of infection. This possibility is sometimes mentioned to justify the view that the drastic measures taken to quell outbreaks are unnecessary in the ordinary way. It seems that before any real progress can be made the precise frequency of hospital infection of all types in medical, surgical, and obstetric units up and down the country must be ascertained. We believe that the results of such an inquiry would be surprising. (MELENEY[6] records that a senior surgeon, asked to estimate the frequency of wound infection in his unit, said ' two per cent.' Investigation showed it to be 14%.) We also believe that the time has come for a new appraisal of methods of preventing hospital infection. Usually the effect of such methods is guessed, and the guesses are often influenced by personal prejudice. Those who conscientiously try to measure the effects find that the measurement must be made over a long time, during which new factors may come into play. Much effort would be saved if the environmental and other factors that could serve as indicators of the risk of infection were established by detailed studies. Once the relation between each factor and the frequency of infection was determined a preventive measure could be rapidly evaluated by *determining its effect on the relevant environmental factor*—not by a long and inaccurate comparison of infection-rates ' before " and " after '.

The factors worth investigating are many. Methods for ridding the human nose of *Staphylococcus aureus* have been described, but it has yet to be shown that infections with this organism depend on, rather than control, the carrier-rate in the surrounding population. The infection of surgical wounds is sometimes attributed to unsatisfactory methods of treating the patient's skin before an operation. But before new ways of doing this are devised, and before judgment is passed on the old ones, would it not be best to find out whether skin carriers of pathogenic organisms are especially liable to wound infection?[2] Expensive and complex ventilation-plants and ultraviolet-light barriers are devised for operating-theatres and hospital wards; but the relationship between the number of airborne organisms in these places and the frequency of wound and chest infection or infantile diarrhœa has not yet been defined.

The definition of relationships such as these calls for painstaking observation and ingenious statistical method. Both of these have been applied in two recent studies from the Air Hygiene Laboratory at Colindale. In the first WILLIAMS et al.[7] examined the air in school classrooms and related the numbers of bacteria of different types to factors such as temperature, humidity, ventilation, and various kinds of activity. In a second study bacterial counts on the air were correlated with the occurrence of infections that might be airborne.[8] The organisms counted were not those causing the diseases under consideration; indeed this cannot be done for some pathogenic organisms or for viruses. Most use was made of estimations of the general bacterial population and of *Streptococcus salivarius* in the air. The use of these organisms as indicators of air contamination is comparable to the examination of drinking-water for fæcal coliforms rather than for typhoid bacilli. The *Strep. salivarius* count was significantly related to the risk of classroom transfer of measles, and can be reasonably used as an index of this risk. The general bacterial counts were related to the incidence of certain respiratory diseases (and not to that of measles) but this relationship was such that it could not be used as a reliable index of the risk. The Colindale workers are careful to point out that bacterial contamination of the air is not necessarily related to the incidence of these diseases as cause and effect, since each might depend on another and unknown factor.

All this work was done in classrooms; the results cannot be applied to hospital wards and the infections that arise in them. But we are not here concerned so much with results as with the demonstration that scientific techniques can reveal the relation of environment to infection. The methods used by WILLIAMS and his colleagues could now well be applied to problems of air hygiene in hospitals, and we hope that they will be. Different bacteriological but similar statistical methods should help to answer some of the questions that we have mentioned.

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[1] See *Lancet*, Jan. 12, 1957, p. 92.

[2] See *ibid*, April 6, 1957, p. 723.

[3] Cook, J., Elliott, C., Elliott-Smith, A., Frisby, B. R., Gardner, A. M. N. *Brit. med. J.* March 9, 1957, p. 542.

[4] See *Lancet*, March 23, 1957, p. 631; *ibid*, April 13, 1957, p. [illegible]

[5] Williams, R. E. O. *Bull. Hyg., Lond.* 1956, 31, 965.

[6] Meleney, F. L. *Int. Abstr. Surg.* 1940, 71, 403.

[7] Williams, R. E. O., Lidwell, O. M., Hirch, A. *J. Hyg., Camb.* 1956, 54, 512.

[8] Reid, D. D., Lidwell, O. M., Williams, R. E. O. *Ibid*, p. 524.

hospital with such good reason In style, presentation, and price we hope this book will set a new fashion for surgical monographs

Battle for the Mind

A Physiology of Conversion and Brain washing WILLIAM SARGANT, M A, M B Camb, F R C P, consultant psychiatrist, St Thomas's Hospital, London London Heinemann 1957 Pp 248 25s

SURPRISING confessions of guilt have been elicited in some countries from political prisoners who seemed to have retained their sanity and who bore no obvious signs of torture Often these have been accompanied by a change of political faith which has outlasted the convert's release from prison These changes in personality have puzzled both doctors and laymen, and the descriptive term "brain-washing" *has come to* be applied Techniques change, but, as Mr Robert Graves shows in his chapter in Dr Sargant's book, brain-washing was used in ancient times

Dr Sargant was struck by a common thread running through sudden political and religious conversion, war neuroses, possession by Voodoo loa, abreactive techniques and shock treatments in psychiatry, the fantastic confessions of women accused of witchcraft, some of the changes in patients receiving psychoanalytic treatment, and certain confessions obtained by police after intensive questioning (even with the best intentions) He believes that all these changes can be described in terms of pavlovian psychology "Much human behaviour is the result of the conditioned behaviour patterns implanted in the brain, especially in childhood" In humans, as in Pavlov's dogs, these *patterns can be destroyed or even reversed by* intense nervous stimulation, especially when the resistance has been lowered—for example, by fatigue, fasting, illness, drugs, or endocrine changes The hellfire sermons of Wesley, the inquisitor's threats of torture, the psychoanalyst's insistence on dragging up painful images, the steady drumming and energetic dancing of Voodoo rites, the denial of sleep in a Communist prison, and constant questioning by police, all predispose to a breakdown in resistance If treatment is sufficiently sustained and protracted, nobody but a psychotic can survive unchanged Recent work in North America, not quoted by Dr Sargant, indicates that men starved of stimuli (by being kept in total darkness at a steady temperature and lightly restrained) can be made similarly suggestible their minds create fantasies which they cannot test against reality

This fascinating book is addressed mainly to laymen, but doctors will find it instructive Some will be upset by the mechanistic approach and some will disagree with certain by-the-way conclusions, but they will find it hard to refute Dr Sargant's facts and main conclusions Our legislators would do well to consider the evidence he presents that, even in this country, the confession of a prisoner may have been largely suggested by the examiners It seems questionable whether a prisoner's confession should be allowed as evidence of guilt

A particular merit of the book is that it will provoke a critical approach to evidence of every kind, including that of science

Novant'anni delle Leggi Mendeliane

Edited by Professore LUIGI GEDDA Rome Instituto *Gregorio Mendel 1956 Pp 494 £6 5s*

IT has been written that in the ten years that Gregory Mendel worked on his peas in the garden of a monastery, he made the greatest discovery in biology that has been made in the past five hundred years This lavishly produced and superbly illustrated book, written in many languages, recalls and honours the discovery of the laws of heredity ninety years ago

It is divided into three parts The first contains a facsimile reproduction of the original manuscript, Mendel's fundamental paper *Versuche uber Pflanzen Hybriden*, which few people have really read and digested, together with a translation into Italian There is also a short biography in Italian, an account of the Mendelian laws in German, and a history of Mendelism in later years in Japanese, with an English summary The second part contains original papers on general and human genetics written in honour of Mendel The third consists of fifteen studies of medical genetics

Of the twenty six papers in these parts, written by experts from all over the world, eleven are in English, and summaries in English are appended to the others Harry Harris writes on genes and enzymes in man and W G Lennox on transmission of the cerebral dysrhythmias and seizures in epilepsy An article on the colour of the iris in certain families is especially notable for its illustrations

This, then, is not a book of purely historic interest It points to the practical development of the studies to which Mendel gave so great an impetus by launching them from the start in the right direction, thanks to his genius and to his modern approach to scientific research Anyone interested in genetics will find this an exciting book

The Organisation of the Cerebral Cortex

D A SHOLL, reader in anatomy in the University of London London Methuen 1956 Pp 125 18s

THE keynote of this monograph is reason, and there is an impressive modesty about the way in which Dr Sholl puts forward his own hypothesis and attempts to evaluate those of others

The book begins with an account of the histological techniques which have been used in analysing the structure of the cerebral cortex, and refers to the work of histologists in assessing the effects of artificially produced lesions in the brain There is a short account of the results of electrical stimulation, but attention is then drawn to the limitation of the cyto architectonic approach to the interpretation of cerebral structure and its function Dr Sholl believes that mathematical and statistical methods are likely to be much more valuable and he gives a clear and concise account of the quantitative analysis of certain aspects of cortical organisation He then goes on to describe the technique of the quantification of neuronal connectivity, which he thinks is most important His work relates very largely to the visual cortex of the cat, but serves to illustrate the relevance and validity of mathematical analysis in human cortical structure

After this outline of structure, Dr Sholl turns to function He is dubious about the views of the cyberneticists and of those who construct machines in the hope of explaining cerebral function Later he states the value of mathematical theories in the interpretation of cortical organisation, and expounds very clearly the validity, of the mathematical approach

Even those who disagree with Dr Sholl's views will own that his ideas on cortical structure and function are well worthy of consideration by all interested in neurology, neuro-anatomy, and neurophysiology The main point which he makes is that it is the interconnections *of the various types* of cells within the cerebral cortex which are important, and it is probable that these interconnections constitute the real clue to the understanding of cerebral function

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This classical monograph will remain an invaluable guide to all otologists and neurologists et al[16] have pointed out Yet problems remain of 9 patients in whom **TELFORD** divided the lumbar splanchnic supply, 6 remained well three to seven years later[1] Why was sympathetic denervation of the chronically obstructed but otherwise normal bowel sometimes effective?

Day Hospitals

THOSE who visit a mental hospital for the first time are usually surprised to find that only a few of the patients—between 1% and 5% perhaps—are treated in bed Indeed, if the space used by patients in the traditional mental hospital is analysed according to its purpose, recreation and sleeping are found to take the largest share, with occupation next and specific treatment last This division of function was dictated by the need for custodial care the hospital was the permanent home of some 80% of its inmates, and it aimed at providing within its boundaries a facsimile of life outside But the recent advance of curative (or at least palliative) psychiatry has had a profound effect on the function of mental hospitals and on the types of patient who enter them Though the long-stay patients still form about 80% of those resident at any one time, they are a diminishing proportion of those admitted The average length of stay of all classes of discharged patients is now about seven months and is shortening, and nearly half are discharged within two months of admission Because so many can thus be returned to their homes in a matter of weeks, the question arises whether the complex social organisation of a hospital is needed for their care The day hospitals now being established are an attempt to find an alternative, and at least one positive advantage can be claimed for them, in that often, if not usually, the patient benefits by maintaining daily contact with his home and normal interests while he is having treatment

Day hospitals are hard to classify, because most of them have grown up in response to specific needs, and no two are alike In an industrial area, for example, the object may be to cater for the patient who could attend a clinic for treatment but has to be admitted as an inpatient because all his family go out to work and he is too depressed to be alone all day Those provided for old people are also in a special class Nevertheless, two main kinds of day hospital may be recognised among those at present in action in this country (1) those attached to a mental hospital or bedded unit of some kind and accepting only patients who would otherwise need inpatient care, and (2) independent units, usually combined with outpatient clinics and prepared to treat all but the most disturbed patients The latter kind have been criticised on the one hand as being no more than elaborate outpatient clinics (and, as such, uneconomical), and on the other because, in attempting to deal with all comers unsupported by inpatient facilities they are said to be accepting undue risks But if we look at the Maudsley and Bromley day hospitals described in these columns on April 6 and in our present issue, they seem to satisfy—though in different ways and for different reasons—both the test of need and the test of economy they offer a special sort of service, and they are economical compared with other forms of care The Maudsley day hospital is one of those designed for a selected class of patient who would otherwise need inpatient attention The running costs are low because it uses the parent hospital's facilities for feeding, occupation, and physical treatment Because of its existence, at least twenty beds in the parent hospital are freed for other cases, but patients attending the day hospital can still be admitted immediately to the main hospital if emergency arises The Bromley day hospital is a multiple-purpose unit, but, unlike some others, it does not undertake physical treatment, and does not therefore need a nursing staff and elaborate equipment Though it is independent and cannot draw on the resources of a hospital, it is inexpensive But perhaps its most interesting characteristic is the use it is making of voluntary help and its association with other social agencies

These Maudsley and Bromley day hospitals show the extremes of the range of function of this kind of unit One clearly belongs to the hospital service and derives its usefulness from the closeness of its association with an inpatient establishment The other is an offshoot of the social life of a community It is still in the experimental stage, and, though opinions may differ as to its advantage for the patient who would normally receive full hospital care, it may serve as a prototype for local health authorities in providing for the aftercare of patients who have been discharged

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[16] Bowden D H Goodfellow, A M Munn J D *J Pediat* 1957 50 321

Annotations

5% AND AFTER

UNDER the Government's "interim adjustment," described in our Parliamentary columns this week, all consultants and senior hospital medical officers will have a 5% rise in remuneration from May 1 This will, of course, give the largest money increases to the specialists who have the largest N H S incomes, and, since the main purpose of the interim adjustment should have been to give help where this is most acutely needed, we regret that the £1,200,000 provided for specialists does so little for the junior who (unlike many of his elders) is gaining little or nothing from the Budget's surtax changes Perhaps more attention can be paid to need in deciding on the distribution of the 5% rise for general practitioners This adds £2,500,000 to the total sum available to them as a group, and the Minister of Health is prepared to discuss with their representatives the best way of dividing it

The special representative meeting of the British Medical Association called for next Wednesday may have to decide, among other things, whether acceptance of this interim award is compatible with the "planned withdrawal" from the National Health Service which the B M A council has proposed as a means of exercising pressure on the Government We have already stated our opinion that the only kind of withdrawal they would in fact be justified in considering is permanent resignation from the service[1]—the possibilities of which could be explored while accepting the interim adjustment and cooperating with the Royal Commission The policy of direct action has won some victories, and, for all we know, it might still win more But their cost, though intangible is likely to outweigh the gain, and we earnestly hope that the representatives will now feel that they can safely take the longer view

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[1] *Lancet*, March 30, 1957, p 673

Hirschsprung's Disease

"MEGACOLON" is an inapt name for Hirschsprung's disease, since dilatation and thickening of part of the colon is simply the outcome of chronic obstruction in normal bowel due to immotility of abnormal bowel beyond, yet for many years this misnomer conditioned our approach to the disease Thus it is not long since the condition was explained on the hypothesis that autonomic imbalance in favour of the sympathetic nervous system caused atonia and dilatation, both being enhanced by sympathetic increase of sphincteric tone, and accordingly patients were treated by lumbar sympathectomy[1] or lumbar ganglionic block[2] "That sympathetic overaction is the cause of the condition is confirmed by the fact that appropriate sympathectomy leads to a relief of the condition"[3] Though the conception was wrong the trail was nevertheless leading in the right direction, for it was postulated that O'BEIRNE's "sphincter" at the recto sigmoid junction was most commonly affected by the spasm[1], and, as we now know, this is often the proximal end of the aganglionic segment causing the obstruction HURST noticed that the rectum was not appreciably dilated or only slightly so in comparison with the pelvic colon above it[4] At that time TELFORD[1] and PATERSON ROSS,[5] both exponents of sympathectomy, doubted whether overaction of the sympathetic system could be the cause, and felt that the operation might succeed by restoring balance in a disorder due to parasympathetic defect at the level of the dilated bowel To PATERSON ROSS it seemed possible that vagal and sacral autonomic nerves might fail to meet in these cases, leaving an area without parasympathetic supply Perhaps the misnomer was responsible for the fact that evidence of defects in the myenteric plexus beyond the dilated areas was so long ignored In 1920 DALLA VALLE[6] first noticed such evidence, and in 1927 CAMERON[7] found the ganglia replaced by inflammatory cells, both observed that the plexuses were normal in the dilated areas, and others reported likewise[8] In 1948 SWENSON[9] switched the surgical attack to the segment of bowel beyond the dilatation, on radiological evidence of "spasm" in 20 cases of Hirschsprung's disease at the lower limit of the area of dilatation he resected the rectum in 3 children, performing a colo anal anastomosis of the pull-through type which he had already practised in dogs The following year BODIAN and his associates[10] reported their neurohistological studies of 15 cases, revealing that the parasympathetic system is indeed at fault, since its ganglia are absent from the narrow bowel and a small adjoining segment of dilated colon Further studies by SWENSON[11] of peristalsis showed strong waves in the hypertrophied colon, but none in the distal segment

1948-49 is therefore the *annus mirabilis* in the treatment of Hirschsprung's disease, because of the work of SWENSON and of BODIAN therapeutic effort came to be based on facts instead of speculation Surgery acquired a new growing-point requiring its confines to be determined in terms of indications, of management, and of pre- and post-operative care These are outlined by Mr WYLLIE elsewhere in this issue A series of 152 patients have been operated upon at Great Ormond Street by DENIS BROWNE's modification of SWENSON's operation by which resection is deferred until the bowel has been delivered through the anus 102 patients are now over 3 years old, and 55 are normal in every way, in the remainder constipation and incontinence, temporary but sometimes protracted, have been the chief imperfections These difficulties have arisen partly because the inability to develop the normal habit of defæcation before operation impedes its institution subsequently, and partly because the operation robs the patient of the sensory area in the lower rectum (SWENSON reported that each of 150 patients had done well after operation apart from occasional incontinence immediately afterwards, except for 3 children aged 2-3 no recourse had had to be made to laxatives or enemas[12]) WYLLIE's report is perhaps less important for the assurance it gives of the effectiveness of rectosigmoidectomy than for its guidance on the management of cases, the indications for operation, the feasibility of one-stage operation with the appreciation of the need to act early, and in some cases the urgent need to relieve obstruction by colostomy[13]

Biopsy per anum is a recent diagnostic advance It is not always easy to be sure that a patient with "megacolon" in fact has Hirschsprung's disease Hitherto the diagnosis has rested on the radiographic demonstration of the cone at the junction of hypertrophied with abnormal bowel (indeed WYLLIE points out that in order to reveal this it is necessary to undertake barium enemas during a period of constipation and not after the bowel has been cleared by washouts) This cone is not always visible—for instance, when a short low segment is affected, or after defunctioning by a colostomy undertaken previously to relieve obstruction SWENSON[14] makes an incision *in the* anal canal extending upwards along the columns of Morgagni to obtain a specimen of the internal sphincter and circular muscle-fibres above it, together with the longitudinal fibres externally, the absence of ganglion cells between these layers can then be determined BILL et al[15] have found the method of wider value, for they have seen cases of constipation regarded on clinical and radiological grounds as Hirschsprung's disease but proved by biopsy to have a normal ganglionated myenteric plexus The Great Ormond Street group have carried a biopsy a stage further by using frozen sections at operation to determine where normal intestine ceases and abnormal begins, so ensuring complete excision and obviating recurrence The aganglionic area may extend even as far as the small intestine, as WYLLIE and BOWDEN

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1 Telford, L D *Proc R Soc Med* 1939, 32, 1145
2 Hawksley, M *Brit J Surg* 1944, 31, 245
3 Maingot, R Postgraduate Surgery London, 1936
4 Hurst, A *Proc R Soc Med* 1939, 32, 1151
5 Paterson Ross, J *Ibid* p 1148
6 Dalla Valle, A *Pediatria Napoli* 1920, 28, 740
7 Cameron J A M *Arch Dis Childh* 1928 3 210
8 Perrot A, Davon L *Ann Anat path méd chir* 1935 12, 157 Tiffin M E Chandler, L R Faber, H K *Amer J Dis Child* 1940, 59 1071
9 Swenson, O, Bill A H *Surgery* 1948 24 212
10 Bodian M Stephens F D Ward B C H *Lancet* 1949 i 6
11 Swenson, O Rheinlander H F, Diamond I *New Engl J Med* 1949 241 551
12 Swenson O *Arch Dis Childh* 1955, 30 1
13 Sieber W K See *Lancet* March 16 1957 p 508
14 Swenson O Fisher J H MacMahon H E *New Engl J Med* 1955, 253, 632
15 Bill A H Creighton S A Stevenson J K *Surg Gynec Obstet* 1957 104 151

of the time at least at less than peak efficiency. Some may be dazed others hyperactive and furiously energetic, but in either case their judgment and performance is below their best. Williams and Rayner suggest that in relief work there is a compelling urge to act and a tendency to think that every act must be completed as quickly as possible, and "this inner compulsion may lead to action which is more rapid than necessary even in the emergency situation." The sense of urgency is often accompanied by an intense concentration on the task in hand, however trivial, to the exclusion of all else. Victims and helpers "seem to operate within a field of narrowed perception or limited awareness." The ability to recognise changing patterns and to anticipate future developments declines, and many may lose their capacity for adapting (or abandoning) familiar responses however inappropriate they have become. Doctors often face a conflict of rôles. The effort needed for leaving behind victims at hand in order to fulfil tasks assigned to them in distant hospitals may be immense. In major disasters, especially when they work without rest, many develop a profound and debilitating feeling of guilt. They may realise that they simply cannot help all those who need their help, but their repeated, conscious assertion that they are doing all they can is a sign of mental fatigue (though unfortunately they will be the last to recognise it as such). Against this the emotional "inoculation" of training and experience affords a high degree of protection, but this is possible only with planning and advance selection of personnel.

The need for such planning was underlined by the Harrow railway disaster in 1952.[4] The Ministry of Health then suggested improvements in organisation[5], and the Sutton Coldfield disaster was successfully dealt with under the scheme agreed for Birmingham.[6] Certainly the country is better prepared for civilian disasters than it was five years ago; but it may still be doubted whether in each area the plans fully integrate the considerable resources of the Armed Forces with those of the civilian services.[5]

HYPERTHYROIDISM IN CHILDREN

FEW pædiatricians have much experience of treating hyperthyroidism; for only 1–2·5% of all cases of Graves's disease are found in children.[7] It is especially important that such children be correctly treated, for prolonged hypothyroidism from over-treatment retards growth, and conversely under-treatment may result in accelerated growth.[8] There is an almost bewildering array of remedies.

In congenital hyperthyroidism iodine is probably the drug of choice. The stimulus to over-production of thyroid hormone by the infant seems to be derived from the mother and regresses gradually after birth. Iodine rapidly controls the hyperthyroidism, and the effect usually lasts until the natural remission develops, but some infants may require additional anti-thyroid drugs, and Lewis and MacGregor[9] have described a case treated with carbimazole and potassium iodide.

In juvenile hyperthyroidism iodine cannot be expected to bring about permanent remission. There is universal reluctance to administer radioactive iodine to young people, and external irradiation of the thyroid gland, formerly favoured,[10] has rightly fallen into disuse. (Of 28 young patients with carcinoma of the thyroid 10 had received irradiation of the thymus in infancy.[11])

On the whole, the results of subtotal thyroidectomy are not encouraging. In children this operation is especially difficult; for the risks of damage to the recurrent laryngeal nerves and to the parathyroid glands are greater, and the effects of postoperative œdema and hæmorrhage more serious than in adults. Moreover, it is hard to decide how much of the gland to excise: to remove too little is to court recurrence, and to remove too much is to condemn the child to thyroid medication for life. Van Wyk et al.[12] describe 4 surgically treated cases: 1 child died after operation, and the remaining 3 became hypothyroid; in 1 hypoparathyroidism developed. Kunstadter and Stein's[13] series contained 5 surgically treated cases with the following formidable complications: hypothyroidism (3 cases), hypoparathyroidism (1), obesity (2), retarded growth (1), and severe keloid scar (1). In each of 5 other children under their care who were treated by thyroidectomy some endocrine complication ensued. Crawford,[14] who advocates surgical treatment, noted no recurrence of the disease in 18 cases so treated, but of 10 children followed for more than two years only half could dispense with substitution therapy after twelve months. McClintock et al.[15] treated 45 of their 50 patients surgically, but they now favour selection based on definite criteria. We cannot dispute that partial thyroidectomy has a place in the treatment of the hyperthyroid child, but it should be reserved for those who fail to respond to proper medical treatment and those with large goitres.

The arguments for and against a conservative regime lose their sharpness in view of the modern dictum that no hyperthyroid patient should undergo any operation until he has been made euthyroid by medical means. The decision, therefore, may safely be postponed for several months. Long courses of medical treatment may have bad emotional effects in adults, but most children do not resent medical attention provided that admission to hospital and unpleasant special investigations are avoided. With methimazole or carbimazole undesirable side-effects are less common than with thiouracil or its derivatives. Using the thiouracil group of drugs and methimazole, Kunstadter and Stein[13] achieved remissions of more than two years in 8 patients, 6 of whom remained well for over five years. They estimate that medical treatment is successful in 65–85% of children. A similar remission-rate was obtained by Allen et al.[10] In these series exophthalmos did not get worse, and after an initial increase in size the thyroid gland regressed eventually. In some cases the regression could be hastened by the addition of desiccated thyroid *U.S.P.* 15–30 mg. daily, to inhibit the production of pituitary thyrotropin.[16] It seems clear that the longer treatment is continued, the greater the likelihood of a permanent cure.

The results of carbimazole therapy in juvenile hyperthyroidism have not yet been reported. This drug is almost certainly safer than the thiouracil derivatives[17]; but it is not entirely free from side-effects, and fatal agranulocytosis in an adult has been reported.[18] The pædiatrician therefore looks hopefully to potassium perchlorate. In doses of 200–800 mg. daily in adults this was found to be virtually free from side effects and clinically effective in nearly all cases by Godley and Stanbury[19] and Morgans and Trotter.[20] But the response was slower than with other anti-thyroid drugs, and where this is likely to be a serious drawback it would be reasonable to combine this treatment initially with carbimazole and to use perchlorate alone for maintenance when the patient is

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[4] *Lancet*, 1952, ii, 1117.

[5] See *Ibid* 1954, i, 1225.

[6] *Ibid* 1955, i, 295.

[7] Atkinson, F. R. B. *Brit. J. Child. Dis.* 1938, 35, 165.

[8] Schlesinger, B., Fisher, O. D. *Lancet*, 1951, ii, 289.

[9] Lewis, I. C., MacGregor, A. G. *Ibid*, Jan. 5, 1957, p. 14.

[10] Allen, R. F., Rose, E., Rose, K. *Pediatrics*, 1954, 14, 38.

[11] Duffy, B. J. jun., Fitzgerald, P. J. *Cancer*, 1950, 3, 1018.

[12] Van Wyk, J. J., Grumbach, M. M., Shepard, T. H., Wilkins, L. *Pediatrics*, 1956, 17, 221.

[13] Kunstadter, R. H., Stein, A. F. *Amer. J. Dis. Child.* 1955, 90, 373.

[14] Crawford, J. D. *Pediatrics*, 1956, 17, 437.

[15] McClintock, J. C., Frawley, T. F., Holden, J. H. *J. clin. Endocrin.* 1956, 16, 62.

[16] Fraser, R., Wilkinson, M. *Brit. med. J.* 1953, i, 481.

[17] Burrell, C. D., Fraser, P., Doniach, D. *Ibid*, 1956, i, 1453.

[18] Tait, G. B. *Lancet*, Feb. 9, 1957, p. 303.

[19] Godley, A. F., Stanbury, J. B. *J. clin. Endocrin.* 1954, 14, 70.

[20] Morgans, M. E., Trotter, W. R. *Lancet*, 1954, i, 749.

GRAFTS AND AORTOGRAPHY

In the past five years the indications for vessel grafting have been broadened and in many centres the demand for homografts has outrun the supply This has led to considerable investigation of various synthetic substitutes, of which at least eight are in use 'Vinyon-N,' 'Orlon,' 'Terylene,' 'Ivalon' (polyvinyl alcohol), 'Teflon,' 'Fortisan,' and stainless steel As any one worker's experience must necessarily be limited, the Society for Vascular Surgery in 1955 appointed a distinguished committee to investigate contemporary opinion among vascular surgeons Of sixty seven surgeons who replied to their questionary twenty-nine stated that synthetic materials were not used at all in their clinics [1] In those centres using synthetic material the aorta had been grafted 256 times with a failure-rate of only 0 7% peripheral arteries had been grafted 160 times with a 37% failure-rate

The failures with aortic prostheses were due to disruption, thrombosis, hæmorrhage, or infection all occurred in the late follow-up period after the grafts had initially functioned satisfactorily This experience compares favourably with that from homografts Like homographs these synthetic materials produce a moderate inflammatory reaction and eventually (with the possible exception of ivalon) become bonded to the neighbouring tissues by fibroblastic ingrowth The final fate of these grafts has yet to be determined, but from studies after two years degenerative changes seem likelier to develop in homografts Synthetic materials are more difficult to apply and they may cause considerable bleeding through the interstices when the clamp is released, but pre-clotting, finer weaves, or chemical treatment will probably overcome this difficulty This evidence is encouraging, but neither the aorta nor the large intra abdominal vessels are good proving grounds for vascular prostheses, for the amount of connective tissue laid down as a new intima never encroaches seriously on the large lumens Grafting a peripheral artery is a much more stringent test, and the failure rate of 37% at centres widely experienced in vascular surgery probably does not reflect the general rate The difficulties in the periphery are the small bore of the artery, the length of the graft, and the crossing of flexion sites Of the available synthetic substances crimpled nylon tubes and terylene taffeta have been most successful in peripheral arteries, and terylene and teflon in the aorta Nylon loses much of its tensile strength within twelve to twenty four months, and the failures were most numerous with ivalon

Whether direct surgery should be inevitably preceded by aortography is discussed by Crawford et al [2] This valuable diagnostic method has been criticised because of its complications, among which are pain, hæmorrhage, aortic thrombosis, embolism, organ infarctions, dissecting aneurysm, spinal-cord damage, and allergic manifestations Crawford et al review their experience with 300 aortograms, complications were few, and even these can be largely attributed to errors in selection of patients, in choice and dose of contrast medium, and in technique of injection Multiple punctures must be avoided, and Crawford et al. believe that the aorta should be pierced only once, well above its major abdominal branches, to avoid flooding these with a high concentration of organic iodide Only 15–25 ml of contrast material is manually injected, after a preliminary test injection has determined the location of the needle These workers conclude that in the great majority of vascular diseases involving the abdominal aorta there is no need to undertake preliminary aortography In a series of 280 aneurysms of the abdominal aorta treated surgically, only 1[illegible] involved the segment of aorta from which the major visceral arteries arise Crawford et al therefore prefer to assess the aneurysm by direct exposure at operation, for, as they point out, involvement of the renal and other vessels no longer constitutes a contra indication to resection and grafting Of a further 215 cases of occlusive atherosclerotic aortic disease, half had incomplete and half complete occlusion In patients with complete aortic occlusion, they always found, distal to the major vessel block, patent arterial segments which were suitable for anastomosis In fact Crawford et al would limit aortography to the occasional patient in whom the diagnosis of aortic disease is in doubt—for instance, the fat person with a suspected but impalpable aneurysm, or the patient with partial aortic occlusion and palpable femoral pulses Possibly aortography, which since its introduction in 1929 has helped so much in defining the anatomical problem before the surgeon, is now becoming redundant because widening clinical experience has shown the constancy and predictability of the arterial disease processes Certainly the doctrine of Crawford et al brings hope of relief to overburdened X-ray departments

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[1] Creech O jun., Deterling R A jun., Edwards S Julian O C Linton R R, Shumacker, H jun *Surgery*, 1957 41 62

[2] Crawford E S Beall A C Moyer J H DeBakey, M E *Surg Gynec Obstet* 1957 104 129

PLANNING FOR DISASTER

Planning for disasters is an awesome task Their site, their moment of impact, and their force cannot be fore seen Modern industrial communities have means of mass relief on a great scale, but the proper use of these potentialities demands a high degree of preparedness and skill Williams and Rayner [1] emphasise that the medical services can be among those most severely hampered by the disruption of normal organisation, and they insist that plans for emergency medical services must therefore be integrated with the general plans for disaster relief The problem is at heart logistical how to get the right services and the right victims together in the right place at the right time For this Williams and Rayner regard three things as essential.

First, good *two way communication* is necessary not only for mobilising relief but also for bringing order into the initial and unplanned mass assault and for maintaining it as circumstances change The second main need is transport Inefficient traffic control affects the medical services mainly by delaying the distribution of patients to suitable hospitals At hospitals close to the disaster area which receive most of the injured and become overloaded, little more than first aid can be given to those most urgently in need of specialist help If they could have been removed to more distant (and perhaps better equipped) hospitals, the waiting time there—and often the total interval between injury and definitive surgery—would have been considerably less Sorting, or *triage*, the "key to management of victims of disaster," [2] can be effective only when transport is adequate and free to move Thirdly it must be known where and in what quantities resources can be found, and how these are to be distributed In peace time disasters over supply may cause embarrassment or even obstruction (During the 1953 flood in Holland, the help of a surgeon and some cattle fodder were repeatedly requested in nation wide broadcasts, and next day, over miles of angry water, six surgeons and ten tons of cattle fodder arrived [3])

Research in America has shown that in disasters few people—and very few doctors—lose their head or break down in the usual sense of the word, but many (possibly a substantial majority) work, for part of the time at least at less than peak efficiency. Some may be dazed, others hyperactive and furiously energetic, but in either case their judgment and performance is below their best. Williams and Rayner suggest that in relief work there is a compelling urge to act and a tendency to think that every act must be completed as quickly as possible, and "this inner compulsion may lead to action which is more rapid than necessary even in the emergency situation." The sense of urgency is often accompanied by an intense concentration on the task in hand, however trivial, to the exclusion of all else: victims and helpers "seem to operate within a field of narrowed perception or limited awareness." The ability to recognise changing patterns and to anticipate future developments declines, and many may lose their capacity for adapting (or abandoning) familiar responses however inappropriate they have become. Doctors often face a conflict of rôles. The effort needed for leaving behind victims at hand in order to fulfil tasks assigned to them in distant hospitals may be immense. In major disasters, especially when they work without rest, many develop a profound and debilitating feeling of guilt. They may realise that they simply cannot help all those who need their help, but their repeated, conscious assertion that they are doing all they can is a sign of mental fatigue (though unfortunately they will be the last to recognise it as such). Against this the emotional "inoculation" of training and experience affords a high degree of protection, but this is possible only with planning and advance selection of personnel.

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[1] Williams H B Rayner J F *Med Ann D C* 1956, 25 655

[2] Ziperman H H *J Amer med Ass* 1956 162 1438

[3] Studies in Holland Flood Disaster 1953 Instituut voor Sociaal Onderzoek van het Nederlandse Volk, 19[illegible]

The need for such planning was underlined by the Harrow railway disaster in 1952.[4] The Ministry of Health then suggested improvements in organisation,[5] and the Sutton Coldfield disaster was successfully dealt with under the scheme agreed for Birmingham.[6] Certainly the country is better prepared for civilian disasters than it was five years ago; but it may still be doubted whether in each area the plans fully integrate the considerable resources of the Armed Forces with those of the civilian services.[5]

HYPERTHYROIDISM IN CHILDREN

FEW pædiatricians have much experience of treating hyperthyroidism, for only 1–2·5% of all cases of Graves's disease are found in children.[7] It is especially important that such children be correctly treated, for prolonged hypothyroidism from over-treatment retards growth and, conversely, under-treatment may result in accelerated growth.[8] There is an almost bewildering array of remedies.

In congenital hyperthyroidism iodine is probably the drug of choice. The stimulus to over-production of thyroid hormone by the infant seems to be derived from the mother and regresses gradually after birth. Iodine rapidly controls the hyperthyroidism, and the effect usually lasts until the natural remission develops, but some infants may require additional anti-thyroid drugs, and Lewis and MacGregor[9] have described a case treated with carbimazole and potassium iodide.

In juvenile hyperthyroidism iodine cannot be expected to bring about permanent remission. There is universal reluctance to administer radioactive iodine to young people, and external irradiation of the thyroid gland, formerly favoured,[10] has rightly fallen into disuse. (Of 28 young patients with carcinoma of the thyroid 10 had received irradiation of the thymus in infancy.[11])

On the whole the results of subtotal thyroidectomy are not encouraging. In children this operation is especially difficult; for the risks of damage to the recurrent laryngeal nerves and to the parathyroid glands are greater, and the effects of postoperative œdema and hæmorrhage more serious, than in adults. Moreover, it is hard to decide how much of the gland to excise: to remove too little is to court recurrence, and to remove too much is to condemn the child to thyroid medication for life. Van Wyk et al.[12] describe 4 surgically treated cases: 1 child died after operation, and the remaining 3 became hypothyroid, in 1 hypoparathyroidism developed. Kunstadter and Stein's[13] series contained 5 surgically treated cases with the following formidable complications: hypothyroidism (3 cases), hypoparathyroidism (1), obesity (2), retarded growth (1), and severe keloid scar (1). In each of 5 other children under their care who were treated by thyroidectomy some endocrine complication ensued. Crawford,[14] who advocates surgical treatment, noted no recurrence of the disease in 18 cases so treated, but of 10 children followed for more than two years only half could dispense with substitution therapy after twelve months. McClintock et al.[15] treated 45 of their 50 patients surgically, but they now favour selection based on definite criteria. We cannot dispute that partial thyroidectomy has a place in the treatment of the hyperthyroid child, but it should be reserved for those who fail to respond to proper medical treatment and those with large goitres.

The arguments for and against a conservative regime lose their sharpness in view of the modern dictum that no hyperthyroid patient should undergo any operation until he has been made euthyroid by medical means. The decision, therefore, may safely be postponed for several months. Long courses of medical treatment may have bad emotional effects in adults, but most children do not resent medical attention, provided that admission to hospital and unpleasant special investigations are avoided. With methimazole or carbimazole, undesirable side-effects are less common than with thiouracil or its derivatives. Using the thiouracil group of drugs and methimazole, Kunstadter and Stein[13] achieved remissions of more than two years in 8 patients, 6 of whom remained well for over five years. They estimate that medical treatment is successful in 65–85% of children. A similar remission-rate was obtained by Allen et al.[10] In these series exophthalmos did not get worse, and after an initial increase in size the thyroid gland regressed eventually. In some cases the regression could be hastened by the addition of desiccated thyroid *U.S.P.* 15–30 mg. daily, to inhibit the production of pituitary thyrotropin.[16] It seems clear that the longer treatment is continued, the greater the likelihood of a permanent cure.

The results of carbimazole therapy in juvenile hyperthyroidism have not yet been reported. This drug is almost certainly safer than the thiouracil derivatives,[17] but it is not entirely free from side-effects, and fatal agranulocytosis in an adult has been reported.[18] The pædiatrician therefore looks hopefully to potassium perchlorate. In doses of 200–800 mg. daily in adults, this was found to be virtually free from side-effects and clinically effective in nearly all cases by Godley and Stanbury[19] and Morgans and Trotter.[20] But the response was slower than with other anti-thyroid drugs, and where this is likely to be a serious drawback it would be reasonable to combine this treatment initially with carbimazole and to use perchlorate alone for maintenance when the patient is euthyroid Potassium perchlorate acts by inhibiting the iodide concentrating mechanism of the thyroid (unlike the thiouracils and methimazole, which interfere with thyroglobulin synthesis), and increase in exophthalmos and size of goitre, and swings into hypothyroidism, are less likely Since treatment must usually be continued for at least two years and preferably until puberty, a non-toxic drug which effectively controls the disease would be a great boon, and the evidence merits a trial of potassium perchlorate in the management of hyperthyroidism in children

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[4] *Lancet*, 1952, ii, 1117.

[5] See *Ibid*, 1954, i, 1225.

[6] *Ibid*, 1955, i, 298.

[7] Atkinson, F. R. B. *Brit. J. Child. Dis.* 1938, 35, 165.

[8] Schlesinger, B., Fisher, O. D. *Lancet*, 1951, ii, 289.

[9] Lewis, I. C., MacGregor, A. G. *Ibid*, Jan. 5, 1957, p. 14.

[10] Allen, R. F., Post, E., Pett, F. K. *Pediatrics*, 1954, 14, 38.

[11] Duffy, B. J. jun., FitzGerald, P. J. *Cancer*, 1950, 3, 1018.

[12] Van Wyk, J. J., Grumbach, M. M., Shepard, T. H., Wilkins, L. *Pediatrics*, 1956, 17, 221.

[13] Kunstadter, R. H., Stein, A. F. *Amer. J. Dis. Child.* 1955, 90, [illegible]

[14] Crawford, J. D. *Pediatrics*, 1956, 17, 437.

[15] McClintock, J. C., Frawley, T. F., Holden, J. H. *J. clin. Endocrin.* 1956, 16, 62.

[16] Fraser, R., Wilkinson, M. *Brit. med. J.* 1953, i, 481.

[17] Burrell, C. D., Fraser, R., Doniach, D. *Ibid*, 1956, i, 1453.

[18] Tait, G. B. *Lancet*, Feb. 9, 1957, p. 303.

[19] Godley, A. F., Stanbury, J. B. *J. clin. Endocrin.* 1954, 14, 70.

[20] Morgans, M. E., Trotter, W. R. *Lancet*, 1954, i, 749.

THE BOMB TESTS

BEFORE long a certain number of thermonuclear weapons of unknown power will be exploded in the Pacific—unless the British Government change their mind Unhappily, they show no sign of doing so or of taking urgent action to secure international control of nuclear bomb tests In his reply[1] to the Japanese prime minister, Mr Macmillan again declared his confidence in the safety of the forthcoming tests, but added nothing new in the way of reassuring facts The most gloom-provoking passage in his letter is that in which he speaks of working for the abolition of nuclear tests "at the appropriate stage" in a scheme of general disarmament Mr Macmillan's statements after his return from the Bermuda conference suggested to many people that a full scale fusion bomb—the so called "dirty" bomb that releases enormous quantities of radioactive isotopes—would not be exploded in the tests on Christmas Island[2], but nothing more has been officially said about "clean" bombs, and fears remain Further alarm has been caused by the recent fusillade of Russian explosions, which were presumably big ones since they were detected

Whatever bombs they plan to fire, the Government again find themselves following a much criticised course, and they must be listening carefully and uneasily to every opinion, scientific and non scientific, from at home and abroad Mr Macmillan has been unresponsive to the appeals from Japan and elsewhere, but we hope he will be more impressed by the sombre statement of the Atomic Scientists' Association, which appears on p 878 This careful analysis of the situation concerning strontium 90 shows plainly how feeble is the case of those who argue against the immediate abandonment of all further nuclear explosions The only safe assumption is that the damage produced is proportional to the radiation received, and that there is no threshold dose On this assumption, the committee of the Atomic Scientists' Association calculate that a hydrogen bomb of Bikini type, exploded high up, may eventually produce bone cancers in 1000 people for every million tons of T N T of equivalent explosive power It has been estimated that bombs hitherto exploded are equivalent to 50 million tons, so far as strontium 90 fallout is concerned Thus, the damage may well have been done for thousands of people

Proposals for nuclear disarmament[3] have been put before the United Nations disarmament subcommittee by Mr Stassen, Russia avows her eagerness to call a halt to testing, and from many sides there come signs that people and governments realise that something must be done very quickly[4] The British Government should acknowledge that the situation is a new and deadly one in which it has become an urgent duty to negotiate an agreement with all speed, so that tests can stop very soon and not at some vague "appropriate stage" Perhaps no single act could do more to bring an agreement nearer than the abandonment of the British tests

RETIREMENT OF PROFESSOR MEULENGRACHT

NOBODY has done more to enhance Denmark's high reputation in the field of medicine than Prof Einar Meulengracht, who retires next week from the staff of Bispebjerg Hospital, Copenhagen, after thirty three years as a chief physician

Meulengracht's original work has been mainly in hæmatology and gastro enterology In his youth he worked out a simple colorimetric method for estimating the degree of jaundice, and this icteric index was widely used for many years His investigations of chronic hereditary hæmolytic jaundice are fundamental, and he has contributed much to the understanding of pernicious anæmia and its treatment, notably through his studies of the pylorus in pigs (In these columns a fortnight ago he and two colleagues showed that the response to administration of heterologous intrinsic factor contained in hog pyloric mucosa differs from that to administration of homologous intrinsic factor) But he is best known for his revolutionary work on bleeding peptic ulcer Abandoning the usual treatment by starvation, he found that mortality was reduced, and recovery hastened, by feeding the patient amply from the start

Through the years many British and other foreign doctors have visited Meulengracht's department and observed his outstanding ability as a clinician and teacher On ward rounds he shows himself as a clear thinker who abjures speculation on the one hand and displays of erudition on the other His style is concise, his manner friendly, quizzical, and urbane It seems highly improbable that, at a spirited 70, this man will relax and enjoy the peaceful retirement he has earned

WELLCOME TRUST

The Wellcome trustees have announced the following benefactions

(1) £95,000 to the University of Birmingham as a contribution to the cost of building an extension to the clinical research block at the Queen Elizabeth Hospital The extension, which will substantially increase the accommodation for research workers in the university departments of medicine and surgery, will be known as the "Wellcome Wing"

(2) Up to £11,000 to the Middlesex Hospital Medical School for the cost of providing an extension, to be known as the "Wellcome Annexe," to the Institute of Clinical Research, *Hanson Street, London,* W 1

(3) £10,000 to the Christian Medical College Hospital, Vellore, South India, for the cost of setting up a metabolic research unit and maintaining it for five years *The* unit is to be used in the first instance for a study of fat metabolism in relation to tropical sprue

(4) The trustees have also agreed to purchase the following items of special equipment for indefinite loan to research centres (*a*) a nuclear magnetic resonance spectrometer (costing approximately £17,000), for the department of chemistry, University College, London, and (*b*) a photo electric spectropolarimeter (costing approximately £3000), for the department of biochemistry, Postgraduate Medical School of London

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[1] *Times* April 18 1957

[2] See *Lancet* April 6 1957, p 726

[3] *Times* April 13 1957

[4] The organisations concerned in the campaign in this country against the testing of nuclear weapons include the National Council for the Abolition of Nuclear Weapon Tests, to which we refer in a note on p 892

Special Articles

THE STEPPING STONES CLUB

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MENTAL illnesses encroach not only on the life of the patient but also on the lives of his family and close friends These encroachments can be greater than those of even severe physical illness, which is socially far more acceptable to the general public and to many hospital workers Today we are beginning to recognise that some of the important roots of psychological upset are to be found within the community Social circumstances influence the unfolding of character, and are as important as genes, and probably more so than orthodox education More than any other factor perhaps, social isolation drives the patient to eccentricity or to a frank behaviour disorder Not only does social isolation evoke mental illness, but the illness, which is unacceptable to the community, heightens isolation Mental hospitals are by no means a complete answer to this problem, for the patient remains an embarrassment to his family, quite apart from the burden which he imposes on society

As a result of this state of affairs, psychiatric departments of general hospitals, unattached to a mental hospital, have often more patients than they can cope with During the past ten years we have been trying to run a psychiatric unit of the kind which offers not only diagnosis, but also treatment outside a mental hospital. Our difficulties and our attempts to solve them have led, one step at a time, to the formation of the Stepping Stones Club

THE TOWN

Bromley, in Kent, was originally a satellite town of London, it is now virtually a suburb It is a mixed community which still has some fairly wealthy members There is some light industry, but it is mainly a dormitory town and the main shopping centre for the surrounding housing estates There are many churches an orchestra, choral societies, a repertory theatre, an amateur dramatic society, and many other cultural and recreational groups The town has a strong civic sense

THE HOSPITAL

Bromley Hospital was founded by the local community as a voluntary cottage hospital Before the start of the National Health Service it had become a general hospital, with visiting consultants from the London teaching hospitals, the general practitioner specialists who had originally staffed it still take an active part in clinical work and administration

Outpatient psychiatry was started in 1945, one of the three present psychiatrists holding a monthly session By 1948 three psychiatrists took 13 sessions with the help of a full time and a part-time psychiatric social worker (P S W), a part time educational psychologist, a part time nurse, and a full time secretary, and larger premises were being sought Once the N H S started there were more urgent priorities and the psychiatric work continued in a consulting room, an office and a waiting room curtained off from the chiropody or orthoptic clinics Two other consulting rooms were sometimes available

A pioneer occupational-therapy unit had been started in the hospital grounds in 1946 About half the patients were physically disabled and half were referred from the psychiatric clinic The results, particularly in paraphrenics whom we had assumed it would not be possible to treat outside a mental hospital, were surprisingly good The success appeared to be due to the patience and skill of the occupational therapists and to the mixture of disablements within the department Both staff and patients came to understand that mental illness is as severe a disablement as the traumatic and disease processes also being treated there Both groups of patients were doing creative work; the psychiatric patient's first sign of recovery was usually an offer to help another patient who seemed to him more seriously disabled than himself

VOLUNTARY HELP

Lectures were given to local organisations from the first days of the clinic Doctors and P S W s in this way met their colleagues, and also parent-teacher associations, church groups, and many other clubs The Townswomen's Guild started branches in Bromley at the request of the clinic, and the lectures began to break down the prejudices about mental illness and to bring offers of help often from ex-patients and their relatives. Church members found accommodation for the homeless the Friends of Bromley Hospital helped patients both financially and by visiting elderly lonely patients The W V S provided meals-on-wheels, and the British Red Cross handicraft instructors and escorts Many of these groups welcomed patients and ex-patients, bridging their initial shyness with great understanding It became clear that this sort of help often sped the patient's recovery In 1951 members of the Board of Control suggested that the hospital should apply for a grant to help to house and formalise these activities The suggestion was premature but provided a focus for planning

During 1953–54 the senior P S W visited many of the people who had offered to help in the work and discussed with them the possibility of doing so It was pointed out that volunteers should be interested and in sympathy with the work, unafraid of mental illness, and prepared to enter into normal social relations with patients Helpers who were skilled in some art or craft, such as music, handicraft, painting cooking or acting, would make a valuable contribution by joining in such activities with the patients It was also pointed out that helpers would have to attend regularly, whether once a week or only once a year, and that they would either have to provide a deputy or give due notice when they could not come

The response to these discussions was so encouraging that a meeting was called with the help of the Friends of Bromley Hospital Members of the hospital management committee and the hospital administrative officers attended The Bromley League of Churches, the Doctors Christian Union, and the Trades Council all sent observers and the Stepping Stones Club was formed The elected committee started groups alongside the existing drama and discussion groups, they strongly advocated an approach being made to the Board of Control to ask how financial help could be obtained Groups were conducted in the clinic, in private houses, and in church halls

Last year the King Edward's Hospital Fund for London allocated the H M C £18,000 to buy, convert, and furnish a house After many vicissitudes a house has now been bought which will house both the clinic and the club It should be opened within three months

FROM THE CLINIC

New patients are sent by general practitioners, school medical officers, and hospital staff at the rate of over 300 annually A third of these are children under 15, but a quarter of the adults are seen as emergencies on domiciliary visits Fortunately these seldom need admission to hospital, though 8–10% of the adult patients are sent to local mental hospitals, to the Bromley Hospital, or to neurosis centres

Many acute patients can be maintained outside hospital by daily visiting during the first week, and the general practitioner and P S W s together, sometimes with the domiciliary nurse, undertake this responsibility In these circumstances the patient is seen at least twice weekly by a member of the clinic staff Relatives have proved extremely cooperative, these methods often avoid the break-up of the family which can be a tragedy where there are young children As soon as possible patients are persuaded to attend the occupational-therapy department We do not insist on compulsory daily attendance, but the patient who is given something to occupy him for even a small part of each day can be much more easily kept at home with relatives

As soon as they are well enough patients are encouraged to attend one of the evening groups During the day many come to read in the small waiting-room of the clinic This has been so helpful that in the new house the Friends of Bromley Hospital intend to provide a daily hostess who will relieve the clerical and other staff

Mental breakdown in older patients is often accompanied by severe malnutrition or major physical disease These patients are often investigated as inpatients in the psychiatric beds of Bromley Hospital

In the outpatient clinic each new patient is usually seen for three quarters of an hour, and old patients are allotted half an hour When possible each patient has ten psychotherapeutic sessions, and one or more home visits from the P S W We gave up the use of physical treatments in 1952 though we refer any patient who asks for it to a suitable clinic

TO THE CLUB

During the past year, the club's membership has grown from 200 to 300, of whom 100 are helpers, including the clinic staff All active members take part in different club activities without distinction as to whether or not they are patients This rule, the most fundamental rule of the club, has been extended to visitors

At the moment ten groups meet regularly, most of them weekly, usually in the evening at a time when both housewives and patients who have returned to work can attend most easily The numbers in each group fluctuate between 7 and 25 The two original groups —the children's play club and the mothers' discussion group, which were run concurrently—have had to be temporarily abandoned until our new house is ready Each year the club gives four parties for its less mobile or more scattered members The groups contribute to these parties in turn and ex-members often attend

Since the first meeting the direction and control of clinical treatment have remained in the hands of the psychiatric clinic staff, but the organisation of the club has been entirely the responsibility of the voluntary body This body has shown a high degree of social responsibility The club committee consists of a representative of each group or type of group, representatives of the hospital management committee, and representatives of the Friends of Bromley Hospital The clinic staff attend whenever they are able, but have no vote The club is a registered charity and has been helped financially by the League of Hospital Friends, this, together with the subscriptions given voluntarily by its members, has met all its expenses

The activities are determined by the interests of the members Any four or five people who wish to start a new group are encouraged to meet and form a nucleus to which patients can be directed Arrangements are fluid, and voluntary workers are not persuaded to remain in the club once their interest has waned The work is enjoyable but demanding, and freshness of approach is essential In so far as possible voluntary workers are not allowed to overwork

Helpers are recruited from all classes of society, in contradistinction to psychiatrists and social workers who are normally recruited from a narrow stratum The education of the technical worker is long, it leads him away from ordinary everyday ideas and language An intelligent voluntary worker or ex patient, on the other hand, who shares with the patient his background and language, can at times help him, particularly when he is acutely ill and confused, more than the trained worker The trained worker, however, can guide and educate the voluntary worker and provide support in times of stress Hence a trained worker at present attends each discussion group where the more serious problems emerge Other groups are visited when possible and their leaders are given special training and support

The activities of the club are designed to avoid social isolation during the acute stage of mental illness to break it down if it has become established, and to provide a link through which the patient can resume a full life within the community It is too early to estimate the impact of this kind of social therapeutic work on psychological techniques So far the results are encouraging

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STRONTIUM HAZARDS

Statement by Atomic Scientists' Association

IN view of the widespread concern about radiation hazards, and particularly the effect of radioactive strontium produced in nuclear-weapon tests, the council of the Atomic Scientists' Association appointed a committee, under the chairmanship of Prof Joseph Rotblat, to study the problem, and to follow up the implications of last year's Medical Research Council report in the light of more recent information What follows is based on the committee's report issued last week

When an H bomb is exploded at a high altitude, and in an area in which there are no inhabitants—as is said to be the case with the forthcoming British tests—there is very little likelihood of immediate injury to people, or of substantial local contamination of the oceans, even if a large amount of radioactivity is produced in the explosion This radioactivity would be taken up into the upper regions of the atmosphere from where it would spread all over the globe and gradually descend to the ground over a period of some years By that time only the long lived radioactive products of the bomb would remain, and it is the possible effects of these that are of concern

If H bomb tests continue at the present rate, the dose of radiation to the reproductive organs, which may cause damage to future generations, has been estimated in the M R C report to be of the order of 1% of that resulting from the natural level of radiations Of greater import, however, is the damage which may result to the present generation, mainly from one radioactive substance—strontium 90 This substance enters into food, chiefly in vegetables and dairy products, and it accumulates in the human body in the bones, where it remains for a long time Depending on the assumptions made about the distribution of strontium in bone, it is calculated that by the year 1970 the radiation dose to bone from all the tests carried out up to the autumn of 1956 will range from 9% to 45% of the dose received from all natural sources, including the radium which is normally present in bone

It is known that radioactive substances concentrated in the bone may give rise to bone cancers and other damage, and that the irradiation of bone marrow may result in leukæmia The induction of bone cancers by the action of strontium 90 in the bone has been demonstrated in animals, in human beings the same effect has been observed with radium, which in some ways behaves like strontium In all these cases, however, the amounts of radioactivity present in the bone were far greater than those that are likely to accrue from H-bomb tests. The question then arises how to apply these findings to very small doses. There is here a fundamental difficulty, in that the relationship between the damage produced and the amount of radiation is not known. If this relationship is such that there exists a threshold dose below which cancer cannot be induced, then it can reasonably be inferred that the small amount of strontium 90 which will accumulate in bone from the current H-bomb tests would not result in any harm. If, however, the number of additional bone tumours resulting from radiation is directly proportional to the dose, then even a very small dose will give rise to a small but definite probability of bone cancer. This means that in a very large population a certain number of people would contract this disease as the result of their having a small amount of strontium 90 in their bones.

The evidence is as yet inconclusive. Some animal experiments have been interpreted as indicating the existence of a threshold dose. On the other hand, in man, the occurrence of leukæmia caused by radiation suggests a simple proportional relationship. Unfortunately the question cannot be settled by experiment in a short period of time, nor is there strong guidance from theory. There is one theory of the origin of cancer (that it is due to somatic point mutation) which implies a proportional relationship. Where the effects of strontium 90 are concerned the authorities responsible for the M.R.C. report appear to be inclined towards the proportional hypothesis, for they state: "On the whole the experiments seem in favour of a proportionality between the frequency of tumours produced in a given length of time and the amount of radioactive material in the body even at low dose levels."

If the proportional relationship is accepted, it is then possible to make a rough estimate of the number of bone cancers which may result from a given H-bomb test. Calculations show that an H bomb of the type tested at Bikini in 1954, if exploded high in the atmosphere, may eventually produce bone cancers in 1000 people for every million tons of T.N.T. of equivalent explosive power. (It has been stated that bombs hitherto exploded were equivalent, in aggregate, to 50 million tons, in so far as their strontium 90 fall out is concerned.) These 1000 casualties would be spread all over the world and occur in the course of several decades. A somewhat larger number of people might suffer other bone changes, possibly without manifesting any clinical symptoms. There is also the probability of a number of cases of leukæmia resulting, but there are not enough data to estimate this number. At the same time, these casualties, although large in absolute number, represent only a fraction of those due to the natural level of radioactivity; there would be no way of distinguishing one from the other.

If other types of nuclear weapons were exploded, the number of casulaties would vary in direct relation to the amount of fission products released into the upper atmosphere.

In giving these estimates it must be emphasised again that, apart from the considerable margin of error due to lack of adequate data, they are based on the as yet unproved hypothesis of a proportional relationship applying to very small doses. From this point of view they represent the most pessimistic approach. On the other hand, if this hypothesis is correct, then the figures may be an underestimate of the damage, since they do not allow for the radiation dose in children before or after birth. Children are known to take up much larger quantities of strontium than adults, and the likelihood of producing radiation damage in them is probably much greater for the same amount of radiation.

An appendix to the report sets out a method of estimating strontium 90 hazard, assuming a linear relationship between bone tumour *formation* and *dose*:

(1) The measurements of the ^{90}Sr content in human bone in this country, carried out by workers of the U.K. Atomic Energy Authority,[1] show that by the beginning of 1956 the average amount in all age groups from 10 years upwards, was about 0·2 strontium units (S.U.) (1 S.U. $=10^{-12}$ curies of ^{90}Sr per g. of calcium).

(2) If this figure is applied to the data of the world survey of strontium 90 made by the Lamont group,[2] the committee conclude that the ^{90}Sr concentration resulting from all the tests carried out up to the autumn of 1956 will in 1970 amount to about 4 S.U. This value is in agreement with the estimate of 4–10 S.U. made by Libby[3] for the U.S.A.

(3) The total fission yield from the tests carried out up to the autumn of 1956 is estimated[2] to be equivalent to 50 megatons. For one nominal high yield weapon (as defined in the Indian government's document[4]: 20 megatons with high fission yield) exploded high in the atmosphere, one may therefore expect a concentration in bone of 1·6 S.U.

(4) From Hasterlik's survey[5] of bone sarcoma in people with a radium burden, the committee estimate that 0·1 micro curie of radium yields about 0·5% probability of bone sarcoma. (A factor of 2 has been allowed for the possible admixture of mesothorium with the radium.)

(5) Since 0·1 microcurie of radium is accepted[6] *to be* equivalent to 1000 S.U., applying this probability value to the population of the whole world ($2·5\times10^{9}$ people), the number of bone sarcomas from one nominal high yield nuclear test may amount to 20,000–all over the world ($2·5\times10^{9}\times0·5\times10^{-2}\times1·6\times10^{-3}$).

(6) The radium normally contained in the body and the external radiation from natural sources deliver to the bone a dose equivalent to 45 S.U., or 9 S.U., if one allows for the non uniform concentration of strontium in bone.[7] This means that the dose rate from strontium in bone will amount to 4/45 or 4/9 of that due to the natural background.

The report is signed by Prof. H. S. W. Massey, F.R.S., president of the association, and Mr. H. R. Allan, PH.D., hon. general secretary.

Public Health

The Glasgow Campaign

A FULL report of the Glasgow mass-radiography campaign is not yet to hand, but it seems that for once the organisers cannot complain of a poor public response. In the first few weeks it was impossible to be radiographed without standing in a queue. A total of 710,838 people were radiographed. On the closing day hundreds were still queuing at midnight; the staff and equipment were overworked (the tubes became overheated and had to be cooled with wet towels); 46,077 people attended, which is a world record for one day.

Preliminary examination has disclosed 8074 cases of pulmonary tuberculosis needing observation or treatment. The figures per cent. are 0·2 of active disease, 0·7 of doubtful active disease, and 0·19 of healed disease. On April 29 the campaign will shift to other parts of Scotland, heralded by runners carrying torches.

The Early M.O.H.

Few people have known much about the doctors who were working as medical officers of health between the appointment of John Simon to the City of London (with the passing of the Public Health Act of 1848) and the appointment of other London medical officers of health in 1855. Prof. C. Fraser Brockington's researches into the events of that period were published last year in the *Medical Officer*, and have now been reprinted as a small book.[8] This includes the text of Dr. S. E. Piper's report on Darlington in 1851 (in which he decried the overcrowding and ubiquitous smallpox, and called for

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1. Bryant, R. J., Chamberlain, A. C., Morgan, A., Spicer, G. S. A.E.R.E. HP/R 2056, 1956.
2. Kulp, J. L., Eckelmann, W. R., Schulert, A. R. *Science*, 1957, 125, 219.
3. Libby, W. F. *Proc. nat. Acad. Sci.* 1956, 42, 945.
4. Nuclear Explosions and Their Effects. Government of India, 1956. See *Lancet*, 1956, ii, 714.
5. Hasterlik, R. J. Geneva Conference, vol. 11, p. 110.
6. Recommendations of International Commission on Radiological Protection. *Brit. J. Radiol.* 1955, suppl. no. 6.
7. Spiers, F. W. *Ibid*, 1956, 29, 409.
8. Medical Officers of Health, 1848 to 1855. Obtainable from Hodgetts Ltd., 72, Fleet Street, London, E.C.4. 1957. Pp. 51. 10s.

better sewage and scavenging, not only for their immediate benefits but also for the example they would set in cleanliness) and appendices giving the duties of officers of health in 1851, the dates of constitution of local boards of health, and biographical details of the medical officers of health of 1848–55

Tuberculosis in Europe

The death-rate from tuberculosis is declining generally in Europe, according to a statistical report published by the World Health Organisation Thus between 1950 and 1955 the crude death-rate per 100,000 population fell from 36 4 to 14 6 in England and Wales, from 13 8 to 6 3 in Denmark, from 143 6 to 63 0 in Portugal, from 39 4 to 20 1 in Western Germany, and from 78 5 to about 16 7 in Eastern Germany Deaths from respiratory tuberculosis are now commoner in people over 60

But in 1954 the disease still caused 0 9% of deaths in Denmark and Iceland, 1 6% in Britain, and 5 6% in Portugal

Parliament

Interim Adjustment of Remuneration

On April 16 the **Prime Minister** made the following statement in the House of Commons

Before the Royal Commission was appointed I explained that its appointment did not preclude an interim adjustment in advance of and without prejudice to its recommendations An adjustment was made in the remuneration of the junior hospital staff, both medical and dental, at the beginning of this month, when their remuneration was increased by 10% In announcing this increase, I said that we were considering what should be done by way of an interim adjustment for the other doctors and dentists covered by the Commission's terms of reference

The Government have now decided to increase the basic remuneration of senior hospital medical and dental staff including consultants and specialists and all dentists engaged in general dental services by 5% from May 1, and from the same date to add 5% to the aggregate net remuneration of general practitioners—that is, remuneration after the deduction of practice expenses We propose to consult representatives of the profession as to the best method of distributing this sum between individual practitioners

In the meantime, the Royal Commission has been asked to regard its work as a matter of urgency and has, in fact, already, I understand, held six meetings I hope that the letters I have exchanged with the then president of the Royal College of Physicians, together with the statement issued by the chairman of the Royal Commission, will reassure those who have expressed concern about the terms of reference

I hope now that all concerned will turn their thoughts to the task of working out a satisfactory basis for future remuneration, and for keeping it under review

Dr **Edith Summerskill** What was the basis used to arrive at this award? Why has this decision been made in an arbitrary fashion without negotiation with the doctors? Why has the decision been made without any consideration of the findings of the Royal Commission? Will the right hon Gentleman say whether the distribution from the central pool will be similar to that made in 1952? The **Prime Minister** It was always stated by the Government that we intended to make an interim award while the Commission was sitting The 10% was given to the junior staff and now 5% is given to the general body The reason this procedure is adopted is that the present dispute is on a matter of the interpretation of the Spens report Therefore, there could not be any agreed basis for negotiation in the ordinary way The object of the Commission, which is really an independent body, is to find and recommend what should be the basis of remuneration both now and in the future As to the method of calculation, I do not know whether it is similar to that in 1952 In the case of the 10%, it is as I have already stated In the case of the 5% to certain senior hospital medical and dental staffs and the dentists engaged in the general service, and of the doctors in ordinary practice, it is by adding to the aggregate net remuneration, and then we propose to consult the doctors' organisations as to the best method of distributing this money

Mr **Hugh Gaitskell** Can the Prime Minister say how much this will cost? The **Prime Minister** The senior medical staff, about £1,200,000 The general medical practitioners, £2,500,000 The general dental practitioners £1,200,000, to which I should add a 10% increase to the junior hospital staff, which is £900,000 Mrs **Jeger** Cannot the Prime Minister give us a better explanation of the basis of these calculations? Is he saying that he thought up 10% in his sleep one night, and that on another night he thought up 5%? What is the arithmetic behind a suggestion which provides the same increase for highly paid consultants as for the humbler and overworked general practitioners? The **Prime Minister** As I have explained, we appointed a Royal Commission because, in this case, there is a disagreement as to what should be the whole basis for calculating remunerations both now and in the future I hope that this independent body, with terms of reference which I have explained to be very wide, will reach that basis Meanwhile, since the Commission must take a considerable time—a substantial time—to make its report, it was thought right to make this advance I hope and believe that it will be regarded on the whole as equitable and reasonable

Mr **Arthur Woodburn** Can the right hon Gentleman say what steps are to be taken to see that fairness is done to the assistants? In some parts of the country quite a lot of empire building is going on among doctors and assistants The public would like to know that the assistants were to get proper treatment under these arrangements The **Prime Minister** No doubt my colleague the Minister of Health will take that point into account in consultation with the doctors' representatives as to the methods of distribution

Mr **Marcus Lipton** How does the Prime Minister expect employers and workers to accept the principle of collective bargaining if he ignores this principle in dealing with the doctors' increment of pay? Is he aware that this contempt for established machinery is regarded as a very grave injustice by the medical profession? The **Prime Minister** I do not think that that is really quite fair It is a prerequisite of any arbitration that there should be common agreement on what the arbitration has to be about The difficulty here is disagreement about the interpretation of the Spens report The most practical way—I think there is general opinion in the country supporting this—is to get the most independent body we can—and I think we have in the Royal Commission a very good independent body—to try to reach an agreed basis from which, in future, these adjustments can be made without difficulty

Dr **Donald Johnson** May I ask the Prime Minister whether he will press, or ask the Minister of Health to press upon the medical organisation the necessity of bearing in mind in distributing this 5%, that there is quite serious concern at the differences in remuneration among various practitioners within the same service, and that it will give this point very serious attention in the distribution of the extra sum? The **Prime Minister** Yes, Sir

Mr **Arthur Blenkinsop** Can the Prime Minister assure us that at last the Minister of Health will have real power to carry out negotiations in this matter, and that he will not only take account of the position of assistants but of the position of doctors with smaller lists and will try to make a constructive settlement that will help to reduce the large lists of the richer practitioners? The **Prime Minister** It is not a question of negotiation but of consultation, and of how this interim award had better be distributed and applied When we get the Royal Commission's report, I hope that we shall have a permanent solution of how the whole service will work in the future

Mrs **Jeger** When did the Royal Commission start work, and from whom has it so far taken evidence? The **Prime Minister** I am informed that the Royal Commission held its first meeting on March 13, the day after I announced its appointment, and that it has already held six meetings I understand that it has not yet received any formal evidence but has held preliminary and informal discussions with representatives of the consultants, the dental profession, the Bar, architects, chartered surveyors, accountants and different branches of the engineering profession Representatives of the consultants and the dentists made it clear at that stage that their presence did not commit their organisations to giving evidence

Mr **J E Ramsden** In view of the business like way in which the Commission is proceeding has my right hon Friend some hope that the doctors will, in these changed circumstances, modify their attitude towards the Commission? Will he make it quite clear, once and for all, that it will be within the competence of the Commission to have regard to the general relevance of the Spens report in its consideration of *the matter?* *The* **Prime Minister** *All these points of the* competence of the Commission were cleared in the exchange of letters which took place I think that the Spens report is generally regarded as wise and satisfactory On the question of the acceptance of the Commission, I can only repeat that I very much hope that everyone concerned will now turn his labours to the work of creating a satisfactory basis for the future remuneration *and future management of the health* service

The **Earl of Home** made the same statement in the House of Lords **Viscount Alexander of Hillsborough**, for the Opposition, welcomed the Government's retreat from their original *non possumus* attitude **Lord Rea** suggested that the Government were changing their point of view in a most favourable way, possibly using the Victorian example of Eric, or Little by Little, rather than agreeing on a final arrangement

QUESTION TIME

Health-service Contribution

Mr J A **Boyd Carpenter**, Minister of Pensions and National Insurance, in a written reply, stated On March 19 after taking the full advice available to me, I said that the existing health-service element in the National Insurance contribution was in that part of the contribution which is not allowable as a deduction for tax purposes I have now ascertained that this is not so It is, however, the intention that the contribution to be imposed on the insured person under forthcoming legislation should not be deductible for tax purposes, and I am authorised by the Chancellor of the Exchequer and the Minister of Health to say that the National Health Service Contributions Bill will deal in this way with the new health service contribution (which will subsume the National Health Service element in the present National Insurance contribution)

National Marriage Guidance Council

Mr E G **Fletcher** asked the Secretary of State for the Home Department what representations had been made to his department for an increased grant to the National Marriage Guidance Council—Mr R A **Butler** replied The National Marriage Guidance Council has expressed to me its disappointment at the amount of the grant of £10,000 proposed to be paid to it in the financial year 1957–58 In addition, since the Home Office estimates were published I have received 13 representations that the grant to the council should be increased Mr **Fletcher** Will the Home Secretary bear in mind that at present the taxpayer is spending about £1 million a year in subsidising divorce under the Legal Aid and Advice Act, 1949? Will he bear in mind also that the Royal Commission, while divided on the issue, was unanimous in recommending a marked extension in the work of education, premarital instruction, marriage guidance, and conciliation? Does he remember that the Royal Commission urged that every encouragement should be given to the existing agencies dealing with matrimonial conciliation?—Mr **Butler** I am sympathetic towards the aims of the council, and I should like to do my best for it The Royal Commission recommended a relatively modest increase in expenditure and the grant of £10,000 represented a 25% increase on the amount being paid at the time of the Royal Commission's recommendation. That does not mean that I regard it as entirely adequate, but it does mean that an *attempt has* been made

General Medical Services

The number of general practitioners under contract to provide unrestricted general medical services under the National Health Service in England and Wales on July 1 1956, was 19 082 The average number of visits by patients to doctors is in the region of 3 a year, and by doctors *to patients* in the region of 2

Group-practice Loans

So far the number of applications for loans from the Group Practice Loans Fund in England and Wales is 231 of which 107 have been granted The fund is now increasing by over £100,000 a year

In England Now

A Running Commentary by Peripatetic Correspondents

The doctor had seen Anne, aged three, on two successive evening visits to her dirty, crowded home She lay curled up, pale, mute and utterly miserable She refused all food He could find no clinical signs, and was puzzled and worried On the third day he asked for the help of the pædiatric department Could this sudden change from her normal cheerful behaviour mean an encephalitis or the onset of a tuberculous meningitis? The pædiatrician was puzzled too, and though, like the family doctor, he could find no clinical signs he thought the child looked ill enough to justify admission

In the ward, she remained curled up, pale, and apathetic Hospital investigations showed nothing significant Three days after admission we asked the psychiatrist to see her He was even more puzzled "The picture," he said, "is clear, quite typical, and immediately recognisable—this is the Child in Hospital The odd thing is that this is what you took her in for and she is now beginning to improve a little"

After further inquiry it all came out The other children, the mother said, had nagged and begged for a television set until finally she had given way and bought one—a 21 in model, she added This meant she had to go out to work to pay the instalments So Anne had been left for long hours sometimes quite alone

She is much better now, playing happily, and warm and friendly both to us and to the parents when they visit in the evening

The problem is one of disposal

* * *

Bang goes another link into the chain as we forge the destiny of our Nation No thermonuclear rumble, no supersonic crack, just another hallowed proverb pushed over the frontiers of human knowledge We have discovered how to make sows' ears into silk purses, to line them with gold, and wax fat on the profits *Meat Marketing* (March 23) reports that thanks to technology we now have a vibration colloid mill which makes more economical and more versatile sausages than ever before The manufacturers of this mighty maw claim, by grinding, emulsifying, and homogenising, to entice the last decimal return from rinds, sinews, cartilages, paunches, greaves, ears, and udders, and to offer as an end-product a mass paste which can be used to cheer our mash Real toad may yet line the hole

But surely the grinding emulsifying, and homogenising action of the mill does no more than reflect the changes in the world today? Changes which on one hand may strengthen our fibre and benefit mankind, or on the other wreck our vested interests and leave us even more crazily mixed-up kids If crusts from the bread and butter made our hair curl, rinds may make it stand on end The sinews of war have ever been strengthened by *armies* marching on their bellies The grinding of paunches may come perilously near to infringing the copyright of haggis, *but the walls of our own* stomachs shall *have ears to* hearken unto our borborygmi And as for udders, maybe emulsifying and homogenising will squeeze *out a* few more drops of the much-needed milk of human kindness The foie gras must look to its *pâte* *Only* time will tell whether our new breed of hot dogs will have a bark much worse than their bite The inside of our Honest John banger will *soon be a* greater mystery than ever

* * *

Dull surgeries make dull doctors Those G P s whose patients depress them should try the *hilarious* new game of surgery poker The poker-hands are made up from every five patients, in order of their appearance Coloured patients denote spades, red-heads, *blonde*, and dark-haired patients hearts, diamonds, and clubs, respectively Adults count as court-cards, *children* under 10 take the value of their age, and I play the convention which regards all chemists representatives as jokers and "*wild*

My best hand this winter has been a full house, kings high given by (in order of appearance) three adult males (all dark), one school-girl *(red-head)*, and one chemist's representative (bald) However, there are rumours that large families of West Indians are to settle in this area, so I have real hopes of a royal straight flush, which should earn me *The Lancet's* Bedpan of the Month

If anyone would like to sit in on the current game, openers are a pair of conjoined twins

* * *

"Odi profanum vulgus et arceo,' but there seems little one can do (if one must travel at that time) to lessen the crowds that push, fight, and squeeze themselves into underground trains between 5 and 6 P M One of my methods of making travelling more interesting is to study the faces of the people I meet, and from their clothes and accessories give a snap diagnosis of their job and the reason they are in that train But one can make mistakes I was strap-hanging last week in a crowded compartment when I noticed a book which attracted my attention It looked just like a *Synopsis of Surgical Anatomy* by a well-known author This must be a medical student, I thought (noticing his uncreased trousers and college scarf) Lucky young man, probably just rolling in for a quiet morning's dissecting, *or* a friendly lecture on the lymphatics Maybe—I thought as I noticed his age—he is an ex-Forces registrar taking a course for the primary fellowship And my wasted youth rose before me and with it a sorrow for never having taken my primary I might even have been a famous surgeon by now driving to town in my Rolls

I was shaken from my reverie by a sudden jerk, as we pulled up at a station, and some people got out, leaving me a seat next to my student I quickly sat down, determined to examine more closely the anatomical diagrams Yes, clearly "Head and Neck," always a difficult chapter The format of the book seemed a little unusual, however, the layout not quite right for a primary student Perhaps this was a real consultant (forced into a train by the petrol-ration) doing a little cramming before giving his midday tutorial His hair was nicely groomed, and had a most delicate perfume This must be a most fastidious surgeon Again the train pulled up and my student-doctor-surgeon, closed the book, and I followed close behind as we got out of the compartment, determined to see the title and author of his book *Anatomy for Hairdressing Students* loomed in gold letters before my eyes, and my dream vanished, bringing me back to England today, and the crowds trying to push through the ticket barrier But perhaps it is good that modern followers of Tod Slaughter take their studies so seriously—or is it?

* * *

How many of us really understand the physiology, psychology, or anatomy of the steed on whom we used to rely so much—our motor-car? But if what I hear is true, this is all to be remedied with the establishment of a College of Motor Anatomy

The first task of the college will be the clarification of instructional manuals of all popular models Such vague and misleading terms as "petrol pipe" and "jack" will be replaced by "ductus petrolificus" and "levator anguli Currus atque Rotarum" which will be so much clearer to medical men

Naturally the college will begin in a small way, but many of the teaching schools will soon enter into the spirit of the thing, found complete departments, and add a compulsory month or so to medical training Study will be broad and scientific, like all medical training Students will learn, for instance, the reasons for the extinction of the 9 H P Boggle Box Egg in 1932 A degree, bachelor of transport anatomy, will be conferred, with the abbreviation B TR A to distinguish it from the popular B T A, which, of course, stands for "Been to America"

* * *

The nuclear Boffins (God bless 'em all),
Have the 'fall outs' assessed to a decimal,
Yet my nephew and niece
Have got five legs apiece,
And their intellect's infinitesimal

Letters to the Editor

SENIOR REGISTRARS AND CONSULTANT APPOINTMENTS

SIR,—The figures relating to consultants and other specialists staff in hospital (April 13, p 785) will be read by those training or intending to train as specialists not only (as you suggest) with interest, but also with dismay and despondency

For example, the tables show that, whereas in 1957 only 11 general physicians will have reached the age of 65, there are as many as 27 senior medical registrars in their fourth year and 68 "others," which include those holding "transitional" posts Even this high figure of 95 potential candidates for consultant appointments may be an underestimate since university lecturers and research-workers are not included in this group

On the basis of the previous report, Mr Morgan[1] has shown that it would take some eight to eleven years for all senior registrars in the major specialties to be absorbed by retirement vacancies Last October Dr McGregor[2] reported that only a third of the senior registrars in the South East Metropolitan Region who completed their training during the period 1952–56 had so far become consultants, and that this status was achieved from twelve to sixteen years after qualification

It is well known that there may be as many as 40 or 50 men of 35–40 years of age still applying for each consultant vacancy Many of these men have had a few years of war service and the majority have growing families to support, with children at school Periodic moves around the country may involve separation from one's family for many months on end The recent increase of 10% in salary, welcome though it is in helping to relieve financial hardship, cannot be accepted as the only solution to the serious situation which has arisen through lack of security of tenure and poor prospects of promotion

Recent correspondence in the journals and national press has shown that the plight of senior registrars is certainly fully appreciated by our consultant colleagues Mr Harold Dodd[3] offered a constructive contribution when he wrote "I think that it is a national need that the office of assistant physician and surgeon be reintroduced, and that our registrars be given status and reasonable security after their arduous and expensive training"

Sir, can the ever present, yet still urgent, plight of senior registrars be solved? It is recognised that senior registrars may already be doing consultant work for many months in the year In fact, in non teaching hospitals one may deputise for as many as four consultants and therefore be in complete clinical charge of beds and outpatient clinics for at least six months in the year

I would suggest that one possible solution would be to discontinue the posts of senior registrars in non teaching hospitals as they become vacant and appoint assistant physicians and surgeons to the hospital staff in their stead It is important that such appointments should not be regarded as in any way being a sub consultant grade On the contrary, those selected should be given the status of junior consultant with every opportunity for promotion at a later date

These junior consultants would continue to act as deputy to their senior colleagues but, as has been stressed, the appointment should also entail "a few beds, a small outpatient session, and, most important of all, the right to private practice"[4] However, if in certain circumstances this right to private practice is not immediately envisaged, my personal view is that such appointments could be held initially on a whole time basis In any case, it seems unlikely that the cost to the country of this transition would be much in excess of that already entailed under the present day senior-registrar scheme

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[1] Morgan, T H *Brit med J* 1956 ii, suppl p 204
[2] McGregor, H G *Ibid* p 159
[3] Dodd H *Ibid*, p 204
[4] Sewell, W *Lancet*, 1955, ii, 873

Critical analysis of this plan for resolving the senior-registrar problem may well reveal certain flaws and deficiencies, and it may require modification Nevertheless, by limiting new senior-registrar appointments to teaching hospitals and postgraduate centres, a reasonable ratio of senior-registrar to consultant establishment will be maintained Senior house officers and registrars will no longer be fearful of their further prospects, and applications for these posts, which are now far below the vacancies available, will surely increase

Dr Horace Joules[5] has written "as the years pass many senior registrars, excellently trained, are approaching middle age and abandoning hope of obtaining full recognition and employment" Is our long period of training and responsibility to be wasted? All we ask is that our services, which we willingly give, may receive recognition and that some reasonable hope for the immediate future be offered

Bristol   A G FREEMAN

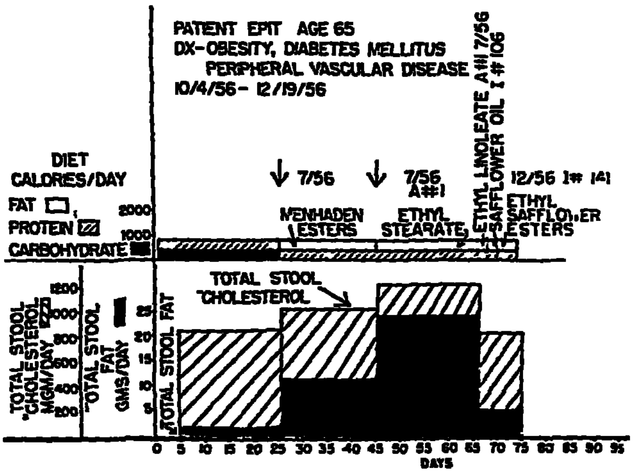
FATS AND DISEASE

SIR,—The paper by Keys, Anderson, and Grande entitled "'Essential' fatty acids, degree of unsaturation, and effect of corn (maize) oil on the serum-cholesterol level in man" in your issue of Jan 12 calls for comment because we believe the authors have not drawn the correct conclusions from their experiments

The authors believe that in general serum cholesterol levels are directly related to the total consumption of fat rather than inversely related to the consumption of essential fatty acids, and that the effect of vegetable oils in lowering serum cholesterol is not the result of the essential fatty acids (particularly linoleic acid) in them They have fed corn oil, sunflower-seed oil, sardine oil, and butter fat to schizophrenics for two weeks The serum total-cholesterol rose after the change from corn oil to sunflower seed oil, and fell after the reverse change, the average difference being 9 3 mg per 100 ml, the values were higher after sardine oil than after corn oil, the average difference being 20 2

There are several objections to the conclusions regarding essential fatty acids that are reached by the authors

1 The actual qualitative and quantitative fatty-acid composition of the oils was completely unknown, and since (as we show below) corn oil appears to produce different effects upon serum-cholesterol in Keys's laboratory at different times, this is crucially important The authors give the iodine numbers of the oils but they take values for linoleic acid from the literature Sunflower-seed oil, with an iodine number of 131, was assumed to have a linoleic-acid content of 61%, "typical variations" given by Hilditch[6] are from 19% to 72% for linoleic and from 14% to 71% for oleic acids, which together are responsible for the iodine number Corn oil, with an iodine number of 120, was assumed to have a linoleic-acid content of 45%, recent commercial samples of U S corn oil had extremes of linoleic acid from 16% to 68% and of oleic from 20% to 76%, a U S corn oil analysed by Lofland et al[7] had an iodine number of 122 and linoleic acid content of 51%, while one analysed by Sniegowski and Baldwin[8] had an iodine number of 121 and linoleic-acid content of 52% It is not apparent to us why Keys and his colleagues have selected a figure as low as 45% Though it is probable that the difference of 11 in the iodine number of the two vegetable oils represents a difference in linoleic-acid content, this is not certain Further, nothing is known of the steric configuration of the linoleic acid in these oils



Absorption of ethyl esters of menhaden oil ethyl stearate and ethyl esters of safflower oil The formula diet used was quantitatively constant. Protein vitamins, and minerals remained unchanged throughout the study

The position regarding the sardine oil is still more unsatisfactory Information is neither given nor available about the content of essential fatty acids in this, and no information is given about any processing or deodorising it may have received Fish oils vary in their growth-promoting activity upon rats deficient in essential fatty acids one of us (H M S) found that samples of herring oil (*Clupea harengus*) and of pilchard oil (*Sardina ocellata*) were each very active in promoting growth when fresh but not when old, whereas samples of Japanese sardine oil (*Clupanodon melanosti*) and of cod-liver oil (Ministry of Food) were without growth-promoting activity If, as is probable, Keys and his colleagues used pilchard oil (probably from *Sardinops caerulea*), the age and treatment of this are important and the iodine number does not give the required information about fatty-acid composition Bronte-Stewart et al[9] found that South African pilchard oil (presumably from *S ocellata*) in fact lowered serum-cholesterol in man It is fantastic to make claims about the relative potency of different oils in essential fatty acids on the basis of iodine numbers

2 The efficiency of absorption of the oils used by Keys and his colleagues was apparently unknown That this may be a factor of real importance is shown in the accompanying figure, representative of studies recently carried out by Michaels and his associates[10] It is obvious from this that absorption of the ethyl esters of menhaden oil (a fish-oil preparation with an iodine number of 139) was extremely poor The same statement applies to esters of palmitic and stearic acid (iodine number=1) whereas the ethyl esters of safflower oil (iodine number=141) are without exception extremely well absorbed

3 In our laboratories, the changes in serum-cholesterol during the two-week periods on corn oil, sunflower-seed oil, and sardine oil—namely, mean changes of 9 3 and 20 2 mg per 100 ml—would be regarded as being within the range of spontaneous fluctuation unless very frequent estimations were made

4 The behaviour of corn oil in Keys's laboratory varies with the passage of time In 1950 he and his colleagues found that corn oil produced a rapid rise in serum-cholesterol in a patient with idiopathic hypercholesterolæmia who had been on a fat-free diet, and Keys concluded[11] that "there is not the slightest evidence for a difference between animal and vegetable fat in this regard [effect of fat intake on serum-cholesterol]" In experiments on 21 male schizophrenics reported in 1952, Keys found[12] that vegetable fat ("mainly corn or maize

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[5] Joules H *Brit med J* 1956 ii suppl p 163

[6] Hilditch T P Chemical Constitution of Natural Fats London, 1956

[7] Lofland H B Quackenbush F W Brunson A M *J Amer Oil Chem Soc* 1954 31 412

[8] Sniegowski M S Baldwin, A R *Ibid* p 414

[9] Bronte Stewart B, Antonis A Eales L, Brock J F *Lancet* 1956 i 521

[10] Michaels G D Chin H P Smyrl S Talpers S J Kinsell L W Absorption of Natural Fats Hydrogenated Fats and Ethyl Esters of Fatty Acids in Human Subjects (In the press)

[11] Keys A *Circulation* 1952, 5, 115

[12] Keys A *Voeding* 1952, 13 539

oil, "as such or hydrogenated to form a vegetable margarine") raised serum-cholesterol the average rise in passing from a diet containing 11 g of vegetable fat to one containing 110 g was 64 mg per 100 ml, and a fall of 61 mg was obtained when the fat in the diet came from two eggs, Keys concluded "that vegetable as well as animal fats have this effect" of raising serum-cholesterol That the serum-cholesterol of the schizophrenics over the past four years had shown "a direct response to change in fat calories, with no indication of an effect of the kind of fat in the diet" was reiterated in 1954[13] At this time

> "most of our demonstrations of the effects of fat intake have been made with corn oil or cottonseed oil or both Recently, however, we have carried out an elaborately controlled experiment on 24 men in which olive oil and cottonseed oil were compared These fats were chosen because, among common food fats of vegetable origin, they have the greatest chemical dissimilarity Besides the use of control (before and after) periods, each subject was studied on both types of fat, and the effect of sequence was also controlled No difference between the effects of olive oil and of cottonseed oil on serum cholesterol concentration could be found"

An average content of linoleic acid in olive oil would be about 6% and of cottonseed oil about 49%, and if indeed these two oils raise serum cholesterol equally the details of this experiment should be published

The similarity in cholesterogenic action of these two oils was repeated, again without details, in September, 1955[14] A year later (October, 1956) Keys had come near to the importance of essential fatty acids which we have been stressing when he concluded[15] that "Hard fats are more [cholesterogenic] than fluid oils The 'essential' fatty acids, linoleic and arachidonic, probably have a different effect than such fatty acids as palmitic and stearic" In a recent paper,[16] Keys is reported to have stated that "coconut oil is outstanding as having the same kind of effect as do meat and dairy fats Some of the oils, however, such as corn oil, do not promote cholesterol increase in the blood As a matter of fact, if taken in large quantities, they depress the cholesterol blood level The level of cholesterol in the blood with a cottonseed-oil diet is about the same as with a fish-oil diet" In his letter of April 13 (p 787) he now recognises that saturated, mono-ethenoid, and poly-ethenoid fatty acids differ in their effect on the blood-cholesterol

Vegetable oils are not immutable nor is man infallible The cause of Keys's altered views might be a change in the composition of the oils he has used, and this possibility, which is not the only one, emphasises again the need for knowledge of this composition if conclusions are to be drawn from slightly different responses to different oils

A great deal more work is required to clarify the effect of feeding different oils upon serum cholesterol The paper of Keys and his associates does little to provide such clarification It is known that the feeding of a synthetic triglyceride containing unsaturated fatty acid is associated with a major decrease in serum cholesterol as compared with the level existing during the ingestion of an equal amount of vegetable fat essentially devoid of unsaturated fatty acid[17] Unpublished data from the same laboratory demonstrate similar effects with purified ethyl linoleate[18] We believe that the essential fatty acid content of dietary fat is the primary factor responsible for the lowering of serum cholesterol, but there are secondary factors as already discussed by one of us in your columns,[19] such as the content of tocopherols and of steric isomers of the fatty acids However, data now being prepared for publication by one of us (L W K) indicate that under appropriately controlled conditions, fresh readily absorbable vegetable oils have serum cholesterol lowering effects that are in fact approximately proportional to their iodine numbers

Oakland, California — L W KINSELL
Oxford — H M SINCLAIR

SIR,—*It should not be too difficult* to ascertain which group of people in this country consume the largest quantities of animal fats—personally I suspect farmers (not farm labourers)—and compare them with a similar group of men (unemployed) for the incidence of coronary thrombosis If the two groups chosen smoked the same number of cigarettes per day, the comparison might be even more helpful Meanwhile, many doctors have cut down their intake of animal fats in the hope of avoiding the disabling consequences of what has been regarded as their own specific vocational hazard Sir John McNee[1] maintains that only in the rabbit has atheroma been proved to be associated with a high intake of cholesterol Will some kind medical statistician please assure me that I can return to my former (modest) ration of eggs and butter?

Hull — L I HARDY

LETTERS FROM HOSPITAL

SIR,—As a general practitioner I am very grateful for the help I receive from consultants, but *this help is* not infrequently marred by the delay in the arrival of their letters, whether they refer to outpatients or inpatients I know that consultants are hard worked, but so are G P s, and yet no patient of ours is accepted as an outpatient without our letter accompanying him Moreover, delay does not diminish the amount of work that has to be done eventually

But there is one way in which consultants could very often save time and labour In the reports I receive half or three quarters is often devoted to repeating the patient's past history and present complaints These are *things* which the G P knows at least as well as the consultant and which were set out in the G P's letter Though the consultant will, of course, want to elicit from the patient his own story, he need not report *it* back to the G P *Shall* we add "*unless he learns something* which he thinks may not have been known before"?

One consultant I know hands his reports (diagnosis and suggested treatment) straight away to the patient to take back to his own doctor This seems to me a very satisfactory arrangement which I would like to recommend

Croydon, Surrey — W J PINCH

POLYNEURITIC REACTION TO AUREOMYCIN

SIR,—I have lately observed a polyneuritic reaction to aureomycin (chlortetracycline) As far as I am aware, such a reaction to aureomycin is rare

A woman of 36 years had pneumonia during the winter of 1948–49 while living under difficult war conditions She has since suffered recurrent bronchitic infections, which seem to be localised in the right lower *lobe* Various chest specialists suspected bronchiectasis, but 2 bronchograms did not show clearly localised lesions The diagnosis has therefore remained uncertain

The bronchitic exacerbations used to be much improved after treatment with penicillin, which she has received repeatedly In September, 1956, the patient *had* a bad anaphylactic shock after an injection of a mixture of benzathine penicillin and procaine penicillin *There* followed a period of disturbed sleep, disturbances of vision, and some feeling of tingling in hands and feet On March 10, 1957, after receiving aureomycin *1250* mg daily for 4 days for an exacerbation of the bronchitis, she had a polyneuritic reaction, glossitis, and disturbances of vision There were paræsthesiæ and hyperæsthesiæ of hands and feet, tenderness of the muscles of the left calf, and some impairment of the sense of light touch and of hot and cold differentiation Vibration sense was normal, as was stereognosis Reflexes were normal All the disturbances in hands and feet, in the typical stocking and glove distribution, ended proximally without sharp limits, and gave way to normal sensation She had difficulty in accommodation. There was no impairment of the function of the external ocular muscles

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[13] Keys A Anderson J T Symposium on Atherosclerosis Washington 1954, p 181
[14] Keys, A Symposium on Arteriosclerosis Minnesota, 1955, p 28
[15] Keys A, White, P D *Nutrition News* 1956 20, 1
[16] Keys A *Modern Medicine*, 1957 25 78
[17] Kinsell L W, Friskey R W Michaels G D Brown, F R *Amer J clin Nutr* 1956 4 285
[18] Kinsell L W Michaels G D Fukayama G, *Dailey J* Effects of ethyl linoleate and ethyl esters of other fatty acids upon lipid metabolism in human subjects 1957 (To be published)
[19] Sinclair H M *Lancet* 1956 i 381

[1] McNee J W *Brit med J* 1956, ii 1172

She was given cortisone 100 to 50 mg daily for a fortnight The condition improved very much during that period.

The allergy department of the central diagnostic clinic "Zamenhoff" of the Workers' Sick Fund (Dr Kessler and Dr Lindenbaum) is kindly trying to find a way of giving the patient antibiotics Dr Itelson, of the same clinic, is the chest physician, and my sincere thanks are due to him as well as to my senior medical officer, Dr Y Shatal, for their help

Dorot Negev, Israel

A YUVAL

HOSPITAL MEDICAL RECORDS

SIR,—Dr Skelton (March 30) and Dr Brocklebank (April 6) both view the problem of preserving medical records and X-ray films from the standpoint of the space needed for their storage

Staffing difficulties must also be considered The retention of medical records is not merely a matter of stuffing them into filing cabinets, or stacking them on shelves To be of value to the clinician or research-worker, records must be suitably indexed and classified (under medical direction), and properly filed by trained clerks An adequate medical records service can be extremely expensive in staff

It is not always appreciated (even by doctors) that the increased number of administrative and clerical staff seen in the hospitals since 1948 is due in large measure to the demands of the vastly improved medical-records service now generally offered Further improvement in this service must result in the employment of yet more clerks

L W HUNT
Hospital Secretary

Aberystwyth General Hospital

STAPHYLOCOCCAL BRONCHOPNEUMONIA

SIR,—The interesting article by Dr Gresham and Dr Gleeson-White (March 30) is timely and of great importance This problem is not confined to one hospital Although it is widespread, some hospitals are much more aware of the problem than others We have been studying the general problem of hospital staphylococcal infections and recently have been concentrating on the patients with pneumonia

An analysis of the first 25 cases of staphylococcal pneumonia obtained from the clinical records of the University Hospitals for the past five years shows that 20 of them were fatal and that a majority occurred in debilitated patients 19 of them were over 50 years of age and there was a slight lessening of incidence in the spring and early summer In 12 cases the disease was not suspected before death Fever, cough, dyspnœa, and mental confusion were the commonest signs A third complained of pleural pain Sputum production was not prominent The X-rays of 19 patients showed that pulmonary infiltration was the only constant finding There were only 4 cases with abscesses and in 2 the hilar glands were enlarged At necropsy the predominant finding in 20 examinations was a diffuse bronchopneumonia, which in 5 instances was described as necrotic Hæmorrhage in the lung was mentioned only once, but it is of interest that 3 other cases had bloody sputum and 2 others clinical purpura These cases, of course, are only indicators of an underlying problem We cannot include patients with undiagnosed antibiotic cured pneumonia and those who died, undiagnosed, without necropsy

Other studies by this group have shown that in the 1935–41 period there were about 20–30 cases of staphylococcal septicæmia seen yearly, whereas after this until 1953 only 5–10 were seen Since then a gradual climb in numbers is evident and in 1955 we saw 27 patients with staphylococcal septicæmia

We made some studies of the prevalence of staphylococcal infections in hospitalised patients similar to those made by Finland and Jones [1] In a group of 634 patients 70 (11%) had proved staphylococcal infection compared with 15% of the patients in the Boston study We had 3% of serious infections compared with 2 6% in their series 56% of our infections appear to have been acquired in hospital (62% in theirs) In addition a study of last year's 484 necropsies, through the kind permission of Dr Emory D Warner, shows that hæmolytic *Staphylococcus aureus* was the prime cause of death in 3 7% of cases and may have been a secondary cause in 12 5% of necropsies

A continuing study of staphylococcal infection is being carried out by a more intensive survey of the wards for incidence and ecology of staphylococcal disease In this study, one of us, a member of the nursing staff, is making observations on nursing and medical procedures and the relationship of these activities to cross-infection

IAN MACLEAN SMITH
MARY E GODFREY
A BARBARA VICKERS
JEAN HATCH

Infectious Disease Division
Department of Internal Medicine
State University of Iowa,
Iowa City, Iowa

CÆSAREAN SECTION

SIR,—I think the conclusions in your leading article on cæsarean section (April 6) are rather misleading I have discussed the problem of the indications for cæsarean section at length,[2] and since my conclusions would seem to be at variance with your own I would like to make the following comments

You say that half the fœtal deaths in deliveries by cæsarean section are attributable to the risks inherent in the operation itself This is certainly not my experience, in fact, I cannot remember a single case in which this was clearly so In some cases where the baby died, earlier resort to cæsarean section might have prevented the death Your recommendation that we should hesitate before deciding to operate solely in the interests of the child therefore needs amplification

Between the periods 1938–47 and 1953–56 the perinatal mortality-rates in booked hospital primigravidæ in Aberdeen fell by more than a third, and the decrease was greatest in the older women, in those of 30 years or more it fell by 75%

Perinatal mortality per 1000 births

Age-group	*15–19*	*20–24*	*25–29*	*30–34*	*35 –*	*All ages*
1938–47	36	35	57	76	101	45
1953–56	40	26	28	17	25	28

The cæsarean-section rate in booked primigravidæ was 1 3% in 1938–47 and 4% in 1953–56 The increase was least in younger and most in older primigravidæ, in those of 35 years or more the cæsarean-section rate is now about 30%

After about 25 years of age, primigravidæ show a progressive deterioration in uterine function which shows itself in a tendency to intra-uterine death of the fœtus and to prolonged labour due to disordered uterine action These dangers are increased if labour does not take place by the 40th week, and may be further increased if pre eclampsia is present The avoidance of protracted pregnancy by induction of labour and of protracted labour by the more liberal use of cæsarean section seems to have been successful in preventing many such deaths without increasing the risks to the mother The overall maternal mortality of 0 99% following cæsarean section, reported by Marshall and Cox [3] for the years 1943–47, no longer applies, since in many maternity hospitals in Britain it is now by no means unusual to perform several hundred consecutive cæsarean sections without a death

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1 *Ann N Y Acad Sci* 1956, 65 191
2 Baird D *Brit med J* 1955 ii 1159
3 Marshall C M, Cox L W Transactions of the 12th British Congress of Obstetrics and Gynæcology, 1949 p 30

Fortunately, cæsarean section is seldom indicated in young women except for disproportion, since it is prejudicial to further childbearing But few primigravidæ over 30 years of age have a second child, so it is particularly important to do everything within reason to ensure that the first baby is born alive My experience is that the chances of a satisfactory outcome can be greatly improved by resort to cæsarean section in cases where there exist one or more potential hazards to fœtal life There seem to be no disadvantages in such a policy except possibly in relation to future pregnancies

Midwifery Department
University of Aberdeen DUGALD BAIRD

SIR,—Practising obstetricians will agree with Mr Higgins (April 20) that the picture painted in your leading article of April 6 is an unjustifiably bleak one of delivery by caesarean section today, but this state of affairs is inevitable as long as figures of mortality surrounding the operation are taken as a yardstick Thirty years ago the mortality connected with the operation was large enough for the statistics to be helpful, but different types of statistics are required today

Mr Higgins quotes his own excellent figures since 1943 of 1114 sections with 2 maternal deaths, in only 1 of which could the operation be considered a contributing factor The real question is, however, what of the 1112 surviving mothers and their babies? Would they have been better dealt with by other means? But it goes further than that What of the other mothers in Mr Higgins's catchment area during these years? Are there any mothers and babies (still and live born) whose situation would have been better today if cæsarean section had been used as a means of delivery?

These are the real questions at issue, and that they are not answered by the mortality figures is obvious It is for this reason that the obstetric art can never be replaced adequately by obstetric technique

In this supersonic age, I find contemplation of this encouraging

South Shields TERENCE G ROBINSON

THE Rh BLOOD-GROUPS

SIR,—Dr Wiener (April 13) suggests that a gene-dosage effect could "readily explain" our findings,[1] and that our use of the CDE notation has led us to make the "blunder" of describing as "Strong D," bloods which are merely homozygous DD But is this really so, and if so, how does Dr Wiener explain these points?

(1) Only 5 examples of Strong D were found amongst 653 random samples tested 227 homozygous DD samples would be expected in this number

(2) Our paper shows tests on 8 CDe/CDe, 3 CDe/cDE and 1 CDe/CDE samples (probable genotypes) These came from unselected individuals, and none gave the reactions of Strong D Are we to assume that the genotypes of all these were really heterozygous Dd? In the English population, 4 5% of individuals of probable genotype CDe/CDe are actually heterozygous Dd Similarly, 11 0% of those of probable genotype CDe/cDE and 2 3% of those of probable genotype CDe/CDE are heterozygous Dd, so that the probability that all the twelve samples mentioned above were Dd is only about 10^{-15} [2]

(3) There are two sisters in our family Tr who must be of identical Rh genotype, yet the D antigen of one shows twice the reactivity of the other

The Rh genotype does appear to have some influence on the reactivity of the D antigen, as, in fact, we pointed out in our paper, but we fail to see, in view of these considerations, how it can be the only factor involved

Furthermore, it seems to us that our observations remain the same no matter what nomenclature they are expressed in, so we do not think the CDE notation ca be blamed for whatever defects there may be in ou paper Our experiments are equally valid, and could b equally well expressed, in either notation

National Blood Transfusion Service,
Manchester 1
P H RENTON
JEANNE A HANCOCK

CHRONIC BRONCHITIS AND SMOKING

SIR,—I disagree with the view expressed by Dr Harl Williams (April 13) that smoking is "an enjoyab habit" I do not think smoking is a habit It is a dru addiction, a disease There is a habit factor— in opium and hashish smoking—but it is utterl unimportant

Nor do I think smoking is enjoyable The pleasure taking drugs is psychopathic—as are the pleasures of th sadists and masochists After-depression is inevitabl and outweighs the immediate pleasure Like D Anderson (March 30), I think it seriously wrong tha a NAPT leaflet should describe smoking as "a ver pleasant social habit"

Wallasey, Cheshire LENNOX JOHNSTON

INSULIN TREATMENT OF SCHIZOPHRENIA

SIR,—The controlled study of Dr Ackner and hi colleagues (March 23) appears to me to be one of the mos valuable psychiatric researches in recent years If the conclusions are borne out by the further results which the promise, they will have conferred an immense benefi on both patients and psychiatrists

Much has been written about the danger of personality deterioration following prefrontal leucotomy A good deal has been said about the possibility of cerebral damage as a result of electroconvulsion therapy (E C T) As far as I can ascertain, very little has been mentioned about the very real danger of insulin-coma therapy to life itself

During the three years that I was directly responsible for an insulin clinic, I never in fact lost a patient, but on three occasions I came very close indeed to doing so In the first case the patient developed status epilepticus which was controlled only by deep anæsthesia He recovered after about 24 hours, but I was at his bedside for practically all of that time The second case was one of "irreversible" coma which required a similar period of anxious and close attention The third was a healthy young hebephrenic who developed peripheral circulatory collapse while recovering from a normal half hour coma She was saved only by very prompt measures. There were, of course, numerous experiences of a less dramatic type I have personal knowledge of two deaths directly attributable to insulin coma therapy, at a time when I was not responsible for the insulin clinic concerned

I have for years had a very strong impression that equally good results could be obtained by less hazardous and anxiety-provoking procedures (for example, E C T) I am sure that this view is shared by many other psychiatrists

It appears to me that if insulin coma can be proved, by scientifically controlled research, to be no more efficacious than safer methods of treatment, a positive advance in psychiatry will have been made

For this reason the remarkable work of Dr Ackner and his colleagues seems to me to be of the utmost importance

Royal Earlswood Institution
Redhill, Surrey G J F FRYER

SIR,—Without taking sides in this controversy, it may perhaps be worth observing that, as so often occurs in learned scientific discussions, what finally separates the two chief disputants appears to be not so much a scientific as a philosophic difference not so much a collision of facts as a collision of emotional convictions Once this is grasped, the rest of us may safely enjoy these ingenious polemics without falling into the dangerous error of

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1 Renton P H Hancock J A *Brit J Hæmat* 1956, 2, 295
2 Calculated from Race, R R Sanger, R Blood Groups in Man Oxford 1954

mistaking them for unbiased testimonies to scientific truth

We may thus read Dr Ackner's paper with such reservations as may be engendered by an awareness of the kindly vitalistic philosophy which colours his conclusions Similarly, a recognition of the fanatically mechanistic outlook of Dr William Sargant will enable us all to appreciate in his reply (April 13) the curious spectacle of a man becoming emotional about the unimportance of emotional factors—an impassioned robot, as it were, fighting for his dear mechanical life

London W 1 ALAN MCGLASHAN

SIR,—As indicated by Dr Ackner and his colleagues, their finding that insulin treatment as such has no great advantage over other therapies has been reported frequently, sometimes with the imitation regime adopted by them

In 1938 Dr Gillman and I[1] found that during the first year after admission of 151 schizophrenics diagnosed by the same observers in the same hospital, 66 1% of 59 who had had 50 or more insulin comas (unless cure was established with a smaller number) went home in an average of 4 3 months, 58 3% of 12 who had had prolonged sleep went home in 5 8 months, and 65% of 80 went home in 7 2 months after no other treatment than ordinary nursing and the psychotherapy of friendly interest Insulin saved time, to which might be added a better doctor patient relationship and the value of a group setting The superiority of the proportion of cures was negligible, but, in general, the bigger the sample, the more certainly does the slight superiority of insulin treatment become significant, and I agree with Dr Sargant that it still has a special place in treatment

I cannot agree, however, with much of his argument —for instance, the phrase "properly selected patients" Are there any impressive follow-ups which show that an appreciable number of schizophrenics treated in mental hospitals, who form the bulk of those about whom statistics are available, were not suffering from schizophrenia at all? (There are such follow-ups which show that many hysterics, &c, were in fact schizophrenics) If not, then "properly selected" really means "thought to have a better prognosis" Again, the "number of comas" contains a fallacy obvious to those with long experience, whether medical or nursing, often after 20 comas it is clear that 120 comas will not produce improvement so that the "more than 40 comas" group tends to include more hopeful cases

Dr Sargant writes " all we used to have at our disposal were the many and varied types of psychotherapy which all proved so very disappointing, when used alone, both inside and outside mental hospitals" I do not know how many schizophrenics Dr Sargant has treated by consistent and time consuming psychotherapy only, but in my experience this is easily the best form of treatment yet available provided that an "acute" episode does not make its continuation temporarily impossible When the early symptoms (difficulty in thinking reduction in the ability to plan, difficulty in separating past thoughts from past events, reduced ability to recognise absurdity and failing insight,[2] to which I would now add mental slowness[3]) develop insidiously, a psychotherapist is at present the most appropriate physician and this despite the fact that such early schizophrenics are usually thought to be psychoneurotic only—a tribute at least to the personal approach of the psychotherapist It is a great pity that more psychiatric time is not available then and for supportive psychotherapy for chronic cases (I think it possible that many of the best results of psychotherapists are achieved with mild undiagnosed schizophrenics)

Further, I agree with Dr Sargant that highly trained near-permanent nursing staff are essential for adequate insulin therapy and that the physician should be able to give E C T. as indicated, and I also agree about the extra value of very deep comas which, I think, should aim at a reversible "irreversible" state, for it is the brain-damaged schizophrenics who do best, as if, at any rate, they now had less but only healthy brain tissue available[4] It is these who provide "the little extra" of insulin treatment I cannot say whether they bear any relation to the group indicated by Dr Batt and his colleagues (April 13)

St Ann s Hospital
Canford Cliffs Dorset D N PARFITT

SIR,—Dr Sargant, after casting doubt on the experience of our medical and nursing staff, says that our " excellent results reported despite these drawbacks suggest what can be achieved with insulin-coma . . by highly trained and experienced therapists in properly selected patients " The fact is that no better validated results have been reported, even though criteria far less strict than ours have been used He asks whether many experienced therapists really believe that insulin is the specific agent of recovery in insulin coma treatment If this has not been their belief we wonder why so much research has been undertaken into the physiological effects of insulin coma, usually with inconclusive results He suggests that we were attempting to demonstrate the psychotherapeutic aspects of the insulin regime and asks why sterile water was not used Our project was designed as a scientific inquiry into the value of insulin-coma treatment and for this purpose we attempted to control as far as possible one variable—namely, insulin It was thus necessary for the patients to go into coma We pointed out that the value of the coma treatment could not be ignored and indicated its possible effect on building up new relationships But we did not conclude that schizophrenia should be treated by psychotherapy alone or that physical treatments should be abandoned We do not deny that coma by itself may have some beneficial physiological effects, though this remains to be demonstrated But if Dr Sargant believes this to be true he must take note of the fact that barbiturate coma is a far less dangerous and expensive treatment than insulin coma and that our results show the outcome to be equally good

Dr Batt and his colleagues in fact assume that insulin coma has a specific physiological effect on properly selected cases They question our method of selecting cases on the basis of clinical criteria, but we can only answer that this is the method which has been used, for over twenty years, by those who have made claims for the value of insulin therapy If selection for treatment could be based on properly validated endocrinological criteria, this would be an advance welcomed by all But in the published work quoted by Dr Batt and his colleagues no figures are given to support their claims and many different patterns of 17 ketosteroid excretion rates appeared compatible with improvement occurring both spontaneously and concomitantly with treatment

Dr Edwards (April 6) has fallen into the old error of assessing the value of a treatment by means of discharge rates Our figures showed similar results for the insulin and control groups when those who were "recovered" or "independent" were considered Social factors and discharge policy may often determine whether a patient who is still unrecovered and "dependent" can return home or must remain in hospital Discharged and not discharged cannot, therefore, be regarded as equivalent to success or failure respectively His statistical criticisms are unacceptable for they fail to take into account previous claims for insulin treatment If the control treatment can produce results as good as those previously achieved with insulin, then naturally spectacular results for insulin would be required for it to be claimed as a significantly better treatment Dr Edwards claims that "it seems very questionable whether such a trial can reveal therapeutic advantages with the precision of the casually acquired beliefs of experienced observers" Casually acquired beliefs are never precise and there is at the moment a marked divergence of opinion amongst experienced observers as to the value of insulin treatment

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[1] Gillman S W Parfitt D N *Brit med J* 1938 ii 16
[2] Parfitt D N *J ment Sci* 1956 102 671
[3] Harris A Metcalfe M *J Neurol Psychiat* 1956 19 308

[4] Parfitt, D N *J ment Sci* 1955, 101 673

BRIAN ACKNER
ARTHUR HARRIS
A J OLDHAM

London, S E 5, and
Coulsdon, Surrey

DAY HOSPITALS

SIR,—Dr Arthur Harris's article of April 6, on Day Hospitals and Night Hospitals in Psychiatry, contains one or two inaccuracies

First, although my first paper on the Day Hospital appeared in 1951, the unit was planned and organised in 1944–45 and was put into operation in 1945–46 It is true that Cameron started his day hospital in Montreal at the same time, but these two independent experiments were conducted simultaneously and without knowledge of each other's existence for two or three years

Secondly, it is misleading to speak of day hospitals when we mean day units There are three distinct forms of day unit which have so far emerged (1) the day ward, which is a ward attached to, and part of, a mental hospital, (2) the day department, which is attached to and part of a teaching or general hospital, and (3) the day hospital, which is an independent unit comprising all the facilities for treatment available in modern psychiatry and is therefore replacing the modern mental hospital

Thirdly, apart from other differences, the cost per head in these various day units also differs The full cost for the treatment of 914 patients last year in the Marlborough Day Hospital, which comes into the third category of day unit, was less than £25,000

Marlborough Day Hospital,
38, Marlborough Place,
London, N W 8

JOSHUA BIERER
Medical Director

HIATUS HERNIA

SIR,—I agree with much of what was said in Dr Phear's article of April 6 I would like, however, to take issue with him over several points

Any surgeon who is working in œsophageal disorders realises that there is a great place for medical treatment For example, in this unit in the past two years, while 70 sliding hiatus hernias have been operated on, 32 have been treated medically with success, and while 16 paraœsophageal and rolling hiatus hernias have been operated on, 5 have been treated medically As regards those cases with an incompetent cardia, 6 have been operated on and 7 treated medically

I could not disagree more with his remark that there is a high recurrence rate after surgery If an Allison repair is carried out, which after all is a physiological and anatomical operation, then the recurrence rate is extremely low—i e, 2% There is no doubt that those cases presenting with gastro-œsophageal reflux which is persistent, and who have to earn their living in occupations which demand bending and stooping, should surely have the cardia rendered competent It is almost fatuous to tell them to follow a medical régime, particularly if their life expectation is another 30 to 40 years

I am sure that Dr Phear did not really mean it when he said that surgery should be considered when the hernia undergoes strangulation or torsion Gastric strangulation is a lethal condition and demands urgent treatment, and certainly if a patient with a paraœsophageal pouch has any symptoms of obstruction, surgery should be undertaken forthwith There is a mortality rate for medical treatment of a paraœsophageal hernia

Thoracic Surgical Unit,
Southampton General Hospital

E F CHIN

INFUSION NEEDLES

SIR,—I was interested to read of Dr Furniss's difficulties with the needle provided with giving sets (April 6, p 739)

Some years ago when I was a resident I obtained an intravenous trocar and cannula, of which I believe there are several types on the market, and found this not only more satisfactory for getting into veins, but less likely to result in thrombosis when in situ The cannula was fitted with a 'Record' mount so that the rubber tubing of the standard giving set could be easily attached to it If the cannula should become blocked it was possible to free the block by inserting the trocar

With this instrument I rarely found it necessary to cut down, even on the patient with the most difficult veins

London, W 1

N A THORNE

MOSQUITOES AND MYXOMATOSIS

SIR,—In your annotation of Feb 2 you mention that the aedes mosquito is not attracted by healthy domestic rabbits, which remain uninfected though exposed to the bites of mosquitoes carrying the virus of myxomatosis

It is interesting to note that Hagedoorn[1] argues that the domestic rabbit is possibly a leporoid, a hybrid of the wild rabbit and the hare, and though this is not universally accepted it may offer an explanation for the difficulty in passing on the infection One would like to know whether the experiment has been tried with caged wild rabbits

Brightwater,
Nelson, N Z

R L HAVILAND MINCHIN

SUBUNGUAL HÆMATOMA

SIR,—The methods outlined in your annotation of April 13 for treatment of this common injury suggest the use of bayonet or red hot poker to burst a balloon I have abandoned their use, over the past year or two in favour of a technique which is quick, safe, and usually painless, and I have so dealt with several dozen lesions

The subungual hæmatoma almost always has a margin which approaches the surface very nearly, usually at the distal edge of the nail, the tip of the finger is swabbed with antiseptic and any type of sterile sharp point is then introduced under the nail, penetrating only a hair's breadth of epidermis to provide immediate decompression and free drainage

This method needs no anæsthetic and has not produced a single case of sepsis, whereas infection is not uncommon after the drilling procedure owing to the smallness of the drainage hole and subsequent intermittent reflux of serum through it and its not infrequent blockage

Southport General Infirmary,
Southport

P J W ROWELL

SIR,—May I point out that the method you attribute to Ashford (using a red-hot needle or wire to penetrate the nail) is also quite painless and that no local anæsthetic is necessary ? I do not have access to Ashford's paper but I saw the method described elsewhere over eight years ago and have used it repeatedly ever since, a medium-size safety pin is about right, and I sometimes make two holes without any protest

Amble by Morpeth
Northumberland

R P ROBERTSON

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[1] Hagedoorn A J Animal Breeding London 1954

GOVERNMENT AND PROFESSION

SIR,—I wish to comment on your two editorials (March 30 and April 13) It is obvious that somewhere we have parted company, in my opinion quite unnecessarily, and somehow the gap has to be bridged. It is enlarged by the action of the Royal College of Physicians in offering to cooperate with the Government by giving evidence to the Royal Commission—an action which recalls to the majority of the profession the 1948 betrayal

Firstly, let me restate the very basis on which our action rests and which you deny

1 The power of the Executive to do what it likes, for reasons of expediency, in dealing with what Lord Home describes as one of the "great skilled professions," must be broken

2 The policy of appealing to "the sense of fairness of British Governments" in "the knowledge that they were dealing with a profession which in no circumstances would use its political weapons" is completely barren because no such "fairness" exists

3 We are therefore left with two courses Either we take the Government to court, as they suggest, to get a "declaratory judgment" on the validity of the contract implied by Government promises on the Spens reports and the consequent Danckwerts judgment or we withdraw and negotiate a new basis for return (This time taking care that we get a written contract)

Secondly my criticism of your editorials is based on the fact that you accept with very mild criticism the autocratic arbitrary methods the Government as new employers "with no inherent virtues" (to quote Lord Home again) have used to date and expect us as a profession to sit down and do nothing about them Surely, Sir, this is destitute leadership? This is complete resignation without argument Do you really imagine that in spite of all the legal arguments (which you dismiss as being far too many) the profession can put any trust in your advice to be good little boys and accept what the Government (which is embarrassed) is doing? Do you think that assurances can get over two separate statements, only two weeks apart, made by the Government in Parliament

(*a*) That an increase for junior hospital staff will be negotiated through Whitley machinery

(*b*) That a flat 10% will be paid to junior hospital staff from a date to be fixed by the Government

Where in this is the sweet "prestige of a profession, whose strength lies in the merits of its case"? I suggest it is in your statement that you expect Sir Harry Pilkington will come to feel the need of one or two colleagues with a good background knowledge of the N H S or the profession (guaranteed non-medical, of course) This is the most monstrous statement ever made by the editor of a medical journal in any country At its very best it amounts to rank betrayal of the profession it purports to advise On what conceivable grounds could the medical profession submit to having its future determined by people "guaranteed non-medical of course"!

Thirdly, having expressed my fundamental objections to your approach and detailed the basic differences with the Government (which are not—in my opinion—anything to do with pay), let me suggest a workable agreement By the time this letter is published we may be faced with an interim award, made without consultation Let us together say that we do not want the award—we want a proper negotiated agreement (not a Royal Commission)—with an agreed basis for future negotiation and the setting up of agreed arbitration machinery for future problems In this way we may save the Government money (temporarily) and we may achieve—what is far more important than any pay claim—a proper mechanism for settling our differences if any, in the future

To enlarge on the results of what this might achieve A new conception of a National Health Service with the *medical* people who are working in it satisfied—the patients therefore better served and the auxiliaries not at loggerheads with the profession It would certainly allow the profession scope for presenting ideas for the better running of the service which might save the country vast sums, and which are at present hamstrung by the very *non medical* persons you admire so much

London, W C 1   J L McCALLUM

⁂ We should not expect much good to come of direct negotiations with the Government in which the profession's avowed object was to limit the power of the Executive At present the best hope of obtaining useful changes in the arrangements for remuneration is to persuade the neutral Royal Commission that they are necessary As for the non-medical membership of the commission, we should perhaps have made it clearer that the reaction of our remarks was slightly acid —ED L

SIR,—It is most disturbing that the British Medical Association, which professes to respect the consciences of its members, should be adopting the tactics of the big unions, where the headquarters policy must be pushed through regardless of the feelings of the minority.

The policies of phased withdrawal and of boycott of the Royal Commission, which seem to many unethical, were decided on by central committees of the B M A without knowledge of the views of the rank and file which could readily have been ascertained by a postal ballot Having failed to do this, it seems quite incredible that a professional organisation should then endeavour to get a mandate for the policy which they had already publicised in the manner I am about to describe

Last week at a meeting of my own division of the B M A I proposed that our local members should decline to support the G M S Committee's proposals I knew, of course, that it would be a difficult path to follow, as it always is when one is not blindly following the majority, but I did not anticipate that there would be present members of the B M A council and of the G M S Committee (neither of them members of our division) ready to spring to their feet every time a point was made against the party line In addition there was a member of the headquarters medical secretariat on hand to chide backsliders with gentle irony and even to question the sincerity of their views by scoring debating points like any other professional politician

All this, I may say, from an association which claims to spurn trade-union methods and at the same time complains that the Government has behaved like dictators!

If the original Negotiating Committee had negotiated terms of service in the years before 1948 instead of talking about principles until the eleventh hour, when they suddenly panicked, the Spens reports *could* have formed the basis of an agreement duly signed and sealed

BLACKLEG

SIR,—The time is obviously coming for a revision of the system of payment for general practitioners Those aspects of general practice which give personal satisfaction and which may involve philosophy and the "art" may be difficult to assess financially, but one might reasonably expect payment to be on the basis of efficiency

The most obvious injustice at present seems to be that efficiency in running a practice is usually associated with financial disadvantage

For example, a practitioner, who successfully runs a practice with one patient less in an acute hospital throughout the year than another practitioner with a similar list, is costing the National Health Service about a thousand pounds less

Some measure of practice efficiency from a business point of view could be obtained by considering in relation to the total numbers on the list

(1) The total certified days off work (obtained from the Ministry of National Insurance)

(2) The total prescribing costs (obtained from the Pricing Bureau)

(3) The number of inpatient days and outpatient appointments (obtained from the hospital)

By some sort of a points system in each of the above items taken respectively over a year, I feel sure that a payment in addition to ordinary capitation fees could be made, which would provide incentive to good practice and would in effect be a merit award to the good general practitioner

Workington R N R GRANT

SIR,—I am disturbed more than I care to admit by the current wrangle with the Government caused by the profession's 24% salary claim, though there are doubtless many worthy reasons why some feel justified in this claim

There is an atmosphere of wronged virtue in the profession's publications, which assumes that we have not broken *our* obligations to *the* Government, can we honestly say all doctors have done their work as they should in the National Health Service? In my opinion the answer is No I am not surprised the Government's attitude is unhelpful when so many doctors have abused the N H S

Before we press our claim further I believe doctors should come forward with a scheme embodying the much-needed reforms in the N H S I cannot agree that this is primarily the Government's obligation to us I would like to see the following incorporated

(1) General practitioners should be paid according to work done, not for the number of patients on their lists

(2) Patients should pay for treatment and advice up to a certain fixed annual amount according to a means test

(3) Diagnostic facilities should be made available to general practitioners

(4) Casualty departments should receive part time staffing at consultant level

Doctors' position of esteem has been won by service to the public without counting the remuneration If we take arbitrary action, as is at present recommended, we shall do ourselves a great disservice

Kettering EDWIN J WRIGLEY

ASEPTIC MENINGITIS

SIR,—I have seen several cases in Marche, in Central Italy, in 1955, with clinical features partly resembling those described by Dr Garnett and his colleagues and by Dr Rotem (March 9)

Between June and November, 1955, 38 patients with this illness were admitted to hospital in Urbino [1] [2] Many patients were from mountainous places (the Urbino area is mainly mountainous) and most of them were children and young adults There was no difference in sex prevalence The predominant signs and symptoms were fever, frontal headache, vomiting, photophobia, and neck rigidity

The cerebrospinal fluid (C S F) was under increased pressure There was a positive reaction for globulin and moderate increase in albumin, the number of cells was raised (20–1500 per c mm), with lymphocytes *predominant*

30% of our patients had rather different signs and symptoms In many cases the liver was involved, with abnormal function tests, 3 patients had nephritis and 1 herpangina 10 had signs of myelo encephalitic disorders (ataxia paresis of the limbs, lethargy, mental changes) Electrocardiographic examination often indicated myocardial damage of diffuse type, of which there was no clinical indication Wassermann and Paul Bunnell tests were constantly negative At the virus laboratory of the University of Siena, Coxsackie virus was isolated from fæces and C S F in about half the cases

Recovery was quick and complete in all except 1 patient who had severe *encephalitic manifestations* and died The virus was not isolated from this patient, but we presume, on epidemiological grounds, that *it* was present

Owing to the presence in our cases of disturbance related to different parts of the neuraxis (central nervous system), we have called this illness acute epidemic neuraxitis due to Coxsackie virus

Urbino, Italy G CARNEVALI

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[1] Cuppini, R , Carnevali, G Carotti, A *Aggiorn Mal Infez* 1956, 2 21

[2] Cuppini R. Carotti A , Carnevali, G *Acta cardiol* , *Brux* (in the press)

UTERINE ELECTROLYTES IN PREGNANCY AND LABOUR

SIR,—In their article of April 6 Dr R L and Dr J H Cort drew attention to the possible occurrence of potassium depletion in pregnancy and suggested that an inadequate intake of potassium may have contributed to such a loss in their patients

It is likely that if potassium salts were given by mouth there would be a high proportion of digestive disturbance The concentrated orange juice provided by the Welfare Food Service for pregnant women in this country contains a considerable quantity of potassium Analyses of samples from several batches show that the concentration is of the order of 250 m eq per litre At present it is possible to obtain 1 bottle (171 ml) each week, containing about 43 m eq of potassium This is not a significant addition to dietary potassium, but it would be possible to achieve this if the dose were increased and with little likelihood of patient resistance

The Queen Elizabeth Hospital
Birmingham 15
C T G FLEAR

Obituary

THORVALD JOHANNES MARIUS MADSEN

Hon C B E , M D Copenhagen

DR Thorvald Madsen, who died on April 15 in Denmark, was long known in his own country as the head of the State Serum Institute In the rest of the world he will also be long remembered for his work with the League of Nations and later with UNICEF

He was born in Copenhagen in 1870 and he took his medical degree at the university there in 1893 A year later he became an assistant in the university laboratory for medical bacteriology In 1902 he was appointed head of the State Serum Institute Many scientists from all over the world were drawn to the Institute by his work on diphtheria toxin and antitoxin, and this was one of the subjects which he discussed in the lectures which he gave, in faultless English, to the University of London in 1929

His work for the League of Nations began after the 1914–18 war, when as chairman of the League's Health Committee he was faced with the task of containing the epidemics raging in Eastern Europe Cholera, typhus, and smallpox were being brought by refugees returning from Russia and Turkestan to the newly formed Eastern European States whose health services were still incomplete Through Madsen's administration the League was able to give timely and practical help to these governments and also to Greece, where severe epidemics had broken out after the return of refugees from Asia Minor In 1928 when dengue fever became rife in Athens the Greek government again turned to Madsen for advice, and with his help the health services of the country were reorganised

Dr Madsen had served so many countries so well that his record of international honours was as impressive as it was deserved In this country he was a member of the Society of Medical Officers of Health and the Pathological Society He was also an honorary graduate

Glasgow University, and a holder of the Buchanan edal of the Royal Society In 1921 he was appointed n honorary C B.E

N M G writes

Madsen was a great doctor for a much longer span of me than is usually given to men to be ' great " He won a ational reputation long before the first world war as head f the Danish State Serum Institute and an international ne between the wars as chairman of the Health Committee f the League of Nations Yet for some years after the second orld war he worked actively in the international field with NICEF, and even after he returned to Denmark his inquiring ind was constantly at work on the problems of his first love, pidemiology Only a few months ago I had a letter from im making some inquiries on the incidence of infectious isease in this country

Spare and very upright with bright blue Danish eyes and soft voice, he would when over eighty, run up the stairs o his office in Rome and arrive on the fourth floor in better ondition than the relatively young men with him In the vening you might find him dining and dancing at the Bibliotheke " and when we left him still dancing, at midight, he would cheerfully remark " See you in the office at 30 "

As chairman he was always courteous and unruffled and ad a special kindness for the younger members of the Health ommittee With the director, Dr Rajchman, at his elbow, e and his committee, which included men such as Buchanan, arisot, Cumming, Stampar, Lutrario, Jitta, and Velghe, laid he foundations of the work which W.H O continues today

STANLEY GEORGE JAMES

M.D Sydney, M R C.P , D.P M

Dr S G James, medical superintendent of Broadmoor Institution, died on April 11 at the age of 56

Dr James was born in Sydney and graduated M B from the university there in 1926 After holding resident appointments at Sydney Hospital he came to this country and became senior house-physician at the West End Hospital for Nervous Diseases, London. In 1931 he took the M R C.P and in 1936 the D P.M. He held appointments as assistant medical officer at Friern Hospital under the London County Council and as deputy superintendent to the Rampton State Institution, Retford, before he was appointed, in 1949, superintendent of Moss Side Hospital, Maghull

During the three years he held this post he established many contacts with his medical and psychiatric colleagues throughout the Liverpool region, and the value of his counsel and work to the region as a whole was recognised by his appointment as physician to the Liverpool psychiatric clinic

In 1952 he took up his post at Broadmoor where he quickly became popular with his staff and patients, and a colleague describes him as ' a strong advocate of modern forms of treatment and a delightful companion "

J E H, who knew him during his Liverpool years, writes

Quiet and unassuming and of great personal charm, Dr James possessed a profound knowledge of psychopathic states and the large psychiatric no-man's land between mental deficiency and psychosis His capacity for calm cool judgment combined with an equable temperament were qualities that ensured his outstanding success in his own chosen sphere His hobbies were cars, electronics, and work He will be greatly missed by his many colleagues and associates, not only in the Liverpool district but throughout the psychiatric world

In 1954 Dr James married Miss Winifred Boshier, at that time matron of Broadmoor

Births, Marriages, and Deaths

BIRTHS

BLACKSTOCK.—On April 20 at 1264 Coventry Road Birmingham, to Pamela wife of Dr A M Blackstock—a son Charles.

DORMANDY —On April 13 to Dr Katharine Dormandy (née Baker) wife of Captain T L Dormandy F.R.C.S E., R.A.M.C—a daughter

Notes and News

UNIVERSITY APARTHEID

NINETEEN vice chancellors and presidents of British universities and university colleges have joined in making a statement[1] of the policy of the government of South Africa towards the universities there[2] Having set out the main provisions of a Bill which was lately introduced into the parliament of the Union, they point out that, if such a Bill becomes law, the universities in South Africa will comprise the four Afrikaans medium universities (which admit only white students), the Universities of Cape Town and Witwatersrand (which will then be allowed to admit only white students) and the University College at Fort Hare and the Medical School for non Europeans in Durban, which will then be organised as part of the University of South Africa and controlled by the government

Such proposals, they say, are open to the gravest objections Firstly, it is contrary to the interests of university education that students should be completely segregated on grounds of race and colour Secondly, the proposed action is contrary to the expressed wishes of the Universities of Cape Town and Witwatersrand, where it is thought that both white and non white students will suffer Thirdly, " it is a very serious matter that university institutions should be arbitrarily dealt with by the Government of the day through legislative processes " Fourthly, substantial powers of control of the non-white colleges will be vested in ministers, the development of academic self-government will be prevented. Furthermore, it is provided that a member of the staff who publicly criticises any department of the government will be liable to discharge, this is described as " intolerable "

The statement notes that the Bill described has been withdrawn for technical reasons,[3] but says that the government has not changed its policy Apparently the provisions of the Bill are to be achieved piecemeal thus a Bill establishing segregation has been introduced in the present session, and legislation concerning Fort Hare and the medical school in Durban will be introduced later The signatories conclude -

" we would express the hope that this opportunity might be taken for further consideration of the academic implications of the policy which the Government is pursuing and of the manner in which it proposes to give effect to it "

MEDICINE AND THE MINES

TEN years ago the National Coal Board, which had been charged by statute with the duty of securing the health of its employees appointed a chief medical officer Since then the medical service has expanded till there is now a doctor (some times two) for each area, and the board employs 300 State-registered nurses and 2000 medical room attendants. An account of the service and its functions is given by Dr J M Rogan, the chief medical officer, in a new book[4]

Since 1952 all new entrants to the mines under the age of 21, and most of the older men, have been medically examined by the board's doctors This examination includes chest radiography Rescue workers, and those liable to skin cancer, are examined yearly Periodic radiography of miners is planned. The medical service also advises on hygiene (e g on dust suppression, ventilation, lighting, and underground sanitation) as well as on the medical aspects of safety and the resettlement of disabled men The doctors, nurses, and attendants help to train the 20,000 first-aid men.

The number of medical centres has risen from 8 in 1946 to 346 in 1956, allowing more efficient treatment of accidents and illnesses at work. Further treatment is normally provided by the National Health Service, except where there would be clear saving in time and convenience in treatment at the medical centre, and the family doctor has agreed to this.

Dr Rogan surveys medical topics which have specia relevance to the mining industry The occupational mortality of miners has steadily fallen since 1911, though it is still above the national average Research on pneumoconiosis is in progress, including a survey of its prevalence The incidence of beat disease (an inflammation of tissues near joints devital ised by repeated blows) does not diminish, but antibiotic treatment shortens the period of disability The incidence of nystagmus is falling as lighting is improved Fungus infection of the feet affects a third of the miners who use pit-head baths and a twentieth of those who do not, experiments are in progress with fungicidal foot sprays and fungistatic material incorporated in the floors of these baths Weil's disease is combated by unremitting destruction of rats, in the past ten years there has been one serious outbreak with 23 cases and 9 deaths

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[1] *Manchester Guardian* April 15 1957

[2] See *Lancet* March 30, 1957, p 675

[3] *Ibid* April 6 1957 p 746

[4] National Coal Board—The First Ten Years London, 1957, p 35

Research is carried out by the board's medical service itself, by the Medical Research Council (which has set up several units including the pneumoconiosis research unit at Cardiff), and by universities The board gives grants towards the cost of research

GENERAL MEDICAL SERVICES COMMITTEE

Dr Talbot Rogers has resigned from the chairmanship of this committee and Dr A B Davies has been elected in his place In a statement to the press on his resignation Dr Rogers said that in his view the doctors had now received from the Royal Commission sufficient assurance to make it possible "for us to deploy our arguments and put our whole case before them" His colleagues felt that, despite the exchange of letters with the Prime Minister and the Commission's statement on how it had decided to proceed, they still had not any real assurance that their views would be fully heard and cognisance taken of them

NUCLEAR-WEAPON TESTS

THE National Council for the Abolition of Nuclear Weapon Tests was formed to give expression to public concern about the continuation of nuclear weapon tests A leaflet has been prepared setting out some of the hazards of nuclear explosions and suggesting ways in which public opinion can express itself Copies of this leaflet (*2d* each, *8s 6d* per 100) and other information can be obtained from the secretary of the Council, c/o 29, Great James Street, London, W C 1

The Council has organised a meeting on Tuesday next, April 30, at 7 30 P M at Friends House, Euston Road, N W 1 The speakers will include Prof Joseph Rotblat, professor of physics at St Bartholomew's Medical College, and chairman of the committee of the Atomic Scientists' Association, whose statement appears on p 878

STRANRAER HEALTH CENTRE

THE first annual report of this centre, which was opened in May, 1955,[1] is the record of a successful beginning The second health centre in Scotland, it serves a small Lowland town and is an interesting and modest contrast to its elder sib at Sighthill

The Stranraer centre has five consulting suites for general practitioners The rent of each, fully furnished and equipped and including heating, lighting, cleaning, and nursing and clinical assistance, is £200 per annum It also accommodates the local authority clinics and has a room for minor surgery and a small laboratory As it is beside the local hospital, X ray and other services are available at all times and this has proved a convenient arrangement Nine doctors, in five firms, provide family doctor services and now have 13,551 patients on their lists The record service of the centre only got under way in September, 1955, but for the last eight months of 1955–56 the number of attendances at surgeries was 19,353 7437 patients attended clinics held by visiting consultants The local health authority holds a weekly child-welfare clinic, mothercraft classes, and an ophthalmic clinic The school medical service has a weekly minor ailments clinic Dental clinics for school children and the priority classes are held three times a week

In the first year, the reports says, all the doctors have become enthusiastic and none of them would now like to go back to the old system of practice The convenience of having X ray investigations and opinions, surgical opinions, and anæsthetists at hand has proved a boon both to doctors and patients The time saved by having a dressings room with a nurse in attendance has also been appreciated and the clerical and telephone help has been valuable The main deficiencies have proved to be the inadequacy of the office accommodation and the waiting space for patients requiring dressings After an initial suspicion lest they might be divorced from the doctor of their own choice, the patients are now strongly in favour of the centre, and a feeling of local pride in it is becoming manifest The report ends "It is thought that the advantages of modern equipment and personnel have been successfully grafted on to the old family tradition and that the intimate personal relationship which has always existed between doctor and patient in this area has not been disturbed"

CONTROL OF THERAPEUTIC SUBSTANCES

UNDER the Therapeutic Substances Amendment Regulations 1957, which come into force on May 1, the following substances are added to the first schedule of the Therapeutic Substances Act, 1956

(*a*) Any absorbent or protective material capable of being absorbed by the body tissues which is offered for sale for use in surgical operations

(*b*) Tetracycline, polymyxin B, and viomycin (or preparations containing them) which are intended for parenteral injection

(*c*) Hyaluronidase, streptokinase, streptodornase, and streptokinase streptodornase (or preparations containing them) which are intended for parenteral injection

(*d*) Heparin and preparations thereof

(*e*) Corticotrophin and preparations thereof

The regulations (S I 1957, no 550) also modify and amend the requirements for preparation and testing of various substances including B C G vaccine, smallpox vaccine, poliomyelitis vaccine, antibiotics, serum albumin, and surgical materials

CARCINOGENS IN TOBACCO

AT a recent meeting of the American Institute for Cancer Research, Dr E L Wynder, of the Sloan Kettering Institute New York, reported experiments on the carcinogenic effects of tobacco tar on the skins of mice[1] He had removed the waxy coating of the leaves and stems, using hexane as a solvent A solution of the tar obtained by combustion at 880°C was painted on the skins of mice A 5% solution of the tar derived from the waxy coat produced carcinoma in 23% of the mice in five months, but a 50% solution of the tar derived from the dewaxed leaves produced only one carcinoma (the report does not specify the number of mice used) after a year Dr Wynder also said that tar obtained by burning at 720°C (which he gave as the temperature of tobacco burning in a pipe) had much less carcinogenic action than tar obtained by burning at 880°C (the temperature of a lighted cigarette) He had found that filter tips did not selectively remove carcinogens,[2] though the report of his remarks implies that an efficient filter may possibly reduce the total amount of tar inhaled

OUR FELLOW CREATURES

THE ascetics of the Jains, an Indian sect, sweep the ground before them as they walk, lest they crush any living creature The Christian religion has seldom been interpreted as requiring such action, but Major C W Hume, director of the Universities Federation for Animal Welfare, thinks that the Church ought to do more to promote the well being of non human animals The founder of the Royal Society for the Prevention of Cruelty to Animals was an Anglican priest, but even today the Church of England has taken no official cognisance of animals' rights indeed, "during the past thousand years consideration for animals has, on the whole, lain outside the Christian theology"

In his little book, *The Status of Animals in the Christian Religion*,[3] which is illustrated by Fougasse with his wonted charm and wit, Major Hume traces the attitude of Christian Churches from the earliest times He suggests a practical programme for the Church of England, ranging from additions to the liturgy and the hymnals to the laying down of rules of conduct that would condemn, for example, the atrocious cruelty of much trapping (he estimates that a musquash coat costs up to 7 months of extreme suffering directly comparable to that of crucifixion and breaking on the wheel), and inhumane methods of slaughtering animals for food "The major cruelties practised on animals in civilized countries today arise out of commercial exploitation"

Major Hume's book is distinguished by clarity of thought lack of sentimentality, and much scientific and theological learning presented in an engaging fashion He allows that killing may be necessary (e g, of vermin) but points out that this need not involve hatred and should be done as painlessly as possible He makes clear the moral difference between killing and hurting, thus he says that men are more important than animals, and killing a man is therefore more important an killing an animal, but hurting an animal is just as ong as hurting a human He answers Auden's criticism that loving birds is easy but it's hard to love the louse," showing that love must be understood in terms of behaviour ther than feeling His attitude to experiments on animals is oderate and commands respect, medical men will be rticularly interested in what he has to say about scientific ethod

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[1] See *Lancet* 1955, i 1032

[1] *New York Times* April 13, 1957

[2] *Times* April 13, 1957

[3] Published by UFAW 7A Lamb's Conduit Passage London, W C 1 1957 Pp 102 *8s 6d*

PEPTIC ULCER AND INDUSTRY

In 1955, the British Council for Rehabilitation set up special working party, under the chairmanship of Dr Avery Jones, to "consider the problem of the peptic ulcer industry" The working party has now issued its report[1] hich briefly summarises what is known about peptic ulcer is desirable, the report says, for each patient to coöperate ith the doctors, and for each canteen to provide a palatable ght meal as an alternative for those who need it, and ght-shift work may be harmless in individual cases, if there a canteen The report is intended to guide industrial anagement and personnel officers

BEDWETTING

A new addition to the booklets published by the National ssociation for Mental Health in their parent-guidance ries is a straightforward account of enuresis by Dr Portia olman[2] Its opinions are orthodox and judicious What arents of bedwetters seldom understand is that enuresis common, has many causes, and is not a sign of laziness or aughtiness which can be overcome by discipline or will-ower Dr Holman makes it clear that there is no quick and mple remedy and that much patience is needed Her advice ill prove helpful to many, but the dangers in writing for ymen have not been entirely avoided. Having read this ook, parents will expect their own doctor, whom they are roperly advised to consult, to approach the problem on the nes suggested, and the authority of the written word may etract from, rather than reinforce, the doctor's spoken ord The case histories may encourage attempts at differ ntial diagnosis by parents, but they will do much to help in he better understanding of enuresis

OCCUPATIONAL THERAPISTS

To celebrate its 21st birthday the Association of Occupational Therapists held a reception in London on April 12 in the hall of the Goldsmiths' Company, to which it has long been indebted for interest and support With 1774 members, the association awards a diploma to students from the seven recognised training schools in London Oxford, Liverpool, Chertsey, Derby, Exeter, and Northampton, and it works closely with the sister association in Scotland in the Joint Council of Occupational Therapists of Great Britain, through which both countries are represented in the World Federation of Occupational Therapists

The guests were received by Mr L G Allbon and Miss M L G Bunting, chairman and vice chairman of council Lord Amulree, F.R C P, the president pointed out that occupational therapy dates not from 21 years ago but from prehistoric times, and is now seen to be indispensable to medicine Dr Janet Aitken, as a past president, said that though occupational therapists are increasing faster and faster, the increase is not nearly fast enough great needs are still not met notably in mental hospitals Mrs Glyn Owens, principal of the Liverpool School, who (as Miss Constance Tebbit) was first principal of the pioneer school (Dorset House) established by the late Dr Elizabeth Casson at her psychiatric clinic in Bristol, spoke of occupational therapy's debt to Dr Casson and paid tribute to many others who have made the history of the association, including Sir Hubert Bond, its first president The first occupational therapy department to be opened at a London hospital started in 1938 at the Royal Free when Miss Muriel Tarrant, now co principal of the London school, was given charge of it on the understanding that she would also supervise the diet kitchen One of the early students at Bristol was Miss E M Macdonald, the present principal of Dorset House which is now at Oxford

On the following day the association held its annual meeting when Dr J G Sommerville presided at a brains trust on the Piercy report on rehabilitation of the disabled

MALARIA IN THE BALKANS

In March, 1957, the second malaria conference for South-Eastern Europe was held in Belgrade In all countries in this area and in the Soviet Union, malaria is receding rapidly —even in Greece, the only country where mosquitoes resistant to insecticides have appeared All these countries expect to eradicate the disease in 3–5 years It is hoped to achieve this at about the same time in all the countries, to make frontier prophylaxis and quarantine unnecessary

Several reports from individual countries emphasise the economic benefits of malaria control thus in Greece malaria used to cost the country 80 times more than it does now In the Soviet Union and some other countries treatment is compulsory

ANNALS OF PHYSICAL MEDICINE

The journal of the British Association of Physical Medicine, which is edited by Dr A C Boyle, is now published by Messrs Baillière, Tindall, & Cox It has been restyled and the format enlarged The first issue of the new volume contains the first in a new series of revision articles The *Annals of Physical Medicine* is published quarterly Subscriptions (30*s* or $5 50 annually) should be sent to the publishers, 7, Henrietta Street, London, W C 2

University of Oxford

Dr E D Acheson has been elected to a Radcliffe travelling fellowship

University of London

On March 27, the following degrees were conferred

M.D —E A. Boyse, Margaret R Dix, P W G Tasker
M S —W J Atkinson

University of Manchester

On May 15 the honorary degree of LL.D is to be conferred on Sir Geoffrey Jefferson, F.R S

Royal College of Physicians of London

On April 15, Dr Robert Platt, professor of medicine in the University of Manchester, was elected president of the college

Royal College of Surgeons of England

Dr D J Lyle, lecturer in neuro ophthalmology at the medical college of the University of Cincinnati, will deliver the Moynihan lecture on Wednesday, May 8, at 5 P M, at the college, Lincoln's Inn Fields, London, W C 2 He will speak on the causes and treatment of exophthalmos

Royal Australasian College of Surgeons

Alan Newton prize —The subject chosen for the next award of this prize is the surgery of malformations of the heart and great vessels Candidates must hold an Australasian or British fellowship in surgery, and the closing date for entries is Dec 1, 1958 Further particulars may be had from the secretary of the college, Spring Street, Melbourne, C 1

The prize for 1956 has been awarded to Mr L I Parton of Auckland Mr C R Davidson, of Ballarat, *proxime accessit*

University College of the West Indies

Dr Robert Mitchell has been appointed lecturer in anatomy

Sanderson-Wells Lecture

Mr R F Milton, PH D, will give this lecture on Tuesday, May 21, at 4 P M, at the Middlesex Hospital, London, W 1 He is to speak on trace elements in the biological relationship *of soil, plant, and animal*

Faculty of Homœopathy

A meeting of the faculty will be held at the Royal London Homœopathic Hospital, Great Ormond Street, W C 1, on Thursday, May 2, at 8 P M, when Dr James Connor will speak on homœopathy and obstetrics

Biochemical Society

A meeting of this society will be held in the department of biochemistry of the Physiology Institute, Newport Road, Cardiff, on Friday, May 24, at 2 P M

Pharmaceutical Society

Dr William Lane-Petter, director of the Laboratory Animals' Bureau of the Medical Research Council, has been appointed by the Privy Council a member of the council of the society in succession to Dr J A. Giles who has retired

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[1] Gastric and Duodenal Ulcer a Modern Industrial Problem British Council for Rehabilitation Tavistock House South Tavistock Square London W C 1 Pp 6 1*s* 6*d*

[2] Children Who Wet Their Beds By Portia Holman M D M R C P London Family Health Publications Pp 20 1*s* 3*d*

Mental Retardation and Epilepsy

Dr D A Pond and Dr B H Kirman will speak at a meeting on this subject to be held at the Fountain Hospital, Tooting Grove, London, S W 17, on Tuesday, April 30, at 5 30 P M

World Health Organisation

The U S S R has informed the World Health Organisation of its decision to resume active membership as from the current year The U S S R became a member State in March, 1948, but in February, 1949, discontinued active participation

Neurotics Nomine

About a year ago some ex-patients, patients, and other people interested in nervous and mental illnesses formed this group They are holding their first public meeting at Caxton Hall, London, S E 1, on Monday, April 29, at 7 30 P M , when Dr Joshua Bierer will be in the chair

Royal Commission on Doctors' and Dentists' Remuneration

Any person or organisation wishing to submit evidence to the commission is invited to send a written statement as soon as possible to the secretary of the commission, 10, Carlton House Terrace London, S W 1

Royal Society of Health

Nearly 50 foreign and Commonwealth countries will be represented at the annual congress of this society which is to be held at Folkestone from April 30 to May 3 The Soviet Union will be represented by Prof Viktor Zhdanov, a deputy minister of health, and Chile is sending its minister of health and social service The subjects for discussion include smoking and drinking among school-children , shortage of dentists , emigration of doctors , fluoridation of water-supplies , world health , irradiation of food , effect of the hire purchase system on mental stability , marriage hygiene, tall buildings , and the dangers of cracked pottery

Medical Art Society

The annual exhibition of this society will be held at Walker's Galleries, 118, New Bond Street, London, W 1 from Friday, April 26, to Saturday, May 11

London Medical Orchestral Society

This society will give a concert in aid of the Imperial Canc Research Fund on Saturday, May 18, at 8 P M , at the Royal College of Surgeons, Lincoln's Inn Fields, W C 2 The solo will be Miss Liza Fuchsova, and the programme will includ works by *Beethoven, Schubert, and Schumann* Tickets (10*s* , 7*s* 6*d* , 5*s*) may be had from the hon secretary, 6 Oxford Court, Queen's Drive, W 3, or at the door

Prof Robert Kellar is visiting New Zealand and Australia during June, July , and August as the guest lecturer of Auckland University College and the Australian Postgraduate Federation in Medicin

At a meeting of the National Smoke Abatement Society held in London on April 11 it was unanimously agreed that the society should seek incorporation as a company limited by guarantee and without share capital, and with the new name ' National Society for Clean Air '

The meeting of the Dental Implant Society of Great Britain on Wednesday May 15, at 1, Wimpole Street London W 1 will begin at 7 30 P M (not at 7 P M)

Some Medical Problems as they affect Adoption Practice —Copies of this report of the Standing Conference of Societies Registered fo Adoption may be had from the hon secretary Mr A Rampton Gort Lodge, Petersham, Surrey (2*s* 6*d* post free)

CORRIGENDUM *Antigen antibody Responses in Multiple Sclerosis* —*In our annotation of April 13, the second paragraph* should begin .

" Another slant is suggested by a preliminary report from Honor Smith and her colleagues[12] on studies at Oxford which show that on intrathecal injection of tuberculin, sensitised (Mantoux positive) patients with multiple sclerosis react differently from otherwis *normal subjects* [not other patients with the disease] "

Diary of the Week

APRIL 28 TO MAY 4

Monday, 29th

HUNTERIAN SOCIETY
7 P M (Talbot Restaurant, 64 London Wall, E C 2) Mr C R Rudolf Hunteriana Part IV

POSTGRADUATE MEDICAL SCHOOL OF LONDON Ducane Road, W 12
4 P.M Dr Walter Somerville Diagnosis and Treatment of Atrial Septal Defect

MANCHESTER MEDICAL SOCIETY
9 P M (Medical Library, University of Manchester) *General Practice* Dr W E Savage Vitality (Presidential address)

Tuesday, 30th

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, London W C 2
3 45 P M Dr J B Walter Histological Aspects of Early Cancer (Erasmus Wilson demonstration)

ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W 1
8 P M *Medicine* Dr Raymond Daley, Mr Andrew Logan Prof J B Duguid Aortic Stenosis

Wednesday, 1st

UNIVERSITY OF LONDON
5 30 P M (Senate House W C 1) Dr Else Frenkel Brunswik (University of California) Logical Analysis of Psycho analytic Concepts

ROYAL SOCIETY OF MEDICINE
5 15 P M *History of Medicine* Dr Gandevia Pattern of Australian Medical History
8 P M *Surgery* Dr Henry Doubilet, Mr Rodney Smith Dr W I Card Chronic Relapsing Pancreatitis

POSTGRADUATE MEDICAL SCHOOL OF LONDON
2 P M Dr D A Long Influence of Hormones Upon Immune and Allergic Responses to Bacterial Infection

INSTITUTE OF DERMATOLOGY Lisle Street W C 2
5 30 P M Dr R W Riddell Pathogenesis of Ringworm Infections

INSTITUTE OF DISEASES OF THE CHEST Brompton S W 3
5 P M Sir Russell Brock Surgery of Pulmonary Stenosis

MEDICO CHIRURGICAL SOCIETY OF EDINBURGH
8 30 P M (Royal College of Surgeons 18 Nicolson Street, Edinburgh) Dr F S Fiddes Medical Malpraxis

Thursday, 2nd

ROYAL COLLEGE OF SURGEONS OF ENGLAND
3 45 P.M Dr F C Chesterman Transplantation of Human Tumours and Normal Tissues to Laboratory Animals (Erasmus Wilson demonstration)
5 30 P M Prof Gösta Dohlman Physiology of the Cupula of the Ampulla in Relation to Vertigo

ROYAL SOCIETY OF MEDICINE
8 15 P M *Neurology and Psychiatry* Dr Hugh Garland Dr D Stafford Clark, Dr Miles Weatherall Toxic Effects of Drugs Used in Neurological and Psychiatric Practice

ST JOHN'S HOSPITAL DERMATOLOGICAL SOCIETY, Lisle Street W C 2
5 P M Dr Graham Weddell Some Recent Investigation into Leprosy

NUFFIELD ORTHOPÆDIC CENTRE
8 30 P M (Wingfield Morris Orthopædic Hospital Oxford) Prof J Trueta Bone Growth and Enchondral Ossification—an Experimental Study

HONYMAN GILLESPIE LECTURE
5 P.M (University New Buildings, Teviot Place Edinburgh) Dr Wilfred Sircus Recurrent Aphthous Ulceration of the Mouth

UNIVERSITY OF ST ANDREWS, Queen's College, Small's Wynd Dundee
5 P M Dr Sheila Callender Absorption of Vitamin B_{12} in Man

Friday, 3rd

ROYAL SOCIETY OF MEDICINE
10 30 A M *Otology* Dr J D Hood Conduction Audiometry Dr E A Carmichael Miss M R Dix, Mr C S Hallpike Vestibular Manifestations of Vascular Lesions of the Brain Stem Dr J Corvera New Method For The Anatomical Reconstruction of The Human Macular Planes Mr Lewis Citron Mr D Exley Biochemistry of the Labyrinthine Fluids
2 30 P M *Laryngology* Dr T J Wilmot, Mr James J Mason Brown Dr Edwin James Tuberculous Cervical Adenitis
5 30 P M *Anæsthetics* Sir Robert Macintosh Anæsthesia in U S S R and Poland

ST MARY'S HOSPITAL MEDICAL SCHOOL, Paddington, W 2
5 P M Prof W C W Nixon Prolonged Labour

POSTGRADUATE MEDICAL SCHOOL OF LONDON
10 A M Prof W A Mackay Postoperative Complications

Appointments

CONWAY J S F R C S D O M S S H M O , ophthalmic department Westminster Hospital London

HEADLEY, S R T , M B Lond F F A R C S , D A consultant anæsthetist, Royal Masonic Hospital London

JAMIESON, J G O B E , M B Lond , F R C S consultant surgeon West Cumberland group of hospitals

TOYE D K M M B Lond , D M R D consultant radiologist United Birmingham Hospitals

East Anglian Regional Hospital Board

COOK G E M B Witwatersrand registrar in psychiatry, St Andrew's Hospital Norwich

HEALD I N S M B Birm registrar in psychiatry, Hellesdon Hospital, Norwich

JAFFERY S S A M B Osmania anæsthetic registrar West Norfolk and King's Lynn General Hospital

THE NORMALITY OF AGEING

THOMAS RUDD
M D Lond , M R C P
CONSULTANT PHYSICIAN, TIVERTON HOSPITAL, DEVON

THOUGH it is a truism that old age is a natural state, the truth of this evident fact is not always recognised Old age, it is generally agreed, is inevitable, subject to the chances of mortality That it is also natural is less generally accepted If old age is unnatural, then old age is a bad thing, as bad for others as for ourselves, and the origin of resistances and resentments in the human mind The unnaturalness of old age, as generally conceived, places a barrier between the age-groups

In our moments of calm reason we admit that the barrier is imaginary But the important thing, psychologically, is that it is so often imagined And not only do we thus split off old age, as a separate part of life, a kind of postscript or appendix, but we try to do something similar with the other end of life when we split off childhood and adolescence as phases for special treatment, the nature of which is decided by those of us who, in middle life, govern affairs, and call the tune, even if we do not always pay the piper This splitting of life into hard and-fast compartments is at once unhistorical and unpsychological, making no allowance for human individuality Social historians can perhaps trace its origin in the past two hundred years The injustice and tragic consequences of making children and adolescents fully responsible for their actions have made the pendulum swing too far the other way Adults now decide what is fit and proper for people at the two extremes of life It is no wonder that the old sink into apathy while the young express their unfulfilled and frustrated powers in reactions and delinquencies

Psychological development through life is difficult enough at any time, and the modern tendency to split people into children, adolescents, adults, and the elderly places a further obstacle in the way of normal mental progress More unfortunately still, it allows the mature adult, from his point of vantage, to react emotionally to the other groups Children become "kiddies" to be pampered and denied the responsibilities they crave, while the aged become "old folks" to be patronised and amused The result is irritating to young and old alike and arouses much resentment for the adult, the effect may be tragic, because his attitude splits him off from the natural development of man through the stages of life, each one of which is necessary for the complete maturation of the personality

* * *

A safe journey to normal and happy old age is not easy Anyone with experience of children, or having insight into his own mind, recognises the psychological difficulties inherent in growing up, and indeed in passing from any stage of life into the next We cling, not unnaturally, to what we have, to the safety and comfort of the present, and draw back from the unknown tomorrow, with all its possible dangers The child, however much it may long to spread its wings, enjoys the advantages of shelter and may cling to childish attitudes, even when the responsibilities of early maturity are offered The child may well be afraid of life, but many years later when it has accustomed itself to responsibility it may be reluctant to surrender it The fear now is not of living but of renunciation and of dying As Jung says "His neurosis comes mainly from his clinging to a youthful attitude which is now out of season,"[1] and the basic fear derives from the false premise that only the mature state is desirable, and that old age means only decline and waiting for death

This fear colours the approach of many mature people to their future and their attitude to older people Their reaction may be one of pity, expressing itself in patronage, or it may show itself negatively in resentment and the desire to brush the unwanted aside It is important that these false attitudes should be recognised in ourselves and in others, because of their power for harm, not only in the home but in medical and social care, as well as in industry

Psychological development, though often both difficult and painful, is generally achieved to a greater or lesser degree by most young people But the passage to healthy old age is less often satisfactorily made The promises of maturity are glittering enough to the adolescent to make the adventure into manhood or womanhood attractive The promised joys of old age are considerably less inviting to the materialist which is in most of us It is not surprising that many of us "stick," unaware that, by refusing normal development and clinging to outgrown attitudes, we are inviting frustration

This difficulty has been created by man himself When a civilisation places so great an emphasis on material success, puts the zenith of life in the sixth decade, and refuses employment to anyone past the middle 60s, it produces old people who have been split off from the main stream of life, and a mass of neuroses among those who are still active but who dread being relegated to the have beens

* * *

As a result of this approach life has become truncated, as it were, in the 60s, after which useful development is restricted and the value of life denied Such an attitude is contrary to the Christian conception of the wholeness of life every stage of life should be characterised by its own appropriate activity, each has its own lessons to be learnt, its own contribution to make to communal life, as well as its own dangers to be faced The activity of infancy is not that of later childhood, nor is that of adolescence the same as that of maturity Anyone occupied in the activities of age groups other than his own shows up his own abnormality Progress in development is made by surrendering the attitudes and characteristics of the former stage for those of the succeeding one Old age has its own characteristics, and it is the old people who show only characteristics of the earlier age groups that should be regarded as the "abnormals"

The instincts of self-preservation, power, and reproduction properly dominate the middle stages of life when children have to be reared As the child's dependence lessens, the strength of these instincts in the parents should also wane Ambition dwindles, things of the moment seem less vital, and present experiences are viewed in the light of past events Old age thus becomes a period of toleration and tranquillity Opinions are not less strongly held, but they should be held with greater toleration than in maturity It is, however, clear that this mellowing and broadening of understanding does not always come Instead, things are held so lightly that they are despised, nothing is considered good or worth while, and life itself peters out in bitterness and disillusion However common this reaction may be, it is still abnormal, and must not be accepted as a norm for old age

Old age challenges mature man to give up middle aged attitudes in favour of more seasonable ones If the challenge is faced squarely, the attitudes of old age will bring with them a new and different kind of happiness, as the assertions of maturity die down But if the challenge is not accepted, the whole of life becomes blighted Romano Guardini gives a picture of can tankerous old age "Beyond the mere drifting towards the end lies nothingness, dark, empty horror To save himself from it, the old person grasps at the nearest thing, this special food, that particular armchair, his bank account, his having the last word at home"[2] This state, however, is not the result of growing old but of refusing to grow up

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[1] Jung C G Modern Man in Search of a Soul London 1945, p 17

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It is impossible for us to look on old age except in terms of our own ageing, our approach is determined, for good or for ill, by our conception of our own future Man in maturity is inclined to view his future old age, and that of the present older generation, in one way Old age, on the other hand, may view itself differently Successful social work depends largely on bringing together these diverging viewpoints Old age's view of itself may be entirely correct, but the view of the younger generation is none the less important for two reasons In the first place, the kind of old people the young will become will be the direct outcome of their attitude to their own future Secondly, the helplessness of many old people today places them at the mercy of wage earners who may be not only their sole supporters but also their planners, legislators, and administrators

It is therefore doubly unfortunate that middle life so commonly looks on old age not as a challenge but as a threat As has already been said, if the challenge is consciously faced, and its implications worked out and accepted, only good can result But if the issues are evaded and repressed, the potentiality for harm is enormous This explains the undesirable attitudes towards old age often seen today in the individual and the community the antipathy which looks on old age as dirty and repellent, to be avoided at all costs, and the aged themselves as better dead, the self-pity which emotionalises old age, and tends to spoil good works by sentimentality, the patronage, which fundamentally despises old age and which tries to help in only material ways All these approaches fail because they deny identification between young and old, the helper and the helped, and refuse to recognise old age as a normal state Identification between individuals is often harmful, but identification between age groups, such as the mature and the elderly, is essential for successful case work Its absence is responsible for ill attended old people's clubs and and visiting To say "There but for the grace of God, go I" is to utter a characteristic Victorian feeling It goes nearer to the heart of truth to exclaim, with John Donne "Any man's death minishes me, because I am involved in mankind, and therefore never send to know for whom the bell tolls it tolls for thee"

When maturity views old age, then, it often does so with a disfavour which may be so deeply rooted as to persist into the viewer's own old age Healthy normal old people, however, look on themselves in a different way They are often only too aware of the physical limitations which prevent them striding over the moors, and meeting the fierce competition of existence, and which may be great enough to prevent any useful activity The personality can, however, remain surprisingly intact, and be, to the individual, his most cherished possession Miss Margery Fry,[3] gave a wonderful description of the feelings which so many older people share "To the administrator an individual may be just 'that old woman, I think her name is Jones,' but to herself she is the Katie Jones who won a prize for scripture and had the smallest waist in her class—with a thousand other distinctive features—who just happens to be old" Is it any wonder, then, that people who have, throughout their lives, grouped themselves into societies and clubs, according to their interests and achievements, should object to being classified into undifferentiated old people, *on* the sole ground of the disability they share in being old ?

To retain one's personality, and the respect attached *to it, is one of the great desires of old people* It is all the more regrettable that personality should be so commonly disregarded by younger people who have charge of their elders in hospitals and residential homes A man or woman who has borne an honoured name, in however humble a sphere, has surely the right to be called by it, even if his legs are too frail to carry the weight of his body even if breath is short and memory failing, he has surely some right to a say in arrangements made for his care The ability to choose, so important to us throughout life, does not fail as years creep on, and its denial to the old is prejudicial to their happiness and to their mental health So often choice in the greater things of life is impossible, only one place of abode or set of attendants may be possible But minor choices may be offered and provide minor, but worth while, satisfactions All who care for the older generation should ponder on this, and consider whether alternatives between the little things of life, between tobacco and sweets, tea or coffee, this or that chair can be arranged to enliven the monotony of living

Moreover many, indeed most, aged people have their own approach to religion for which they can demand respect, even if it is a matter they will not readily discuss with their somewhat preoccupied juniors False attitudes to religion in old age exist, as they do at other times of life most workers are familiar with the egotism and fears of senile neurosis, with the constant complaints of the grumbler who projects his self dissatisfaction on to his surroundings, and, above all, with the apathy—the Seventh Deadly Sin of Religious Sloth which in the middle ages was called accidie The characteristics of true religion in old age are as clear and definite as its characteristics in childhood and maturity They comprise a sense of true proportion, a valuation of material things at their true worth, and a greater tendency than formerly to view events *sub specie aeternitatis*

* * *

But though old age is a normal stage in life, as necessary as any other to human experience, and having its own problems, challenges, hazards and possibilities, it can be a time of disability and deterioration which frustrates happiness, and indeed any useful purpose—physical, mental, or spiritual All the same, the gross deteriorations of physique and mentality so often seen are the abnormal state and not the normal Only too often, moreover, they are the result of wrong methods of living and of thinking, in earlier life The ill effects of unwise eating and drinking are well known, although it is insufficiently appreciated that excessive intake of starches and sugars is as great a national problem as the overuse of alcohol Obesity, with its sequels of high blood pressure and diabetes, is a killing disease Smoking gives rise to lung ailments, including chronic bronchitis and cancer, and air-pollution in big cities and factories introduces another hazard Perhaps even more important are the neurotic fears to which the present age is a prey They are fundamental in producing, not only the frank anxiety states, but psychosomatic conditions of stress, such as gastric and duodenal ulcer, asthma, and high blood-pressure These groups of disease are responsible for a large proportion of illness in old age Even senile dementia, formerly thought to be caused by hardening of the cerebral arteries, is now held often to have an emotional background Gitelson,[4] summarising original work based on pathological studies, writes "Elderly patients, with more or less balanced personalities, are able to withstand a considerable amount of cerebral damage, while less-balanced personalities may produce a frank psychosis with a minimum of cerebral pathology. It seems to be the case that cerebral organic pathology is only a final precipitating factor in persons already excessively burdened by such emotional problems." It is, moreover, important to realise that just as anxiety and fears may affect physical and mental health, the opposite is equally true. As Paul D. White[5] points out: "We have paid perhaps undue attention to the harmful effects of fear, sorrow and anger. It is quite certain that biologic effects also result from cheerfulness, optimism, courage and joy." Though disability and ill health in old age are not entirely preventable, healthy living in the mature years will help to preserve health later, while a philosophy of life which excludes fears and anxieties and which teaches patience and cheerfulness is likely to prolong useful living.

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[2] Guardini, R The Faith and Modern Man New York, 1952, p 108

[3] Fry, M Old Age Looks at Itself London, 1954, p 4

[4] Gitelson, M *Geriatrics*, 1948, 3, 135

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The problem now arises of how to use the time afforded to us, when the productive years are over, and physical capacity is greatly reduced. If old age is a normal phase, what activity is appropriate to it? There are lessons to be learnt, some special to the time of life and some which should have been learnt earlier.

Willingness to renounce is perhaps the prime (and often the hardest) lesson to learn, including as it does not only the surrender of responsibility and authority, normal to maturity, but also the gradual loss of companionship of one's own age group, the impairment of vision, hearing, and powers of movement and thought. Against this background of renunciation the mind becomes detached from material things and each individual finds a meaning of life valid for his personality. In this mental development, which, for most people at least, cannot take place until old age is reached, lies the value to the community of its older members. The wisdom of simple experience can leaven the whole community, and show that the meaning of life transcends material success and ambition, and that true happiness is independent of both. A community without these values is poor indeed.

To regard old age as the stepping stone to eternity is the last and the great reorientation that we have to make in our approach to life, for as Monsignor Baunard points out: "notre vieillard à nous n'est pas un mortel qui finit, c'est un immortel qui commence,"[6] and this fact revolutionises our view of what we now see, not as a decrescent phase, but as a stage of life of supreme and immortal importance.

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[5] White, P. D. *Ann. intern. Med.* 1951, 35, 1291.

[6] Baunard, M. J. Le vieillard. Paris, 1926; p. 8.

"Though three generations can muster more resources than two, there are still many essential services which no family can possibly provide for itself. Few grandmothers can perform operations or teach algebra. Few grandfathers can, on their own, maintain children stricken by illness or unemployment. Children unaided, cannot support their parents through the years of retirement. The family is not a society on its own, merely part of the wider society, and, if it is to perform its proper function within its own sphere the family needs the support which only the wider society can give. This vital support the social services in some measure already supply. The health services have made a great and obvious difference to the well being of the family, especially to mothers and children. Old age pensions, inadequate though they often are, have enabled children to care for their parents all the more effectively. . . . The social services have in many ways already made the family of three generations or two not less, but more, viable."—MICHAEL YOUNG and PETER WILLMOTT. *Family and Kinship in East London.* London, 1957; p. 160.

A HEPARIN PREPARATION WITH PROLONGED ACTION

ITS CLINICAL APPLICATION

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IN the treatment of thrombo-embolic conditions with anticoagulants, it is important to prolong the clotting-time as soon as possible and to retain this effect for a suitable time.

The coumarin derivatives are valuable because they are effective when administered orally, but at least 24 hours must elapse after the first dose before the clotting-time is increased sufficiently. When dicoumarol—in many respects one of the most convenient of these drugs—is given, the full effect is not reached for 48 hours, and sometimes longer. On the other hand, heparin given intravenously attains the full effect almost immediately, but this effect is rather short lived; usually it lasts 1–4 hours, depending somewhat on the dose. Hence, to maintain a sufficient increase in the clotting time, intravenous injections must be given at intervals of about 4 hours. To cover the time till the effect of a starting dose of dicoumarol has developed, eight to twelve intravenous injections must be administered, which is cumbersome. Intravenous drip infusion necessitates frequent determinations of the clotting-time, and the infusion-rate will have to be varied to obtain a smooth effect. The method demands experience and constant supervision. Using subcutaneous injections of concentrated solutions of heparin, a longer but also comparatively weak and variable effect has been obtained, and hæmatomas may arise on the site of injection (Raaschou et al. 1954). Intramuscular injections of aqueous solutions of heparin may cause large hæmatomas, which may remain unrecognised for some time, even causing anæmia.

Long-acting Heparin Solutions

One method of tackling this difficulty is to prepare a solution with prolonged effect for intramuscular injection, by dissolving the heparin in a 15–30% solution of gelatin (Pitkin's menstruum). But the viscosity of this solution is so high that it has to be warmed immediately before the injection and wide bore needles must be used. Moreover, the sterilisation of gelatin solutions is so difficult that it is better to avoid the use of this substance. But it would be rational to use other hydrophilic colloids which can safely be sterilised without being denatured.

Tonnesen and Pedersen Bjergaard (1950) have shown that the absorption of chorionic gonadotrophin is delayed when carboxymethyl cellulose has been added to the injection. In accordance with these observations, we tried to prepare a heparin preparation for intramuscular injection, and found that an aqueous solution of 1.25% carboxymethyl cellulose, after autoclaving, has a suitable viscosity. The pH of the autoclaved mucilage is regulated to 7.2 by means of a normal sodium hydroxide solution. Heparin is then added to the solution to give a concentration of 100 mg. (10,000 international units) per ml. The solution is heated for 15 minutes at 100°C. It is perfectly easy to inject intramuscularly through a long needle of narrow gauge.

Experimental Results

Before using the preparation for treatment we tested it in six healthy volunteers—four medical students and two young men who had recovered from slight acute diseases not known to influence blood coagulation Each was given 2 ml of the preparation once (equal to 200 mg heparin, or 20,000 international units) The injection was given intramuscularly in the gluteal region Blood samples were drawn just before and 2, 4, 8, and 24 hours after the injection The clotting-time was determined by the Lee-White test (fig 1)

The clotting-time had risen markedly after 2 hours, and a little further after 4 hours, after 8 hours it was still higher than normal The longest clotting time 2 hours after injection was 56 minutes, the normal was 5 minutes (before injection) In all these experiments the clotting-time at 4 hours was longer than at 2 hours, the longest being 58 minutes In five of the volunteers the longest clotting-time was between 30 and 58 minutes In the sixth the longest was 16 minutes 8 hours after the injection the clotting time was still much prolonged—in the first five subjects to between 18 and 27 minutes, and in the sixth to 11 minutes—still considerably longer than the pre-heparin time of 5 minutes

In the four persons who continued their usual work, there was some tenderness at the site of the injection which began after 5–6 hours The next day the tenderness had completely disappeared In the two who stayed in bed during the trial, no tenderness at all was felt

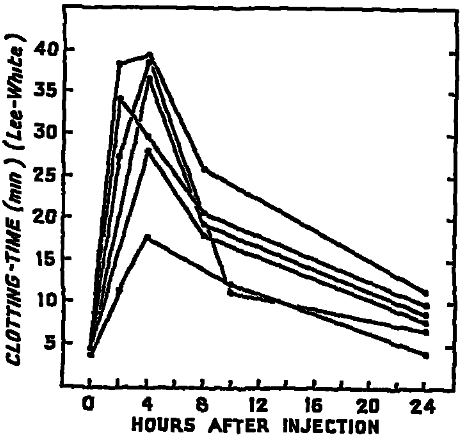

Fig 1—Clotting-time before and after intramuscular injection of 2 ml heparin prolongatum in 6 normal subjects

Clinical Trial

Since this preliminary test, we have used heparin prolongatum in almost all cases in which anticoagulant treatment has been employed It has been given in doses very roughly adapted to the estimated weight of the patient The initial dose has usually been 2 ml, followed by five 8 hourly injections of 1 ml each Obese patients have had the same initial dose, but the subsequent doses have been 1 5 ml In underweight patients the initial dose has been 1 5 ml and the subsequent doses 1 ml

Dicoumarol in doses of 300–600 mg was given at the same time as the first heparin injection No further dicoumarol was given for at least 72 hours The use of heparin prolongatum was started in February, 1955 Up to Dec 31, 1956, one hundred and thirty-five patients had been treated with heparin prolongatum, and altogether well over eight hundred injections had been given In no case was there any local reaction, tenderness, or infiltration, and no hæmatomas were observed

In forty-eight of the patients, altogether one hundred and seventeen blood samples have been drawn for Lee-White tests The patients tested were chosen at random. Thirty-one samples were drawn before heparin was administered Clotting times varying from 3 to 8 minutes were found, the vast majority being 4–5$^1/_2$ minutes, only four were below 4 minutes and three above 5$^1/_2$ minutes

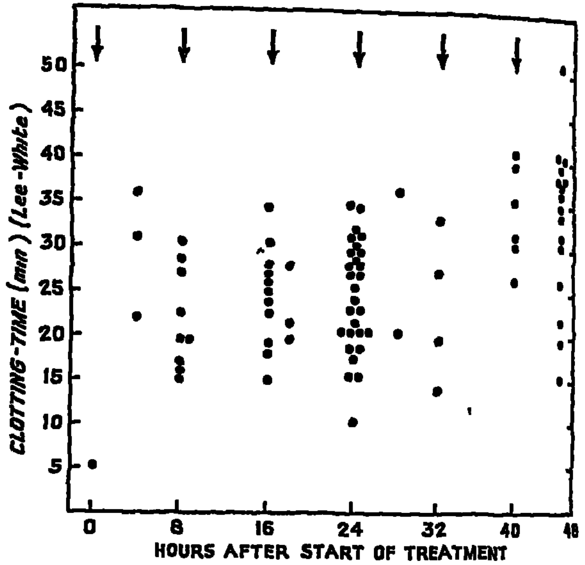

Fig 2—Clotting-times in random patients under treatment with intramuscular injection of heparin prolongatum (see text) Arrows mark times of injections

The remaining eighty-six samples were drawn 4, 8, 16, 24, 32, 40, and 46 hours after the first dose of heparin prolongatum The samples at 8, 16, 24, 32, and 40 hours were drawn immediately before the next dose on the schedule was given, the samples at 4 and at 46 hours were drawn 4 hours after the first and 6 hours after the last dose respectively Fig 2 shows that the clotting time is much prolonged in all samples, but, as could be expected, the times vary considerably, the lowest being found at 8, 16, 24, and 32 hours—i e, immediately before the next dose on schedule At 40 hours—also just before a scheduled injection—the times seem to be a little higher, possibly because the dicoumarol given at 0 hours has begun to have some effect These samples seem to show that on the whole a suitable effect was attained In two cases the clotting-time was followed for the whole period of treatment with heparin prolongatum (fig 3) The clotting-time was evidently much prolonged, and fairly constant values are found for the whole period

We have no established knowledge of what should be the *therapeutic level* of the clotting-time to prevent new thrombosis and impede the growth of thrombi already formed Indeed, it is probable that the optimal level differs under different conditions It will depend on the condition of the vessels (especially that of the intima of the vessels in which thrombosis is to be prevented), and on the rate of the blood-flow and all factors influencing this It is obvious that, by and large, the prevention of thrombosis in the venous part of the circulation would

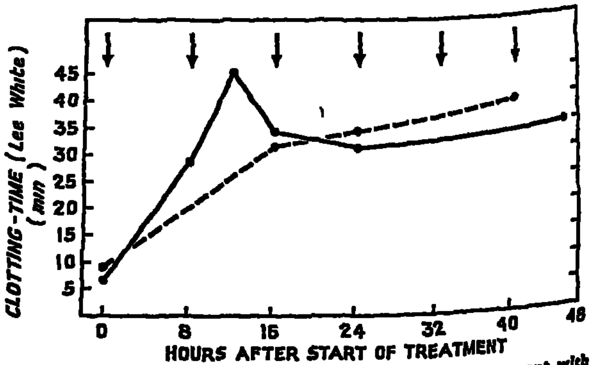

Fig 3—Clotting times in 2 patients followed during treatment with intramuscular injections of heparin prolongatum Arrows mark times of injections

emand a greater prolongation of the clotting-time than ı the arterial part Thus no optimal level suitable for all onditions can be decided On the other hand it must e kept in mind that too big doses involve a very real sk of hæmorrhage

It is a more or less accepted rule that the normal e , pre treatment) clotting-time must be prolonged no ss than three times to attain the "therapeutic level" his rule may not have sufficient factual and statistical ackground, but will serve as a practical guide until ufficient evidence for defining a correct therapeutic level an be procured

Without discussing them at length, we should mention hat heparin has actions other than prolongation of the lotting-time Important qualitative and quantitative ffects on the platelets and a notable action on the clotetraction are well recognised, but little is known of heir importance in thrombo embolic conditions Other ctions of heparin (i e , on the lipids and lipoproteins) are lso known, and they may also be important in these onditions

Our main object has been to prepare a heparin solution or intramuscular injection with long-continued action out without the risk of causing local reactions and hæmatomas On the strength of the observations here elated, we believe this has been attained , also we believe hat these observations show that the preparation is useful, at any rate for "bridging the gap" till the action of dicoumarol (or any other anticoagulant of this group) has fully developed

Summary

A heparin preparation suitable for *intramuscular* injection with prolonged action has been prepared by adding 1 25% carboxymethyl cellulose to heparin solution containing 100 mg per ml We have called the preparation heparin prolongatum

In six normal volunteers we have found that the effect of a single dose of 2 ml of heparin prolongatum is considerable 2 hours after injection, maximum effect is seen 4 hours after injection, and the clotting-time is still clearly prolonged 8 hours after injection

Heparin prolongatum has been used as initial anticoagulant treatment to bridge the gap between the first administration of anticoagulants of the coumarin group and the full effect of these drugs Usually six 8 hourly injections have been given A hundred and thirty-five patients, most of them with coronary occlusion, have been treated Well over eight hundred injections have been given Tenderness, infiltration, and hæmatomas have not been seen

Blood-samples drawn at intervals from patients chosen at random during the treatment with heparin prolongatum indicate that a suitable increase in the clotting-time has been attained

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"The differences between a man s attitudes in his personal and domestic concerns and in his national and international ones, are indeed great , and they do actually correspond to the differences we should expect to find in him between his attitudes as private individual and as a member of a regressive group Mr Smith, who feels greatly for the sufferings of his countrymen, has no care for the sufferings of foreigners, opining that that is none of his business Signor Cappello, who has no wish to attack or oppress his neighbours at home applauds Italy s colonial expansion , M Duval a solid bourgeois of France with an eye to the main chance, gladly risks material ruin for a war of glory Even the most peaceable citizen admires and supports his country s conquering heroes and makes no enquiry into the harm their conquests have done to other countries, or to his own "
—ALIX STRACHEY, *The Unconscious Motives of War* London, 1957 , p 201

A LACTOBACILLUS PREPARATION FOR USE WITH ANTIBIOTICS

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REPORTED side effects of treatment with antibiotics include intestinal disturbances which vary in severity from mild diarrhœa to fatal superinfection by resistant organisms With the increasing use of antibiotics these side-effects are causing widespread anxiety

Their chief cause is thought to be the partial destruction of the natural intestinal flora (Garrod 1955) In the absence of competition and of inhibitory substances such as lactic acid and hydrogen peroxide, produced by the normal flora, antibiotic resistant pathogens can flourish , and the risks of this happening grow greater as resistant strains become more prevalent

Such side effects could perhaps be prevented if, during antibiotic therapy, saprophytic organisms were introduced into the bowel in sufficient numbers to become established Since the beginning of the century this type of therapy has been suggested for a variety of conditions but has fallen into disrepute for a number of reasons

(1) It is essential to provide an organism such as *Lactobacillus acidophilus* which is a normal inhabitant of the intestine and can therefore be established Organisms of doubtful pathogenicity, and species of lactobacilli such as *L bulgaricus* and *L casei* which cannot establish in the gut, have been used because of their less exacting growth requirements

(2) Owing to faulty classification, cultures have been used which were not in fact *L acidophilus*

(3) The viability of liquid cultures declines rapidly, and they usually contain mainly dead or inactive material when used

(4) The growth requirements of *L acidophilus* are complex They are satisfied under normal intestinal conditions, but when various other organisms are destroyed during antibiotic therapy certain factors are lost These must therefore be added at the same time as the culture

(5) It is also of course essential that the strains of *L acidophilus* used be made resistant to the antibiotics if they are to survive during therapy

'Enpac' *L acidophilus* preparation has been developed to meet these requirements It is a culture of strains of *L acidophilus* together with complete growth factors and nutrilites, which has been dried in a manner preserving full viability

The richest sources of these nutrilites and growth factors were found to be unprocessed tomato, autolysates of certain yeasts, and some of the bacterial degradation products of casein For the preparation of the base only crude extracts and concentrates of these materials were used, in view of the labile nature of some of the factors These were blended with full cream milk to which dextrose was added

The lactobacillus used was a human intestinal strain made resistant to penicillin, streptomycin, chloramphenicol, neomycin, chlortetracycline, oxytetracycline, tetracycline, and erythromycin

We have investigated the bacteriological effects of this preparation on the intestinal flora of patients receiving an oral antibiotic

Methods

The 66 patients studied were mainly between the ages of 1 and 13 years, and all received tetracycline 10 mg per kg body weight daily for five days No other antibiotic was used Alternate patients were given 3 g of enpac four times a day, in the intervals between anti-

EFFECT OF ENPAC ON INTESTINAL FLORA DURING ANTIBIOTIC THERAPY

—	Antibiotic and enpac					Antibiotic alone				
	No of samples	Lactobacilli counts $>5 \times 10^5$		Staphylococci counts $>5 \times 10^3$		No of samples	Lactobacilli counts $>5 \times 10^5$		Staphylococci counts $>5 \times 10^3$	
		No of samples	Per centage	No of samples	Per centage		No of samples	Per centage	No of samples	Per centage
Before treatment	33	21	64	14	43	33	21	64	12	36
During treatment	33	14	42	22	67	33	10	30	20	61
At end of antibiotic treatment	29	20	69	11	38	25	4*	16	19	76
At end of enpac treatment	16	14	88	2	12	4	0	0	4	100

* Staphylococci were not isolated from the samples which contained lactobacilli

biotic doses, during administration of the antibiotic, and for four days afterwards

Materials

Fæcal specimens were examined (1) before treatment, (2) at the beginning and (3) at the end of antibiotic treatment, (4) at the end of enpac administration, and (5) a week later The fourth and fifth specimens were not always obtained since some patients had already left hospital

Bacteriological Examinations

Each specimen was diluted in saline and counted by the technique of Miles, Misra, and Irwin (1938) on the following media

(1) Beerwort agar for yeasts,
(2) MacConkey s agar for coliforms,
(3) Ludlam s agar (Ludlam 1949) for staphylococci,
(4) Reinforced clostridial medium (R C M) (Hirsch and Grinsted 1954) for enterococci and lactobacilli
(5) R C M plus tetracycline for resistant lactobacilli

A preliminary bacteriological examination of some specimens made it possible to select the dilutions to be counted on the various media The beerwort agar was incubated at room-temperature for five days, the remaining media at 37°C for three days Only the two R C M media were incubated anaerobically The colonies were identified by the catalase test and microscopic examination of Gram-stained films No attempt was made to identify the actual species of each organism, but the coagulase test was used to identify pathogenic strains of staphylococci

Clinical Considerations

The choice of clinical case to be used in this experiment was limited by certain factors Each patient had to suffer from a disease for which tetracycline is a reasonable treatment, but enteric disease had to be excluded as it might complicate interpretation of results, and a simple, reasonably mild, easily treated disease had to be chosen to eliminate as far as possible fallacies associated with severity or diversity of disease Furthermore, the timing, collection, and quick transmission of stool samples proved difficult for the nurses, and arrangements could be entrusted to only one ward of 36 beds

Hence, the series was limited to children suffering from respiratory streptococcal infections and scarlet fever In every case the streptococcal disease cleared up uneventfully The antibiotic caused no evident bowel or other side effects in either the test or the control series The acidophilus preparation was taken by the children with relish and caused no symptoms

Bacteriological Results

Staphylococci (see table) —Initially counts of staphylococci exceeding 5000 per g of stool were found in 39% of all cases Soon after the start of treatment, the staphylococcal counts increased in both groups, and 64% yielded staphylococci The count continued to rise in cases receiving tetracycline only, and by the end of treatment there was a large increase in 76% of these In the group treated with enpac, however, the numbers had decreased, and by the end of the antibiotic treatment samples from only 38% had more than 5000 staphylococci per g After a further two or three days of enpac, this number fell to 12 5% Some strains of staphylococci, isolated at the end of treatment in cases receiving the antibiotic only, were tested for their antibiotic sensitivity, all were resistant to the highest concentration used

Lactobacilli (see table) —In 64% of the cases lactobacilli before treatment numbered over 500,000 per g The number fell when the antibiotic was given alone, and by the end of antibiotic treatment lactobacilli could be isolated in only 4 cases, one strain was resistant In the cases receiving enpac there was a rapid build up of resistant lactobacilli after the initial destruction of sensitive strains by the antibiotic Finally, in all but 2 cases, there were counts in the range of 10^6 to 10^8 Specimens were obtained in only 4 cases a week after the end of enpac treatment, and high levels of lactobacilli were maintained in all

Enterococci —Over 500,000 enterococci per g were found in nearly all specimens, initially and throughout both courses of treatment There was a marked increase in numbers during administration of the antibiotic with and without enpac In specimens obtained a week after treatment had finished, the enterococci had returned to the original level

Coliforms —Only half of the initial specimens showed over 500,000 coliforms per g, and this level was not exceeded at any stage in 20% of cases During treatment there appeared to be no definite relation between the numbers present and the administration of antibiotic, this may or may not have been due to inter species differences It was impossible to count coliforms below 500,000 since the enterococci overgrew them This may be one reason why the percentage of samples showing coliforms is lower than might have been expected

Yeasts —A few yeasts were present initially in about 20%, and a few were isolated at the end of antibiotic treatment, in only 1 case, however, were there many

Discussion

The administration of enpac can check the increase of potentially pathogenic staphylococci and reduce these to the pretreatment levels or lower Competition, the production of inhibitory substances, and the effect of lactic acid on intestinal pH, may all be contributory factors to the suppression of these organisms In the group receiving only antibiotic, at the end of treatment 4 patients still had natural lactobacilli in the stools, and it is interesting that staphylococci could not be found in these cases

Rapid establishment of lactobacilli demands a large number of viable cells, but 6 g of a preparation containing 10^9 lactobacilli per g tended to cause loose stools When the dose was decreased to 3 g of the 10^7–10^8 preparation, this fault disappeared It is of interest that enterococci and lactobacilli were the predominant organisms in initial specimens Coliforms were present in smaller numbers and exceeded 500,000 in only 52% of cases The numbers normally present are very variable (Thomson 1955)

The results of the bacteriological examination of pecimens from the group receiving antibiotic only are n close accord with those of Loh and Baker (1955)

The choice of media and dilutions when examining pecimens with such a mixed and varied flora is always ifficult, and in the absence of completely specific elective media some overlapping is inevitable The nedia used in this work were by no means ideal, but eemed the most satisfactory of those available during rial experiments The use of tomato-dextrose agar Briggs 1953) for counting the lactobacilli had to be disontinued, since its content of Tween 80 allowed the drops o spread during incubation and it was impossible to ount the plates R C M was substituted, though it did iot give as good growth of these organisms and required onger incubation

Summary

66 patients receiving oral antibiotic were divided into two groups and one was given a preparation (' Enpac ') incorporating antibiotic-resistant strains of *Lactobacillus* *acidophilus* Fæcal specimens from all cases were examined bacteriologically at intervals before, during, and after treatment

It was found that the staphylococci increased in both groups at the beginning of antibiotic therapy Staphylococci continued to increase in the patients taking the antibiotic alone, but in those taking enpac there was a pronounced drop in numbers following the initial rise Simultaneously, in this latter group the lactobacilli were rapidly established and continued to multiply This followed the elimination of the normally non-resistant lactobacilli by the antibiotic during the early days of treatment

The 'Enpac' and other material for this work was provided by Messrs Aplin & Barrett, Yeovil

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SERUM-CYANOCOBALAMIN LEVEL IN CHRONIC INTESTINAL DISORDERS

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In temperate climates a deficiency of cyanocobalamin (vitamin B_{12}) is found in pernicious anæmia , idiopathic steatorrhœa , strictures, blind loops and anastomoses of the small bowel , and malnutrition Since this deficiency may cause optic atrophy, mental changes, glossitis and subacute combined degeneration of the cord without significant change in the hæmatopoietic system the only reliable method of detecting it is to demonstrate a low serum-cyanocobalamin level by microbiological assay Victor and Lear (1956) emphasise the need of such assays in clarifying certain neurological diagnoses

We describe here a method which is suitable for routine use , report results obtained in certain gastro intestinal disorders some of which we feel are of therapeutic importance , and indicate the need for such determinations

Methods and Material

The level of cyanocobalamin in body-fluids can be determined by microbiological assay using *Euglena gracilis* (Hutner et al 1949), *Lactobacillus leichmannii* (Thompson et al. 1950), or *Ochromonas sp* (Hamilton et al 1952) The *E gracilis* technique, though probably the most sensitive, requires special apparatus and skill and is unsuitable for routine use. Ochromonas though extremely specific, does not appear to be sufficiently sensitive

The method we have adopted is essentially that described by Thompson et al (1950) modified by using the pH change instead of turbidity to measure growth We also emphasise the importance of washing the test organism carefully before transfer to the assay medium, to obviate the carry-over of small amounts of cyanocobalamin which would give inaccurate and high readings This point was also made by Spray (1955)

All the media are obtainable in this country in the dehydrated state from Difco Laboratories through Baird & Tatlock London Ltd They are bacto micro inoculum broth, bacto micro assay culture agar, and bacto B_{12} assay medium *U.S P* (' Difco Certified ')

The organism used is the *L leichmannii* (National Collection of Industrial Bacteria 7854) This is maintained on micro-assay culture agar and subcultured fortnightly

Before an assay a subculture is made into micro inoculum broth and incubated for twenty-four hours at 37°C The growth is centrifuged and washed thrice with single strength B_{12} assay medium and then resuspended in 1 0 ml of the medium 0 1 ml. of the latter is added to a further 10 ml. of the medium and used for the inoculum

Test Solution —About 20 ml of blood is allowed to clot in a sterile universal container The serum is pipetted off as soon as it reaches the laboratory and placed in screw capped sterile containers, which may be stored in the deep freeze refrigerator at −10°C if desired (In this laboratory all assays are performed within a few days of receiving the specimen, and these are kept frozen in an ordinary household refrigerator) An equal quantity of acetate buffer pH 4 6 and 20 ml of distilled water is added to 5 ml. of serum in a boiling-tube, giving a 1 6 dilution of serum at pH 5 1 After thorough mixing a tight-fitting rubber bung with a glass outlet is inserted, and the tube is placed in a water-bath at 100°C for 30 minutes The tube is then cooled and centrifuged. 9 ml of the supernatant fluid is taken and its pH is adjusted to 6 9 with N sodium hydroxide , 6 ml of distilled water is added to give a final total volume of 15 ml , giving a serum dilution of 1 10 For the assay amounts of 2, 3, 4, and 5 ml. of this solution are added to 6 in × $^5/_{8}$ in. tubes and made up to 5 ml. by adding amounts of 3, 2, 1 and 0 ml of distilled water to each tube respectively

Standard Solution —Solution A a stock solution of 0 02 g of cyanocobalamin per 100 ml is made up in sterile buffer 0 62 *M* Na_2HPO_4/KH_2PO_4 pH 6 8 Solution B 0 25 ml of solution A is added to 500 ml of buffer=0 1 µg per ml A drop of toluene is added, and the solution is stored in the dark at 4°C Solution C for the standard solution 1 ml of solution B is made up to 500 ml with distilled water The standard curve is prepared as follows

	Solution C (ml)	*Amount of distilled H_2O to each tube*	*Final concentration of cyanocobalamin (mµg per tube)*
Tube no 1	0	5 000	0
2	0 125	4 875	0 025
3	0 25	4 750	0 050
4	0 375	4 625	0 075
5	0 5	4 500	0 100
6	0 625	4 375	0 125
7	0 75	4 250	0 150

Assay —To both standard and test solutions 5 ml of rehydrated bacto B_{12} assay medium is added so that all the tubes have a final volume of 10 ml All the tubes are sterilised by steam autoclave for three minutes at 15 lb pressure (121°C) Each tube is cooled and inoculated with 1 drop of the prepared inoculum The tubes are incubated for seventy two hours at 37°C, and the production of acid is measured with a pH meter (Pye no 11066) The highest dilution falling on the lowest part of the curve (fig 1) is taken as the reading and the result (which is the total activity of cyanocobalamin) calculated from this is expressed in µµg per ml.

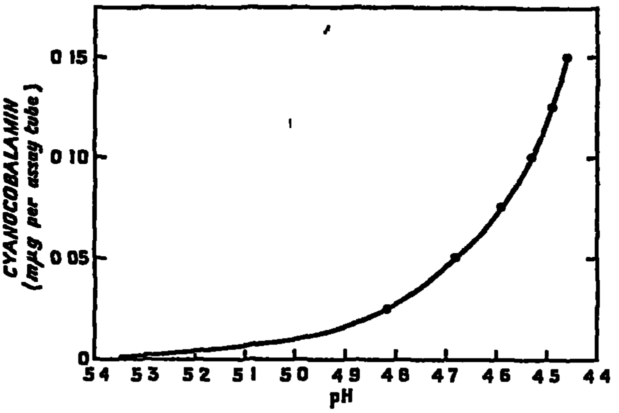

Fig 1—A standard curve of growth

Clinical Subjects—The 43 healthy people used for this investigation were medical students and hospital personnel aged 20–50, two-thirds of them being aged 20–25 The 90 hospital patients used as controls were selected at random, except that patients receiving antibiotic therapy and patients with leukæmia were excluded The diagnosis of cirrhosis of the liver was confirmed by either biopsy or necropsy Most of the 78 patients with idiopathic steatorrhœa and of the 43 with regional ileitis were outpatients attending the nutritional and intestinal follow-up clinic at intervals of three, six, and twelve months and seen during the past twelve months

Results

Mean difference expressed as a percentage of the mean in 34 duplicate observations was 2 97%—S D 2 95, range 0–9 5%

The results of duplicate assays of a pooled serum estimated weekly over fourteen weeks gave a mean of 171 μμg per ml, S D 9 2, range 162–192

In table I our results in healthy people and hospital patients used as controls are given and compared with those reported by other workers and in patients with pernicious anæmia in relapse From these figures we have adopted a normal range of 100–450 μμg per ml of serum

Table II gives the serum cyanocobalamin levels in idiopathic steatorrhœa, regional ileitis, cirrhosis of the liver, ulcerative colitis, and enterocolitis In 22 of 78 patients with idiopathic steatorrhœa the serum-cyanocobalamin levels were below 100 μμg per ml, and in 14 others a deficiency of cyanocobalamin was diagnosed from their hæmatological response to cyanocobalamin therapy In 4 cases it was impossible to know if a deficiency had ever existed, because treatment with cyanocobalamin had not caused any appreciable hæmatological or neurological improvement

Of the 43 patients with regional ileitis 23 had abnormally low serum cyanocobalamin levels and 3 others were being treated with cyanocobalamin for previously diagnosed megaloblastic anæmia Most of these patients and of those with steatorrhœa had no hæmatological manifestations, but some had mild macrocytic anæmia

The serum cyanocobalamin levels in idiopathic steatorrhœa and in regional ileitis contrast with the normal levels found in enterocolitis and in ulcerative colitis and, even more strikingly with the levels in cirrhosis of the liver, where the range was 280–1250 (mean 577) μμg per ml (S D 229) These levels were significantly higher than those found in the healthy people and in the hospital patients used as controls

A more detailed comparison of these groups is made in fig 2

Discussion

All the patients with untreated pernicious anæmia had serum cyanocobalamin levels below 100 μμg per ml, and the lowest level in the healthy controls was 105 μμg per ml We finally adopted 100 μμg per ml as the lowe normal value In the hospital controls 2 patients had values below this 85 and 95 μμg per ml Both had peptic ulcers, one having been admitted after a hæma temesis, and the other having been on a strict diet for many years

As the highest normal value we adopted 450 μμg per ml 3 healthy people had levels above this 475, 500, and 670 μμg per ml The 3rd was an African Of the hospital controls, 1 patient with congestive cardiac failure and hepatomegaly had a serum cyanocobalamin level above 450 μμg per ml, the result of a single assay being 625 μμg per ml Thus 96% of the healthy and the hospital controls had normal levels (100–450 μμg per ml)

Girdwood (1954) included in his controls 3 patients who could have had a deficiency of cyanocobalamin 2 possibly had pernicious anæmia, and 1 had chronic hypochromic anæmia with a gastro enterostomy If these 3 patients are excluded, Girdwood's lower limit of normal was 130 μμg per ml, which level he subsequently adopted (Girdwood 1956)

Unglaub et al (1954) found that 75 μμg per ml was their lower limit Such variations may result from individual differences in assay technique

TABLE I—CYANOCOBALAMIN LEVELS (μμG PER ML.) IN HEALTHY PEOPLE AND IN PERNICIOUS ANÆMIA

Reference	Healthy persons	Hospital patients used as controls	Pernicious anæmia	Organism
Present results				*L leich mannii* with serum
No of persons	43	90	20	
Mean level	281	244	41 1	
Range	105–672	85–625	5–95	
S D	117	104	28	
Mollin and Ross (1952)				*E gracilis* with serum
No of persons	65	83	43	
Mean level	358	318		
Range	100–720	60–680	16–105	
S E	16 1	20 2	±33	
Unglaub et al (1954)				*L. leich mannii* with serum
No of persons	31		6	
Mean level	210		40	
Range	70–420		10–70	
S E	13		7	
Nieweg et al (1954)				*L leich mannii* with whole blood
No of persons	36			
Range	300–1050		5–175	
Lear et al (1954)				*L leich mannii* with serum
No of persons	20		33	
Mean level	532		39	
Range	292–856		0–85	
S D	161		26	
Girdwood (1954)				*L. leich mannii* with serum
No of persons		50	36	
Mean level		320	95	
Range		50–870	50–200	
		3 below 130	2 over 130	
Rosenthal and Sarett (1952)				*L. leich mannii* with serum
No of persons	24			
Mean level	200			
Range	80–420			
	1 below 110			
Pitney et al (1954)				*E gracilis* with serum
No of persons	13			
Mean level	195			
Range	122–460			
Spray (1955)				*L leich mannii* with serum
No of persons	111			
Mean level	437			
Range	150–860			
Rachmilewitz et al (1956)				*Escherichia coli*
No of persons	25			
Mean level	340			
Range	200–500			

TABLE II—SERUM CYANOCOBALAMIN LEVELS IN GASTRO-INTESTINAL DISORDERS

Disorder	Serum cyanocobalamin level (µµg per ml)			Previous response to cyanocobalamin therapy	
	< 100	100–450	>450	Positive	Negative
Idiopathic steatorrhœa	22	35	3	14	4
Regional ileitis	23	17	0	3	0
Cirrhosis	0	7	13	0	0
Enterocolitis	0	11	1*	0	0
Ulcerative colitis	0	9	0	0	0

* This patient had associated cirrhosis of the liver

Spray (1955), using traces of cyanide in preparing the extracts of serum, found a normal range of 150–860 µµg with *L leichmannii*

Lear et al (1954) obtained higher values, and Mollin and Ross (1952) obtained results similar to ours Both these groups of workers used *E gracilis* Only in patients aged more than 70 with miscellaneous diseases did Mollin and Ross report results below their normal range of 100 µµg per ml

In 18 patients aged more than 70, most of them with senile vascular disease, we found a mean of 245 (range 90–625) µµg per ml (S D 112 2) None of the patients with pernicious anæmia had levels above 100 µµg per ml

Girdwood (1954) found levels up to 200 µµg per ml

Nieweg et al (1954), using whole blood, found an upper limit of 175 µµg per ml in 6 cases of pernicious anæmia

Unglaub et al (1954) found a range of 10–75 µµg per ml in serum, and Spray (1955) reported 16 of 17 cases of pernicious anæmia in relapse with levels below 100 µµg per ml

Mollin and Ross (1952) and Lear at al (1954), working with *E gracilis*, had ranges of 16–105 µµg per ml and 0–85 µµg per ml respectively

Our findings are in keeping with those of other workers, and we feel justified in regarding levels below 100 µµg per ml as evidence of a deficiency of cyanocobalamin

Our results in patients with cirrhosis of the liver confirmed those of other workers

Lear et al (1954) found that of 29 patients with cirrhosis 5 had abnormally high serum cyanocobalamin levels, and Jones and Mills (1956) found similar values

Baker et al (1956) found in addition a decreased urinary excretion of cyanocobalamin in patients with hepatic disorders after an injection of 50 µg

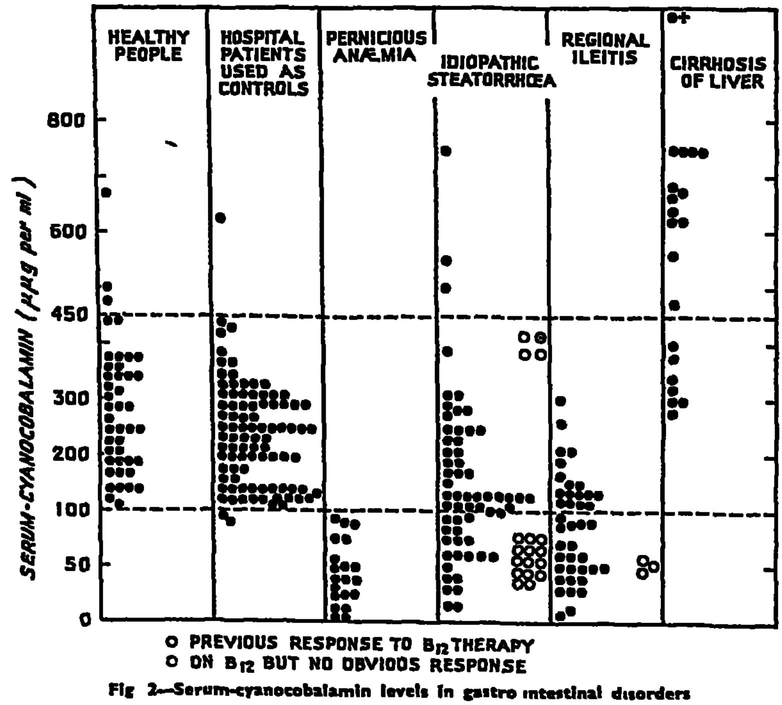

Fig 2—Serum-cyanocobalamin levels in gastro intestinal disorders

Rachmilewitz et al (1956) found that the cyanocobalamin-binding capacity of the serum of patients with cirrhosis and of patients with infectious hepatitis was increased but they could not find any correlation between raised serum cyanocobalamin levels and the amount of serum globulin, which is said to be the cyanocobalamin-binding protein (Pitney et al 1954) At present there is no adequate explanation for these observations

A deficiency of cyanocobalamin in idiopathic steatorrhœa has previously been recognised by the hæmatological response to therapy, but the incidence (36 of 78) in our group was somewhat surprising

Girdwood (1956) found only 1 patient with a low serum-cyanocobalamin level among 29 patients whom he investigated because of intestinal malabsorption of the sprue type

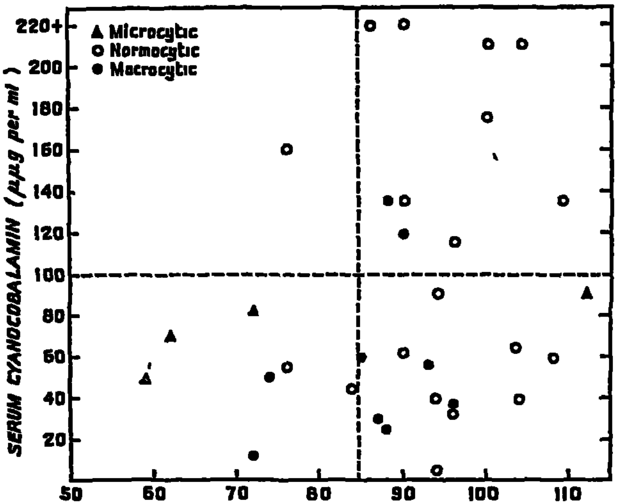

Fig 3—Hæmatological picture compared with serum cyanocobalamin level in regional ileitis

Callender and Evans (1955) found, in 7 of 13 patients with steatorrhœa, defective absorption of cyanocobalamin comparable to that found in pernicious anæmia

A large proportion of our patients had some hæmatological abnormality, shown by the number already being treated with cyanocobalamin Others, however, developed a deficiency of cyanocobalamin although their blood counts were relatively normal or they were already well controlled with folic acid

Megaloblastic anæmia has been reported in patients with regional ileitis and in patients with small-bowel lesions (Barker and Hummel 1939, Jensenius 1945, Cameron et al 1949, Watson and Witts 1952, Thompson and Ungley 1955, Halsted et al 1956), and in most of them a deficiency of cyanocobalamin was shown by, or seemed probable from, their response to cyanocobalamin Poor absorption of radioactive cyanocobalamin in regional ileitis was found by Halsted et al (1956) in 3 patients, by McIntyre et al (1956), and by us in 2 patients Nevertheless, the high incidence of low serum cyanocobalamin levels found by us in regional ileitis was unexpected Most of these patients had free hydrochloric acid in their stomachs and but little anæmia (fig 3), but some had loss of weight, energy, and concentration, and irritability and other personality changes, including occasional psychoses The fact that both in the patients with idiopathic steatorrhœa and in the patients with regional ileitis these symptoms cleared up under treatment with cyanocobalamin leads us to suppose that a low serum cyanocobalamin level indicates an absolute deficiency of cyanocobalamin in the body

Summary

A method suitable for a routine laboratory is described for determining the serum-cyanocobalamin level

The normal range of values of the serum-cyanocobalamin level was taken to be 100–450 μμg per ml

Serum cyanocobalamin levels above 450 μμg per ml were found in 13 of 20 patients with cirrhosis of the liver

Serum-cyanocobalamin levels below 100 μμg per ml or therapeutic evidence of deficiency were found in 36 of 78 patients with idiopathic steatorrhœa and in 26 of 43 patients with regional ileitis

We are glad to acknowledge financial support from the medical research endowment fund of the United Birmingham Hospitals for technical assistance

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LESIONS OF THE HYPOTHALAMIC REGION AND SERUM-PROTEIN LEVELS

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IN view of the importance of the brain in regulating bodily functions it is surprising that focal damage to the brain has not been more frequently associated with metabolic changes It is well known that the hypothalamus is either directly or indirectly concerned with regulating the metabolism of carbohydrate and fat, water balance, and vasomotor activity, and that lesions in the hypothalamic region can disturb these functions No report of disturbances of protein metabolism in association with focal lesions of the brain seems to have been published

The qualitative and quantitative alterations in the serum-proteins have been studied in a wide range of diseases (Gutman 1948)

Roboz et al (1955) found changes in the serum protein levels both with benign and with malignant neoplasms of the central nervous system but did not discover any correlation between the site of the lesion and the disordered pattern Magraf (1953), Shetlar et al (1950), and other workers found abnormal protein levels with malignant but not with benign tumours in other parts of the body

Mider et al (1950) was of the opinion that the protein change was independent of the site of the tumour, but only two of his patients had intracranial growths

I report here alterations in the serum-protein pattern in certain neurosurgical conditions and suggest that lesions affecting certain not yet accurately localised basal regions of the brain are responsible for these changes

Attention was first drawn to the serum protein levels in connection with checking the adequacy of nutrition of comatose patients, especially those with head injuries These patients were given, through a Ryle's tube, a diet of about 2000 calories daily containing 90–100 g of first class protein

Methods

Estimation of Serum-protein Levels

The serum-protein levels were estimated in the department of chemical pathology at Manchester Royal Infirmary The biuret method, as described in the American Association of Clinical Chemists' publication, Standard Methods in Clinical Chemistry, vol I, was used With this technique standard normal values are as follows

Serum albumin 3 8–4 6 g per 100 ml
Serum globulin 2 2–3 5 g per 100 ml

Feeding of Unconscious Patients

All the patients who were unconscious or unable to swallow were fed by Ryle's tube with a feed based on 'Complan,' Glaxo, which was modified because the protein content of 140 g in a 2000 calorie daily feed seemed to be too high

The feeds were prepared daily in the dietetic department and kept in the ward refrigerators Immediately after admission frequent feeds of small volume were given, and, as the patient improved, the volume and the time between each feed were increased From 3½ to 4½ pints of the feed was given daily, the total volume of fluid being made up to 5 pints with water, usually given in a small amount after each feed to clear the Ryle's tube

The mixture consisted of water 5 pints, complan 12 oz, lactose 8 oz, sodium chloride 5 g, and vitamin C 50 mg

Illustrative Case-reports

CASE 1 —A man, aged 42, was involved in a road accident on Oct 9, 1955 He was admitted unconscious with no history of a lucid interval Radiography revealed extensive fractures of the right temporofrontal region Shortly after admission both pupils became dilated and fixed, respiration became irregular, and the blood pressure began to rise At operation a large left sided hæmatoma was removed and a right temporo parietal bone flap was taken out to decompress the swollen lacerated brain After this his respirations became regular and blood pressure fell to 80/55 mm Hg Next day his temperature rose to 104°F, and for the following eight days ice packs to the skin and chlorpromazine were used to keep his temperature down to normal On Oct 14, 1955, tracheostomy was done, and he remained in an oxygen tent until Nov 10, 1955, when his respirations were satisfactory and he was beginning to take fluids by mouth He slowly improved and by Feb 27, 1956, could reply to questions and was taking a normal diet There was, however, severe mental deterioration, his behaviour was primitive and childlike, with periods of violence He was transferred to a mental hospital on May 2, 1956

Serum protein levels were as follows

Date	*Albumin (g per 100 ml)*	*Globulin (g per 100 ml)*
Oct 22 1955	2 4	5 1
Nov 2	1 9	5 2
8 ,	2 2	5 0
„ 16, „	2 7	4 7
28	3 0	4 7
Jan 2, 1956	4 0	3 7
Feb 7	4 0	3 1

On Nov 2, 1955, electrophoresis showed a low serum-albumin level with increased globulin, especially the gamma fraction

Case 2 —A woman, aged 48, was admitted to hospital after a car crash on Oct 29, 1955 She had a laceration over her left frontal region, was deeply unconscious, responding only slightly to painful stimuli and had a dilated and fixed right pupil Four days later, still unconscious, she was transferred to Manchester Royal Infirmary There was no localising sign other than the unreactive pupil, both plantar responses were extensor, and radiography of the skull revealed no evidence of a fracture Bilateral burr holes revealed the brain to be under normal tension with no evidence of either extradural or subdural hæmatoma The patient's general condition slowly deteriorated, pulmonary congestion developed, and she died on Nov 7, 1955

Serum protein levels were as follows

Date	*Albumin* (*g per 100 ml*)	*Globulin* (*g per 100 ml*)
Nov 4 1955	3 1	2 6
7, ,,	2 4	2 7

Necropsy was ordered by the coroner of the area in which the accident happened and was not done at this hospital We could not procure a detailed report of the findings No significant amount of intracranial clot was said to have been present, and there was " no evidence of a pressure cone at the tentorium " Death was regarded as being immediately caused by the pulmonary condition

Case 3 —A man, aged 69, was knocked down by a car on Jan 14 1956, and admitted to hospital in deep coma His pupils were equal and reactive, and there were no localising neurological signs He had a laceration over the occiput, but no fracture of the skull was seen on radiography He was still unconscious on Jan 17, 1956, when his left limbs showed increased tone over the right, and the left plantar response became extensor Bilateral burr holes revealed a subdural hæmatoma about 2–3 mm deep covering the right parietal and left frontal cortex Lumbar puncture on Jan. 19, 1956 revealed a bloodstained cerebrospinal fluid (C S F) under a pressure of 120 mm Tracheostomy was done on Jan. 24, 1956 The patient made a slow return to consciousness and by Feb 7, 1956, was trying to talk and taking food by mouth By March 3, 1956, he could walk unaided, but there were signs of gross organic dementia, and he was eventually admitted to a mental hospital in May, 1956

Serum protein levels were as follows

Date	*Albumin* (*g per 100 ml*)	*Globulin* (*g per 100 ml*)
Jan 21 1956	3 7	3 3
30	3 2	5 3
Feb 4	2 9	4 6
8	2 8	4 6
22 ,,	3 1	4 3
March 3	3 4	4 0
April 30	3 9	3 7

On Feb 4, 1956, electrophoresis showed low serum albumin and raised serum globulin levels, most evident in the gamma fraction

Comment —It seemed unlikely that these changes could be regarded as nutritional because the patients were all receiving an adequate intake of protein and calories In case 1 there had been evidence of severe damage to the mid-brain the pupillary changes, the respiratory and cardiovascular changes, and the loss of temperature control Thus the possibility arose that lesions of the mid-brain might be responsible for the altered protein levels Accordingly the serum-protein levels of other neurosurgical patients were determined especially those with lesions of the mid brain

Case 4 —A woman aged 43, was admitted to hospital on Dec 14, 1955 Three years previously she had begun to have attacks in which she " had become hazy for a moment " and had visual hallucinations of people she had known previously In 1953 she began to get frequent headaches and associated with these ' spots before the eyes During the twelve months before her admission her vision had gradually deteriorated sometimes almost disappearing and then recovering She also slept more than formerly was becoming increasingly thirsty, and was having more severe headaches

On examination she had bilateral anosmia and severe bilateral papillœdema with venous engorgement and exudates Her visual acuity was J10 right and J12 left Small but definite supraclavicular pads of fat were present Charting of the visual fields showed an enlarged blind spot on each side, her C S F contained 280 mg of protein per 100 ml and air encephalography and 'Myodil' ventriculography showed a filling defect of the anterior end of the third ventricle

Craniotomy on Jan 28, 1956, revealed a greyish-pink tumour involving the chiasma and extending upwards towards the floor of the third ventricle A biopsy specimen was taken and the flap was closed. Histologically the specimen showed dense fibrillar gliosis with spindle shaped nuclei, suggesting a benign tumour of the chiasmal type

Postoperatively the patient's vision improved to J6, J4 (similar improvement had taken place on previous occasions) She was discharged from hospital on Feb 15, 1956, and was seen as an outpatient on April 9, 1956, when her vision showed no change but her optic discs now showed consecutive atrophy Her weight was increasing, she had polydipsia and polyuria, and during the previous few weeks she had been having attacks, lasting a few minutes, in which she felt faint and giddy and became flushed and hot

Serum-protein levels were as follows

Date	*Albumin* (*g per 100 ml*)	*Globulin* (*g per 100 ml*)
Jan 13 1956	2 9	4 5
20 ,,	2 9	2 9
Operation		
Jan 29 ,,	3 7	3 7
Feb 4	3 4	3 4
April 9,	3 3	4 2

On Feb 4, 1956, electrophoresis showed a slight rise in the level of α_2 globulin

Case 5 —A woman aged 52, was first admitted to the neurosurgical unit on Dec 28, 1954, with five years' history of progressive increase in weight, lack of energy, hypersomnia, and failing vision. On Feb 3, 1955, her optic chiasma was explored, and a purplish tumour was seen protruding from behind it A needle introduced into the tumour yielded 0 75 ml of yellow fluid It would have been impossible to obtain a biopsy specimen without dividing the optic nerve, so the flap was closed The patient made an uneventful recovery from the operation, her sight remaining unchanged In March, 1955, she was given a course of radiotherapy.

Readmission —On Sept 29, 1955, she was readmitted to hospital because of rapidly failing vision and increasing drowsiness She was still gaining weight and had severe polyuria On examination she was confused and her speech was slurred Her optic discs were severely atrophied, her blood-pressure was consistently low, and she had slight left-sided pyramidal signs Cortisone improved the blood pressure without altering her general condition The original flap was reopened on Nov 4, 1955 Tumour tissue was seen indenting the right optic nerve and spreading up behind the chiasma A biopsy specimen of this appeared histologically to be a glioma The patient went steadily downhill, lapsed into coma, and died on Dec 1, 1955

At necropsy a carpet of glioma was found growing from the floor of the third ventricle

Serum-protein levels were as follows

Date	*Albumin* (*g per 100 ml*)	*Globulin* (*g per 100 ml*)
Nov 7 1955	2 6	4 3
23	3 3	4 4

On Nov 23, 1955, electrophoresis showed an increase in the gamma globulin

Case 6 —A woman, aged 54, had complained since 1953 of headaches failing memory, and, later, unsteadiness of her limbs and vomiting Air encephalography and air ventriculography revealed an obstruction at the posterior part of the third ventricle and proximal part of the aqueduct (fig 1) and internal hydrocephalus This was regarded as being due to a slowly growing mid brain tumour In June, 1955, a right sided Torkildsen s ventriculo-cisternostomy was done After this she improved considerably and went home at the end of July In October, 1955, her condition suddenly deteriorated and she became unresponsive, mute, and incontinent After admission to hospital, however, she slowly but spontaneously recovered Radiography showed that the lower end of the tube was about 5 cm above the cisterna magna, so the posterior fossa was reopened and the tube replaced in the cistern

Postoperatively the patient rapidly recovered and went home in mid April When she was next seen as an outpatient

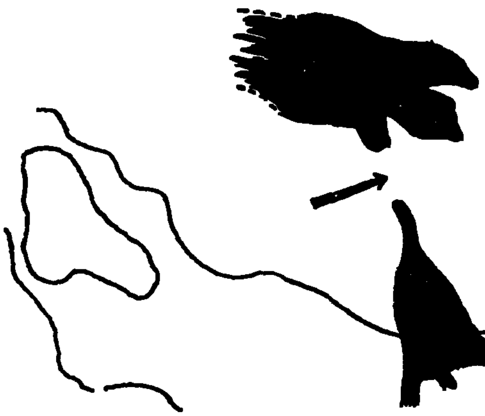

Fig 1—Case 6 composite drawing of air encephalogram and air ventriculogram, showing obstruction of proximal end of aqueduct

in June, her only complaints were of sleepiness and increased weight

Serum protein levels were as follows

Date	*Albumin* (*g per 100 ml*)	*Globulin* (*g per 100 ml*)
Dec 19, 1955	3 2	3 3
,, 30	3 3	3 7
March 14, 1956	2 9	4 0
21 ,,	2 9	3 9
Operation		
June 11, ,,	3 6	3 8

On March 21, 1956, electrophoresis showed a low serum albumin level with a normal globulin pattern

Case 7—A woman, aged 50, was admitted on March 13, 1956, having first noticed failure of vision in 1948 Her sight remained stationary until mid 1955, when it rapidly deteriorated further, the left eye being more affected than the right

On examination there was primary atrophy of both optic discs, and the left eye was blind, but there was some remaining vision in the right nasal field Radiography revealed erosion of the dorsum sellæ, air encephalography showed a midline tumour extending into the third and fourth ventricles (fig 2), and the C S F contained protein 180 mg per 100 ml There was no clinical or biochemical evidence of pituitary failure

Operation—A left frontal osteoplastic flap was turned, and a meningioma was found attached to the orbital roof and extending 1 5 cm in front of the orbital ridge The left optic nerve was bowed forwards over the main mass of the tumour, which lay behind it The meningioma was growing from the dorsum sellæ and raised the floor of the third ventricle, making the risk of attempted removal prohibitive The patient made a good postoperative recovery, but her eyesight remained unchanged She subsequently received a course of radiotherapy

Serum protein levels—On March 16, 1956, the serum albumin level was 2 9 g per 100 ml and serum globulin level 3 4 g per 100 ml

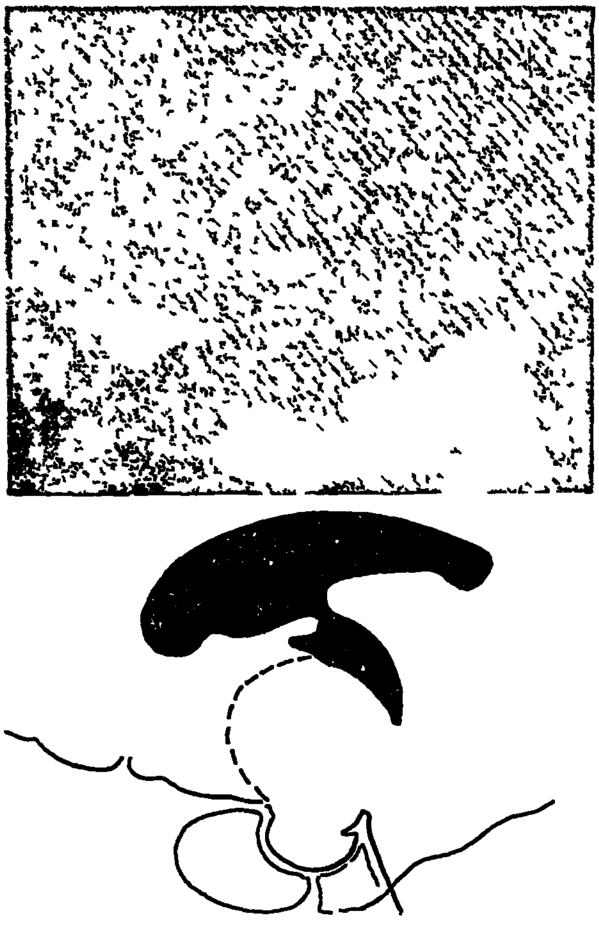

Fig 2—Case 7 air encephalogram and drawing, showing large suprasellar tumour extending into third and fourth ventricles

Controls

During the period of the investigation the serum protein levels of 44 other patients were determined These control patients cannot be regarded as a completely random group, because (1) the aim was to cover a wide variety of lesions, and (2) all patients with suprasellar tumours were investigated In all the following cases the serum albumin and serum-globulin levels were within normal limits

Condition	*No of cases*
Malignant supratentorial glioma	9
Craniopharyngioma	5
Chromophobe adenoma	5
Supratentorial meningioma	4
Acoustic neurinoma	2
Subdural hæmatoma following head injury	4
Extradural hæmatoma following head injuries	3
Subarachnoid hæmorrhage from aneurysm	2
Acromegaly	3
"Pseudotumour"	1
Frontal tuberculoma	1
Cervical prolapsed disc	1
Cord meningioma	1
Brain stem glioma	1
Congenital stricture of iter	1
Brain stem thrombosis	1

Several of these patients were unconscious for periods varying from a few days to several weeks and were fed by the procedure used for head injury patients In these cases the serum-protein levels were estimated at intervals, but no abnormality was found

The patients with tumours arising from the pituitary fossa all showed moderate suprasellar extensions on air encephalography, and in most of them the third ventricle was displaced In none of these patients was there any radiological sign of tumour growth into the third ventricle All the patients with craniopharyngioma and two with chromophobe adenoma presented clinical and biochemical evidence of hypopituitarism, and in all these cases the serum protein levels were estimated before cortisone was administered

Discussion

The various structures and connections of the base of the brain are not yet precisely defined, and rarely are pathological lesions sufficiently circumscribed to allow accurate localisation of the part mainly affected Because of this difficulty of localisation the broad term "hypothalamic region" has been used in the title of this paper

In the seven cases studied there is adequate evidence that this region was primarily involved, and in none of them is there reason to believe that other areas of the brain might be seriously damaged except in case 1, where, however, the bilateral dilated pupils, loss of temperature control, and long period of unconsciousness bore witness to trauma suffered by the brain stem.

It is unlikely that the disorder of protein metabolism in such cases is due to environmental circumstances, because several of the controls had periods of unconsciousness and tube-feeding. Moreover in cases 4, 6, and 7 abnormal serum-protein levels were present while the patients were ambulant and receiving a normal diet. Although there is a relationship between the duration and degree of unconsciousness and the serum-protein levels in cases 1 and 2, it seems reasonable to assume that both are a reflection of the original focal damage to the brain.

That the protein change is not due to the type of tumour seems certain; meningiomas and gliomas in *other areas did not alter the protein pattern.*

It was at first thought that the change might be due to disruption of the hypothalamic-pituitary mechanism, but none of the seven patients provided any clinical or biochemical evidence of pituitary insufficiency, and in patients with severe panhypopituitarism no qualitative alterations in the serum-protein levels were found.

The first change to develop appears to be a fall in the serum-albumin level, and this is closely followed by a rise in the serum-globulin level. With recoverable lesions the serum-albumin level returned to normal before the increased serum-globulin level fell to normal. Where electrophoresis was done no specific change was found in any one fraction. *At all times the total serum-protein* level was normal. In none of the seven patients was there any abnormality in either the serum electrolyte levels or the blood-urea level when the serum-protein levels were estimated.

All but one of the patients were incontinent of urine and fæces during the period in which abnormal serum-protein levels were present. In case 4, however, the nitrogen balance was studied. From Feb. 3 to Feb. 7, 1956, this patient received a diet containing 70–90 g. of protein daily. Urine and fæces were collected, and their nitrogen content was estimated, from Feb. 5 to Feb. 7, 1956. During this time case 4 excreted 3500 ml. of urine containing *17.6 g. of nitrogen and her fæces contained* 19.4 g. of nitrogen. Thus during the test period the intake and output of nitrogen were about equal. Bodansky (1938) found the normal daily total nitrogen output in the urine to be 13.2 g. Thus in case 4 the urinary output of nitrogen was abnormally low, and probably there was incomplete absorption of protein during the test period. In this respect it is interesting to recall the work that has been reported, particularly that of Kabat et al. (1935), showing that stimulation of the lateral nuclei in the hypothalamic region leads to a decrease of gut motility and gastric secretion in laboratory animals.

The mechanism by which these alterations in serum-protein levels take place and the significance of the change are obscure; but determination of the serum-protein levels may be of value in the diagnosis of lesions involving the hypothalamic region and in assessing recovery in certain head injuries before there is any clinical improvement in consciousness.

Summary

Seven cases of lesions involving the hypothalamic region are described.

In all of them the serum-protein levels were changed, the serum albumin level being lowered and the serum globulin level raised.

In 44 control patients the serum-protein levels were normal.

The disturbance of protein metabolism is probably due to a specific cerebral disorder rather than an alteration in the environmental circumstances.

Determination of the serum-protein levels may be of diagnostic and prognostic significance in patients with lesions of the hypothalamic region.

I wish to thank Mr. H. Varley and the Department of Clinical Pathology for estimating the serum-protein levels; the Department of Neuroradiology; the Department of Medical Illustration and Miss D. Davison for the illustrations; and especially the nurses for their untiring efforts over many weeks, particularly in the care of the patients with severe head injuries.

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MANAGEMENT OF FRACTURES THROUGH FEMORAL METASTASES

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IT is important to know the prognosis of any disease syndrome as precisely as possible before planning its treatment.

Petit described in 1723 multiple fractures in a woman with carcinoma of the breast. How to treat such fractures is not easily decided. The introduction of intramedullary nailing by Küntscher (1940) suggested the possibility of internal fixation instead of traction or plaster in the treatment of femoral fractures, and since then this or some other surgical technique has been used and reported by numerous workers. Internal fixation in anticipation of a fracture has also been advocated and practised (Griessmann and Schüttemeyer 1947).

Altman (1953) originally described the successful use of trifin nails and of nails and plates to stabilise fractures through deposits in the femoral neck and trochanteric region.

D'Aubigne (1951) described the insertion of an acrylic prosthesis to replace a carcinomatous femoral head.

Ehrenhaft and Tidrick (1949), Rossi (1953), Altman (1953), and Devas et al. (1956) have discussed the management of pathological fractures through metastases and have described their own cases.

Bickel and Barber (1951) from the Mayo Clinic and Fitts et al. (1953) have given brief descriptions only of substantial numbers of patients.

All these workers dealt with management or described operations but rarely stated how long the patient survived *operation.*

I review here the cases of all 22 patients treated in University College Hospital between 1943 and 1956 for fractures of the femur through secondary carcinomatous deposits. This analysis seems to show that the treatment of a fracture of the femur at the site of a secondary deposit should be influenced by one fact—i.e., whether the metastasis is solitary or one of several. If it is solitary, the expectation of life is longer, and therefore an attempt probably successful should be made to achieve osseous union. If there are multiple metastases, there is no likelihood of long survival, and the object should be to make the patient comfortable. *Osseous* union, which demands more stringent *treatment,* is unnecessary for this.

The Patients with Fractured Femurs

All were women with carcinoma: in 17 the primary tumour was in the breast, in 4 in the thyroid gland, and

TABLE I—PATIENTS WITH MULTIPLE METASTASES OF MAMMARY CARCINOMA AT TIME OF FEMORAL FRACTURE

Case no	Age at start of history (yr)		Histology of carcinoma	From start of history to fracture (mos)		Site of fracture	Survival after fracture (mos)	Time for fracture to unite (mos)	Special treatment of fracture	Year of fracture
1	38	Pre menopausal	Anaplastic duct	40		Upper $^1/_3$	2	Ununited		1953
2	38		Spheroidal cell	21		Upper $^1/_3$	6	,,	Androgens	1950
3	40		Scirrhous adenocarcinoma	36	Both femurs	Middle $^1/_3$	3	,,		1951
				38		Middle $^1/_3$	1	,,		1951
4	40			32		Upper $^1/_3$	1		Androgens	1948
5	41		Mucoid	34		Middle $^1/_3$	3			1951
6	44			32		Middle $^1/_3$	1			1955
7	45 ?			25		Lower $^1/_3$	4	,,	Radiotherapy	1947
8	58	Post menopausal	Small duct	5		Neck	10	,,	Androgens	1955
9	59		Anaplastic small duct	15		Middle $^1/_3$	5		Radiotherapy	1956
						Lower $^1/_3$				
10	66			83–94		Lower $^1/_3$	4–15	,,	Amputation	1951

Case 10 lived ninety eight months in all, but the month of the year in which her fracture occurred is unknown

TABLE II—PATIENTS WITH SINGLE METASTASIS OF MAMMARY CARCINOMA AT TIME OF FEMORAL FRACTURE

Case no	Age at start of history (yr)		Histology of carcinoma	From start of history to fracture (mos)	Site of fracture	Survival after fracture (mos)	Time for fracture to unite (mos)	Special treatment of fracture	Year of fracture
11	37	Pre menopausal	Scirrhous adenocarcinoma	48	Upper $^1/_3$	29	?	Radiotherapy	1948
12	44		Anaplastic small duct	21	Neck	17	Ununited	Radiotherapy androgens	1955
13	63	Post menopausal	Undifferentiated	18	Upper $^2/_3$	4 +	? United in 4	Intramedullary nail, radiotherapy, androgens	1956
14	63		Duct	21	Neck	6	Partially united in 6	Radiotherapy	1951
15	64			23	Upper $^1/_3$	12 +	Ununited	Radiotherapy nail and plate	1955
16	67			47	Upper $^1/_3$	16 +	United in 4	Intramedullary nail, radiotherapy	1955
17	67			33	Neck	10	United in 4	Radiotherapy	1953

"Partially united" in case 14 is a quotation from a necropsy report +, Still alive on last day of 1956

in 1 in a bronchus (The principal primary site of the carcinoma in previously published cases was the breast)

Tables I and II contain details of the eighteen fractured femurs in the 17 patients whose primary tumour was in the breast The youngest woman in each group is put first and the others follow in order of age recorded at the time of the first symptom caused by their primary carcinoma The age distribution in the two groups is similar The same histological types of carcinoma occur in both Details of external splinting in a Thomas's splint, plaster spica, or walking calliper have been omitted from the treatment column

One criterion alone was adopted in separating the two groups the question was asked, "At the time the fracture occurred was there clinical or radiological evidence of other bloodborne metastases ?"

The femoral fractures of the women in table I who at the time showed definite evidence of other metastases were all ununited at death, and none of the women lived longer than ten months after her fracture

In table II are listed the women who showed no evidence of other bloodborne metastases, they lived much longer after their fracture—up to two and a half years They were confined to bed initially In the patients in whom the fracture did unite it did so in about four months, judged on clinical examination and on radiological evidence that osseous union was taking place

Living with a leg stabilised by an internal splint of metal is a vast improvement on life with a Thomas's splint or a plaster spica Radiotherapy can be given as soon as the surgical incision has healed, and sex hormones may be prescribed in cases of mammary and prostatic carcinoma With internal splinting pain is relieved, nursing and radiotherapy are facilitated, and some patients learn to get about on crutches two weeks after their operation

Surgery is contra indicated when a large mass of tumour infiltrates the soft tissues of the thigh at the site of the fracture I have not been able to find any published case in which death was attributable to an operation on a femur with a fracture at the site of a metastasis, either from fat embolism or any other cause

Though early mobilisation is desirable, it delays union of the fracture and may prevent it When the expectation of life is short, this is of little consequence

Conclusion

The history of these 17 patients suggests that the correct surgical management of a woman with a fracture of her femur through a metastasis from a carcinoma of the breast depends on whether or not there is clinical or radiological evidence of other bloodborne metastases If such metastases are present, she will probably die within six months, and her fracture will remain ununited even with complete rest in bed If no other bloodborne metastases are found, it is justifiable and correct to confine the patient to bed, making every effort to secure union of the fracture, because there is a good chance that it will unite in about four months, and the patient may live for two and a half years

Although the prognosis of the patients in the two groups differs considerably, they may all be considered for treatment by operative stabilisation of their fracture with an intramedullary nail for a shaft fracture, and a trifin nail, or a nail and plate, for fractures at the upper end of the femur

I wish to thank the consultant staff at University College Hospital, London, for permission to publish details of the patients under their care For advice and constructive criticism freely given during the preparation of this paper, I am indebted to Dr Gwen Hilton, who has cared for all the patients in this series, and to Mr C W Flemming, who has treated many of the patients and who performed all the operations on the femurs

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MIXED ADRENOGENITAL-CUSHING SYNDROME FOLLOWING THYROIDECTOMY

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THE relationship of the adrenal cortex to the thyroid has been extensively investigated, and clinical and experimental observations have shown that corticotrophin and cortisone, or other adrenal cortical steroids, can modify the activity of the thyroid gland The nature of this adrenal thyroid relationship has been investigated in rats and guineapigs with reference to the production of exophthalmos (Aterman 1952, 1954, Aterman and Greenberg 1954), organ weights, growth, and food utilisation (Greenberg and Aterman 1955), and the prevention of hepatic necrosis (K Aterman, personal communication), and it has been shown that the thyroid and adrenal cortical secretions have mutually antagonistic actions In particular, thyrotoxicosis can suppress the effects of hypersecretion of the adrenal cortex or cortisone administration, and thyroidectomy can cause the appearance of hitherto suppressed symptoms of cortical hyperactivity

In the case described here the appearance of a mixed Cushing-adrenogenital syndrome closely followed thyroidectomy in a patient with an adrenal carcinoma which had shown no characteristic hormonal effects

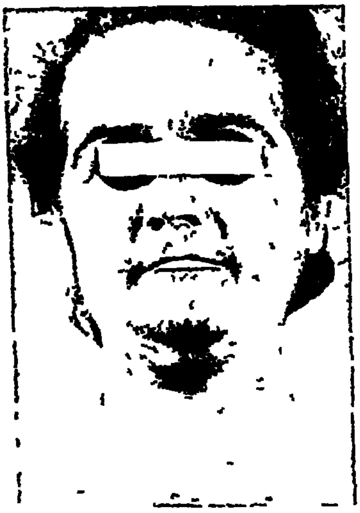

Fig 1—Patient showing hirsuties, acne, moon face, and thyroidectomy scar

Case-report

A married woman, aged 35 (fig 1), with three children, presented in November, 1954, with slightly irregular menstrual periods, dyspnœa and choking, sweating, agitation, and recent enlargement of a goitre which had been present for twelve years She had a diffuse goitre, tremor, moist palms, tachycardia, and blood pressure 160/80 mm Hg, but no exophthalmos Mild thyrotoxicosis was diagnosed, and subtotal thyroidectomy was done at another hospital on Feb 24, 1955 Her thyroid gland had large colloid filled acini lined by flattened epithelium, resembling those found in simple colloid goitre (fig 2)

The patient developed amenorrhœa in March and swelling of the ankles in May In June she noticed increasing growth of hair on her upper lip and chin, increased deposition of fat on her abdomen, and the appearance of striæ on her legs and abdomen like the striæ which appeared after her pregnancies She was advised by her doctor to take less salt and on this regime her ankle swelling subsided for two weeks She developed pain in the small of her back, later radiating down the inside of her thighs to her knees She was admitted to hospital on Oct 5, 1955

Examination

She was well nourished, with hirsuties and fullness of the face, and acne of the face and chest Her skin and hair were coarse, she had very slight pitting œdema of her ankles and striæ on her thighs and abdomen resembling striæ gravidarum A large hard mass in the right lumbar region moved on respiration and was not tender or fluctuant Her clitoris was slightly enlarged and her pubic hair of female distribution Her blood pressure was 135/95 mm Hg

Investigations

Serum sodium 136 m eq per litre, serum potassium 5 6 m eq per litre, serum chloride 105 m eq per litre, serum alkaline phosphatase 7 4 units per 100 ml (These values are within the range accepted as normal) White cells 8600 per c mm (no eosinophils seen) Urinary excretion of 17-ketosteroids 52 mg in 24 hr (normal range in Dr A C Crooke's laboratories is 12 ± 6 mg in 24 hr) Intravenous pyelography showed that the right kidney was displaced downwards and rotated by a large vague mass lying above it There was no albuminuria

Diagnosis

In view of the hardness and size of the mass in the loin, the pain in the back and thighs, and the ankle œdema it was decided that a carcinoma of the right adrenal gland was producing a mixed Cushing adrenogenital syndrome

Further Course

On the fifth night after admission, before an operation could be done, the patient suddenly collapsed She became shocked, with pallor, sweating, a small pulse (rate 100), and systolic blood-pressure 80 mm Hg There was no abdominal rigidity or tenderness, but there was gross œdema of the legs and thighs

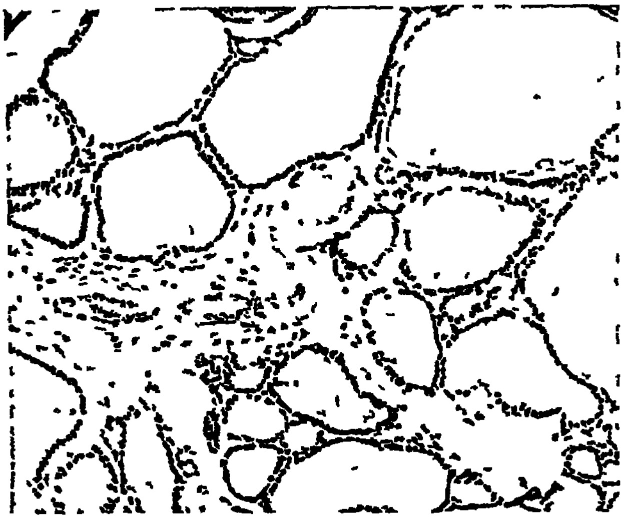

Fig 2—Thyroid gland, showing large colloid filled acini with flattened epithelium

Emergency investigations showed serum sodium 143 m eq per litre, serum potassium slightly raised (6 0 m eq per litre), serum chloride 104 m eq per litre, blood urea 38 mg per 100 ml, some hæmoconcentration, urine sp gr 1 018, albuminuria +++ In spite of the exhibition of intramuscular hydrocortisone 100 mg her condition rapidly deteriorated and she died

From the clinical point of view this severe spontaneous collapse was thought to indicate final adrenal failure due to hæmorrhage or metastasis in the remaining functional adrenal tissue

Necropsy Findings

The body was moderately obese (weight 74 1 kg, length 5 ft 7 in) The extremities were cyanotic, and there was œdema of the legs Hirsuties, facial acne, striæ on abdomen and legs, and clitoral enlargement were confirmed There were two small xanthomas at the inner angle of the left eye The breasts were well developed

The abdominal cavity contained 800 ml of straw coloured fluid There was a mass in the right upper quadrant, attached to the upper pole of the right kidney, measuring 22 × 15 × 15 cm It was encapsulated, and there were many vessels coursing over its surface Its cut surface was soft and brownish yellow, with areas of old and recent hæmorrhage The tumour had invaded the suprarenal veins and, through these, the inferior vena cava immediately below its intrahepatic portion The last centimetre of the hepatic veins and the intrahepatic vena cava were blocked by a cord of tumour ascending and terminating in a globular mass, 2 5 × 2 5 × 4 cm, in the right atrium

Tumour embolus plugged a secondary branch of the pulmonary artery, distal to this the lung had a pale infarction Throughout the lungs were scattered secondary deposits of the neoplasm up to 0 5 cm in diameter There was a massive intrabronchial hæmorrhage, the source of which was presumed to be the secondary growth

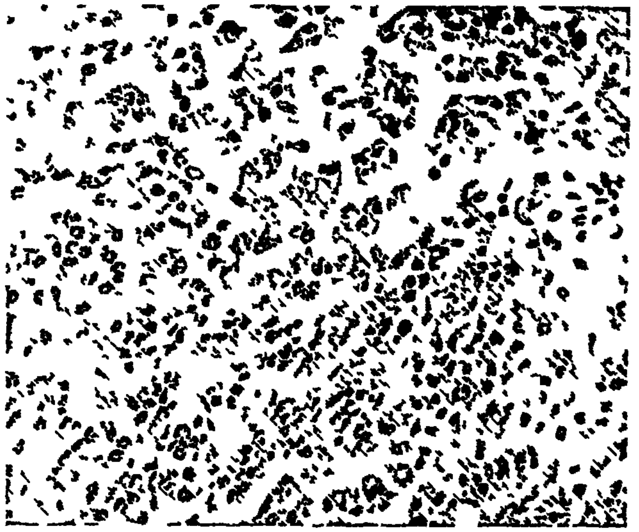

Fig 3—Adrenal carcinoma

The left adrenal gland was much atrophied (4 g) The ovaries were atrophied, there were no corpora hæmorrhagica The uterus was small, and the endometrium normal in thickness The pituitary gland was normal in size On either side of the trachea, embedded in scar tissue, small nodules of thyroid tissue were found The liver was enlarged, its cut surface showing centrilobular congestion

Histology

The tumour was a poorly differentiated polyhedral cell carcinoma of the adrenal cortex, with a scanty stroma (fig 3) The cells were large, with abundant eosinophil and faintly granular cytoplasm and large round or oval nuclei usually with prominent nucleoli Mitoses were uncommon, and there was some necrosis The mass in the vena cava, right atrium, and pulmonary artery consisted of tumour with a little superficial thrombus The cytoplasm contained a little sudanophil lipoid irregularly distributed throughout the tumour Broster and Vine's ponceau fuchsin stain showed fuchsinophil granules very irregularly distributed, within the cells were very occasional granules which stained with periodic-acid-Schiff and proved to be glycogen by the diastase control method The left adrenal cortex was much atrophied, especially the zona fasciculata The cells were packed with sudanophil lipoid, except a narrow zone at the outer part of the zona glomerulosa Ponceau fuchsin staining did not show fuchsinophil granules, occasional cells containing granules stained by periodic acid Schiff were seen in the zona fasciculata

The pituitary gland showed marked alteration of the basophil cells, which were hypertrophied and vacuolated, and 60% of them were hyalinised (Crooke 1935) This hyalinisation was most clearly shown by periodic acid Schiff staining and affected both central and peripheral cells, sparing only those basophils posterior to the intermediate cleft Many of the affected cells were completely hyaline, with practically unstained cytoplasm, within which vacuolation was still present A few cells of the general size, shape, and nuclear configuration of basophils had very clear cytoplasm within which were a few large granules and rods which stained with periodic acid Schiff, such cells were confined to the central portion of the gland Gomori's aldehyde fuchsin stain also showed the hyalinisation, and some basophils were not stained This method was also capricious in differentiating basophils into stained (β basophils) and unstained (α basophils), hence evidence of localisation of either type of cell at the periphery or centre of the gland was lacking Both types of granule, with or without hyaline change, sometimes occurred in the same cell 20% of the cells classified as "chromophobe" from the Mallory stain contained material which took the periodic acid Schiff stain The distribution of this varied from a few large vesicles to a diffuse granulation within the cytoplasm Many of the finely granulated cells resembled small basophils, but none showed hyalinisation Occasional acidophils contained a minute body which took the periodic acid Schiff stain, usually paranuclear in position Phospholipid within the acidophils was normal in amount, the only change noted being a slight degranulation compared with control sections stained on the same slide

Discussion

Adrenal cortical overaction in the adult female commonly presents either as Cushing's syndrome or as the adrenogenital syndrome (Taylor 1955) The adrenogenital syndrome has been defined by Hartman and Brownell (1949) as (1) disturbance and cessation of menstruation, (2) hypertrichosis of face, limbs, hands, feet, and trunk, (3) deeper and coarser voice, (4) enlargement of the external genitalia, degeneration of the ovaries, and diminution in size of the uterus, (5) alteration of bodily contour, which becomes short, thickset, broad shouldered, deep chested, and narrow hipped, and (6) underdevelopment of breasts and obesity Hartman and Brownell emphasise the rarity of adrenal tumours as a cause of this condition

The onset of the Cushing adrenogenital syndrome in our patient dated from the thyroidectomy, this may be interpreted as a "release" of the adrenal cortical steroids produced by the carcinoma, and which—before thyroidectomy—could not produce their characteristic effects The progression of events is similar to that seen in the rat and guineapig by Aterman and Greenberg (1954) who found that thyroid hormone inhibited cortisone induced exophthalmos and modified the characteristic signs of hypercorticism, such as atrophy of the adrenal glands and involution of the thymus Also, thyroidectomy in rats accentuated the signs of hypercorticism or allowed these signs to appear at a lower level of cortisone administration In the case described, transition from a slightly hyperthyroid state to a hypothyroid state led to the appearance of florid symptoms of hypercorticism

The adrenogenital syndrome and Cushing's syndrome can be combined in the same patient, Lucas et al (1955) describe the case of a 34-year old mother of two children with an adrenogenital syndrome due to carcinoma of the left adrenal cortex The tumour was removed but recurred a few months later, this time associated with Cushing's syndrome The patient died five months after the original operation

The only other published case related to thyroidectomy that we have been able to find was described by Hurxthal and Musulin (1953) A man, aged 25, presented with an illness which, in retrospect, was believed to be a Cushing syndrome Thyroidectomy was done, and the patient became much worse, he became fatter and much more weak, and sluggish, and developed generalised osteoporosis with many pathological fractures He died after exploratory craniotomy, necropsy findings are not mentioned The mode of progression of this case is very similar to that of the one recorded above the intact thyroid gland appeared to be controlling or suppressing the symptoms, and thyroidectomy led to the "release" of the abnormal adrenal cortex and the appearance of much more pronounced symptoms of hypercorticism The present case and that of Hurxthal and Musulin (1953), with their similar modes of progression, suggest that this hormonal pattern is of fundamental importance in the adrenogenital syndrome and Cushing's syndrome

We have no direct evidence that the tumour was present before thyroidectomy, but, in view of its massive size five months later and the natural history of this type of growth, there is very little doubt that it was already in existence

The pituitary cytology is of interest There was no selective damage to the central mass of basophils which correspond in position with the thyreotrophs (β basophils) of the rat There were, however, central clear cells which correspond very closely in morphology to the "thyroidectomy cell" of the rat (Purves and Griesbach 1951) and may indeed be of a similar nature

Summary

A case of mixed adrenogenital Cushing syndrome is presented

The precipitating factor is believed to have been thyroidectomy, with the "release" of adrenal cortical secretions, and the appearance of the characteristic symptoms of hypercorticism

Cells like the rat "thyroidectomy-cell' were found in the pituitary gland

We thank Prof F A R Stammers, under whom the patient was admitted, for permission to publish, and Prof J W Orr for valuable advice and criticism

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ACUTE OSTEOPOROSIS WITH HYPERCALCÆMIA

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OSTEOPOROSIS, as an intrinsic disorder of bone, is associated with normal serum-calcium and serum-phosphorus levels The finding of a raised serum-calcium level with radiological evidence of osteoporosis strongly suggests that the disorder of bone is secondary to a disturbance of calcium metabolism such as hyperparathyroidism (Cooke 1955)

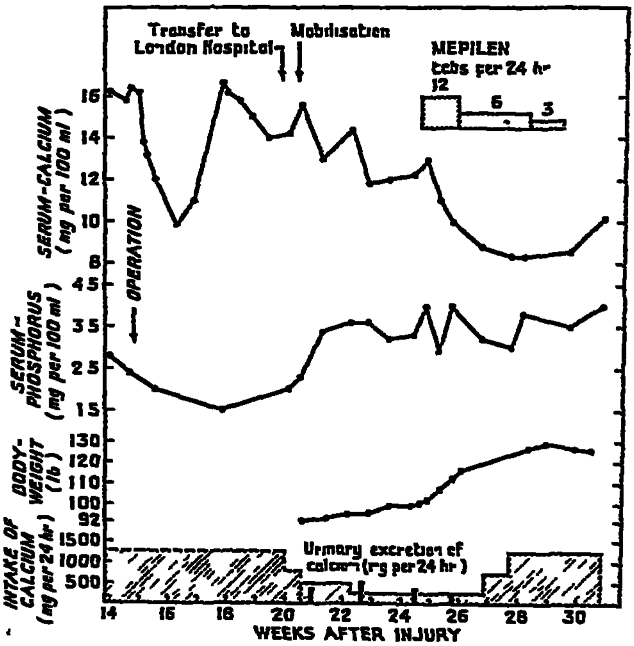
Albright et al (1941) reported osteoporosis with a raised serum-calcium level in a boy, aged 14, with a fractured femur The initial diagnosis of hyperparathyroidism was discarded when exploration of the neck and mediastinum did not reveal a parathyroid tumour It was concluded that the bony injury and subsequent immobilisation were responsible for the osteoporosis and hypercalcæmia When the patient was mobilised the serum-calcium level returned to normal A similar case, also cured by mobilisation, was reported by Halvorsen (1954)

I report here an example of the syndrome in a young adult

Case-report

A woman aged 22 was admitted to another hospital on Oct 15, 1955, after a motor accident Examination revealed a comminuted fracture of the left side of the pelvis a crush fracture of the third lumbar vertebra, and a lesion of the cauda equina which caused weakness of the right leg and almost complete paralysis of the left leg, the bladder and anal sphincters were also affected

Treatment and Progress—Skin traction was applied to the left leg for six weeks When this was discontinued, a back slab was applied to the leg and physiotherapy was started This was confined to passive movement and faradic stimulation of the lower limbs Three weeks after injury the patient lost her appetite and was given milk instead of solid food She became progressively more thirsty and drank up to eight pints of milk daily A week later she started to vomit, and her pulse rate rose to 120 Her general condition steadily deteriorated loss of weight being constant and severe Fourteen weeks after injury her weight had dropped by 50 lb the tachycardia was persistent, and anorexia, vomiting lethargy, and muscular weakness were predominant There was also obstinate constipation, which caused fæcal impaction on one occasion Radiography showed osteoporosis of her legs lumbar spine and pelvis Her urine which had become infected soon after her injury, contained pus despite constant and varied treatment Her blood urea level, which had been normal on three previous occasions was 39 mg per 100 ml



Her serum-calcium level was 16 2 mg per 100 ml, serum-phosphorus 2 8 mg per 100 ml, and alkaline phosphatase 9 0 K. A units

Operation—When the presence of hypercalcæmia had been confirmed on succeeding days, the parathyroid glands were explored on Jan. 28, 1956 but no adenoma was found One parathyroid gland was removed but was found normal on histological examination

Postoperatively the serum calcium level fell rapidly (see figure) and the patient's condition much improved, but this improvement was short-lived and all the previous symptoms returned two weeks after the operation, and the serum-calcium which had been 9 8 mg per 100 ml nine days after the operation, rose again to 16 0 mg per 100 ml The patient was transferred to the London Hospital on March 2, 1956, nineteen weeks after her original injury

On admission she was very ill and wasted, weighing 92 lb and having a pulse rate of 110 and gross atrophic palsy of the legs, particularly the left leg and buttock Her bladder did not empty completely, and her urine was infected

Investigations—Her blood contained sodium 148 m eq per litre, chloride 96 m eq per litre, bicarbonate 35 m eq per litre, potassium 4 6 m eq per litre, urea 48 mg per 100 ml, plasma proteins 8 4 g per 100 ml., alkaline phosphatase 3 0 K.-A units (on three occasions), calcium 14 2 and 15 6 mg per 100 ml, phosphorus 1 9 and 2 3 mg per 100 ml (at this level the rate of urinary excretion of phosphate was 0 2 mg a minute) The urinary excretion of calcium was 383 mg in twenty four hours Radiography showed osteoporosis of the legs, pelvis, and lumbar spine The original fractures had not healed The skull showed no radiological abnormality, and there was no evidence of renal calculi or of nephrocalcinosis

Treatment and Progress—In view of the absence of increase in serum phosphatase level the high serum calcium level could not be attributed to hyperparathyroidism but seemed more probably the result of bony fractures and immobilisation An intensive programme of active movements was therefore started Although the patient's legs were capable only of minimal movement her activity was increased rapidly by exercising all the other muscle groups At the same time her intake of calcium was reduced to 500 mg daily and, two weeks later, to 250 mg daily On this regime she made steady progress vomiting and thirst disappeared, her appetite returned and her weight increased The serum-phosphorus level quickly rose to normal, but the serum-calcium fell slowly until it remained steady at 12 mg per 100 ml The calcium balance remained negative, the urinary excretion of calcium being 372 mg in twenty four hours after two weeks on an intake of 250 mg in twenty four hours This failure to return to complete normality despite adequate mobilisation, was evident twenty five weeks after the patient's injury In a further effort to improve the calcium metabolism

'Mepilin' (ethinyl œstradiol 0 01 mg with methyl testosterone 3 mg per tablet) was administered in an initial dose of 12 tablets daily This treatment produced a rapid rise in weight and a drop in serum-calcium level to 8 4 mg per 100 ml The urinary output of calcium also fell to normal, and the alkaline phosphatase level rose to 6 0 K A units Since the patient's weight continued to rise and her general condition was very satisfactory, the dose of mepilin was decreased and the intake of calcium increased The serum calcium level then returned to normal, and the patient's subsequent progress was only interrupted by an attack of pyelitis Her left ankle required manipulation to restore free movement, but then she could walk well without a stick

Discussion

Within four weeks of injury this patient developed anorexia, vomiting, thirst, constipation, tachycardia, and progressive loss of weight The cause of these symptoms, which had persisted for ten weeks, was attributed to hypercalcæmia The raised serum-calcium level and lowered serum phosphorus level prompted a search for a parathyroid tumour Removal of one parathyroid gland and examination of the others was followed by a transient disappearance of the hypercalcæmia However, the disturbance recurred, suggesting either a parathyroid adenoma in the mediastinum or some other cause of the hypercalcæmia

In appraising the situation nineteen weeks after injury it was noted that the raised serum-calcium level was associated with an alkaline-phosphatase level at the lower limits of normality, and that the lowered serum phosphorus level was accompanied by a normal rate of urinary excretion of phosphorus Furthermore the radiological evidence of osteoporosis was confined to the area of injury and of immobilisation, nor were there any specific radiological signs of hyperparathyroidism These points, taken in conjunction with the patient's initial bony injury and subsequent immobility, led to the diagnosis of acute osteoporosis with hypercalcæmia The appropriate treatment, active movement and restricted intake of calcium (Albright et al 1941) proved partially successful Therapy with œstrogen and androgen, as suggested for postmenopausal osteoporosis (Albright et al 1940), caused an immediate increase in osteoblastic activity with a fall in the serum calcium level, a decrease in the urinary output of calcium, and a rise in the alkaline phosphatase level This good clinical response indicated the effectiveness of hormone therapy in a case of bony atrophy from disuse, confirming the experimental findings of Armstrong et al (1945)

The changes in calcium balance which follow bony injury and immobilisation were studied by Howard et al (1945), who found that the urinary loss of calcium increased for four weeks and continued at a maximal rate for at least two months, and that the loss of nitrogen was maximal within a few days and disappeared within a month This work supported the contention of Albright et al (1941) that immobility was a more important factor than the initial injury in producing a negative calcium balance The prime importance of immobilisation was proved by the observation of a sustained loss of calcium in healthy men encased in plaster (Dietrick et al 1948) This effect is confirmed by the radiological demonstration of osteoporosis in the legs of all patients immobilised for three or more months (Stevenson 1952)

Only a small amount of activity is required to inhibit the loss of calcium from immobilisation, healthy men encased in plaster do not develop a negative calcium balance if placed on a rocking bed (Dietrick 1948) The patient whose history is recorded here was never fully immobilised by splinting but did not respond to mobilisation so satisfactorily as the patients of Albright et al (1941) and Halvorsen (1954) The major difference between their patients and the present one lies in her neurological lesion, which prevented active movements of her legs Wilkins (1945) reported losses of calcium up to 1 g daily in patients with poliomyelitis, and Orr (1941) reported a serum-calcium level of 18 mg per 100 ml in a child with poliomyelitis Furthermore the use of a rocking bed does not prevent loss of calcium in a paralysed patient (Wyse and Pattee 1954)

Immobilisation causes atrophy of bone because it removes the stresses of movement which are the normal stimulus to osteoblastic activity Healthy bone is in a constant state of flux, bone deposition balancing resorption, hence a cessation of osteoblastic activity due to immobilisation allows resorption to continue and leads to osteoporosis In the rare cases of osteoporosis with hypercalcæmia, such as the one described here, the resorption of bone must be very rapid to allow so much calcium to enter the circulation Hence the condition is unlikely to arise unless the bone was previously in a state of rapid metabolism Paget's disease provides an example because both the formation and the destruction of bone proceed more rapidly than normal If a patient with Paget's disease is immobilised, acute osteoporosis with hypercalcæmia develops (Albright and Reifenstein 1948) Similarly the increased metabolic activity of young bone compared with the adult skeleton (Leblond and Greulich 1956) probably explains why hypercalcæmia after immobilisation alone is confined to children But these observations do not explain the sustained hypercalcæmia in the present patient, who had no previous bone disease and was fully grown

In the present case it seems possible that there may have been a breakdown in the homœostatic relationship between the blood-calcium level and the activity of the parathyroid glands Under physiological conditions the rate of secretion of the parathyroid hormone varies inversely with the serum-calcium level (McLean 1956) Hence the hypercalcæmia due to skeletal immobilisation should be self-limiting owing to inhibition of parathyroid function In this patient, however, hypercalcæmia persisted although the parathyroid glands were structurally normal Indeed the only occasion when the blood-calcium level fell was after operative exploration at which one parathyroid gland was removed—i e , when, on the analogy of subtotal thyroidectomy, a temporary inhibition of parathyroid secretion may have been induced If this is true, the reappearance of hypercalcæmia would coincide with the resumption of secretion of the parathyroid hormone If indeed there was in this patient a breakdown in the homœostatic relationships between the serum-calcium level and the secretion of the parathyroid hormone, we have no evidence to suggest the reason for the breakdown or for the restoration to normal which took place when the negative calcium balance was corrected by mobilisation and hormone therapy

Summary

A case of acute osteoporosis with hypercalcæmia in an adult without previous bone disease was successfully treated by mobilisation, restricted intake of calcium, and hormone therapy

It is suggested that a breakdown in the normal homœostatic control by the parathyroid glands was responsible in some measure for this syndrome

I am deeply indebted to Dr J Kidd for the early records of this patient and his kindness in transferring her to the London Hospital, to Mrs E Scott and her staff for nursing and dietetic care of the patient, and to Mrs M N Hryniewicz for the biochemical work

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References continued at foot of next column

BENIGN GASTRIC ULCER PERFORATED CHRONICALLY INTO THE SPLEEN

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PERFORATION and hæmorrhage are said to complicate about 6% of perforated ulcers Uncommon chronic perforations into aorta, portal vein, pleura, pericardium, heart, and other organs have been reported In the case described here a benign gastric ulcer was associated with hæmorrhage and had perforated into the spleen

Case-report

A white man, aged 36, had had, from 1946 to 1951, attacks of epigastric burning pain after meals and pyrexia (102°F) of several days' duration

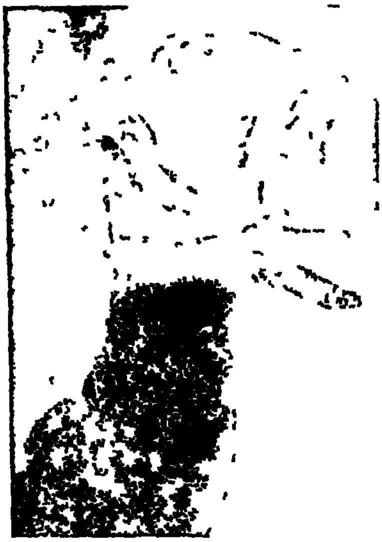

Fig 1—Stomach showing barium level and gas bubble on its left side

On admission on April 5, 1951, he had severe melæna hæmatemesis, and consequent anæmia Radiography disclosed a strange barium level and gas bubble on the left side of the stomach (fig 1) This cavity filled with barium from the stomach when the patient bent over to his left Urography and an opaque enema showed no relations of colon or kidneys with the cavity At exploratory laparotomy no lesion was found, and the patient was discharged

A year later, in 1952, he had another hæmatemesis and melæna This time he underwent subtotal gastrectomy, but the abnormal barium level and gas bubble still appeared to the left of the resection

On April 10, 1956, after three and a half years of calm, he had a sudden severe melæna, with anæmia (2,000,000 red cells per c mm) He was given a blood transfusion and operated on

On laparotomy the stump of the duodenum appeared normal, and no jejunal ulcers were found On the greater curvature were thick adhesions to the spleen and the splenic flexure of the colon The spleen was large and divided into two lobules, diffuse perisplenitis made it adherent to the peritoneum of the abdominal wall The splenic flexure of the colon was bound to the spleen by the same fibrotic process These adhesions were freed with difficulty and the spleen was exteriorised but, when this had been done, the greater curvature of the stomach was seen to fit into the spleen's hilum Longitudinal gastrostomy revealed an ulcer situated high on the greater curvature, perforating into the hilum of the spleen, and having a crater 1 cm wide The spleen was removed and the gastrostomy closed, and the patient recovered uneventfully

Pathology

The spleen measured 11 × 8 × 5 cm and was deeply indented on its external wall Its hilum was covered by a rhomboidal segment of gastric wall, whose centre corresponded to an ulcerous niche 20 mm across and 2 mm deep (fig 2) Section revealed a fibrotic bed, with large blood vessels, continuous with fibrotic intrasplenic tissue The niche was covered almost completely by simple cylindrical gastric epithelium There were a few small areas without epithelium, probably the remains of a primitive ulcer Nearby and beneath the epithelised area were large blood spaces, covered with thin endothelial walls, and arteries, resembling an angioma Thick bands of connective tissue containing much iron pigment invaded the splenic parenchyma

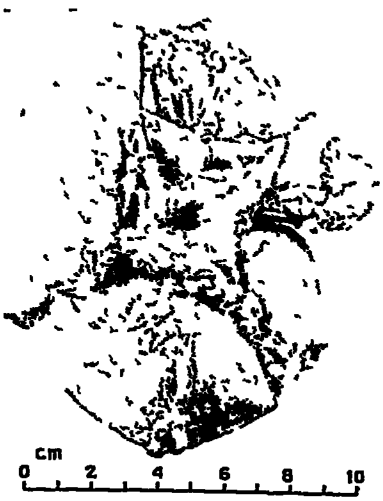

Fig 2—Spleen with adherent gastric wall

Summary

A case is reported in which a benign chronic ulcer of the greater curvature of the stomach perforated into the hilum and parenchyma of the spleen

This ulcer was not found at operation for subtotal gastrectomy A second operation revealed the ulcer which had provoked massive severe hæmorrhage by damage to the splenic vessels

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CARDIAC COMPLICATIONS OF COXSACKIE-VIRUS INFECTION

EVAN FLETCHER
M D Belf, M P C P, D[illegible]
PHYSICIAN

C F B[illegible]
M B Bel[illegible]
SENIOR [illegible]

BELFAST [illegible]

DURING *our* [illegible] the causes of benign pericarditis, we found [illegible] of Coxsack[illegible] virus *infection*, [illegible] special [illegible] is [illegible] Myocarditis has [illegible] dis- [illegible] son- and W[illegible] 19[illegible] [illegible] 195[illegible] how Coxsac[illegible] disea[illegible] into (Ja[illegible] treet, [illegible] w [illegible]

ANTIBODY TITRES TO SEVERAL VIRUSES

Test	Specimen (days after admission)	Results					
Neutralisation test	Convalescent serum (10)	Virus (Coxsackie subgroup)	B1	B2	B3	B4	B5
		Titre	<1/8	<1/8	<1/8	1/128	<1/8
Complement fixation test		Virus	Influenza		A P C group	Q fever	Psittacosis L G V
			Sol A	Sol B			
	Serum 1 (29)	Titre	<1/8	<1/8	<1/8	<1/8	<1/8
	Serum 2 (46)	Titre	<1/8	<1/8	<1/8	<1/8	<1/8

electrocardiographic tracings in our case over a period of four months

Case-report

A woman aged 28 was first seen in her own home for an influenza like illness 5 days previously she had taken suddenly ill, with sore throat, fever, headache, profuse sweating, cough, and sharp pains in the chest Her parents were the only other occupants of the house, and her mother had similar symptoms of the same duration, and was confined to bed in an adjacent room Her father, though ambulant, had malaise, headache, cough, and sweating attacks

The daughter's temperature was 100°F and the skin was moist There were fine crepitations at both lung bases, the pulse was slow and irregular, and a pericardial friction rub was audible over the precordium The heart sounds were normal, and there were no murmurs, blood pressure 140/80 mm Hg The fauces were inflamed but no vesicles were seen The mother was also examined and was found to have a pericardial friction rub and a temperature of 100°F The father was not examined The patient was admitted to hospital next day for investigation Her parents declined further study, and remained at home

On admission, the patient's temperature had fallen to 98°F, and she had no further pyrexia The basal crepitations had completely cleared up on the 3rd day after admission The pericardial friction rub persisted for a further 3 weeks, but she was symptom free a few days after admission Radiography of chest showed normal heart shadow and clear lung fields (day of admission), repeat radiography and fluoroscopy at weekly intervals during her 29 days in hospital showed no evidence of pericardial effusion, or any other abnormality White cell count 3500 per c mm Blood sedimentation rate (Westergren) 27 mm in the first hour on day of admission, 10 mm on 6th day Mantoux negative (1 in 1000) Throat swab *Streptococcus viridans*, pneumococci, *Neisseria catarrhalis* Samples of the patient's convalescent serum were submitted to the Virus Reference Laboratory, Colindale, London, for virus antibodies, and titres obtained are shown in the accompanying table These results indicated a type-B4 Coxsackie infection

Because of the evidence of cardiac involvement, serial electrocardiograms were recorded during the patient's stay in hospital and thereafter at follow up examinations as an out patient for 3 months In addition to evidence of pericarditis, there was a persistent extrasystolic arrhythmia, the ectopic focus apparently situated in the A–V node Fig 1 is from lead 2 recorded on the day of admission It shows sinus arrhythmia, complicated by a non compensatory extrasystole, which disturbs the basic sino auricular rhythm by retrograde auricular activation closely related in time to its ventricular complex This appears to indicate that the ectopic focus is situated in the A V node, the ventricular complex being moderately aberrated The T waves are inverted—that of the beat following the extrasystole more than the others Fig 2 was recorded 3 weeks later It differed in no way from previous serial tracings The extrasystolic arrhythmia persists, and the significant abnormality is the negativity of the T waves in leads 2, 3, and V_3–V_6 Subsequent serial tracings over the following 2 months resembled fig 2 Thereafter the extrasystoles diminished in number, and after a further few weeks the electrocardiogram reverted to within the normal range

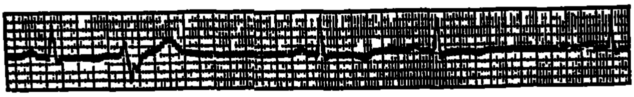

Fig 1—Coxsackie pericarditis Lead 2 (time marker 0 02 sec) Sinus arrhythmia with nodal extrasystole Abnormal T waves, more negative in post-extrasystolic beat.

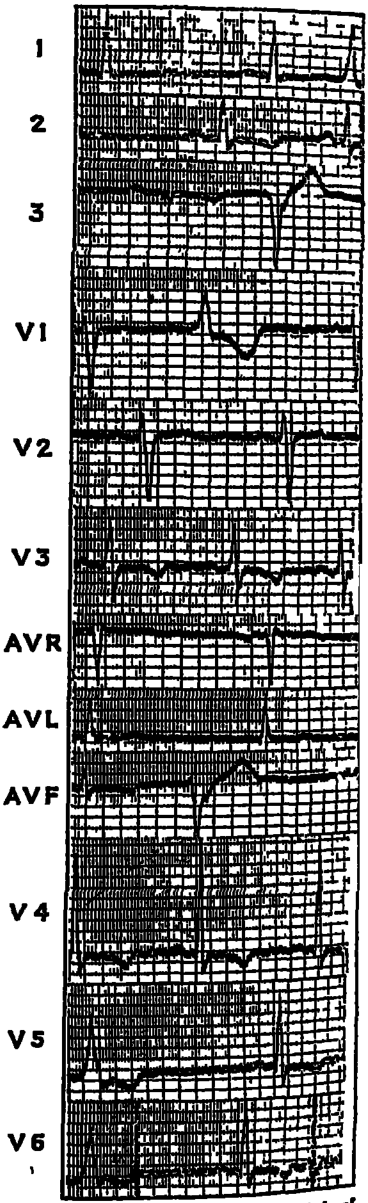

Fig 2—Coxsackie pericarditis End of third week Extrasystolic arrhythmia T negative in leads 2 3, and V_3V_6 (time marker 0 02 sec)

Discussion

Little is known about the pathogenesis of Coxsackie-virus infection in man Herpangina has been attributed to group-A Coxsackie-virus infection, and pleurodynia and aseptic meningitis to group B Viruses of group B4 have lately been isolated from the heart muscle in fatal myocarditis in newborn babies (van Creveld and de Jager 1956, Verlinde et al 1956) The viruses are probably universally distributed, and they have been isolated from sewage and flies (Jawetz et al 1956) Household exposure is important, and it is significant that the parents of our patient had a febrile illness at the same time Group B infection is usually associated with clinical illness, and it appears very likely that the case described—with a few days' fever and evidence of pulmonary and cardiac involvement—was related to the high titre of subgroup B4 There is no specific treatment The unique feature in our patient was the benign pericarditis, and possibly also myocardial involvement producing the persistent extrasystolic arrhythmia The electrocardiographic abnormalities remained in our case for some months after clinical recovery As Coxsackie virus infection may produce only minor symptoms which may be overlooked or forgotten by the patient, the discovery of abnormal electrocardiographic tracings, especially with regard to T wave changes in an otherwise healthy young adult, may raise the question of an unrecognised virus infection some months previously

Summary

A case of benign pericarditis is described in which it seemed very likely that infection with Coxsackie virus, ubgroup B4, was the cause Symptoms lasted only a ew days, but clinical signs of pericarditis persisted for ome weeks, and abnormal electrocardiographic records were present for some months As Coxsackie infection may produce only minor illness which may be overlooked, the possibility of its occurrence should be borne in mind when otherwise healthy young adults have abnormal electrocardiograms

We wish to acknowledge the valuable help of the Virus Reference Laboratory, Colindale London, and the useful advice and criticism of Dr C Cotton Kennedy, consultant clinical pathologist, Belfast City Hospital

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Preliminary Communication

A NEGLECTED SOURCE OF BLOOD-GROUP ANTIBODIES

FOR practical purposes the supply of rhesus (and other) antibodies comes from the serum of women who have been immunised by pregnancy They are usually of the common anti-D variety Less frequently antibodies are found in patients of either sex who have received repeated transfusions of blood containing antigens they themselves lack These are more likely to be the less common anti-E, anti-C, or anti-c, since they may arise in Rh(D)-positive recipients of blood which, although D-positive, is not necessarily compatible for the antigens E, C, and c

Only limited amounts of serum can be obtained from such people Clinicians are often reluctant to allow their obstetric patients to donate in the puerperium, even with the promise of compatible blood to replace any withdrawn

A large number of repeatedly transfused Rh(D)-positive patients will receive C or E or c incompatible blood, and immunisation particularly to the latter two, is to be expected in a few but often these patients have one or other of the blood dyscrasias, and their clinical condition rarely justifies venesection for the purpose of preparing test sera

Any additional source of antibodies therefore becomes of great value, especially when it can be obtained in really large quantities and with no inconvenience to the donor

The ascitic fluid from patients with such conditions as cirrhosis of the liver, who have received multiple transfusions and become immunised to a blood group antigen may form such a source It is surprising that this has received so little attention in the past There is practically nothing in the voluminous literature on the subject of blood group antibodies to suggest that the possibilities of this "by-product" have been properly explored Pickles,[1] however refers to the presence of the antibody Yt^a in a case of ascites and, in a personal communication describes an anti-c in the ascitic fluid of an R_1R_1 patient immunised by pregnancy

CASE REPORT

A female, aged 58, group O Rh positive and suffering from cirrhosis of the liver with œsophageal varices received several uneventful blood transfusions in 1956 Nothing unusual was found on cross matching until October of that year when she was found to be incompatible with one of four bottles of group-O Rh positive blood prescribed for her At this stage her genotype was determined as R_1R_1 (CDe/CDe), those of the three compatible bottles as R_1R_1 (CDe/CDe) or R_1r (CDe/cde) and that of the fourth the incompatible bottle as R_2r (cDE/cde) As was expected, her serum contained the antibody E

Her ascitic fluid was examined for anti-E, and this was found in appreciable amount, the best results were obtained by Löw s papain technique, visual reactions appearing in tubes incubated for an hour at 37°C Surprisingly good results were also obtained by Stratton s[2] "sandwich" technique, but with Löw s papain substituted for albumin[3]

Many litres of this valuable fluid have already been obtained, and, since her cirrhosis yields four or five litres of ascitic fluid a month, the supply of antibody is at present limitless

With the patient's consent and her doctor s coöperation, bi-weekly injections of EE (R_2R_2) blood are being given intravenously to boost the titre of her serum and, it is hoped, of her ascitic fluid The antibody appears to be fairly stable and can be stored frozen or freeze dried. It withstands at least twenty freezings and thawings and it has been reconstituted from the dried state without loss of potency

COMMENT

A programme of ab-initio immunisation of other cases of ascites has been planned Meanwhile, it is suggested that the serum and ascitic fluid of any patient with ascites who has had multiple blood-transfusions should be examined for the presence of the rarer Rh and other blood-group antibodies If only a fraction of 1% is found to be immunised the large yields of reagent will be ample compensation for the work involved

I have great pleasure in acknowledging the enthusiastic coöperation of Dr T C Jameson Evans, who has charge of the case, and of Dr C C Thomas, group pathologist, Farnham County Hospital, Surrey

South London Blood Transfusion Centre
Sutton Surrey

R A ZEITLIN
M R C S

[1] Pickles, M M *Brit J Hæmat* 1956 2 343

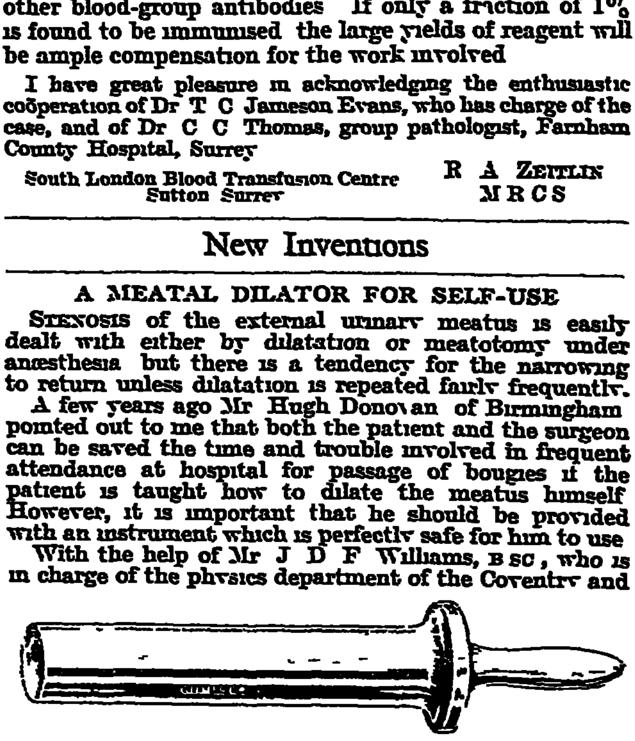
New Inventions

A MEATAL DILATOR FOR SELF-USE

STENOSIS of the external urinary meatus is easily dealt with either by dilatation or meatotomy under anæsthesia but there is a tendency for the narrowing to return unless dilatation is repeated fairly frequently.

A few years ago Mr Hugh Donovan of Birmingham pointed out to me that both the patient and the surgeon can be saved the time and trouble involved in frequent attendance at hospital for passage of bougies if the patient is taught how to dilate the meatus himself However, it is important that he should be provided with an instrument which is perfectly safe for him to use

With the help of Mr J D F Williams, B SC, who is in charge of the physics department of the Coventry and Warwickshire Hospital, I have devised a small instrument which has proved very satisfactory for this purpose It is made from 'Perspex,' has a very smooth surface, is boilable, and has a flange so that the instrument can only be passed for a limited distance The size of the instrument corresponds to 18 Ch, and this size has in practice, been found to be the only one necessary. After the initial dilatation the patient is given one of these instruments together with a supply of sterile water-soluble lubricant and is instructed how to cleanse the penis with dilute 'Dettol' solution and to introduce the instrument after it has been sterilised by boiling At first the instrument is used daily, but with the passage of time it is used at increasing intervals In many cases the tendency for the meatus to contract seems to disappear after a few months, and the patient, if reasonably intelligent can usually be left to determine how often he should introduce the dilator



The instrument has been made for me by the Genito-Urinary Manufacturing Company 28A, Devonshire Street, London W 1

Coventry and Warwickshire
Hospital

RICHARD E SHAW
CH M Leeds F R C S

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[2] Stratton F *Brit med J* 1955 i 201
[3] Löw B *Vox Sanguinis* 1955 5 94

Reviews of Books

The Child and the Outside World

Studies in Developing Relationships D W WINNICOTT, F R C P Edited by JANET HARDENBERG, M B London Tavistock Publications Ltd 1957 Pp 187 16s

IN several papers which form the main body of this collection, Dr Winnicott shows how the evacuation of town children to the country in war-time led to deeper understanding of the needs of children deprived of home life The evacuated children were all at first sent to private homes, but under the stress of separation from their families many became psychologically ill The experience gained in providing hostels for these children has greatly influenced the care given to children who, in peace-time, cannot be looked after at home It is clear how great a part Dr Winnicott has played in applying war-time understanding to peace-time difficulties

Those concerned with children who have to live away from home will find much to help them, and those whose responsibility is "placement" or "disposal" will find encouraging support for the view that "home is best" Since many of the children reacted to their deprivation by antisocial behaviour, the work in hostels has also had an important bearing on the treatment of juvenile delinquents

In quite another vein is the lecture to the 8th form of St Paul's School—Towards an Objective Study of Human Nature This little masterpiece should certainly be read by anyone seeking a simple and lucid description of what psycho-analysis is about

But this leads us to the paradox of Dr Winnicott's writings on the one hand, there is a deep understanding of the strong unconscious forces of love and hate at work in all children, and, on the other, the concept of a "normal" parent who has come to terms with his unconscious forces in a way which is seldom, if ever, found The standard for "normal" parental behaviour and feeling appears to be unattainable and may not even be desirable

The Visual Fields

A Textbook and Atlas of Clinical Perimetry DAVID O HARRINGTON, A B, M D, F A C S, clinical professor of ophthalmology, University of California School of Medicine London Henry Kimpton 1956 Pp 327 £6

THIS book may well become a successor to Traquair's famous monograph Professor Harrington, like the late H M Traquair, is an ophthalmologist with a deep interest in neurology, and his book shows Traquair's influence, particularly in the description of techniques for examining the visual fields

Simple non mechanical methods are Professor Harrington's first choice, but he has experimented with and accepted several novel procedures which more conservative schools would do well to examine For example, he has been able to eliminate many of the drawbacks of the older methods by using ultra violet illumination and fluorescent test objects for his perimetry and scotometry He has elaborated an ingenious system by which large numbers of subjects can be quickly screened—an outstanding need for busy eye clinics Patients fix the centre of a series of ten cards and are asked to describe the simple patterns which fluoresce for $^1/_4$ sec Incorrect answers lead to more extensive tests by orthodox methods

The second part of the book is devoted to the interpretation of defects in the visual fields, with chapters on each part of the visual pathway and many excellent diagrams of abnormal fields Where possible anatomical pictures indicate the proven position of the lesion Much effort has been spent on clear classifications, some of which are original Vast experience clearly lies behind the discussion of the many illustrative cases, but the uninitiated are kept constantly in mind Many full page illustrations show diagrammatically the field defects which can result from lesions at various anatomical levels The author's laudable attempt to keep the book self explanatory makes for rather dull reading in places and his style sometimes suffers for the sake of teaching

This is an excellent textbook for the beginner who intends to take visual-field testing seriously It has a good index and a fairly full bibliography and is therefore a useful reference book as well

Social Policies for Old Age

A Review of Social Provision for Old Age in Great Britain B E SHENFIELD, formerly a lecturer in social studies at Birmingham University London Routledge & Kegan Paul 1957 Pp 236 25s

BY gathering together much information, statistical and sociological, that has hitherto been hidden in various blue-books, Government publications, surveys, and elsewhere, the author has done a useful service Few doctors derive much regular intellectual nourishment from such sources, and many will be grateful for the help of this book

It sets out to present, in relation to the general problems of old age, the basic facts upon which social policies should be founded, and it succeeds A short but illuminating account of the demographic factors that underlie the recent rise in the number and proportion of old people in the population is followed by a long discussion of employment for the older worker and pensions Finally, the author deals with housing and the pattern of medical and other services available for domiciliary care

Her book will have a wide appeal, particularly to doctors and social workers concerned with old age who wish to enlarge their outlook on the subject

Manual of Anesthesiology

For Residents and Medical Students HERMAN SCHWARTZ, M D, S H NGAI, M D, E M PAPPER, M D, from the Anesthesiology Service, Presbyterian Hospital, New York Springfield, Ill Charles C Thomas Oxford Blackwell Scientific Publications 1957 Pp 170 32s 6d

UNLIKE most of its counterparts in this country, this introduction to the subject of anæsthesia concentrates on the scientific rather than the purely practical aspects, and in doing so it provides a good balance between the basic sciences and their applications to anæsthesia The text is derived from talks given to beginners and it effectively fulfils its aims of supplementing practical theatre work and encouraging the reading of original papers

Group Psychotherapy

The Psycho Analytic Approach S H FOULKES, M D, physician to the Bethlem Royal and Maudsley Hospitals, E J ANTHONY, M D, senior lecturer in child psychiatry, University of London, physician to the Bethlem and Maudsley Royal Hospitals Harmondsworth, Middx Penguin Books Ltd 1957 Pp 263 3s 6d

A CLEAR and comprehensive account is here provided of a method of psychotherapy that is making rapid strides and attracting much interest in psychological circles

In the first part of the book an introductory survey traces the history of group psychotherapy and relates the various methods since developed to the theories held by their authors. In the next three chapters, the group structure, the therapeutic process, and the technical and practical aspects of the treatment are discussed from the standpoint of group analysis, the method developed by Dr Foulkes in 1940

The second part is devoted to clinical illustrations with a commentary, and the third to chapters on the natural history of the therapeutic group, the phenomenology of the group situation, general dynamic theory and "metatheory" (speculations on theoretical and practical developments)

This book will inform the novice and stimulate the expert in this or other kinds of psychological treatment

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Physiopathology of the Reticulo-endothelial System (*Oxford Blackwell Scientific Publications* 1957 Pp 314 45s)—Among the participants in this symposium organised by the Council for International Organisations of Medical Sciences were Prof A A Miles, who spoke on local defences against infection in relation to the general reticulo endothelial defences, and Dr P G H Gell, who discussed the nature of some tissue hypersensitivity reactions The papers, edited by Dr B Benacerraf and Dr J F Delafresnaye, under the direction of Dr B N Halpern, are in English, there are summaries of each, and an introduction to the conference in French

THE LANCET

LONDON SATURDAY, MAY 4, 1957

Pulmonary Hypertension

THE many clinical features related to pulmonary engorgement, and the finding of atheromatous plaques in the pulmonary arteries at necropsy, led our predecessors to deduce that the pulmonary vascular pressure was raised in mitral stenosis as well as in other forms of left-sided heart-failure This was confirmed and put on a quantitative basis just over a decade ago when a cardiac catheter was first purposely passed into the pulmonary artery[1] Since then measurement of the pulmonary-artery pressure has become commonplace in all modern cardiological departments, and appreciation has grown apace of the circumstances in which pulmonary hypertension arises, and of the natural history of its various forms Clinical and laboratory assessment has led to renewed interest in the physiology of the pulmonary vessels, and opportunities are taken during catheterisation to gain information on such important matters as the innervation of the pulmonary vessels The results of these investigations are controversial Some suggest that the pulmonary vascular pressure-resistance may fall considerably under the influence of ganglion-blocking drugs[2] or minute doses of acetylcholine[3] given through a catheter into the pulmonary artery This supports the view, taken by **DALY**[4] after many years of painstaking study, that the pulmonary arterioles have an active autonomic innervation But in the treatment of patients with severe pulmonary hypertension ganglion-blocking drugs have failed, and **LEE** et al[5] have shown beyond any doubt that the pulmonary arterioles are not constricted in some of the baroceptor pressor reactions in which sympathetic vasoconstriction in the systemic vessels is easily demonstrated Yet, although the sympathetic innervation of the lung arterioles does not readily come into action in healthy people, it may become more active in pathological states

In mitral stenosis the rise in pulmonary arterial pressure is not always due to simple passive transmission of pressure from the left atrium Moderately raised at first, the pressure tends to become very high on moderate exercise, and later it may become persistently elevated at a level about or even above that in the systemic arterioles[6] This extreme pulmonary vasoconstriction is thought by some to protect against pulmonary œdema from extreme rises in alveolar capillary pressure , but this explanation tells us nothing of the mechanism Others believe that pulmonary œdema is not uncommon in the presence of extreme pulmonary hypertension[7]

In bronchitis and emphysema the pulmonary arterial pressure is at first raised only during acute exacerbations of bronchitis with intensification of cyanosis, and the pressure falls to normal when the attack passes off[8] In the more advanced stages of emphysema the pressure becomes more persistently raised between attacks The early reversibility of bronchitic pulmonary hypertension yielded a new concept of functional and reversible pulmonary hypertension, which was at first thought to be related to the alleged anoxic contraction of the pulmonary *vessels exposed to low oxygen tensions*[9], *but* subsequent investigations showed that this reaction is not so simple as was at one time thought[10] retention of carbon dioxide may be more important in its pathogenesis than oxygen lack[11] For example, it was found impossible to lower the pulmonary arterial pressure in emphysematous patients by giving them oxygen to breathe[8] Improved understanding of these questions will be important to the rational management of chronic bronchitis and its complications

Another group of pulmonary hypertensions are those complicating lesions which usually give rise to left-to-right shunts, such as atrial septal defects, ventricular septal defects, and patent ductus arteriosus Increased pulmonary vascular resistance may develop in these conditions at any age A young child may have it though an elderly patient with the same disorder does not[12] Such random development has been thought to be due to some such accidental circumstance as persistence of the strong fœtal muscular coat of the lung vessels[13] Among a series of cases of unexplained pulmonary hypertension, **WADE** and **BALL**[14] reported one with abnormally narrowed muscular arteries in the lungs resembling those found in fœtal lungs They do not, however, consider that persistence of the fœtal form of vessels causes the hypertension, but rather that hypertension provokes this type of anatomical reaction New development of muscle in the arterioles of patients with mitral stenosis has been noted by **HEATH** and **WHITAKER**[15]

In Egypt, and possibly less commonly in other tropical areas, bilharzial eggs may reach the lungs as emboli, setting up an organising obstructive lesion[16] In peripheral venous thrombosis recurrent small emboli may do the same[17] In some cases of pulmonary hypertension related to pregnancy the cause seems to be small thrombotic emboli , and **WOOD**[3] emphasises that these patients, in whom the disease begins sub acutely, should be treated with anticoagulants **Harrison**[18] has shown that multiple small fibrin thrombi lodging in the lung vessels can cause pulmonary arteriosclerosis, but pulmonary hypertension was not consistently established in such experiments[19] The complication of pulmonary arterial embolism plagues the pathologist in his analysis of the lung vessels in all forms of heart-disease, including pulmonary hypertension Two of **Wade** and **Ball**'s cases were thus obscured, but the emboli could be identified as complications, for abnormally small arteries were found beyond them There may even be local thrombosis—often as a complication of embolism, but sometimes as a primary local process in the main trunks of the pulmonary arteries[20]

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[1] Bloomfield R A Lawson H D Cournand A Breed E S Richards D W jun *J clin Invest* 1946 25 639

[2] Gilmour H R Kopelman H McMichael J Milne I G *Lancet* 1952 ii 898

[3] Wood P Diseases of the Heart London 1956

[4] Daly I de B Pulmonary Circulation and Respiratory Function University of St Andrews 1956

[5] Lee G de J Matthews M B , Sharpey Schafer E P *Brit Heart J* 1954, 16 311

[6] Bayliss R I S Etheridge M J Hyman A L *Lancet* 1950 ii, 889

[7] Davies L G Goodwin, J F Van Leuven B D *Brit Heart J* 1954 16 440

[8] Mounsey J P D Ritzmann L W Selverstone, N J Briscoe, W A McLemore G A *Ibid*, 1952 14 153

[9] Von Euler, U S , Liljestrand, G *Acta physiol scand* 1946, 12 301

[10] Fishman A P Himmelstein A Fritts H W jun , Cournand, A *J clin Invest* 1955 34 637

[11] Yu P N G Lovejoy, F W jun Joos, H A , Nye R E jun. *Ibid* 1953 32 130

[12] Campbell M. *Brit Heart J* 1955 17 511

[13] Gilmour J R. Evans W *J Path Bact* 1946 58, 687

[14] Wade G Ball J *Quart J Med* 1947, 26 83

[15] Heath D , Whitaker W *J Path Bact* 1955, 70 291

[16] Girgis B *Amer Heart J* 1952 43 606

[17] Davison P H , Armitage, G H McIlveen D G S *Lancet* 1956 ii, 224

Rarely pulmonary hypertension may appear in collagen disorders such as scleroderma, dermatomyositis,[21] pulmonary polyarteritis, and possibly rheumatic arteritis[14] This ill-defined group leads us into the unexplained pulmonary hypertensions, on which several reports have lately appeared[22–24] This idiopathic disorder often appears in young women Dyspnœa is an invariable symptom, but orthopnœa has not been recorded except by **Evans** et al[23] Effort syncope is a notable feature, and a remarkable study by **Howarth** and **Lowe**[25] showed that this was due to a form of acute right ventricular failure **Wade** and **Ball** observed a death in one such attack Substernal pain on effort is common and hæmoptysis unusual There are signs of right ventricular hypertrophy with an accentuated second sound, and the electrocardiogram shows right ventricular preponderance The characteristic large venous "a" wave described by **Wood**[26] is an important physical sign Peripheral cyanosis is, for the most part, related to a low cardiac output, but reduced oxygen-saturation of the arterial blood is sometimes found, which **Wade** and **Ball** think may signify the development of arteriovenous shunts in the lungs In some cases **Evans** et al,[23] in fact, showed by injection methods collateral and anastomotic communications Radiologically the larger pulmonary arteries at the root of the lung are enlarged, but the distal branches are grossly narrowed Hilar dance is absent **Shepherd** et al[24] emphasise that inhalation of oxygen induces significant relaxation of the arterioles in the lung in congenital cardiac disorders with pulmonary hypertension This relaxation may be recognised by a significant increase in arterial oxygen-saturation It is not seen in primary pulmonary hypertension, and in this condition they found it impossible to measure the "wedge pressure" in the pulmonary capillaries —no doubt because of anatomical arterial obstruction

The study of pulmonary hypertension is one of the great new fields opened up by cardiac catheterisation New facts are still being accumulated rapidly Much has been learned but much more remains to be done Perhaps in a few years it will be possible to reach a better synthesis than seems possible today

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18 Harrison C V *J Path Bact* 1951 63 195
19 Barnard P J *Circulation*, 1954 10 343
20 See *Lancet*, March 23 1957 p 625
21 Caldwell I W Aitchison G D *Brit Heart J* 1956, 18, 273
22 Heath D Whitaker W Brown J W *Ibid* 1957 19, 83
23 Evans W Short, D S, Bedford D F *Ibid*, p 93
24 Shepherd J T Edwards J E Burchell H B Swann, H J C, Wood E H *Ibid* p 70
25 Howarth S Lowe J B *Ibid* 1953 15 47
26 Wood P *Brit med Bull* 19 2 8 348

The Anatomy of Memory

Abnormalities of memory, perhaps even more than those of perception, take doctors within the terrain of philosophy In some ways the difference between an object and its memory-image epitomise the problem of mind and matter Memory, in any wide sense, is concerned in all learning and the ability to make use of past experience, and all conditioning is an aspect of memory, which must be admitted very early in the phylogenetic scale In man the term commonly has a more precise and limited usage the conscious recall or recognition of past experience—a process suggesting far greater psychological and physiological complexity Normal memory is capricious, and the defects associated with cerebral disease are highly varied It has been recognised since the time of **Hippocrates** that injury and disease of the brain may produce defects of memory, but it is only in the past century that memory has been correlated with focal brain lesions In 1888 **Hughlings Jackson**[1] reported a case of epilepsy in which the aura comprised a dreamy state where things seemed familiar, as if they had happened before, clinical evidence suggested a lesion in the "temporo-sphenoidal lobe" Some ten years later **Jackson**[2] reviewed other such cases, in one of which necropsy showed a lesion in the left uncinate gyrus Since then "uncinate fits," with a *deja vu* aura, have generally been considered to reflect discharge from the medial temporal region

Scoville and **Milner**[3] have now described 8 cases in which bilateral removal of the anterior part of the medial temporal lobe, including the uncus and hippocampus but leaving the lateral temporal cortex intact, permanently impaired memory for recent events The resections were made blindly through frontal trephine holes, and some were combined with orbital undercutting, but it is reasonable to suppose that the damage was in fact mainly in the antero medial aspects of the temporal lobes The memory defect was essentially one of "memorising," and there was no evident loss of preoperative memories or of intellectual ability Such findings seem to be the obverse of **Jackson**'s "discharging" lesions with their sense of diffuse reminiscence, but the precise rôle of the uncus remains in doubt, since in a further case, where the bilateral ablation included the uncus but fell short of the hippocampus, the memory defect was not noted Necropsies in Korsakow's amnesic syndrome (where the characteristic picture is gross loss of memorising combined with confabulation or pseudo-reminiscence to fill in the memory gaps) have shown maximal damage in the hypothalamic region and especially the mamillary bodies This is found not only in alcoholic cases but also when the syndrome is caused by cerebral neoplasm Thus two distinct anatomical sites seem to be involved in laying down memories, but they do not necessarily represent two disparate mechanisms, since the hippocampus projects by way of the fornix very largely on to the mamillary bodies, thus providing an anatomical basis for functional entity

These observations throw light on the process of memorising, but do not touch directly on the problem

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1 Jackson J H *Brain* 1888 11 179
2 Jackson, J H *Ibid* 1898, 21, 580
3 Scoville W B, Milner, B *J Neurol Neurosurg Psychiat* 1957, 20 11

of specific memories or what a past generation would have termed ' memory engrams ' Information on this is being provided by the study of epilepsy and its surgical treatment Occasionally the aura of epilepsy involves a memory, either visual or auditory, or both In some such cases **Penfield**[4] has located the epileptic discharge in the posterior temporal region of the dominant hemisphere He has elicited the visual and auditory "memory" by electrical stimulation of the cortex and occasionally the memory was not a static isolated affair but showed something of the normal march of naturally recalled happenings In a study of epilepsy following focal brain wounds **Russell** and **Whitty**[5] recorded cases of occipito-parietal and occipito-temporal wounds where specific remembered scenes arose as a visual aura In one case the memory aura was more complete and involved the re-experiencing of a past event including the sights, sounds and emotional content of the original situation. In such cases we see the storehouse of memory being artificially opened and the sites involved seem to be widespread in the posterior temporal temporo-occipital and even posterior parietal cortex. But the relation between the function of such areas and individual memories is certainly not a simple one It is impossible to say that this or that memory is contained in this or that area of cortex ; for if the cortex is excised the memory is often largely unaffected. Even in the sphere of word-memory where we can say with some certainty that excision of one area of cortex will produce an amnesic aphasia the correlation is far from precise What the excision brings about is not loss of the memory of a number of words but rather loss of memory of a diffuse skill in the use of symbols in which a surprisingly variable loss of individual word-memory is included. Indeed to think of memories in terms of locality may be to search for a chimæra for every memory must contain something that is the function of many (perhaps all) cortical areas—visual, auditory, motor, and sensory Nevertheless the evidence enables us to picture a mechanism with a subcortical and cortical substrate concerned in memorising: a mechanism which invokes the cortex to supply the specific content of individual memories

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[4] Penfield W Jasper H Epilepsy and the Functional Anatomy of the Human Brain London, 1954

[5] Russell W R Whitty C W M *J Neurol. Neurosurg Psychiat* 1955 18 79

Annotations

VIROLOGY AT GLASGOW

Glasgow University is to have a department and chair of virology the first of their kind in Britain[1] The department which is to be beside the main university site at Gilmorehill is expected to open in or about 1960. The Scottish Hospital Endowments Research Trust has given £225,000 to cover the cost of construction and equipment (estimated at £200 000) and the initial running costs. The Medical Research Council is to attach a research unit to the department. Dr. J. W Howie professor of bacteriology in the university, said last week that some fundamental research in human virology is being done in Great Britain but not nearly enough because our material resources for such work do not compare favourably with those overseas—notably in the U S A and Australia Professor Howie expressed his confidence that the new department will at least equal anything in existence elsewhere "We are hoping,' he declared. to establish a centre that will attract researchers from all parts of the world "

THE GROUP TEACHES ITSELF

Methods of teaching undergraduates are a perpetual source of argument, Lectures tutorials textbooks—all have their champions and detractors Prof J M Mackintosh[2] describes an interesting method used in postgraduate teaching in the department of public health at the London School of Hygiene and Tropical Medicine in which groups of students study some particular questions and present a report on each

Before the beginning of the academic year members of the teaching staff meet and discuss possible topics and 6 to 8 projects are decided on about the end of October Each is briefly described on the students' note-board The students state their preferences and are then allocated to study groups Each group has one tutor and about a dozen students—chiefly those taking the D P.H course with one or two qualified nurses and perhaps a psychologist. Many of the students have come from overseas In the first few meetings of a group its members get to know each other and appoint a chairman and secretary. By the end of term a provisional programme has been arranged ; some students will be keenly interested some hostile, some apathetic By the beginning of the Spring term some work will have been done and some proposals abandoned. There is usually a period of frustration when disappointments are met with, the members disagree, students from tropical countries feel the cold of a London winter, and the pressure of other work becomes distracting But the enthusiasm of a few members usually keeps the group going, and the camaraderie of the group may be helpful to the lonely visitor from abroad

Gradually the material accumulates The group may split up For instance, the men of action may prefer to go afield to interview, to examine, and to collect facts, while the men of thought plan the campaign sort the evidence and analyse it The chairman can be valuable in this reconciling opposing temperaments. The next stage is to decide on presentation Possible schemes include a series of short reports with linking remarks by the chairman , a dramatic presentation : or film strips and exhibitions Some groups prefer a statistical, some a descriptive, approach The last few days are marked by alternating enthusiasm and despair, till the great day when the presentation is made.

Many advantages are evident in this scheme The students of a group have the opportunity of making friends and of working as a team Excessive classroom teaching is avoided The project is an exercise in method ; for example much more is learned by actually planning and carrying out a social survey using a questionary than by hearing lectures about it Statistical methods are seen in action in the analysis of real material and not just as an academic exercise Finally, the presentation gives valuable training in health instruction and propaganda which is a very important part of public-health work.

The topics dealt with by study-groups in 1955–56 included an exhibition showing the development of health services and the work of medical officers of health through the hundred years since their society was founded , studies of the common lodging-houses in London, of the little markets, of the work of the National Assistance Board, of a railway terminus and of the questionaries sent to parents before school medical examinations and a discussion of many aspects of health education

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[1] *Times* Apr 27 1957 *Manchester Guardian* April 27 1957

[2] London School of Hygiene and Tropical Medicine, Keppel Street, Gower Street, W C.1 Report for 1955–56

CONTRACEPTION IN CHINA

THE Chinese People's Government is reported to have reversed its policy on family planning and contraception Previously, like most other Communist governments, it had been bitterly hostile to such practices, but the change is not unexpected The infant death rate in China is reported to have fallen by 2,000,000 a year, and in any case contraception by various methods (including abortion) is already a *fait accompli* a government newspaper recently *put the proportion of women workers* and clerks who have used contraceptive appliances or traditional herbs at 70% (This probably refers to the urban public, but figures in the villages may not be much lower) Accordingly a campaign to disseminate information on contraception is to be undertaken such campaigns, on other topics, have been prosecuted with enormous energy, and have proved highly effective in teaching simple hygiene At the same time abortion is legalised—chiefly to bring it under supervision—but not specifically encouraged

There is little to surprise us in the change of front—what will be really interesting will be to see exactly what methods of contraception are to be taught The mechano chemical methods used in the West are effective and more or less adequate under urban conditions, but experience in India has already shown that for rural populations, especially those which have climatic and literacy problems and live under simple conditions, they are quite unsuitable Research on fundamentally new methods is at present scanty While government planners might be quite content with any method which merely reduced the overall birth-rate, individuals will not be so easily satisfied They will expect a reasonable measure of certainty in action, and one or two notorious failures may, very reasonably, determine the future attitude of a whole village to further instruction of this kind Given some measure of reliability the demand for instruction is no doubt enormous There may be traditional opposition in China to any restriction of fertility, but the influence of the old economic and religious significance of fecundity and posterity must be very heavily offset by the demand of the newly emancipated generation of Chinese women for relief from continuous compulsory pregnancy

The best approach for the organisers of contraceptive education in the villages will probably prove to be the advocacy of a simple female occlusive method, possibly combined with the sheath and the "safe period"—any two of these would probably effect a substantial reduction in the incidence of pregnancy Tampons of paper or other materials are the basis of most of the effective folk methods—male appliances are certainly familiar in the towns, but the sheath as such might conceivably arouse opposition based on a long standing belief in Chinese medicine that the male absorbs virtue from the female secretions

Few Western observers would probably now advocate the "safe period" alone as a contraceptive method in any community where it was not preferred for religious or similar reasons But it might be worth seeking other behavioural methods of reducing fertility the results of research on infertility, carried out with the opposite *intention, already suggest* that such an approach is possible There are, for example, individuals who can keep their sperm count below the fertile level by maintaining a high frequency of ejaculation, and it seems likely that some couples could live a relatively or wholly infertile sexual life by adjusting their coital habits But owing to the enormous range of individual variation in fertility and capacity, this method would require careful individual laboratory study and failures would be frequent even in countries with expert fertility clinics A cheap mechanochemical method is probably the only effective contraceptive which could be promoted on a national scale by a Communist type education drive Our failure so far to find a relatively simple biological o pharmacological contraceptive is partly the result of our ignorance of the actual mechanics and pattern of human coital behaviour The adoption by the Chinese Communists of a positive attitude towards contraception may very well lead, for practical reasons, to the revision o another doctrine—that which condemns the study o human sexual ethology If so, it will be yet anothe instance where practical needs exert the same compulsio on the attitudes of societies as different *as our own, th* American, and the neo-Chinese

CONSERVATIVE MANAGEMENT OF URETERIC CALCULI

IT is often difficult to decide whether a ureteric ston will be passed spontaneously *Gartman*[1] *points out tha* surgical treatment has been found necessary in proportions of cases ranging from 7% to 54%, and h suggests *that* the figures at the upper end of this scal relate largely to cases sent for specialist advice on accoun of resistance or chronicity In the U S Armed Force all cases of ureteric calculus are referred at the outset t a urologist In 218 consecutive military cases referre to him, Gartman applied expectant treatment wheneve practicable Of 237 ureteric stones (in the 218 patients) 186 (78 5%) were passed spontaneously without complications, 38 were dealt with instrumentally, and onl 13 (5 5%) had to be removed by ureterolithotomy

Undoubtedly these figures reflect fairly the likelihood of natural passage, but some qualification is necessary in applying them to civilian practice Interference with business or other urgent activities by recurrent symptoms sometimes influences the decision when to interven Moreover in the general population there will always be a few with renal insufficiency in whom the removal o a stone is a matter of urgency Gartman's account i important because it provides some idea of the prospect of spontaneous cure in uncomplicated cases

PERFORMANCE IN PRACTICE

AN attempt has now been made to assess the performance of general practice in an American State by combining observation with use of the statistical method Of 102 representative general practitioners in North Carolina whose cooperation was sought, 94 agreed to allow their methods of work to be observed by two observers from the programme planning section of the Division of Health Affairs of the University of North Carolina These observers visited each practice separately, "sitting in" on each doctor for a few days at a time, *sometimes revisiting at a different season*, and so ordering their journeys from practice to practice as to eliminate statistical error where possible Considerable pains *had been taken to study the range of difference* in observations between the observers and also the within observer error arising in the interval between observations The great care in *allowing* for such *errors* as this gives authority to the results

The performance of the doctors was measured in two ways One observer awarded *an* ordinal grading from I up to V (mediocre to outstanding) which could be statistically matched to a quantitative numerical score This score was obtained by *allotting* "weights" to different aspects of the diagnostic and therapeutic processes examined Emphasis was placed on the diagnostic process in internal medicine, such qualities as surgical or obstetric technique being expressly excluded When the ordinal and numerical rankings were found to be statistically comparable, attempts were made to see how and why the doctors distributed themselves within the gradings as they did Little was overlooked from performance in medical school to age, type of

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1 Gartman E *U S Armed Forces med J* 1957, 8, 313

2 Peterson, O L Andrews L P Spain R S, Greenberg B G *J med Educ* 1956 31, no 12, part 2

practice, previous hospital experience—all the factors which must contribute to the performance of the doctor in Cheltenham as well as North Carolina—and the figures show much that was expected as well as much that is new

The evidence shows that the better medical students become the better practitioners, and that clinical merit cannot be directly related to the number of patients cared for nor, even under conditions of private practice, does it appear that the best doctor achieves the highest income Opportunities for postgraduate education were neglected by doctors in the lower groups In some practices both history taking and examination showed little clinical knowledge or skill, and one of the objects of the study was to identify the fundamental reasons for this

Though the conclusions of this report are valuable they may not be applicable under different conditions of practice elsewhere, and the main merit of the work lies in the methods of investigation Clearly the observer of general practice should be detached from it yet experienced in it, and when he is joined by a statistician scientific appraisal is feasible Studies of this sort should be encouraged wherever there are standards of general practice to be improved—and this means wherever there are doctors in general practice

CORTISONE AND IMMUNITY IN TUBERCULOSIS

CORTISONE or related drugs are now administered to tuberculous patients with less hesitation than in the past The indications for the use of these drugs in tuberculosis are now said to include obstructive lesions due to adhesions, stress,[1] exhaustion after major operations,[2] and hypersensitivity[3], and simultaneous administration of antimicrobial drugs is believed to deal adequately with the tubercle bacillus But opinions on the advisability of cortisone therapy for patients with pulmonary cavities are still conflicting

Cortisone aggravates tuberculosis in mice,[4] and cortisone and corticotrophin diminish tuberculin sensitivity in guineapigs previously sensitised with B C G [5–7] From this it might be inferred that these agents lower resistance and hence promote spread of tuberculous infection, but guineapigs which have been vaccinated with B C G apparently suffer no impairment of acquired immunity through administration of cortisone before being infected with virulent tubercle bacilli[8]

Light has lately been thrown on the cellular response to tubercle bacilli in animals receiving cortisone Pagel and Treip[9] injected heat killed tubercle bacilli intradermally into guineapigs which had been sensitised by a previous injection of bacilli of the same type During the period of developing sensitivity one group was treated with cortisone and a second (equally sensitised) group was left without cortisone and served as controls In all animals the first injection was followed by the usual sequence of histological events

> By the sixth day an abscess replete with tubercle bacilli had formed, from about the sixteenth day the abscess was gradually replaced by a tuberculoid granuloma consisting of large macrophages and many giant cells filled with acid fast rods Bacillary disposal was not complete until the sixth or seventh week, when only acid fast dust remained

After the second injection in the controls, the process was much faster on the sixth day a granuloma was present and tubercle bacilli were no longer visible, and the histological picture resembled that at the fiftieth day after the sensitising injection In the cortisone-treated animals disposal of tubercle bacilli was hardly less rapid than in the controls, but the histological picture differed conspicuously mononuclear, epithelioid, and giant cells had taken no part in removing the bacilli, which had all perished virtually in the abscess itself, suggesting a humoral rather than a cellular mechanism

These interesting findings are consistent with the observations of Long and Miles[5] on the depressant effect of cortisone on tuberculin sensitivity cortisone apparently reduces the cellular response without preventing (though it slightly delays) disposal of tubercle bacilli[9] These findings also explain the lack of interference by cortisone with the efficacy of B C G vaccination In short, cortisone does not seem to impair acquired resistance in guineapigs This encouraging revelation surely invites experimental study of its effect under conditions of natural resistance

EPITHELIAL HYPERPLASIA IN THE LUNGS

MUCH attention is being paid to areas of epithelial hyperplasia forming small nodules, almost like tumours, in the lung parenchyma in relation to terminal bronchioles and alveoli The cells in the nodule may be tall columnar with or without mucous secretion or cilia,[10 11] cuboidal, or flattened[12], but often they are small and oval,[13–16] reminiscent of the oat cell carcinoma or carcinoid tumours of the appendix, though without argentaffin granules in the cells Rarely, the cells show squamous characters[16] The cells may be seen in clusters of acini round terminal bronchioles, or they may line alveoli or form masses filling alveoli The main points of interest about these cells are the conditions in which they are found and whether or not they are to be regarded as precancerous, either for bronchial carcinoma or for alveolar cell carcinoma

So far, it is not claimed that the condition is common Whitwell[15] examined 2300 surgical specimens of lung (including 900 resected for bronchiectasis, 600 for tuberculosis, 500 for carcinoma, and 80 for abscess) and 1400 necropsy specimens, and found these nodules in 24 cases (22 surgical) The sex-distribution of the material was roughly equal, but in 18 of the 24 affected cases the patient was female The nodules were multiple in three-quarters of the cases and developed from bronchi, bronchioles, alveoli, or even pleura Whitwell claimed to see hyperplastic cells in dilated bronchial and pulmonary lymphatics (King[16] points out that the identification of lymphatics in these nodules is very difficult), but he could find no extension to lymph glands in the 15 specimens which could be examined for this He remarks that these islets of hyperplasia are a serious trap in sputum cytology and may account for the occasional false positive reports of malignancy, especially in cases of bronchiectasis He found such nodules almost exclusively in cases of bronchiectasis or chronic abscess, they bore no relation to the occurrence or distribution of carcinoma of the bronchus Spencer and Raeburn[14] and King[16] hold that most of these nodules are innocent proliferations of bronchiolar epithelium related to non-specific inflammatory or fibrotic lesions in the lungs They are thought to be becoming commoner partly because of the increase of viral and atypical pneumonia which heals by fibrosis rather than by resolution, and partly because organisation of exudate and subsequent fibrosis often follow the administration of antibiotics[17] in bacterial pneumonias These proliferations have not so far been associated with tuberculosis [18]

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[1] Wasz Höckert O Seppälä K, Raito M *Acta tuberc scand* 1956 32 232
[2] Edge J R *Tubercle* 1956, 37, 166
[3] Houghton L E *Lancet* 1954 i, 595
[4] D'Arcy Hart P Rees R J W *Ibid* 1950 ii, 391
[5] Long, D A Miles A A *Ibid* 1950, i, 492
[6] Birkhaug K *Amer Rev Tuberc* 1954, 69, 511
[7] Houghton L E Davies D *Tubercle*, 1954 35 2
[8] Davies D, Nassau E Houghton L E *Ibid* 1955, 36, 23
[9] Pagel W, Treip C S *Int Arch Allergy* 1956, 9 1
[10] Swan, L L *Arch Path (Lab Med)* 1949 47, 517
[11] Spencer, H, Raeburn C *J Path Bact* 1956 71 145
[12] Ewing J Neoplastic Diseases London 1931, p 859
[13] Prior J T, Jones D B *J thorac Surg* 1952 23, 224
[14] Spencer, H Raeburn C *J Path Bact* 1954, 67, 187
[15] Whitwell F *Ibid* 1955, 70, 529
[16] King L S *Arch Path (Lab Med)* 1954, 58, 59
[17] Auerbach S H, Mims O M, Goodpasture, E W *Amer J Path* 1952 28, 69

The presence of a few mitotic figures and some local extension of the hyperplastic cells by natural passages are compatible with simple hyperplasia, but in some cases definite carcinoma of the terminal bronchioles or alveolar epithelium has been identified by secondary spread—e g, to hilar glands [19, 20] This diagnosis should be accepted, however, only if there is no demonstrable carcinoma elsewhere,[10, 11] either at necropsy or for some time (e g, five years) after operation In particular, there must be no small primary growth higher up the bronchial tree,[21] especially where there appear to be multiple primary foci in the periphery of the lungs, and where there is extensive mucoid spread throughout one or more lobes [22] In another type of primary growth, described as pulmonary adenomatosis,[23] a peripheral mass spreads by many small outgrowths, causing progressive involvement of large areas of the lung, this does not seem to be related to the nodules of epithelial hyperplasia following scarring of the lung, but it confuses the *nomenclature*

Rare disorders have an extraordinary propensity for coming in small runs There are many reports [11, 18, 19] of series composed of a few cases with these nodules of apparently simple hyperplasia and a smaller number of cases with superimposed malignant changes, and there is a tendency to assume that the simple hyperplasia is inevitably followed by malignancy Then comes the assumption that the epithelial hyperplasia, bronchiolar or pulmonary adenomatosis, and alveolar-cell or bronchiolar carcinoma are phases of a single process [24, 25] From this, it is taken as proved that the sex-distribution of carcinoma of the alveolus (almost equal in males and females, or even commoner in females) is very different from that of carcinoma of the bronchus (about 5 males to 1 female) But it must be realised that many of these so-called carcinomas of the lung alveoli or of the bronchioles were originally reported as areas of hyperplasia and were not proved or claimed to be malignant even some claimed originally to be malignant [26] might not now be so classified in view of the later reported series [14, 15] Further, several cases of true alveolar carcinoma have been reported in series of bronchial carcinomas with strong male predominance [22, 27], and if these were added to the cases reported separately the sex-distribution would be very different Spencer and Raeburn [11] recognise the reported equality in sex-distribution but point out that 5 of their 6 cases were in males so also were the cases with extrapulmonary spread in Beaver and Shapiro's series [18]

Similar reasoning is used to show that cancer in the alveoli is due to chronic inflammation [11, 17] It has long been known that epithelial hyperplasia arises at the edges of chronic infections or sites of irritation—e g, in skin ulcers, gastric ulcers, and erosions of the cervix—but that this change is rarely supplanted by true malignancy Now that lung pathology is receiving increased attention vis-a-vis cancer, surely the same caution must be exercised here, and it may well be shown in the future that other agents besides infection are needed to induce the actual malignant change—perhaps the same agents as in bronchi Auerbach et al [28] have shown that, in the mucosa of the trachea and bronchi, areas of basal cell hyperplasia, stratification, squamous metaplasia, and even "carcinoma in-situ" are seen in unexpected numbers, certainly more commonly in smokers, but even in non-smokers who die from causes other than carcinoma of the lung, and these changes are found even in the trachea, in which carcinoma is very rare

At present it seems advisable to restrict the names used as far as possible—reserving pulmonary adenomatosis for the condition described by Hutchison and Fraser,[23] and pulmonary adenoma (simple or multiple) for true simple tumours [29], the term epithelial hyperplasia nodular or diffuse, should be used for the effects of chronic inflammation or fibrosis Exacting criteria should be fulfilled before carcinoma of the alveoli or terminal bronchioles is diagnosed

HARVEY'S TERCENTENARY

William Harvey died on June 3, 1657, and the tercentenary of his death will be commemorated next month in London by the Royal College of Physicians and the Harveian Society and by many distinguished guests from abroad On June 3 at 9 30 A M at the Royal College of Surgeons, Lincoln's Inn Fields, W C 2, Mr A Dickson Wright, the president of the Harveian Society, will open an international congress on the circulation of the blood, and on the same day at noon the Royal College of Physicians will hold a memorial service at St Paul's Cathedral The congress will continue in London till June 7, and the speakers will include Prof C Heymans (Ghent), Prof Gustav Nylin (Stockholm), Dr Donald E Gregg (Washington), Dr Claude S Beck (Cleveland, Ohio), Dr Andre Cournand (New York), Dr S Radner (Lund), Prof G d'Allaines (Paris), Dr Seymour S Kety (Bethesda, Maryland), Prof T Alajouanine (Paris) Dr Stanley E Bradley (New York), Dr J F Fulton (Yale), Dr F A Wilkins (Mayo Clinic), Dr L W Katz (Chicago), Dr S Weidmann (Berne), Prof K Matthes (Heidelberg), Prof A D Volta (Padua), and Dr Louis Chauvois (Paris) Sir Russell Brain will give the concluding address in London at 2 P M on June 7 On June 8 the congress will hold a historical meeting, under the chairmanship of Sir Geoffrey Keynes, in Folkestone which was Harvey's birthplace There will be a service at Canterbury Cathedral in the afternoon

During the congress an exhibition will be held in the library of the Royal College of Physicians, Pall Mall East, S W 1, to illustrate Harvey's life and work It will include his demonstrating rod, his diploma, the drawing of his Stemma, letters, and the earliest extant Harveian oration (by Edmund Wilson in 1658) A new translation of *De Motu Cordis* by Prof K J Franklin, F R S, has been sponsored by the college A new edition has also been made of the black and white silent film prepared in 1928 by Sir Henry Dale, F R S, and the late Sir Thomas Lewis to illustrate some of Harvey's most important experiments The 1957 version, for which a grant was given by the Wellcome Trustees and which has been made by the Wellcome Film Unit, uses colour, animated diagrams, and a sound-track Happily it retains Sir Henry Dale as one of its stars and he contributes an introduction From June 3 to 7 the film will be shown daily at the college at 5 P M and 5 45 P M

During the week of the congress a Harvey exhibition will also be on view at the Wellcome Historical Medical Library, Euston Road, N W 1 Later in the month, on Sunday the 23rd, at 3 P M, there will be a commemoration service at Hempstead Parish Church, Essex, where Harvey is buried

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Public Health

INFLUENZA BETWEEN EPIDEMICS

A SEROLOGICAL STUDY

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Our knowledge of the attributes of the influenza virus is now very detailed, but there are many gaps in our knowledge of the relationship between it and its host Not unnaturally, most investigations of this have been made during epidemics, and, owing mainly to the difficulty of recognising the disease clinically and so distinguishing it from many other acute respiratory infections, we are comparatively ignorant of the position which obtains between epidemics Relatively few studies aimed at elucidating these problems have been reported, the most important are those of Hoyle and Fairbrother (1947) and of Stuart Harris et al (1954)

The present investigation was initiated by the recovery of influenza-A virus from two localised outbreaks in the vicinity of Dublin in May, 1954 In view of the possibility of an autumn epidemic following these outbreaks (Isaacs and Andrewes 1951) it seemed that an opportunity might have arisen to study the genesis of such an epidemic, using the complement-fixation test, and particularly to see whether silent seeding of the virus throughout the population could be detected before it In the event, no autumn epidemic occurred, but the study continued from June, 1954, to August, 1955 during which time an outbreak due to influenza B and yet another due to influenza A were recorded, in January, 1955, and March, 1955, respectively The viruses responsible were isolated in each case The 1955 influenza-A strains were antigenically distinct from those of 1954, being the prototypes of the Eire '55 strains which were isolated almost simultaneously in this country, Great Britain Albany, N Y and India (Isaacs 1956) We were able therefore, to investigate the population concerned before, during and after those periods at which virus was known to be circulating

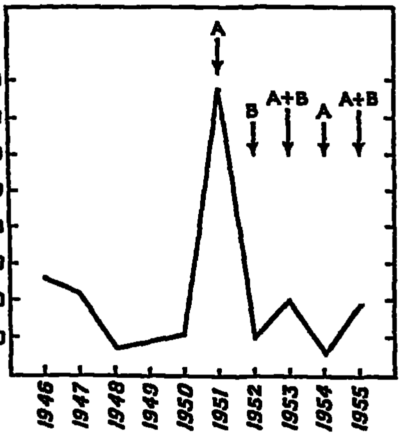

Fig 1—Mortality rates and viruses isolated

As it has been suggested that antibodies demonstrated by the complement fixation test between epidemics may derive from infection in a previous epidemic, the background to this study is shown in fig 1, which records the mortality rates and the viruses isolated in this country in recent years It should be noted that, except for 1951, when a severe epidemic with a high mortality occurred early in the year (Meenan and Clarke 1951) the recent isolations were from localised outbreaks, and there was no subsequent large epidemic By June, 1954, therefore more than three years had elapsed since the previous epidemic of influenza A, the most recent epidemic of influenza B had probably been in 1946 In our experience localised outbreaks were as likely to have been due to A viruses as to B

Materials and Methods

During the period of the study 5084 sera were examined by the complement-fixation test for antibodies to influenza A and B

Except for a few specimens received for the Wassermann reaction, the sera were all obtained through the National Blood Transfusion Service from donors with no history of recent illness They were collected locally in different parts of the country by teams from Dublin, which meant that the areas more remote from Dublin were visited only at intervals, and a continuous sample was not obtained from them During December and January the vast majority of the specimens received were from Dublin The specimens examined could, however, be taken as representing a fair cross section of a healthy portion of the adult population at the time they were collected.

The sera were examined at an initial dilution of 1 8, and those positive at this dilution were further titrated For the purposes of the investigation a positive result at 1 8 dilution was regarded as significant and recorded as positive In patients with an illness of the respiratory tract a titre of 1 16 in a convalescent specimen examined by the complement-fixation test is taken as pathognomonic of influenza Our specimens were collected from a sample of the general population who, as blood-donors, could be presumed to be in good health, and our interest was in possible subclinical infection rather than in known convalescents For these reasons a titre of 1 8 was regarded as significant, being not so high as to detect only frank cases yet high enough to ensure that positive results of doubtful significance at low dilutions of serum could be eliminated

Complement-fixation Test—The method used was that recommended by an expert committee of the World Health Organisation (1953) as regards both the preparation of antigens and the technique of the test Soluble antigens prepared in fertile eggs from PR8 and Lee strains were used throughout

Sera were stored at –15°C where necessary before examination As only a few sera were collected in August and September, 1954, the results for these two months were pooled No sera were collected in June, 1955

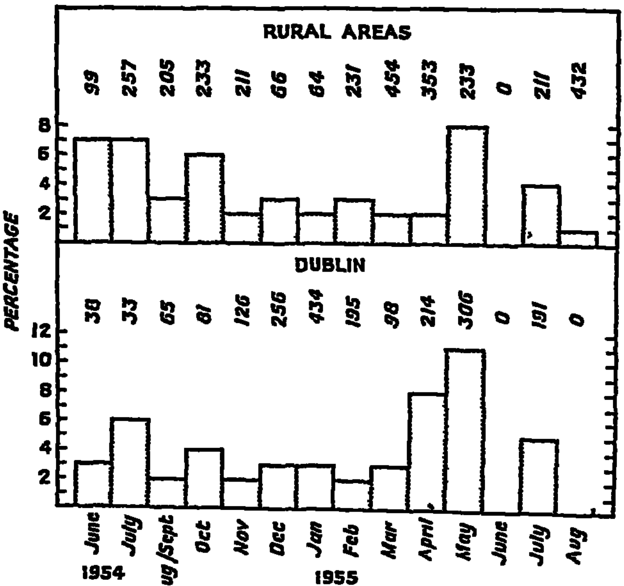

Fig 2—Results of complement-fixation tests for antibodies to influenza A virus

Results

The results for influenza A and B are shown in figs 2 and 3 respectively They are broken down into those for Dublin city and county on the east coast, which is predominantly urban, and those for the rural areas The former, with a population of just under 700,000 in an area of 350 sq miles, contain almost a quarter of the total population of the country The rural areas consist of most of the rest of the country except the south-western region, which is not visited by the National Blood Transfusion Service A very few specimens sent from this area for the Wassermann reaction are included The exclusion of this region means that the rural population investigated numbered about 1,200,000 persons living in a countryside containing only eight towns with populations over 10,000, the largest having 30,000 inhabitants, in an area of about 12,000 sq miles As might be expected, the rather more thickly populated eastern counties within easier reach of Dublin were more intensively sampled than the very thinly peopled western seaboard, but in the results these rural areas showed no great differences between them

The findings for influenza A show two periods of activity One, during the summer and autumn months of 1954, affects the rural areas to a rather greater extent than Dublin This suggests that the viruses isolated near Dublin in May of that year may have spread slowly outwards from Dublin, for the proportion of positive sera was highest in the west during October, when the level had fallen to negligible proportions in the rural areas in the east During the winter months only very slight activity due to influenza A was detected serologically anywhere in the country before it became epidemiologically evident in Dublin during March with the appearance of the Eire 1955 strains there This is reflected in a rise in the number of positive sera found in April, which again increased in May and was still above the winter level in July This rise occurred a month later in the rural areas, although apparently not to the same extent, and appears to have been confined to the eastern part of the country As no specimens were collected in June, it is impossible to be dogmatic on this point, but a large batch of sera from the midlands in August showed less than 1% of positives

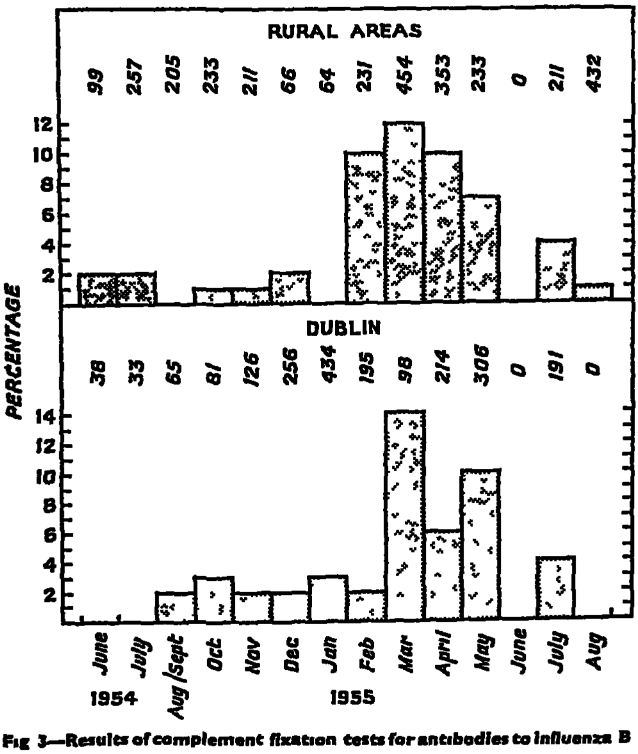

Fig 3—Results of complement fixation tests for antibodies to influenza B virus

Neither in 1954 nor in 1955 did influenza A appear to be frankly epidemic in Dublin or throughout the country Nevertheless the serological results show a fairly sharp increase following the period when influenza virus A was circulating in Dublin in March, 1955, and there is no suggestion of any earlier widespread dissemination of virus such as might happen during a period of "seeding" before an outbreak

The findings in respect of influenza B seem clear cut After months of predominantly negative results there was a sharp rise in all the areas early in 1955 which, in the rural areas at least, had completely died away six months later In Dublin the rise in the number of positive sera took place two months after the epidemic of influenza B The peculiar fall in April may have been due to a sampling defect in either March or April, but it may serve to emphasise that the population from which the specimens were drawn was predominantly healthy The main brunt of the January epidemic appeared to fall on school children rather than on adults, and most schools were closed during the latter part of the month, having opened in the ordinary way after the Christmas holidays

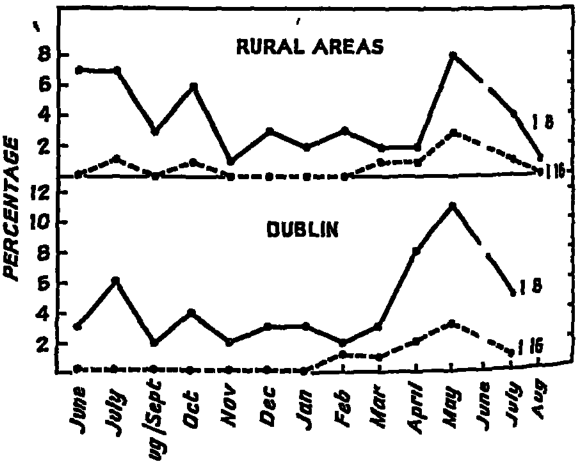

Fig 4—Proportion of sera positive for influenza A at a dilution of 1 16 or higher

The rise is shown in the rural areas a month earlier than in Dublin, this being almost entirely due to the findings in the area north of the city, which, however, was inadequately sampled in the immediately preceding months, and one cannot say whether or not the epidemic may have originated there In any event all the rural areas rapidly became involved, and it is clear that they suffered severely Again one may note (and it is even more conspicuous in this instance) the apparent lack of any build up before the epidemic

Figs 4 and 5 show the proportion of positive sera which, on subsequent titration, were positive at a dilution of 1 16 or higher The two curves parallel each other closely and, for the period covered in 1955, the curve of the 1 16 dilution supports the epidemiological findings Its significance during 1954 is less obvious, except perhaps to suggest that influenza A was slightly more active in the rural areas than in Dublin in the autumn of that year

Discussion

One of the difficulties in a study such as this is to define the proportion of positive sera which one might expect to find during interepidemic periods Stuart Harris et al (1954), working at a serum dilution of 1 4, found 5–9% of positives for influenza A as against 20–30%

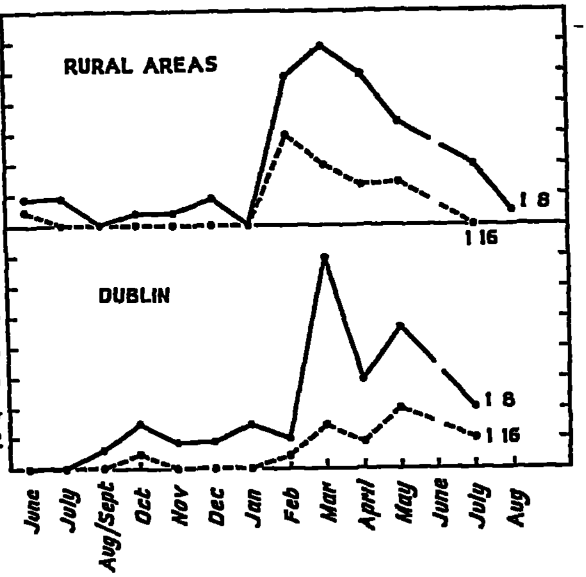

Fig 5—Proportion of sera positive for influenza B at a dilution of 1 16 or higher

found by earlier workers They suggest that their lower levels may have been due either to a real alteration in antibody levels following the introduction of the A-prime viruses or to technical differences Hoyle and Fairbrother's (1947) report shows 7% of positives for influenza A and 4% for influenza B at a dilution of 1 8 and over in inter-epidemic periods Our findings suggest that the corresponding figure in our series is at most 2–3% and may well be less In essentials the technique used in this investigation is the same as theirs, except that the antigens were prepared in fertile eggs instead of mouse lung There is some evidence that the A-prime and subsequent viruses may give rise to a poorer antigenic response than did the earlier A strains, but this change does not, so far as we know, hold for influenza B, hence, though the lower figures obtained by Stuart Harris et al (1954) and, to a much lesser extent, by ourselves might be due to the preparation of the antigens in the fertile egg instead of mouse lung, they could also have been due to differences in antibody levels with recent A strains

If the figure of 2–3% in this series represents a normal finding, it appears that there was no evidence of pre-epidemic seeding in Ireland during 1954–55 before outbreaks of either influenza A or B, but that in each case infection erupted suddenly after a period of minimal detectable activity Evidence for such pre epidemic seeding would be exceedingly difficult to obtain except by serological means, and in this series the evidence suggests that at least it is not necessary for it to occur Similarly, it seems that the methods used in this study would be valueless for forecasting an epidemic, for the rise in the proportion of positive sera lagged behind the epidemiological findings

On the other hand, our results show that almost all evidence of an outbreak, as detected by complement-fixation tests on random samples, may have disappeared by the end of some six months afterwards This being so, it seems improbable that even the low level of 2–3% of positive sera could derive solely from persons infected during a previous epidemic some years before It is more likely that at least a proportion of these positive sera reflect constant low grade activity of virus circulating " underground " in a population essentially immune to it The origin of an epidemic would then depend on the appearance of a new strain of virus, arising either locally or by importation and with sufficient capacity to spread, rather than on a decline of the immunity level of the population and the recrudescence of a pre existing strain The data presented here, however, cast little light on how such a new virus might appear, for one did arise during this study, but the methods used give no clue to its origin Nevertheless it would be reasonable to expect such a new virus to emerge at a time when the population is immune to earlier strains Its subsequent history—as a major problem or as a curiosity—would depend on many factors, of which its own antigenic novelty and capacity for spread are only two

Summary

Between June, 1954, and August, 1955, 5084 sera, almost entirely from healthy blood-transfusion donors, were examined by the complement-fixation test for antibodies to both influenza A and influenza B

Two outbreaks—one of influenza A and one of influenza B—occurred during the period of study Each is reflected in a rise in the antibody content of the sera collected subsequently The pre epidemic level is reached again at the end of about six months, and a few positive sera detected between epidemics probably reflect current low-grade virus activity

No evidence was detected of seeding of virus in the community before the outbreaks, and both outbreaks occurred after periods of minimal activity as reflected by serological tests

This study was carried out with the aid of a grant from the Medical Research Council of Ireland, and Dr Clarke is a Fellow of the Council Our best thanks are due to Dr J P O'Riordan, medical director, National Blood Transfusion Service, for supplying almost all the specimens tested The patients from whom viruses were isolated during the outbreaks were kindly reported to us by Dr W R F Collis, Dr E M Caraher, Dr S McCann, Dr J F Fleetwood Dr C J O'Sullivan, and Dr V J Doyle

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Joint Tuberculosis Council

At a meeting on March 1, the council strongly supported the views expressed in a report by its radiological committee—namely, that much more extensive use should be made of mass radiography In industry both employers and employees should (in their own interest) arrange for pre-employment radiographs For the protection of the public, annual radiographs should be required of workers in public transport and the catering trades

The report recommends improvement of the present mass-radiography service by providing miniature X-ray units in all chest clinics for the examination of persons referred by general practitioners, and of others who wish it The extension of the service in this way would make chest radiography easily available to everyone, and pre-employment films could be provided either by the chest-clinic service or by private arrangement with industry

First Quarter in England and Wales

The Registrar-General has announced[1] provisional figures for the first quarter of 1957 in England and Wales Live births numbered 183,676, or 16 7 per 1000 population The corresponding rate last year was 16 2 There were 134,621 deaths registered—a rate of 12 2 per 1000 population, compared with a rate of 15 3 in 1956 and 13 6 in 1938 in the corresponding quarters The infant-mortality rate was 25 0 per 1000 related live births in 1938 the corresponding figure was 69 3

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[1] The Registrar-General's Weekly Return no 16 1957 H M Stationery Office Pp 20 1s 3d

Special Articles

CARE OF CHILDREN IN HOSPITAL

Report from the College of Physicians

FOR the guidance of individuals and authorities who are planning the care of children in hospital, the pædiatric committee of the Royal College of Physicians of London have recorded their views on this important subject Their report, which does not deal with the care of mentally defective children, was accepted by the college in comitia last week We reproduce the text in full

General Considerations

The proper care of children in hospital is so different from that of adults that their admission to adult wards is to be deprecated It is realised that such admissions may sometimes be necessary to obtain investigation and treatment in specialised units, but when this occurs there is a particular need for close liaison with the pædiatric services

There is no doubt that special children's hospitals offer the best service for children, because the staff, at all levels and in all departments, is attuned to the special needs of the sick child Children's hospitals carry with them a tradition of service which cannot lightly be set aside

In large general hospitals a separate self-contained children's block in close association with the obstetric department of the general hospital is desirable Where there is no separate children's block all children should be in special wards in a single unit under the general supervision of a pædiatrician, with a sister in charge who has had training and experience in nursing sick children A children's unit makes possible such amenities as schooling and facilities for play, &c It is most desirable, as suggested by the Ministry of Health (R H B 48 1) that the consultant pædiatricians of outlying units should, where possible, be connected with central units so that they do not work in isolation

Psychological Needs

The psychological aspects of childhood illness are increasingly recognised, not only in the field of psychosomatic illness, but also in the appreciation of psychological difficulties arising from physical illness and from hospitalisation To prevent these it is recommended that, whenever possible, daily visiting by parents should be allowed, and the importance of admitting mothers with their young children is stressed

The psychiatric needs of sick children should take a prominent place in the training of medical students, nurses, and pædiatricians

Size of Unit

The size of the unit will be determined by the needs of the area and the density of the population, and must have regard to town-planning

In university centres where pædiatrics is taught it is suggested that there should be at least one pædiatric bed or cot for each annual student entry

Small units are undesirable because they are detrimental to satisfactory arrangements for the proper care of children, and to the training of doctors and nurses in this field Units of less than twenty beds are uneconomic, and in closely populated areas children's beds should be concentrated in units of forty beds or more, including beds for both medical and surgical disorders, small units being gradually eliminated

In all units there must be isolation accommodation for infectious cases, enough cubicles for the isolation of babies under one year, for dying and seriously ill children, and for those recovering from operation Accommodation should also be available for the admission of mothers with young children

Where adolescents are admitted there should be separate wards for boys and girls

Site of Unit

There should be a children's hospital or unit of adequate size at each university centre undertaking the training of medical students Much is to be gained from its proximity to the other university departments involved in medical teaching and research, particularly the obstetric department

Inpatient accommodation in general hospitals should be concentrated in central hospitals, but outpatient services should be developed to meet the needs of the population, and a pædiatrician may well conduct a children's outpatient session at a general hospital which has no children's beds The transfer of difficult or obscure cases from smaller units to special children's hospitals should be encouraged It is unnecessary and undesirable to attempt to provide a children's unit in every general hospital or even every area hospital It is essential that the emphasis should be on the best treatment for children and on the best training for those who are responsible for the medical and nursing care of children, and this implies some concentration of children's beds

Medical and Surgical Staff

As stated in the pædiatric committee's interim report of April, 1945, where a pædiatric department is situated at a general hospital it is essential that all children admitted to the hospital should be considered as admitted to the children's department, and should have the benefit of all the facilities available for children, including the services of the pædiatrician

In addition, the need for surgeons interested in and concentrating upon the surgical problems of children, particularly in the newborn period, should be realised, and the larger pædiatric units should provide adequate accommodation for surgical cases

The application and development of special techniques in departments dealing with the investigation and treatment of children is extremely important These specialist facilities clearly could be fully established only in large pædiatric units but these large units should make their resources available to the smaller units in surrounding districts

Particularly there is a need for a personal interest in children and their problems in departments of radiology, anæsthetics physiotherapy, biochemistry, and pathology The staff of such children's departments should be trained and interested in the pædiatric aspects of their specialty

Nursing Staff

The nursing of sick children is one of the most important aspects of their hospital care and requires nursing techniques and experience quite different from those suitable for adult patients Hence the need for nurses with this special education and training in the care of sick children in hospital is obvious

In children's hospitals where training schools for nurses exist and where all nurses have a vocational interest in the sick child, the standard of nursing care for children is likely to be higher than it is in general hospitals where the nurses in training are doing only three months' children's work

The most suitable curriculum and training for sick children's nurses has yet to be evolved Two or three months spent in the children's wards by a nurse training for the general register does not equip her for the care of sick children It is hoped that experiments now running in some centres for combined and integrated training in pædiatric nursing and general nursing may result in a satisfactory solution Nurses undergoing their general training in hospitals without a properly staffed children's unit will need to go for a period to such a unit

The minimum number of trained nursing staff for a unit of twenty beds should be a sister and three staff nurses, all in possession of special training in the care of sick children, to provide such care round the clock

The Staffing of Psychiatric Beds

It is not the intention of this report to set out in detail what specialist departments might usefully be found in large pædiatric units, but the need for psychiatric diagnosis, extended observation, and treatment must be realised

Within the large pædiatric units a child psychiatric unit would be an advantage This could economically be of eight o twelve beds The sister in charge should have had previous psychiatric experience with children In addition to the onsultant and resident medical staff, the part-time services of a clinical psychologist, and a psychiatric social worker will be needed Where treatment is undertaken provision will have o be made for this in staffing the department The whole unit working under the direction of a consultant pædiatric psychiatrist should form a part of the pædiatric service

Education and Recreation

The happiness of children in hospital can be materially nfluenced by the opportunities they have for occupation The use of education in hospital, not only to prevent llness from interfering with educational progress, but also to keep children happy, should be recognised, and a liaison established with local education authorities Provision should also be made for recreation and for play

Branch Outpatient and Casualty Departments

These should be set up both in areas of scattered population and in city areas to meet the needs of the population and to avoid the necessity of small units Such branch outpatient departments should be staffed from the main pædiatric unit, and thus be able to call upon the special facilities of these units

Infectious Diseases

The care of children suffering from infectious diseases should be included in the general pædiatric services for the care of children in hospital The Ministry of Health has stated (R H.B 48 1) "It is of the utmost importance that hospitals or wards for infectious diseases should be closely associated with pædiatric departments, since so many of the patients are children and the problems are similar" Thus the committee fully endorses and considers that when a vacancy occurs on the staff of an existing infectious disease hospital, a pædiatrician should be appointed In every pædiatric unit isolation accommodation is essential, and as large units are developed a block should be included for infectious fevers

Infants in Maternity Units

The committee has already stated that all maternity hospitals and departments should have pædiatricians on the staff and they should undertake full responsibility for the care of the newborn

In the larger units the services of a pædiatric registrar are advisable and the obstetric house surgeons should be directly responsible for the infants to the pædiatric registrar and consultant Every maternity hospital should be linked with a children's hospital or children's department of a general hospital and thus be able to call upon the special facilities of the pædiatric unit

The Family Doctor

Pædiatric units should have the closest relationship with family doctors, who should be encouraged to follow their children while in hospital The proper follow-up of hospital admissions may thus be promoted after they return home from hospital, and the pædiatric unit can perform an educative function

Where pædiatric beds are under the care of family doctors it is important that the pædiatric services should be used and that a pædiatrician should advise on planning as well as policy, taking control, for example, when there is an outbreak of infection

The Local Health Authority

All pædiatric units should have the closest cooperation with these authorities particularly the maternity and child-welfare and school health services and should provide facilities for the postgraduate tuition of clinic doctors and health visitors Through this coöperation the proper follow-up of patients may also be assisted after their discharge from hospital

Regional Hospital Boards

In each region there should be a pædiatric committee to advise the regional board upon questions of planning and policy for the care of children

DISCUSSIONS ON ROYAL COMMISSION

On Tuesday the Special Conference of Local Medical Committees decided to take no decision on the matter of the profession's cooperation with the Royal Commission and to defer the question until the annual conference in June The chairman of the General Medical Services Committee, Dr A B Davies, said that his committee had decided, by 24 votes to 22, at an emergency meeting held immediately before the conference, to put a new recommendation to the conference—namely, "that in view of the latest developments evidence should now be given to the Royal Commission and a decision on withdrawal of services deferred" This decision had been taken after consideration of a letter of April 26 from the Minister of Health to Dr Solomon Wand, chairman of the council of the British Medical Association Confirming what he had said in a talk with Dr Wand, the Minister declared in his letter that there would be full consultation with the profession before implementation of any of the Royal Commission's findings and "that such consultation could of course include any matters relevant to the report or the present dispute" Referring to Dr Wand's fear of some inconsistency between the terms of reference of the Royal Commission and the public statements issued by its chairman, the Minister's letter said that the public statements which had been issued could certainly be regarded as having full validity On the position of public-health medical officers, the Minister repeated his previous assurance that any settlement for others, following the Commission's report, could not fail to be taken into account in considering the position of these doctors, and any claim through the normal machinery would of necessity be considered in the light of the report and of any settlement that followed it Giving the conference his interpretation of this letter, Dr Wand pointed out that the Minister had included the present dispute in the matters for consultation after the Commission's report, and that the broadened terms of reference had been confirmed The issue was now "evidence or fight" If the conference accepted the new recommendation of the G M S Committee, the intervening period would be used to regain unity and strengthen the finances of the Trust, so that action could be taken if later consultations broke down

Many members of the conference were uneasy at taking a hurried decision before they had had a chance to assess how the Minister's letter and the latest statements by the chairman of the Royal Commission had affected the situation Dr Talbot Rogers, on the other hand urged the conference to make an immediate decision His own doubts about the Royal Commission had been resolved and he found it unthinkable that the Commission should go on hearing evidence without having the doctors' case put before it Dr I D Grant warned the conference that to cooperate with the Commission was tacitly to accept unilateral dictation Were doctors to be servants of the Government or equal partners in the National Health Service? Proposing an amendment to defer decision until the annual conference in June Dr Frank Gray remarked that until 9 o'clock that morning the policy of the G M S Committee had been firm Now with almost indecent haste, it had reversed that policy by the smallest possible majority Dr J A Pridham also pleaded for more time to consider the latest developments, and when it came to a vote the conference agreed with him The conference also decided that a decision on withdrawal be deferred, and that the "interim offer of 5% should be accepted without prejudice"

During a discussion on the mechanism of withdrawal from the National Health Service, a proposal that the withdrawal should be total and not phased was defeated, and the conference supported the view that in the event of progressive withdrawal no practitioner should be asked to resign unless 80% of resignations had been collected from the area in which he had been included

The special representative meeting of the B M A held last Wednesday will be reported in our next issue

Central Consultants and Specialists Committee

At its meeting on Tuesday the committee decided to recommend cooperation with the Royal Commission

THE LONDON HOSPITAL RESEARCH BUILDING

FROM its endowment funds the London Hospital has spent £200,000 on a new research building in Ashfield Street, Whitechapel, which will accommodate the research units of the hospital and thus make space in the main hospital for clinical laboratories The new building, which was officially opened last Wednesday, contains

The Hospital Physics Unit

Chief Physicist L A W KEMP, PH D

The London Hospital Physics Laboratory came into being in 1943 but for eight years was concerned almost entirely with radiotherapy physics In 1951 it became responsible to a special physics subcommittee, and was made accessible to all departments Since that time, it has done work for many departments, including the medical unit and the cancer research dental, cardiac, electro encephalographic, ophthalmic, and diagnostic X ray departments, as well as several of the research groups working in the medical college In the field of radiation physics it has come to be known for its specialisation in precision dosimetry

The Hospital Instrument Workshop

Chief Technician E PENFOLD

This workshop has grown out of the initial steps taken to meet the instrument making needs of the physics laboratory In 1951 a full time instrument maker was appointed, but the needs of the laboratory grew rapidly, and it was found that an increasing number of other research departments also required access to first class instrument makers The building of the new research block has therefore been made the occasion for creating the research instrument workshop, administratively separate from the physics laboratory and staffed by five instrument makers (with a storekeeper), provided with 5 lathes, 2 milling machines, 4 power drills, and a surface grinder, together with a guillotine, bending machine, various presses, and welding and spraying equipment The workshop is also equipped, to a more modest degree, for electronic work

Department for Research in Industrial Medicine

Director DONALD HUNTER, F R C P

This department (Medical Research Council) was formed in June, 1943, and its staff includes physicians, chemists, physicists, and technicians Its aim is to study diseases of occupation and their prevention These include (1) acute and chronic poisoning by metals and chemical substances, (2) industrial cancer, and (3) the effects of physical agents such as vibratory tools Field studies are undertaken anywhere in Great Britain and have been made, for example, into fluorosis in an aluminium foundry at Fort William, silicosis among Cornish tin miners, and chronic cadmium poisoning on Merseyside

In the new building there are organic and inorganic chemistry laboratories, a laboratory for radioactive isotopes, a physics laboratory, and a histology laboratory In the animal house a dosing chamber has been built by the staff of the department in which animals can be treated with dust and fume under controlled conditions resembling those of a factory

Venereal Diseases Laboratory

Director I N ORPWOOD PRICE, M R C S

This laboratory (Medical Research Council) is a conjoint laboratory established in 1956 by fusion of the London Hospital Whitechapel Clinic and the M R C Venereal Diseases Reference Laboratories The amalgamation of the two laboratories has made it possible to achieve a much greater output of work without any increase in staff, which consists of the director, two serologists, eleven technicians, and the usual ancillary personnel

Social Medicine Research Unit

Director J N MORRIS, F R C P

This unit of the Medical Research Council was founded in 1948, and transferred to The London in January, 1956 It has a staff of about twelve—medical, statistical, sociological, and clerical In addition, it enjoys much help from the staff of the hospital and from others Depending on the nature of the problem, studies are made on a national or local scale, and though the unit's principal method is that of the field survey, clinical and other methods are used as required

At present it is completing studies on infant mortality, is actively engaged on several inquiries into the causes of coronary thrombosis in middle aged men, and is planning to move into the field of mental disease and the relations of social to hereditary factors Studies are also being made of the working of various parts of the health and social services The advances in the treatment of mental disease mean that many patients are discharged home after a relatively short stay in hospital, and the unit is trying also to assess the needs of such patients in the hope of helping to reduce the considerable relapse and readmission rates In another inquiry the results of teaching and non teaching hospitals in dealing with certain "emergencies" are being compared An intensive study has also been started of the problems of The London Hospital itself

The Dental Research Laboratories

The new dental research department, which consists of four compactly designed laboratories and a small photographic darkroom, will provide much needed space for the expansion of research already being carried out on dental disease by members of the staffs of the dental department and dental school An experimental study of the influence of defective nutrition on the incidence of dental decay is being undertaken by the department of children's dentistry

Cancer Research Department

Director M H SALAMAN, M D

This department was founded in 1930, and transferred to the Medical College in 1948 It is largely maintained by a block grant from the British Empire Cancer Campaign It consists, at present, of six graduate and six technical staff. Members of the department have worked for the most part in two fields (1) chemical carcinogenesis, and (2) the action of tumours on the enzymes of the host Its new, compact, and well equipped laboratories will, it is hoped, enable the department to extend its work

Department of Experimental Surgery

Director Prof VICTOR W DIX, F R C S

This department has been designed in two parts in order to make it possible for work with radioactive isotopes to be done safely The part at present allotted to isotope work consists of a large laboratory, a small animal room, and a dog room, and these rooms are completely isolated from the rest of the department The space allotted to ordinary experimental surgery consists of an operating theatre, two laboratories, a dog room, two small animal rooms, and a larger room which is to be used for X ray work and also as an additional operating theatre It is hoped that it will be possible to do every sort of experimental work in the department except possibly surgical experiments in which long term survival is necessary Later it may be possible to make arrangements to keep animals elsewhere for such experiments

CLINICAL GENETICS RESEARCH UNIT

THE Medical Research Council have established this new research unit, under the directorship of Dr J A Fraser Roberts, at the Institute of Child Health, The Hospital for Sick Children, Great Ormond Street, London, W C 1 The research to be undertaken will include the investigation of congenital malformations and hereditary abnormalities and diseases and studies of the rôle of inheritance in common diseases

In England Now

A Running Commentary by Peripatetic Correspondents

THE forbidding Zeitgeister of *tachisme* and action painting do not haunt the members of the Medical Art Society The keynote of their current exhibition, at Walker's Galleries, 118, New Bond Street, London, is happy innocence The landscape is the most popular form and nearly all the landscapes breathe contentment Dr Terence East's "Douarnenez Bay," Dr Isabel Wilson's "Battersea Reach," Dr Henry Wilson's city ruins, Dr K Shirley Smith's "Wareham," and Mr Ian Robin's "Loch Lomond" are pleasing examples "Near Atcham" is a charming pencil drawing by Dr S Charles Lewsen Among the most attractive of these contemplative scenes are Dr A E O'Donnell's forest glade, "St Martin's Summer," and the sunset-hued oils of Sussex by Sir Philip Manson-Bahr, the society's president, who also contributes a striking picture of a corridor of columns from Karnak

A doctor puts his passion into his work, he is a Sunday painter and perhaps it would be unreasonable to expect passion in his paintings In this exhibition, even where the subject is turbulent, the treatment is often placid, thus the well-drawn windswept moors of Dr Leslie Cole and Mr F N H Maidment do not hammer us to the ground or even gaily whisk off our hats But Sir Harold Gillies's expansive "Flamingoes" has vitality, and Mr T Holmes Sellors, whose water-colours abound in the "wiry lines" beloved by Blake, contributes a small study, "Kitzbuhel," which is one of the most energetic and impressive in the show The deep blue sea in Dr Leonard Simpson's "The Harbour, Monte Carlo" looks as thick and compelling as treacle, and Dr Edith Magill's Connemara landscape is properly sombre, the water is beautifully painted

Mr B N Brooke's romantic imagination is bursting in his two fine pictures His lush "Succulents" is as deeply felt as his portrait "Goan Girl" Dr Josephine Roth has two portraits, of which "The Twisted Smile" is admirable An unusual portrait is Dr Margaret Little's mosaic reproduction Of the still-lifes, Dr Elizabeth Whatley's aquatint is outstanding, and Mr W M Van Essen has a very lively flower piece

He must be a stern critic who has no weaknesses, and mine include primitives (such as the charming oils by Dr Ph Tuttnauer) and Edward Ardizzone, whose strongly individual work is called to mind by Mr G Sparrow's "Pony Sale, New Forest," an accomplished and attractive composition But if I could award a prize for this exhibition, it would go to Dr A Phillips for his splendid bronze head, "Suzanne," in which passion and skill have produced a fine work of art

* * *

Now that the 5% interim tossed into the kitty promises to turn pounds into guineas surely vingt-et-un is the *game for gambling in the N H S ?* Surgery poker, as described by my peripatetic colleague last week, may be all very well for the larger lists with crowded surgeries, but here in the country we have to content ourselves with patient pontoon The profits may be smaller but the returns are much quicker, and in a dispensing practice we have the prescription charges to play with Pontoon is sufficiently flexible to be easily *adapted* to the conveyor-belt routine of hospital casualty and outpatient departments, or local-authority clinics The more sporty-looking patients can even be invited to put their shirts on the luck of the card drawer

As in surgery poker, the preliminaries are much the same for all branches of the service, with the allocation of playing card values to various patient types and the drawing-up of an agreed code of local rules Fate and the buses shuffle the pack before they stack themselves into the waiting-room My partner and I toss for the bank, and then the intercom phone does the rest between our twin consulting-rooms Our receptionist safeguards the spirit of the N H S by seeing that we get a blind deal and she exposes any twists Sticking presents no great problem, but it needs skill not to arouse the suspicions of our more strait-laced patients Poor Miss Prune paled visibly this morning when I greeted her with a disgusted look and absent-mindedly barked "Bust!" Perhaps we have something to learn from the poker-players after all

* * *

The cuckoo has been called the trumpeter of summer Would that I had Jenner's skill as an ornithologist so that I could add something to the natural history of this parasitic bird, which was heard here in the pastoral heart of England on Easter Monday morning I have not yet seen one, though he usually shows himself by his flight and colours as well as announcing his arrival by his voice, still a little hoarse What will his mate do with her eggs this year? The robin, the hedge-sparrow, and the thrush have weeks' start on her Thrushes have already hatched their young The others are well in the middle of the incubation period Even if the foster-mother is deceived, will her own young, several days older, tip the late-hatched intruder out? Perhaps this often happens already, there seems no reasonable explanation why the cuckoo should lay over a dozen eggs except an exceptionally high neonatal mortality

* * *

The American navy, according to the New York correspondent of the *Daily Telegraph* (April 16), is thoughtfully preparing "do it yourself plans" for radio amateurs who wish to tune in on an artificial satellite *during the International Geophysical Year* One of the costly but essential items of this "poor man's version of a million-dollar recordings station" would be a recording device, "but officials believe the amateurs could cut the cost by borrowing a cardiograph from a local doctor"

Local doctors whom we know might offer a choice of stethoscope, auriscope, or hypodermic syringe

* * *

When Cocteau was elected to the French Academy, he said that it is now conformist to be anti-academic He was demonstrating his nonconformity by becoming an academician Perhaps a similar mischievous spirit has prompted Mr Stanley Spencer over the years At this year's Royal Academy exhibition, his alarming *Dinner on the Hotel Lawn* (direct, as they say, from its success at Tooth's) is one sort of splendid painting that is still unexpected in its surroundings Almost equally surprising are his portraits, painted with such sharpness that they seem to lie a foot or so in front of the canvas In the generally romantic atmosphere, earthy realism is *equally surprising It is the keynote of a school of* young painters of whom the best-known are Mr Derrick Greaves and Mr Edward Middleditch Each has contributed *three accomplished* oils, of which Greaves's *Sicilian Subject* and Middleditch's *Irises* are outstanding

In a sense the Academy itself seems to be becoming anti-academic The few abstractions chosen are feeble, and the drawings in the main unexciting, *but* the portraits are often strong and critical, in general they are less than fulsome Fatal charm is dissected, harshness laid bare, rascality hinted at, folly revealed From this exacting test, the medical profession may congratulate itself on coming out so well Mr Harold Knight has painted a presentation portrait of Sir Gordon Holmes, which is *sympathetic and acute*, *and* he portrays both the shrewdness and the humanity of Sir Harold Boldero Mr A R Thomson's sketch of the late Dr Joan Malleson *is charming, Sir Gerald Kelly's Dr John Fulton* is weighty, and Mrs Mary Gillick's medallion of Sir Henry Dale a model of firmness and strength Mr Maurice Codner's *Dr Arthur Bousfield* has quiet dignity Mrs J K Irvine, president of the Pharmaceutical Society, is painted by Mr Norman Hepple, *and* Miss Margaret Smyth, chairman of the General Nursing Council, by Dame Laura Knight There is *a* bust of Dr Douglas Robb by Mr John Kavanagh

The most moving picture in the exhibition is the late John Minton's *Composition, 1957* His reputation among painters was, if anything, even greater than his public reputation The knowledge that it was his last (and unfinished) work adds poignancy to a magnificent painting

Letters to the Editor

MEDICAL STAFFS OF MENTAL HOSPITALS

SIR,—In the light of recent intense interest in the problems concerned with the management and treatment of those suffering from mental illness in its various forms, we should like to draw attention to a matter which has an immediate bearing on the situation—namely, the urgent need for a substantial increase in the medical staffs of mental and mental-deficiency hospitals

This need has already been emphasised in the report of the Central Health Services Council for the year ended Dec 31, 1955, where attention is drawn to both the change in character which is taking place in mental hospitals and the steeply climbing admission-rates After noting that, as psychiatry advances and popular prejudice against resort to mental-hospital treatment lessens, more patients come within the scope of remedial treatment, the report continues

> " These tendencies, encouraging in themselves, are developing in circumstances of great difficulty for the hospitals Most of them were built in the last century and their design is not in accord with modern ideas of the requirements of medical or social treatment They are, for the most part over crowded and short not only of doctors, but of other staff These conditions constitute a challenge alike to hospital committees and their staffs and credit is due to them for succeeding in the face of all difficulties in improving the services available to the community But they need all the help that can be given and more particularly it is essential to strengthen the medical staff "

The wider social and economic aspects of the situation are reflected in a recent public statement to the effect that the loss of man-power in industry due to mental illness of one kind or another is approximately twenty times as great as that which results from industrial disputes

We are satisfied from both our own experience and the information we have received from our colleagues in other parts of the country that the situation is steadily growing more grave Requests for psychiatric advice and treatment steadily increase while the number of psychiatrists to supply this need is woefully inadequate

We would draw particular attention to the fact that the present medical establishments were fixed in 1948 The expansion that is taking place in the volume of work is reflected in the following comparable returns in respect of the mental hospitals and their associated psychiatric outpatient departments in one region for the years 1949 and 1955

	Five mental hospitals (occupied beds 8452)			*Psychiatric outpatient departments*		
	Admissions	*Discharges*	*Deaths*	*No of clinics*	*New patients*	*Total attendances*
1949	3271	2564	587	15	3572	16,159
1955	4741	3864	784	16	4315	21,727

This increase in the turnover of cases in the mental hospitals and the expanding outpatient commitments are two factors which have added to the psychiatrists' work There are others, however, that are important Since the Mental Treatment Act of 1930 there has been a steady increase in the numbers of those seeking admission as voluntary patients with the result that in 1954 and 1955 in one region 70% of the total admissions were in the voluntary category The number certified has diminished proportionately This trend has been mainly responsible for bringing more and more mild and early cases for treatment Such cases demand a much greater amount of the doctors' time since psychiatric management is no longer just a matter of custodial care and attention to intercurrent physical disease, instead, it involves time-consuming psychotherapeutic procedures or the skilled application of the newer physical methods of treatment, together with the social work involved in restoring the patient to useful employment in the community There is a tendency to concentrate the limited medical resources of the hospital on these cases with the consequent danger of neglecting longer-term cases, for whom so much more could be done if time and medical staff were available

With mounting attendances at outpatient clinics the psychiatrist, instead of enacting his proper role of clinician and psychotherapist, runs the risk of becoming a routine prescriber of tranquillising drugs

In the case of mental deficiency hospitals increasing demands on the time of the medical staff stem from the rising numbers of temporary cases, the more frequent review of licence cases, the expansion of extramural activities, and the more thorough investigation of neurological cases, which includes electro-encephalography

With these heavy commitments senior psychiatrists have little or no time in which to perform what should normally be one of their essential functions—that of instructing junior members of the staff and supervising their work

We realise that regional hospital boards are seriously handicapped in dealing effectively with this problem because of the financial restrictions imposed upon them but we are firmly of the view that the situation has become sufficiently serious to merit reference to the highest level

We would therefore urge the Minister to review the matter comprehensively as a pressing national problem, and to introduce without delay effective measures for its control In this connection we submit that a substantial increase in the medical establishments of mental and mental deficiency hospitals, particularly in the senior grades, is a primary requirement

E B STRAUSS
J S HARRIS
B MATHESON
G S NIGHTINGALE
R H F SMITH
G SOMERVILLE

CLEAN BEDS

SIR,—We should like to support the findings of Dr Blowers and his colleagues (March 23) concerning the sterilisation of hospital blankets, and to add some of our own observations For the past six months we have been comparing the properties of woollen and 'Terylene' blankets which have been washed, and then sterilised by autoclaving, after use in a ward in which many full thickness burns are treated

Our method has been to affix to the blankets to be tested squares cut from a similar blanket, which can then be removed for bacteriological tests at each stage of the experiment These test squares were placed in a broth culture and subcultures then plated in the usual manner The blankets were washed at 110°F with a detergent, 'Syndet 4,' using a technique of acid washing conditions with low foam production for maximum detergency They were then dried and autoclaved in a large dressing drum at 20 lb per sq in for 25 min

The proportion of area lost (i e, shrinkage) after only six complete processes (washing and autoclaving) was 47% for the woollen and 4% for the terylene blanket In addition the woollen blanket " felted " into a hard coarse material, the colour changing from cream to light grey, whilst the terylene blanket remained soft, white, and fluffy The bacteriological tests showed that the blankets, when new, were infected with a variety of organisms including *Neisseria mucosus*, *Streptococcus viridans*, and coagulase negative *Staphylococcus aureus* After being used on the patients the test squares then grew, in addition, coagulase positive *Staph aureus*, *Pseudomonas pyocyanea*, *Escherichia coli*, and *Bacillus subtilis* These types of organisms were still found after the washing process, and often further varieties of organisms were isolated, showing that the washing process did nothing to remove the bacteria but merely distributed them throughout the blankets After sterilisation (autoclaving), however, the blankets showed either no growth or the growth of a few types of non pathogenic organisms

The good qualities of terylene blankets are therefore:

(1) There is little change in weight or size after repeated washing and autoclaving.

(2) There is very little change in the texture of the material after washing and autoclaving.

(3) They are non-inflammable.

(4) They are preferred by the patients because of their warmth and softness.

There is one disadvantage, the accumulation of a high static electrical charge. This would prohibit the use of terylene blankets in the operating-theatre, and it is, therefore, suggested that Turkish-towelling blankets, dyed in a distinctive colour to act as a reminder, could be used to accompany the patient to and from the operating-theatre.

Although blankets will quickly become reinfected when used on a patient with full-thickness burns, sterilisation of blankets will ensure that no organisms are added to the patient's wounds at the start of his treatment.

R. P. OSBORNE
A. H. M. LITTLEWOOD
Liverpool W. ATKINSON.

GOVERNMENT AND PROFESSION

SIR,—In your last issue "Blackleg," who does not give his name, complains that members of the B.M.A. council and of the General Medical Services Committee, who were not members of his division, attended its meeting. But what is the job of elected members of the G.M.S.C. and council if not to attend meetings of divisions within their constituencies?

He speaks of a "party line." There is no party line: every decision made has been made by strict majority voting. If "Blackleg" does not attend meetings, it is his own fault if these majorities decide things he does not like. To do everything by postal ballot for 70,000 B.M.A. members plus 10,000 odd non-members would increase the subscription to the B.M.A. by at least a guinea. So even that idea is not a good one.

He says that to many people the policies of phased withdrawal and boycott of the Royal Commission seem unethical. Then perhaps it is unethical for such people to take the money won for them by those who negotiated the Danckwerts increase in 1952 or the hospital increase in 1954? Does your correspondent suppose that a beneficent Ministry of Health looks after his interests and is only too glad to ask the Treasury for what it thinks he needs?

If he regards withdrawal as wrong because it will "hurt the patient," I can assure him that the patient will not get hurt: the Government, for political reasons, will see to that. The only risk is that this Government, being Tory, may be trying to wreck the National Health Service and pin the responsibility on us. (After all, we are on record on two occasions as opposing the imposition of charges on patients.) No, even if we withdraw, the Government when the time comes will make interim arrangements by which the public will have a free service, even if this is done through the National Assistance Board refunding the money that patients have paid out to doctors and for chemists. In any case, as the Government so often remind us, this is not our problem: it is their duty, by law, to provide a Health Service, not ours. We are merely asked to contract to do Government work at *agreed* rates and on *agreed* terms. If one side to this agreement rats, what is the other side to do? It can (*a*) go to court, or (*b*) withdraw from the agreement and negotiate a fresh one. If we had ratted the Government would have been the first to do either (*a*) or (*b*). "Ethics" —apart from the ethics and honour of pledged agreements —do not enter into it.

London, W.C.1 J. L. MCCALLUM.

SURGEON'S "PRIVILEGE"

SIR,—Up and down the country one hears from time to time of attempts by hospital administrators to break a tradition which they are told by the financial representatives of the Government is illegal. I refer to the provision of refreshment to the surgeon and his colleagues during operation sessions when they are prevented from going to their homes or other normal places of refreshment. Sensible administrators, particularly those of the older school, turn a blind eye to any question of restriction. Lest younger men should become overwhelmed by authority, the whole matter should be clarified nationally.

Surgeons and their immediate colleagues do not ask for "privilege": the matter is much more fundamental. Operative surgery is an exacting enterprise concentrated without regard for time upon one purpose. The patient who is the centre of this purpose should, with the surgical team, be identified as a unit and for no matter how many hours the work continues by day or by night every aspect of the comfort and well-being of the complete unit must be safeguarded. The custom of sustaining the surgeon and his colleagues under these conditions is a humane tradition of British hospitals; the ultimate object is the safety of the patient. The exercise is like that of a naval vessel in action: it cannot be measured in the time taken or in the personal service received by the crew.

Exeter NORMAN CAPENER.

INSULIN TREATMENT OF SCHIZOPHRENIA

SIR,—We read with great interest the article by Dr. Ackner and his colleagues (March 23).

We think they and your readers would like to know that we pointed out the non-specificity of insulin treatment as early as 1939.[1] Our findings were based on 419 patients, of whom 118 were given insulin shock and 61 leptazol ('Cardiazol'): 218 had no active treatment (control group).

The follow-up included 283 very carefully investigated cases. Two of our final conclusions were: (*a*) insulin treatment had no effect on new *acute* cases of schizophrenia; and (*b*) in *chronic* cases improvement was no greater than in the control group—i.e., 10%.

We think our experience serves to confirm the conclusions of Dr. Ackner and his colleagues.

St. Istvan Hospital, Budapest.
T. LEHOCZKY
MARGARET LEHOCZKY.

SIR,—Before the two camps in the issue of insulin treatment become too firmly entrenched, it will be appropriate to point out a line of argument which so far has not been adduced. Dr. Ackner's findings, obtained by an incomparably exact technique, are unassailable, though one would have wished for a larger material and for a longer follow-up. A fine demonstration of an object-lesson, the findings must be made the starting-point for unrelenting re-thinking.

While nobody has ever been biologically so naïve as to see in insulin a specific therapeutic agent in schizophrenia, and while everybody has kept in mind that what matters are the neurochemical reactions to hypoglycæmia, very few have proceeded from there to a wider biological field. If one biological lever to the adaptatory mechanisms of the organism can produce good results, then, it can be concluded, other biological levers can produce just the same. The rhythmic training of the homœostatic mechanism which insulin treatment incorporates—in other words, this slow process of restoring elasticity to a system which has been in danger of becoming stiff—can in principle be replaced by any similar technique.

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[1] Lehoczky, T., Fazenyi, M., Horanyi-Hechst, B., Dub, R. *Z. ges. Neurol. Psychiat.* 1939, 160, 24.

White mice weighing about 20 g were given hexo arbitone sodium 150 mg per kg or methylpentynol 400 mg er kg intraperitoneally Fifteen minutes after the induction narcosis, bemegride 50 mg per kg was given intravenously he results are shown in the accompanying table

In a few other preliminary experiments with chloral hydrate, similar tendency to shortening of the sleeping-time was oted In several animals narcotised with hexobarbitone, onvulsions were noted after bemegride had been given o such effects were observed in the methylpentynol group

Our results demonstrate that bemegride is effective gainst a non-barbiturate narcotic, methylpentynol, hich has previously been denied [6] These findings seem confirm the opinion that bemegride acts mainly as a entral analeptic The experiments are being continued

Medical Department
Karolinska Sjukhuset,
Stockholm.

L E Bottiger
L Engstedt
O Strandberg

AN ALTERNATIVE TREATMENT OF OSTEO-ARTHRITIS OF THE HIP

Sir,—My experience of the effects of radiotherapy in steo arthritis of the hip is similar to Mr Murley's April 20), and about a year ago I had to find an alternaive for a woman of 70, who had severe joint damage and was in such pain that she could not sleep at nights

She was almost bedridden, her general condition was eteriorating, and owing to myocardial degeneration she was nfit for operation My colleague, Mr Godfrey Hutchinson, onsultant dental surgeon to the Newcastle group of hosntals, agreed to treat her by hypnotic suggestion The result was very satisfactory She was given physiotherapy during er course of suggestion therapy, but it had to be stopped for ear of acute heart failure

She now sleeps well and her general health has improved he walks indoors at home, but always holding on to the urniture Her range of hip movement is now voluntary whereas previously it was difficult to obtain any movement, even passively, owing to spasm

She is not entirely free from pain and she is still very limited n what she can do, but this is a safeguard for her weak heart

I recommend this method as an alternative to heavy sedation and a prolonged painful bedridden existence I am most grateful to Mr Hutchinson for his cooperation in my dilemma

Newcastle upon Tyne

C C Michael James

EPIDEMIC VERTIGO

Sir,—I have recently seen 5 cases of acute vertigo 2 patients had no associated signs and returned completely to normal within a week, they were not investigated The other 3 had coarse, rotatory nystagmus but no other physical abnormalities

Blood counts, erythrocyte sedimentation rates, radiographs of chest and skull, and examinations of the cerebrospinal fluid were normal Caloric tests were normal in 2, the other patient gave no response on stimulation of the right labyrinth Audiograms in this and 1 other patient were normal All 3 patients were afebrile The longest period for recovery was a month The patient with an abnormal caloric response still had this when last seen, six weeks after the onset His nystagmus had disappeared and he was quite steady with eyes open or closed

The patients were seen over a period of eleven weeks and had had no direct or indirect contact with each other Consequently nothing could be inferred about the epidemiology of the condition It seems likely, however, that sporadic cases do (perhaps regularly) arise The ætiology of the condition was unknown, precipitating infection, emphasised by Dix and Hallpike [7] and Moller,[8] was not evident The lesion was thought to be situated centrally to the labyrinth and the term "central vestibular vertigo" was used Such a term would include affections showing a similar natural history and previously called virus labyrinthitis, vestibular neuronitis, brainstem encephalitis, and epidemic vertigo It should exclude cases with progressive tinnitus or deafness and those where the ætiology is known

Aldershot

T B. Stretton

ÆTIOLOGY OF PRE-ECLAMPSIA

Sir,—The letters of Dr Morris (April 13) and Dr Schuurmans (April 20) suggest that some confusion may exist about structural stress and strain relationships and hydrostatic pressures in the uterus It is important to recognise which factors can and have been measured, and to avoid lax terminology, which leads to the misinterpretation of available evidence

Intra-uterine, or intra-amniotic, pressure arises from the work of the uterine muscle and the intra-abdominal pressure The uterine muscle component is the greater, and, for simplicity, is considered alone in this letter The uterine contents are held together against the forces of gravity by the forces in the walls of the uterus During a contraction the fluid-like contents of the uterus are gathered into a pear-like shape, which tends to become more spherical (largest volume for least surface area) as the contraction increases in intensity The volume of the contents remains nearly constant With the change in shape the hydrostatic pressure is raised For a given shape the rise in intra-uterine pressure is a measure of the average increase of the tensile force over the whole uterine wall

The tensile force is the force required to approximate the edges of an imaginary cut perpendicular to the direction in which the force is being considered Clearly the force depends on the size of the cut and it is therefore better to use the term *stress*, which is the tensile force per sq cm of cross sectional area Where tensile force in the wall is greatest the wall thickness tends to be greatest, thus making for a substantially uniform stress distribution, at least over the corpus

Tensile force at any point is directly proportional to the intra-uterine pressure and to the radius of curvature of the wall in the same direction

The intra-uterine pressure is not uniform throughout the uterus, because of the greater weight of water upon the lower parts It is customary, therefore, to express the pressure related to the highest point of the uterus in the supine patient The pressure difference between fundus and cervix may be as much as 25 cm water in the standing patient

The relation of pressure to tensile force has been very thoroughly discussed by Halliday [1]

The change in length per unit length of a stretching or contracting material is called *strain*—positive strain for an increase in length and negative strain for a decrease in length During a contraction, the myofibrils and their surrounding fibrous tissue show negative strain The interconnecting fibrous tissue between the muscle cells shows positive strain The response of strain-sensitive nerve endings would depend upon the part of the structure to which they were attached

In patients with gross uterine distension the walls are thinned and curvatures decreased, with the result that for the same tensile stress in the walls, and the same strain, if the nature of the muscle is unaltered, intra-uterine pressures are reduced

Measurements upon patients show that

In hydramnios intra uterine pressures both between and during contractions are below normal Hydramnios may be either the cause or the result of the low pressure, but when liquor is removed the pressure rises

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[6] Posen J *Nord Med* 1957, 57, 23
[7] Dix, M R Hallpike C S *Proc R Soc Med* 1952 45, 311
[8] Möller F *Acta psychiat, Kbh* 1956, 31 107

[1] Halliday, E C *J Obstet Gynæc, Brit Emp* 1954, 61, 811

To quote an apparently far fetched example in 1954 Lovett Doust[1] claimed good results in schizophrenia by "rhythmic sensory bombardment" (photic or sonic), which he tried to connect with the principle of desoxygenation. 25 years ago when Mayer Gross[2] reported on the therapy of schizophrenia, he quoted (with due caution) a review[3] of 1600 cases (in the literature) subjected to pyrexial treatment, which was widely advocated in the first quarter of this century. No doubt the third quarter will see an attempt to treat the disease with hypothermia, which now is so much in the *foreground*.[4]

In the present situation, the studies on the relationships between schizopathy and endocrinopathy, inaugurated by Bleuler[5] of Zurich and supported by our Bristol and St Ebba's groups (April 13), must be allowed to ripen. This is nothing more than a revival of the much earlier metabolic idea underlying Gjessing's studies in catatonics.[6] If this trend bears fruit, as it may, we shall not expect the psychotherapists of schizophrenia to retreat into the next trench and to abandon schizophrenics as untouchables. Similarly, there is no need for clinical workers who value the insulin technique for its standardisation, and for the prognostic criteria worked out on an immense material, to abandon it. Some will find all the trouble worth while in selected cases without neglecting *other therapeutic approaches to personality as a whole*.

The biology of the human organism and the theory of its adaptation are very complex matters, and any attempt to claim monopoly for one isolated mechanism, or one isolated level of behaviour, will lead to fallacious conclusions. While neither side is yet victorious, both will continue to share in an honest endeavour to master the problem.

Reading STEPHEN KRAUSS

THIRTY-MINUTE SCREENING TEST FOR PHÆOCHROMOCYTOMA

SIR,—Dr Hingerty's test (April 13) has the merit of requiring no special apparatus, but his reporting of results in terms of µg of pressor amines excreted seems to me open to criticism, for the following reasons.

(1) No results are given for percentage recovery of noradrenaline added to urine. Using the technique described by Dr Hingerty, but taking noradrenaline as comparison standard without prior adsorption and elution, recoveries, in my experience, have been around 30%, and have varied considerably in different estimations. Admittedly the extent of error from this source could be partially reduced if a recovery estimation was included in each analysis. Dr Hingerty's comparison standard, however, is prepared in advance and kept for repeated use on the assumption that the percentage *recovery remains constant*.

(2) Visual comparison of fluorescence intensity is likely to be misleading, particularly at low concentrations, where even a threefold difference of intensity is by no means obvious unless instrumental comparison is made. The presence of other fluorescent substances, not infrequently encountered in urine extracts, could make even semiquantitative assessment impossible unless filters were used, as in commercial fluorimeters.

(3) The details given of the method of preparation of alumina are insufficient to allow of exact repetition; it is, however, known that the temperature of drying and the final water content of the "dry" alumina exert a considerable influence on its adsorptive properties. Dr Hingerty may have been fortunate in having alumina which regularly gave quantitative recovery of pressor amines, but my experience in this respect has been discouraging.

A simple routine method for estimation of pressor amines in urine is certainly required, but I am not convinced that the method described is sufficiently reproducible to be useful, except possibly when excretion is enormously increased. To judge by published data, the output of catechol amines in phæochromocytoma is not *always increased to this extent*.

Lastly, the test might perhaps be more accurately described as a sixty-minute one. If a set of controls and standards is prepared at the same time, two hours is a more likely requirement.

Department of Clinical Chemistry,
Royal Infirmary Edinburgh SAMUEL C FRAZER

BRONCHIAL LAVAGE

SIR,—I wish to thank Dr Trobridge for describing his simple technique of bronchial lavage (March 16). With a little practice, the method may be further simplified by posturing the patient while the saline is poured in (as is done during bronchography). This will avoid the theoretical dangers of "flooding and soiling" other parts of the lung. Recently, I had the opportunity of finding acid-fast bacilli in the bronchial lavage of a woman who had persistently negative sputa and laryngeal swab. She had eosinophilia in the blood and had in fact been transferred to a general medical ward.

In view of Dr Trobridge's report, every patient who has difficulty in raising sputum should have bronchial lavage instead of the traditional swabbing of the larynx or washing of the stomach.

North Middlesex Hospital
London N 18 SAMIR K GUPTA

IS BEMEGRIDE A SPECIFIC BARBITURATE ANTAGONIST?

SIR,—In 1954 Shaw et al[1] described their investigations of bemegride ('Megimide,' ββ methylethylglutarimide) and claimed it to be a barbiturate antagonist. They based their opinion on experiments in which they had found a reduction of sleeping-time in animals of several species that had been narcotised with pentobarbitone, barbitone, or phenobarbitone, as well as on clinical experience. In 1955 Shaw[2] stated that the action of bemegride was specific and that it did not affect the depressant actions of other anæsthetic agents such as ether, chloroform, and morphine.

Lately, voices have been raised against the specificity of bemegride, which is instead believed to act mainly as a central analeptic. Thus Hahn et al[3] have stated that it is "a functional and not a competitive antagonist." Danish work suggests that bemegride does not shorten barbiturate coma in man, that the patients do not wake up at higher serum-barbiturate levels, and that the rate of elimination of barbiturate from the blood is unaltered.[4] Others also emphasise the potent action on reflex activity and respiration. "It is difficult to explain these clinical results and observations as the action of a simple biochemical antagonist."[5]

We believe that bemegride is a valuable drug in the treatment of certain forms of barbiturate intoxication, but we do not think that the mode of action has been sufficiently clarified. We therefore compared the action of bemegride against barbiturates with its action against other narcotic agents.

ACTION OF BEMEGRIDE ON NARCOTISED MICE

Drug	No of animals	Duration of narcosis (min) with standard error of the mean (min)	Difference
Hexobarbitone	29	118 ± 5	38 ± [illegible] P < 0·001
Hexobarbitone, then bemegride	18	80 ± 4	
Methylpentynol	35	29½ ± 2	
Methylpentynol, then bemegride	45	37 awoke at once 8 after 7–180 min	

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[1] Lovett Doust J W Schneider, R A *Dis Nerv Syst* 1954, 15 12
[2] Mayer Gross W *In* Handbuch der Geisteskrankheiten, vol IX Berlin, 1932
[3] Menninger von Lerchenthal E *Z ges Neurol Psychiat* 1925, 97 460
[4] Giles, P Personal communication
Bleuler M Endokrinologische Psychiatrie Stuttgart, 1954
sing, R. *Arch. Psychiat Nervenkr.* 1935, 104, 335.

[1] Shaw, F H Simon, S E Cass N Shulman, A, Anstee, J R Nelson D R *Nature, Lond* 1954 174, 402
[2] Shaw, F H *Med J Aust* 1955, ii 889
[3] Hahn F Oberdorf A, Schunk, R *Dtsch med Wschr* 1956, 81 1580
[4] Pedersen, J *Ugeskr Laeg* 1956 118, 773
[5] Louw, A, Sonne, L M *Ibid*, p 761

White mice weighing about 20 g were given hexo arbitone sodium 150 mg per kg or methylpentynol 400 mg er kg intraperitoneally Fifteen minutes after the induction t narcosis, bemegride 50 mg per kg was given intravenously he results are shown in the accompanying table

In a few other preliminary experiments with chloral hydrate, similar tendency to shortening of the sleeping time was oted In several animals narcotised with hexobarbitone, onvulsions were noted after bemegride had been given o such effects were observed in the methylpentynol group

Our results demonstrate that bemegride is effective gainst a non-barbiturate narcotic, methylpentynol, hich has previously been denied [6] These findings seem o confirm the opinion that bemegride acts mainly as a entral analeptic The experiments are being continued

L E Bottiger
L Engstedt
O Strandberg

Medical Department,
Karolinska Sjukhuset
Stockholm.

AN ALTERNATIVE TREATMENT OF OSTEO-ARTHRITIS OF THE HIP

Sir,—My experience of the effects of radiotherapy in osteo arthritis of the hip is similar to Mr Murley's (April 20), and about a year ago I had to find an alternative for a woman of 70, who had severe joint damage and was in such pain that she could not sleep at nights

She was almost bedridden, her general condition was deteriorating, and owing to myocardial degeneration she was unfit for operation My colleague, Mr Godfrey Hutchinson, consultant dental surgeon to the Newcastle group of hospitals, agreed to treat her by hypnotic suggestion The result was very satisfactory She was given physiotherapy during her course of suggestion therapy, but it had to be stopped for fear of acute heart failure

She now sleeps well and her general health has improved She walks indoors at home, but always holding on to the furniture Her range of hip movement is now voluntary whereas previously it was difficult to obtain any movement, even passively, owing to spasm

She is not entirely free from pain and she is still very limited in what she can do, but this is a safeguard for her weak heart

I recommend this method as an alternative to heavy sedation and a prolonged painful bedridden existence I am most grateful to Mr Hutchinson for his cooperation in my dilemma

Newcastle upon Tyne C C Michael James

EPIDEMIC VERTIGO

Sir,—I have recently seen 5 cases of acute vertigo 2 patients had no associated signs and returned completely to normal within a week, they were not investigated The other 3 had coarse, rotatory nystagmus but no other physical abnormalities

Blood counts, erythrocyte sedimentation rates, radiographs of chest and skull, and examinations of the cerebrospinal fluid were normal Caloric tests were normal in 2, the other patient gave no response on stimulation of the right labyrinth Audiograms in this and 1 other patient were normal All 5 patients were afebrile The longest period for recovery was a month The patient with an abnormal caloric response still had this when last seen, six weeks after the onset His nystagmus had disappeared and he was quite steady with eyes open or closed

The patients were seen over a period of eleven weeks and had had no direct or indirect contact with each other Consequently nothing could be inferred about the epidemiology of the condition It seems likely, however, that sporadic cases do (perhaps regularly) arise The ætiology of the condition was unknown, precipitating infection, emphasised by Dix and Hallpike [7] and Moller,[8] was not evident The lesion was thought to be situated centrally to the labyrinth and the term "central vestibular vertigo" was used Such a term would include affections showing a similar natural history and previously called virus labyrinthitis, vestibular neuronitis, brain-stem encephalitis, and epidemic vertigo It should exclude cases with progressive tinnitus or deafness and those where the ætiology is known

Aldershot T B Stretton

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Sir,—The letters of Dr Morris (April 13) and Dr Schuurmans (April 20) suggest that some confusion may exist about structural stress and strain relationships and hydrostatic pressures in the uterus It is important to recognise which factors can and have been measured, and to avoid lax terminology, which leads to the misinterpretation of available evidence.

Intra-uterine, or intra amniotic, pressure arises from the work of the uterine muscle and the intra abdominal pressure The uterine muscle component is the greater, and, for simplicity, is considered alone in this letter The uterine contents are held together against the forces of gravity by the forces in the walls of the uterus During a contraction the fluid-like contents of the uterus are gathered into a pear like shape, which tends to become more spherical (largest volume for least surface area) as the contraction increases in intensity The volume of the contents remains nearly constant With the change in shape the hydrostatic pressure is raised For a given shape the rise in intra uterine pressure is a measure of the average increase of the tensile force over the whole uterine wall

The tensile force is the force required to approximate the edges of an imaginary cut perpendicular to the direction in which the force is being considered Clearly the force depends on the size of the cut and it is therefore better to use the term *stress*, which is the tensile force per sq cm of cross sectional area Where tensile force in the wall is greatest the wall thickness tends to be greatest, thus making for a substantially uniform stress distribution, at least over the corpus

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The relation of pressure to tensile force has been very thoroughly discussed by Halliday [1]

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In patients with gross uterine distension the walls are thinned and curvatures decreased, with the result that for the same tensile stress in the walls, and the *same* strain, if the nature of the muscle is unaltered, intra-uterine pressures are reduced

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After concealed accidental hæmorrhage both pressure and wall stress is considerably increased for a long time

The changes in strain in the uterine walls occurring from time to time in a normal patient, with changes in posture or with Braxton Hicks contractions, far exceed the differences between one patient and another, and the uterorenal reflex pathway, if it exists in woman, would often be stimulated in all patients

Two facts, however, need to be ascertained before the uterorenal reflex theory of toxæmia is discarded Firstly, do pre-pre eclamptic patients have a phase of raised intra-uterine pressure before they become pre eclamptic? Secondly, do patients before or after they become pre eclamptic have more frequent Braxton Hicks contractions and hence stimulate this hypothetical reflex more often? One might inquire whether they have premature development of the lower segment and cervix, where positive strain sensitive nerve endings would be expected to exist Toxæmic patients certainly have shorter labours for the same weight of baby, as judged by the duration of painful contractions, than normal patients

Obstetric Unit
University College Hospital,
London, W C 1

C N SMYTH

THE STAPHYLOCOCCUS PLAGUE

SIR,—Your leader of April 6 suggests methods of reducing the dissemination of staphylococci but does not refer to the possible use in hospitals of germicidal ultraviolet light for the inactivation of air-borne micro-organisms

The germicidal ultraviolet tube (T U V Philips Electrical) is widely used in laboratories and in industrial processes to produce "germ free" air conditions These discharge tubes are made from a special glass, transmitting ultraviolet of wave-length longer than 2000 Angstrom units, a high proportion of the radiant energy produced is at 2537 Å

Ultraviolet of 2600 Å wave length prevents the reproduction of micro organisms The ultraviolet from a T U V will inactivate *Staphylococcus aureus* in culture with a dose of about 5 micro watt seconds per sq cm

Ultraviolet tubes of 15 and 30 watts resemble fluorescent lamps in appearance and the same type of control gear is required for operation The tubes can be mounted in air ducts or in aluminium reflector units, or used bare in suitable situations Bacteria in the air within the effective radiation of the tube are inactivated, and inactivity of the order of 99 9% can be obtained

There are many possible applications of this germicidal ultraviolet radiation in hospitals—for example, to produce an almost sterile atmosphere in operating theatres, anæsthetic rooms, clean surgical dressing rooms, and wards, and to inactivate the immense numbers of floating bacteria in septic wards, septic surgical dressing rooms, soiled linen rooms, and corridors leading from similar potent sources It should be possible to devise a portable tube carrier for use over a bed when heavily infected dressings are being changed

Patients and staff can be protected from direct radiation by simple means, ordinary glass spectacles or plastic visors protect the conjunctiva, which is especially susceptible to short wave ultraviolet radiation The American Medical Association has approved the use of germicidal tubes in hospitals and has produced tables showing safety limits of intensity of radiation to which patients and staff can be exposed

The movements of patients, staff, and bedding from septic wards to "clean" areas causes heavy air contamination, but if T U V can be used to inactivate these floating millions of bacteria the possibility of cross infection becomes remote and a hospital should then become a "clean and wholesome sick-house"

I believe that the initial cost of installation is greater than that for fluorescent tube lighting, but the running costs should be no higher, the life of T U V is relatively long—averaging 2500 hours

[illegible] Northumberland

JOHN W JAMES

SHERRINGTON CENTENARY

SIR,—A memorial lecture as suggested by your corr pondents (April 20, p 841), seems to me to be inadequate recognition of Sherrington's work as a ve great scientist and a truly great man As, however, t die is cast, may I suggest that "lecture" be replaced "lectures," and that they be founded on the same li as the Silliman lectures, among which Sherringto greatest work *The Integrative Action of the Nervous Sys* is enshrined?

London, W 1

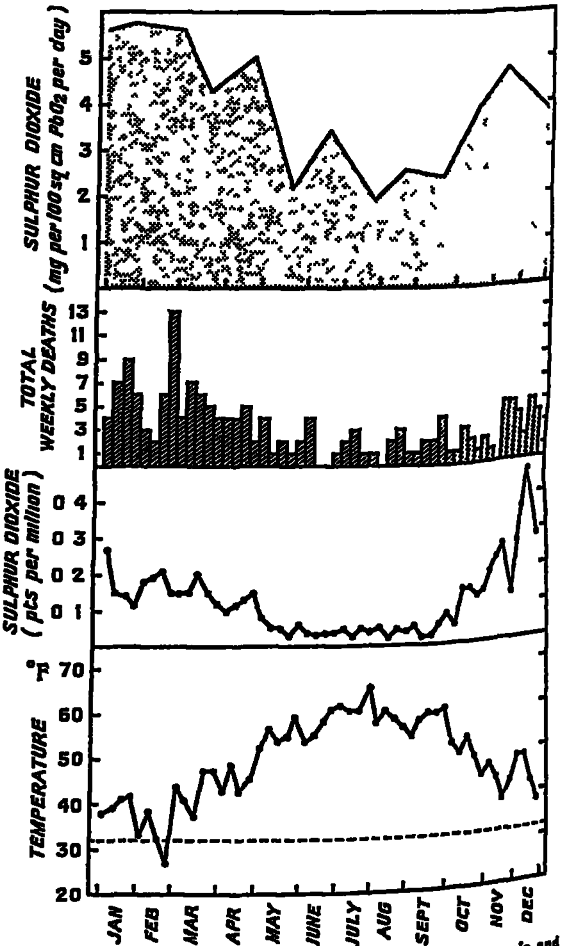
J HERBERT PARSON

ATMOSPHERIC POLLUTION, TEMPERATURE INVERSION, AND DEATHS FROM BRONCHITI

SIR,—Bronchitis is rarely given as the first cause death in this country The deaths shown in the accom panying figure are those recorded as due to respirato diseases (other than lobar pneumonia and cancer) a circulatory failure, where no definite ætiology is give The figures were extracted from the lists reaching th department during 1956

At the top of the figure is given the rate of absorptio of sulphur dioxide on to a lead-peroxide candle T values are the averages of monthly readings taken three sites within the district Below are given, week b week, the mean daily temperature (measured at Kew and the mean sulphur dioxide content of the atmosphe as measured at one point in the district I have n information about the occurrence of temperatu inversion

The general trend of the figures is the same as th recorded by Dr Roberts and Mr Batey (March 16



Deaths due to respiratory disease (other than lobar pneumonia and cancer), sulphur-dioxide readings, and mean daily temperature at Kew out it will be seen that the week ending Feb 25 is exceptional, having 13 recorded deaths Of these, 4 were ascribed to heart-failure, and of the other 9, bronchitis was mentioned in 6 cases This was the week of the great freeze, but the sulphur-dioxide content of the air was not unduly high In the week ended Dec 22 fog was experienced in London and the sulphur-dioxide content rose, but the number of deaths recorded was not unusual

These figures seem to indicate that extreme cold may be inimical to the survival of bronchitic patients

Public Health Department
City of Westminster
G W PIPER

INCREASED PITUITARY GONADOTROPHIN ACTIVITY AFTER DEGENERATION OF SEMINIFEROUS TUBULES PRODUCED BY NITROFURAZONE

SIR,—In his interesting article (Feb 9) Dr Nissim has described the lesions in the testis in mice fed for a period of 2–5 weeks on a diet containing 0 04–0 6% nitrofurazone If a mouse eats 5 g daily of a diet containing 0 6% nitrofurazone, the quantity of nitrofurazone ingested is considerable—the equivalent of 90 g nitrofurazone a day for a man weighing 60 kg

When the diet contained 0 04% nitrofurazone Dr Nissim did not notice any damage of the testis This latter dose is equivalent to 6 g a day for a man weighing 60 kg Such a dose is not in common use

Nitrofurans have been used with effect in the treatment of various infections, and we think that Dr Nissim should have mentioned that the doses given to mice in his experiment represent large doses never used in man

Bucharest Rumania
V BOTGROS

AMIPHENAZOLE

SIR,—We note that Dr Dundee (Feb 16) has confirmed our earlier finding that amiphenazole, in combination with large doses of morphine, is of benefit in the treatment of intractable pain of terminal carcinoma Dr Dundee states that amiphenazole does not always counteract the nausea and vomiting due to morphine We would agree with this In results about to be published, we show that the incidence of vomiting in healthy volunteers due to a dose of 20 mg of morphine is about 30% When morphine is given to carcinoma patients in pain the incidence of vomiting is almost negligible The above-mentioned vomiting in volunteers is not controlled by amiphenazole but it is almost completely, by oral cyclizine and entirely by intravenous cyclizine The low incidence of vomiting when morphine is given in the presence of pain misled us with respect to the antiemetic action of amiphenazole

Dr Dundee finds that the respiratory depression induced by morphine is not always relieved by amiphenazole We would also concur with this finding We have now had some experience in the use of amiphenazole as a respiratory stimulant, both specifically against morphine and non specifically, over the past two years

The variable results obtained by ourselves and others may be due to the use of too small a dose Both from pharmacological evidence and clinical experience one can say that amiphenazole is a very safe drug On two occasions recently we have successfully used amiphenazole in single intravenous dosages of 150 mg to treat non-specific respiratory depression As we have already pointed out[1] doses of up to 300 mg may be given intravenously, at a single injection These large doses may be repeated at hourly intervals for several hours if necessary

Department of Pharmacology
University of Melbourne
F H SHAW
S GERSHON

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[1] McKeogh J Shaw F H *Brit med J* 1956 i 142

THE STUDENT AND SEX EDUCATION

SIR,—Dr Sandler (April 20) is to be congratulated for pointing out the inadequacy of our teaching in the general field of sex education

He goes right to the root of the matter when he says that to be an adviser one must have not only the necessary knowledge and experience but also a basic spiritual depth Last year the Birmingham medical students (perhaps unwittingly) underlined this when they arranged a forum on the subject of marriage guidance, they invited a gynæcologist, an experienced general practitioner, who had for years assisted at the Family Planning Association, and a minister of religion, the Rev H L Tizard

Has the time now arrived, as Dr Sandler suggests, for a set course of lectures on the functional aspects of marriage, the problem of birth control, &c , as outlined in his essay ? My own view is that instruction is best integrated into " medicine "—particularly, of course, into gynæcology and obstetrics

In Birmingham we are fortunate in our clinical material which allows us to " dilute " our student-instruction to 2 or 3 students per firm This allows us to avoid " classes " in outpatients, and although a student in his early days does not probe deeply into the functional side of marriage in his patient's history, nevertheless, there is on our unit case-sheet the heading " dyspareunia " With individual teaching of students the more detailed histories taken in private by the consultant can be gone over with the students when the patient has gone I give these as examples of integrating teaching of the abnormal into gynæcology, but an interest in the normal is also stimulated and our library has a suitable stock of books by authors such as Wright, Macalister, and Tizard Moreover, the Marriage Guidance Council and the Family Planning Association both accept our students as visitors, and of course Roman Catholic students are recommended to visit centres for members of their Church or to discuss problems peculiar to their Church qua sex education and birth control with colleagues in gynæcology who are also Roman Catholics

Lastly, I thought Dr Sandler should have made more of the educational value of a resident three months in an obstetric unit Nevertheless, his main arguments are, I think, proven and those of us who are taking part in the teaching of students must obviously accept greater responsibility But I make a plea for further and improved teaching which will be integrated into the subjects of gynæcology and obstetrics The idea that a further subject (" sex-education ") should be established with its own lecturer and perhaps its own examinations makes no appeal to me

Department of Gynæcology and
Obstetrics University of Birmingham
H C MCLAREN

SIR,—Dr Sandler's excellent article comes at a time when it is particularly welcome The General Medical Council, the Royal College of Physicians, the College of General Practitioners, and the British Medical Students' Association are all earnestly considering the problem of medical education Later this year the General Medical Council will make its recommendations, which, it is sincerely hoped, will give the medical schools a free hand in the rejuvenation of their teaching

Proper instruction in normal marital and sexual relations is sadly lacking from the present curriculum Even though the modern concept is the production of a basic doctor who can then specialise in general practice, cardiology, or whatever he desires, surely normal marital relations in all aspects should be taught wisely and sensibly during the clinical years This is of a far greater importance than watching œsophagectomies and ventriculograms

As that all too rare occurrence amongst British medical students, a married man with a family, I am acutely aware of the inadequacy of the training of my fellow students There can of course be no substitute for marriage itself as a teacher, and it is very much open to debate whether the early marriage of medical students should be approved or frowned upon

At a time when so much of a doctor's life is spent in dealing with functional illness and so much of functional illness stems from sexual and marital difficulties, may I make a plea to our teachers to read with care Dr Sandler's article and implement his suggestions, so that we may produce doctors and not scientists

E J R ROSSITER
Chairman, London Region,
London, W C 1 British Medical Students' Association

FLUORIDATION OF WATER-SUPPLIES

SIR,—Now that some experience has been gained in the fluoridation of water-supplies and that the benefits of fluoride-rich water are so well known, we feel that the time has come for the next step in this campaign for better dental health

It seems to be widely believed that fluoridation is different in principle from other methods of water treatment, particularly as regards the rights of the consumer and the powers and duties of water undertakers

We, however, maintain that the duty to supply wholesome water should now be understood to mean a duty to ensure an optimum fluoride content We propose to make what appears to be the first complaint ever made under the Metropolis Water Act of 1852, which provides for an inquiry by the responsible Minister into a complaint by 20 or more householders as to the quality of the water supplied by the Metropolitan Water Board

Our complaint is that the water contains much less fluorine than does the more wholesome water supplied by certain other water undertakers We invite any of your readers who are interested, and especially those who are parents and householders dependent on the Board for drinking water, to communicate with us at 73, Harcourt Terrace, London, S W 10

J GREENWOOD WILSON
J L PATTON
R B D STOCKER

ANÆSTHESIA FOR FRACTURES OF THE FEMORAL NECK

SIR,—I have read with interest the paper on this subject by Dr Murray and Mr Stuart Young (March 23)

In my experience it is unnecessary to raise the blood-pressure preoperatively or during operation in those patients who have received chlorpromazine as part of their premedication Provided a depleted preoperative blood-volume is remedied and a constant blood-volume is maintained during the operation, the reduction in blood loss and the protection from stress afforded by this drug benefit the patient

Should it be deemed essential, however, to raise the blood-pressure in a patient who has received chlorpromazine, I would have thought an overall vasoconstrictor such as noradrenaline would be preferable, for chlorpromazine, like dibenamine, partially blocks the pressor effect of certain amines such as methedrine, and the pressor effect of intravenous adrenaline may be actually reversed, resulting in a further fall in blood pressure

The dose of lignocaine (' Xylocaine ') recommended for local infiltration (i e, 100 ml of the 1% solution) I would regard as dangerous, particularly in the elderly patient In my view 500 mg of lignocaine should not be exceeded, this restricts the volume of the 1% solution to 50 ml A further safety factor is to use adrenaline with the lignocaine As the latter has no vasodilatory properties the adrenaline is effective in a concentration as dilute as one part in a million, and this local vasoconstrictor effect is not antagonised by the adrenoly properties of chlorpromazine

Furthermore, as adequate analgesia can be obtai with $^1/_2$% or even $^1/_4$% lignocaine, and as the toxicity the drug varies in geometrical ratio to its concentrati it follows that much larger volumes of these dil solutions could be safely used

Hull W N ROLLASON

THE Rh BLOOD-GROUPS

SIR,—Dr Wiener usually deals with points ma against him by changing the subject By contrast propose to deal with the paragraphs of his letter (April one by one, with the exception of his criticism of Renton and Dr Hancock which is, I think, best answer by those authors themselves

There are perfectly good distinct symbols for bo phenotypes and genotypes in the CDE system, and t worker can use whichever suits his purpose best Mo of Medicine involves choosing between possibilities varying degrees of likeliness and it is difficult to see w the serologist alone is debarred from doing this

Since there is no international agreement, no terminolog CDE or Rh Hr, can be considered as "official" Unl Wiener, Fisher and Race have never made false claims to "International Nomenclature" Nevertheless all the sy onyms given can be readily understood, and none wou provoke the user of one of the others to an outburst in pri Most workers would probably prefer to use *CcDee for t* phenotype and CDe/cde for the most likely genotype cannot see that the existence of these synonyms is a "contr diction" But what about Dr Wiener's use of anti Rh_1 a anti Rh_2? In 1943[1] they meant anti D and anti C respe tively, now they mean anti C+D and anti D+E

The designation -D- describes the serology of this blo well, far better than Rh_0^x Whether the dashes denote gen which determine nothing or an absence of genes is rath academic The reasons for thinking this is a deletion a quoted by Race and Sanger[2] but this blood type could, course, be called c°De° without damage to the CD nomenclature as a whole

The "shorthand" symbols are colloquialisms, and lik many colloquialisms are survivals of earlier usage They a not an essential part of the system, and one of their chief us is probably as an aid to transatlantic understanding R_1R_2 *not directly related to CDe/cDE any more than Et is relate* to C_2H_5, but if one remembers the simple equivalence a *serum reactions and all other possible genotypes giving the* can be directly deduced CDE workers have no need fo tables six pages *in length of possible and impossible childre* of various matings such as Wiener[3] gives

The complete sentence on p *181* of Race and Sanger book[2] is "Now that anti f is commonly found in anti c ser we feel doubtful about the identity of these two examples o anti d, their published reactions however exclude anti f"

The derivation of the order DCE from a theory *of extremely* rare crossing over was a suggestion of Fisher and Race,[4] and has never been put forward as incontrovertible *fact* Their actual words were "It is tempting to think that these fou rarer genes in the British population are maintained by suc occasional cross overs" This, surely, does not look like sweeping claim of world wide application Whatever the tru order may be the conventional order is likely to remain a CDE, just as an electric current still conventionally flow against the electron stream

As Race and Sanger say in a footnote on p *113 of the* book, the difference between Fisher s and Wiener's theories "the highly academic and interesting point whether the thre allelomorphic sites of Fisher are to be placed within or withou the boundary of one gene" Dr Wiener tries to give th impression that Fisher and Race have based their whole theor and nomenclature on C, D, E, c, d, and e being independen genes, and have since retreated from this position This is, a Dr Wiener well knows, not true Race's[5] original paper says "These single letters refer to antigens and their correspondin

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1 Wiener A S Blood Groups and Transfusions Springfield, Ill 1943
2 Race, R R Sanger, R Blood Groups in Man Oxford, 1954
3 Wiener, A S *Bull Wld Hlth Org* 1950 3 265
4 Fisher R A, Race, R R *Nature, Lond* 1946, 157, 48
5 Race, R R *Ibid* 1944 153, 771

ntibodies only Every gene of the system seems to be ssociated with a selection of three antigens from these three airs" In his table CDE, CDe, and so on are listed under he heading "genes"

Not all "most likely genotypes" involve high possible rrors, and some can be determined with complete or almost omplete certainty It is well recognised which are subject o error, and how big that error may be Dr Wiener's implied ccusation of recklessly incurring errors of 15% is therefore njust

Probably the only way of differentiating two linked antiodies from one cross reacting one would be the neutralisation f one component with a soluble antigen if this should ever ecome available The distinction between the names of linked nd mixed antibodies can easily be made by the use of brackets —e g , anti ($C+C^w$) but anti $C+D$

The concept of "blood factors" has not been proved, and s not fundamental CDe can quite easily mean an agglutinogen ontaining the three blood factors C, D, and e, and it contains o more characters than its equivalent Rh_1 In Race's original paper C, D, E, c, d, e are in fact considered as possibly being partial antigens, so here again the nomenclature is independent of theory What does it matter to an obstetrician whether his patient is sensitised to part of an Rh_1 molecule or to all of a D molecule ?

In his last paragraph Dr Wiener appears to overlook one thing Most leading workers have previously used (and been proficient in) his terminology, but have abandoned it in favour of CDE Unlearning *his* terminology, therefore, is neither difficult nor painful

Pathology Laboratory,
Essex County Hospital Colchester
J W NICHOLAS

CHRONIC BRONCHITIS AND SMOKING

SIR,—On the likely assumption that Dr Lennox Johnston (April 27) drinks tea and coffee, he is as much the victim of drug addiction as the person who smokes In regard to whether it is enjoyable, let him ask Sir Winston Churchill

Bristol
CHARLES CORFIELD

AMMONIA METABOLISM AND HEPATIC COMA

SIR,—Your leading article of March 23 gave an excellent résumé of current information on the association of ammonia metabolism and the pathogenesis and treatment of hepatic coma

We were particularly interested in your comments about the use of intravenous arginine in the therapy of ammonia intoxication The stimulus for our use of this agent came from Dr Santiago Grisolia, of the McIlvain Biochemistry Laboratories, his suggestion for its use being based on current knowledge of enzymatic reactions Our clinical results from this starting-point have been most rewarding Since you expressed doubt as to the mechanism of action of arginine, I would like to outline briefly our concept of its function

It has become a fundamental principle of enzymatic reactions that given standard conditions the addition of increasing amounts of substrate increases the reaction velocity in a non-linear fashion This principle has been set forth in the classic Michaelis Menten equation A maximum velocity of course is reached wherein the enzyme is saturated with substrate, but this state is seldom reached in the human body Applying this principle to the removal of ammonia as urea via the ornithine citrulline arginine cycle, the addition of any of these substrates should increase the reaction velocity and therefore increase the removal of ammonia as urea The cyclic nature of this series of reactions allows enhancement of the entire urea synthesis by addition of only one of the substrates Greenstein and his co-workers, at the National Institutes of Health, have shown that arginine is the most effective of the agents tried, although ornithine will protect animals from ammonia intoxication when given in amounts three to four times that of the arginine necessary We feel that the effectiveness of arginine is due to the free permeability of arginine into the liver cell and also the high concentration of arginase in the liver The arginine therefore acts as a precursor of ornithine in the urea cycle and is more effective owing to its relatively more easy access to the enzyme system

We feel, as you do, that the most important measure in the treatment of hepatic coma is the complete removal of all protein from the diet, gastro-intestinal tract, or any other source Gastro-intestinal sterilisation is certainly an important adjunctive therapy Our clinical results with arginine, however, have left little doubt in our minds that it is a most important addition to the therapeutic regimen, particularly in getting the patient out of coma rapidly

Department of Internal Medicine,
University of Kansas,
Kansas City
ROBERT T. MANNING

HOSPITAL INFECTION

SIR,—In your leader last week you state that the general frequency of infections is not known Actually, an index is the frequency of infection of "clean" surgical wounds—e g , orthopædic and hernia incisions These should all heal rapidly and without infection If any are infected, the facts are reported at once and the cause is investigated

It is only too true that ideas on cause and prevention have fluctuated rather than progressed This lack of progression is not due to lack of knowledge but to lack of interest and lack of intelligent application of knowledge

The view that "drastic measures taken to quell outbreaks are unnecessary in the ordinary way" is only too popular There is no doubt that reports of hospital infection are prompted by unusually great amounts of infection and by a laudable desire to acquire merit for successful remedial measures Some of these successful remedial measures have passed into routine, after the crisis was overcome—a very praiseworthy decision On the other hand, "The Devil was well, the devil a Saint was he!" often applies

You suggest that "before any real progress can be made the precise frequency of hospital infection of all types in medical, surgical, and obstetric units up and down the country must be ascertained" Surely, the question of dealing with these problems would not arise if the problems did not already exist, in formidable array I submit that a good deal is now known of the frequency of hospital infections

The suggestion that skin carriers of pathogenic organisms might be specially liable to wound infection is a most interesting one, and I am sure that they are specially liable

The work of Williams and others in the Air Hygiene Laboratory at Colindale is important, most hospitals would welcome an investigation on the lines you suggest Very few hospitals have a slit sampler or a statistician Statisticians might be better employed in cutting down expenditure in hospitals than in aiding research

To mention only a few factors concerned in infection in hospitals that have been dealt with recently in published reports contaminated thermometers,[1] baths,[2] noses,[3] fingers,[4] umbilical cords,[5] fomites,[6] blankets,[7] pillows,[8] mattresses,[9] floors,[10] dust,[11] septic wounds,[12] and plasters,[13] and patients with infectious diseases, sometimes admitted undiagnosed or during the incubation period [14]

Investigation of the bacterial contamination of air in hospitals has much to recommend it, but it cannot be the whole answer to the problem Effective measures can be instituted with the knowledge that we now have

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[1] *Lancet* 1956 ii 559
[2] Colbeck J C *Canad Serv med J* 1956, 12, 563
[3] *Brit med J* 1946 i 856
[4] Colebrook, L Ministry of Health Interim Report on Maternal Mortality and Morbidity, 1930
[5] *Brit med J* April 20, 1957 p 925
[6] *Lancet* 1948 ii 845
[7] M R C War Memorandum no 11, 1944
[8] *Brit med J* 1956 ii 840
[9] *Lancet* 1954, i 125
[10] *Ibid* 1940, ii, 133
[11] *Brit med J* 1944 i, 245
[12] *Ibid* 1940, ii 855 895
[13] M.R C War Memorandum no 6, 1941
[14] *J Hyg Camb* 1937 37, 1

There were great men before Agamemnon, a few of them are mentioned in the references

St Margaret's Hospital,
Epping

Frank Marsh

SENIOR REGISTRARS AND CONSULTANT APPOINTMENTS

Sir,—The plight of those aspiring to consultant posts is tragic in the extreme No other learned profession treats its brethren in this way—the insecurity of tenure and constant change of habitat, inflicted on men approaching middle age, is appalling Parents would be well advised to note these facts, and advise their children to enter the promising new fields of electronics and physics, where the prospects are dazzling, compared with medicine

The law of supply and demand can thus be relied upon to adjust matters—nothing else will

Solihull

E S Page

Medicine and the Law

Liaison between Hospital and Practitioner

Disclosures at a recent inquest[1] suggest that there may be need for closer liaison between hospital and general practitioner in cases where the patient is attending an outpatient department

The inquest was into the death of a young man, aged 17, by barbiturate poisoning

Last October he had complained to his doctor of tiredness and of sleeping too much After he had seen a physician, it was suggested that the cause was mental and in January he was admitted to hospital He appeared to do well and was soon discharged, thereafter attending three times as an out patient He was given a tranquilliser to be taken four times a day and 'Tuinal' to be taken at night, he was warned that he must not exceed the dose He also visited his general practitioner weekly and complained to him that he was not sleeping enough, the doctor prescribed paraldehyde in liquid form, and the patient appeared to improve The doctor told the coroner that he would not have prescribed paraldehyde if he had known that tablets had been prescribed at the hospital

A pathologist told the coroner that necropsy had revealed that the young man had taken at least 20 capsules of tuinal in addition to a normal dose of paraldehyde The combination of the two did not have any sinister significance, but normally it would be unwise to give the two at the same time

The acting superintendent of the hospital said that the general practitioner would normally be told that a patient was attending the outpatient department, it would be assumed that the general practitioner would realise that the patient was obtaining drugs from that place "We do not write to the practitioner when they attend In this case one would expect the young man to tell the general practitioner what he was getting" On certain nights the drugs might not give him the desired sleep, and he might take two or three more tablets so that he became intoxicated and might go on taking them without knowing what he was doing He did not think that the patient had suicidal tendencies, or he would not have entrusted him with the tablets

The coroner agreed that the young man did not show any suicidal intent, and returned a verdict of accidental death He said that he was "a little shaken" that there was not more liaison between the hospital and the practitioner, but he had no idea whose fault this might be

Diminished Responsibility

The Homicide Act, 1957, came into force on March 21 Until then, English law knew no defence of diminished responsibility in criminal cases, although it allowed the defence of insanity within the narrow limits of the McNaughten rules Section 2 of the new Act provides that a person shall not be convicted of murder if he is suffering from such abnormality of mind as substantially to impair his mental responsibility, f purpose the abnormality of mind may arise fr arrested or retarded development, (b) any in cause, or (c) disease or injury The section provid in such cases the conviction shall be for manslaug

This new defence was pleaded for the first ti a case at Leeds Assizes last week[1]

Shirley Campbell, a 21-year old coloured mill was charged with the murder of Susan Pickles, aged 17 m While the parents were at the cinema she had been l after the child, who was later found dead with a belt tied the neck Counsel for the prosecution explained th defence and said that he would not resist the defence if Counsel for the defence pleaded the section and called m evidence The jury found the accused not guilty of m but guilty of manslaughter The judge said that this w right verdict on the evidence and sentenced Campbell maximum sentence for manslaughter—life imprisonm

Obituary

JOHN PERCY LOCKHART-MUMMERY

M B Camb, F R C S, F A C S

Mr J P Lockhart-Mummery, consulting surge St Mark's Hospital, London, and for many years c man of the executive committee of the British Em Cancer Campaign, died at Hove on April 24 at age of 82

He was the eldest son of J Howard Mummer Islips Manor, Northolt, and he was educated at School and Caius College, C bridge After taking part the natural sciences tripo 1897 he was appointed assistant demonstrator of a omy in the university continued his medical stu at St George's Hospital, w he won the Thompson medal After qualifying in he held several house-appo ments there and was for a t demonstrator of operative su ery In 1900 he took F.R C S and soon afterwards joined the staffs of the No East Hospital for Children Hackney and the King Edw VII Hospital But his appointment in 1903 to St Ma Hospital showed the true direction of his surgical be and the following year he published in our columns important paper on the use of the electric sigmoidosco "The human mind," he wrote in a characteristic fi paragraph, "is so constituted that we always experien a certain pleasure when we have succeeded in obtaini access to some spot hitherto difficult or impossible explore And in medicine and surgery the perfection a method by which we are enabled accurately to expl hitherto inaccessible portions of the human body alwa arouses our interest and helps to perfect our art" 1908 he was awarded the Jacksonian prize of the Ro College of Surgeons of England for his essay on disea of the colon

His writings, his teaching, and his techniques as surgeon drew many visitors from abroad to his operatin theatre, and the reputation of the hospital and the you specialty of proctology grew with his own In 1913 was the first secretary of the British Proctological Socie and it was largely through his guidance that the societ after a period as a subsection, became in 1939 an ind pendent section of the Royal Society of Medicine I interest in cancer research led him to become one of t founders of the British Empire Cancer Campaign, t first chairman of its executive committee, and for ma years the editor of its annual reports

But despite the claims of hospital, private practice a committee work he found time for a great deal of writin and he continued this art with pleasure after he h relinquished surgery

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[1] *Portsmouth Evening News* April 11 1957

[1] *Times*, April 27, 1957

O E D writes·

Lockhart Mummery had " the pen of a ready writer " and his literary output was truly remarkable as a glance at his bibliography in the *Collected Papers of St Mark's Hospital* shows This centenary volume was published in 1935, when Lockhart Mummery was sixty years of age, and up to that time he had written 6 books, *made major contributions to* 6 other standard textbooks, and published 163 papers in scientific journals During his last five years of hospital work, he wrote another 20 papers After retirement he turned from medical and scientific subjects to writings of a more speculative character which gave scope to his vivid imagination In these he sometimes gave the impression that the subject was running away with him, but his writings were always interesting and original, for he could never be dull

One of his most appreciated contributions was his small handbook, *The After Treatment of Operations* (1903) This ran through four editions, became widely known outside this country, and was eventually translated into Arabic, which gave him much pleasure His larger textbook, *Diseases of the Rectum and Colon*, was almost equally well known It was profusely illustrated, and he pointed out in the preface to the second edition in 1934 that a new feature had been introduced by using photographic reproductions of actual operations to illustrate operative technique He was a keen photographer and worked with enthusiasm to surmount the technical difficulties of those days so as to obtain photographs of operations which might be good enough for reproduction as book illustrations

Cancer research always made a strong appeal to him, and despite the many other claims on his time he made strenuous efforts to keep abreast with it in all its aspects Always a [illegible]uded opinion, in the early 'thirties he made up his [illegible] cancer was best explained as due to a somatic [illegible] in 1934, in *The Origin of Cancer*, he set out

brought all the needed qualities to the task of ensuring that there was one single unit of strength for each important substance which could not be chemically assayed, and that this unit was recognised and accepted throughout the world To him more than to any other man is it due that a ship's surgeon, for instance, can replenish his stock of diphtheria antitoxin or streptomycin in any part of the world knowing that the units marked on the package are the same units that he dealt with in his home port Though Gautier in his work for the League of Nations had from time to time other and wider interests than biological standardisation, one of his happiest moments was when, before the war had ended, he met old friends at a meeting in London to standardise penicillin He had the physique of a rugby forward, and his bustling, somewhat extrovert, manner might give a first impression of sound without substance But his technical knowledge and personal shrewdness made and kept him indispensable through 30 years of kaleidoscopic changes in the world of international health

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THREE London hospitals owe much to Miss Chadburn She served the Elizabeth Garrett Anderson Hospital as a surgeon for 20 years, and only resigned in 1922 because she believed that the time had come when women patients should have greater opportunity of consulting women doctors This belief inspired her work in founding and serving the South London Hospital for Women and later the Marie Curie Hospital

She was born in 1868, the daughter of the Rev James Chadburn, and she studied medicine at University College and the London School of Medicine for Women After qualifying the whole answer to the problem Effective measures can be instituted with the knowledge that we now have

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St Margaret's Hospital
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His writings, his teaching, and his techniques as a surgeon drew many visitors from abroad to his operating theatre, and the reputation of the hospital and the young specialty of proctology grew with his own In 1913 he was the first secretary of the British Proctological Society, and it was largely through his guidance that the society, after a period as a subsection, became in 1939 an independent section of the Royal Society of Medicine His interest in cancer research led him to become one of the founders of the British Empire Cancer Campaign, the first chairman of its executive committee, and for many years the editor of its annual reports

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[1] *Portsmouth Evening News* April 11 1957

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One of his most appreciated contributions was his small handbook, *The After Treatment of Operations* (1903) This ran through four editions, became widely known outside this country, and was eventually translated into Arabic, which gave him much pleasure His larger textbook, *Diseases of the Rectum and Colon*, was almost equally well known It was profusely illustrated and he pointed out in the preface to the second edition in 1934 that a new feature had been introduced by using photographic reproductions of actual operations to illustrate operative technique He was a keen photographer and worked with enthusiasm to surmount the technical difficulties of those days so as to obtain photographs of operations which might be good enough for reproduction as book illustrations

Cancer research always made a strong appeal to him, and despite the many other claims on his time he made strenuous efforts to keep abreast with it in all its aspects Always a man of decided opinion, in the early 'thirties he made up his mind that cancer was best explained as due to a somatic mutation , and in 1934, in *The Origin of Cancer*, he set out the theory that cancer arises as the result of a mutation of somatic cells leading to more rapid growth He preached this doctrine with fervour for the latter years of his working life, but was a little disappointed in the amount of attention the book received

On the other hand he had no reason to complain that his earlier work was disregarded and he had the satisfaction of seeing his advice and teaching widely adopted His classical description of the operation of perineal excision of the rectum for cancer was published in these columns in 1920 and his pioneer observations on familial polyposis in 1925 The latter paper initiated a research into the incidence and inheritance of familial polyposis which has been continued with the aid of a grant from the British Empire Cancer Campaign ever since Lockhart Mummery continued to take an interest in this long after he had left the staff of St Mark s Hospital and it was a source of pride and satisfaction to him when his son was appointed to the staff of the hospital

RAYMOND GAUTIER

Dr Gautier, a former assistant director-general of the World Health Organisation and research director for the International Children's Centre in Paris, died last month at the age of 71

He was born in Geneva and qualified in 1911 He was on the staff of the university laboratory of physiology and of the Institute of Hygiene and Bacteriology at Geneva before he joined the Health Organisation of the League of Nations in 1925 as head of its section of biological standards The following year he was appointed director of its Eastern office at Singapore, where he took a large share in controlling the cholera epidemic of 1928 In 1930 he returned to Geneva and continued his work on biological standardisation till in 1938 he was appointed acting director of the Health Section of the League of Nations Towards the end of the late war he was often in Washington and London discussing and organising health measures for the liberated countries In due course he became deputy to Dr Brock Chisholm on the Interim Commission of W H O and later in W H O itself After he retired at the age of 65 he went to Paris to resume his old association with Dr Rajchman at the International Children's Foundation

An old colleague writes

In his particular sphere—biological standardisation—Raymond Gautier was *sans pareil* With a solid grounding in old style hygiene and bacteriology at Geneva University a varied administrative experience and Swiss nationality, he brought all the needed qualities to the task of ensuring that there was one single unit of strength for each important substance which could not be chemically assayed, and that this unit was recognised and accepted throughout the world To him more than to any other man is it due that a ship's surgeon, for instance, can replenish his stock of diphtheria antitoxin or streptomycin in any part of the world knowing that the units marked on the package are the same units that he dealt with in his home port Though Gautier in his work for the League of Nations had from time to time other and wider interests than biological standardisation, one of his happiest moments was when before the war had ended, he met old friends at a meeting in London to standardise penicillin He had the physique of a rugby forward and his bustling, somewhat extrovert, manner might give a first impression of sound without substance But his technical knowledge and personal shrewdness made and kept him indispensable through 30 years of kaleidoscopic changes in the world of international health

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She was born in 1868, the daughter of the Rev James Chadburn, and she studied medicine at University College and the London School of Medicine for Women After qualifying in 1893 she held house-appointments at the Royal Free Hospital Clapham Maternity Hospital, and the Elizabeth Garrett Anderson Hospital Later she became curator of the museum and surgical registrar at the Royal Free In 1898 she took the degree of M D , and in 1903 she was appointed to the staff of the Elizabeth Garrett Anderson Hospital Very soon she had a large and successful practice in general surgery and in gynæcology for during most of her professional life women surgeons usually did not separate these two specialties At different times she ran two large nursing-homes for her private practice Hospital and private patients alike gave her implicit trust and it is recorded that one went so far as to say " If Miss Chadburn said I was to have my head cut off I should agree '

But her chief work was the South London Hospital for Women which in its early days was so largely dependent on her initiative, courage and foresight A colleague who joined her there in 1916, describes its steady growth

At first we saw outpatients in converted houses near the Elephant and Castle A large house at Clapham Common which was to have been converted for hospital purposes was being demolished and instead a modern hospital built with money derived from anonymous donors' largely through Miss Chadburn s enterprise In the years that followed large properties to the left and right of the new block were incorporated and the number of beds rose from 30 to 260

Miss Chadburn also played a big part in the foundation of the Marie Curie Hospital to which she was surgeon For many years she was chairman both of its medical committee and its research committee In 1931, to mark her retirement from her hospitals she was appointed C B E She was a past president of the London Association of the Medical Women's Federation Despite these heavy professional responsibilities which she had willingly accepted and which she gener ously fulfilled, she also adopted three children whom she brought up and educated

A H B writes

Miss Chadburn's pre eminence was as a practical surgeon She left a tradition of slow, gentle surgery, which gave very good results She was held in high esteem by her colleagues at all her hospitals, but she was not a public figure, and she did not publish reports of her work Only those closely associated with her knew what a remarkable woman she was, and how much was accomplished by her quiet persistence *She was indefatigable, and could spend long hours in the* operating-theatre without strain Those who assisted her in her heyday recall operating sessions which went on through the evening, perhaps into the night Everyone else might flag—but not Miss Chadburn ! She was rather small and without an obviously forceful personality , yet her deceptively mild manner masked an indomitable will power, as those who worked with her on committees well knew She had a long life, and died at the age of 89 on April 24, in the hospital where she had first come as a house surgeon To the end she retained the dignity and quiet charm of manner which distinguished her

Dr G R. MATHER CORDINER

F R B writes

It would be a pity if Dr Cordiner's generous and ready acknowledgment of the help which he had received from the work of Forssell, Akerlund, and Berg were to prevent recognition of his own contributions to gastro intestinal radiology Although the perfection of his technique and the accuracy of his interpretation were clear for all to see, only those who were trained by him could assess his pioneer work, because he published relatively little They saw him in his moments of hesitation when he was trying to assign the exact significance to some particular X-ray finding , there was no book on earth that could help him at these times , this work was absolutely original Too much emphasis has undoubtedly been placed on the use of compression in the techniques which he used, and it is not generally known that he was the greatest advocate of the use of gravity in the demonstration of lesions of the stomach and duodenum The tilting tables which he designed before the late war have never been bettered—in fact a return to many of the features of his original apparatus would be an advantage As long ago as 1936 he showed me the first chapter of his book on the radiology of the gastro intestinal tract—a book that, alas, has never been published The reasons for this were many, among them the war and the difficult times which have followed it Perhaps another reason was his passion for accuracy and exactness in everything He could not bear to think of something being published that was not precise A less busy man would have had time to polish his work , Dr Cordiner never found time to fashion the book to his own liking Much of his work was concerned with rather unrewarding and controversial diseases such as gastritis, duodenitis, and inflammatory changes in the kidneys These diseases are not yet wholly understood and the value of his contributions cannot yet be assessed

Only those who worked for Dr Cordiner could fully appreciate his untiring energy or realise the extent to which he drove himself in the pursuit of his work The last years were undoubtedly a tremendous strain on his health and he could never have continued without the devoted affection and help of his wife

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Mr A H Coughtrey, librarian of St Bartholomew's Hospital Medical College from 1903 to 1939, a vice-president of the Institute of Hospital Administrators, and a former editor of the *Hospital*, died on April 18 at the age of 82

Births, Marriages, and Deaths

BIRTHS

ELITHORN —On April 28 at University College Hospital, to Dr Helen (Wendy) Grant wife of Dr Alick Elithorn—twins, Justin Richard and Sandra Clare

STONE —On April 18 at Wanganui New Zealand to Barbara Mary Stone (née Dana) M B and Arthur Richard Stone, M R C P, M R A C P —a son

MARRIAGES

RILEY—WYLIE —On May 1 at Four Oaks Warwickshire, Ian D Riley, *M D of Glasgow* to Agnes Kent Wylie, M A

DEATHS

FISON —On April 20 James Fison M D Camb of Flat 2, 28, York Place Harrogate

Diary of the Week

MAY 5 TO 11

Sunday, 5th

UNIVERSITY COLLEGE HOSPITAL MEDICAL SCHOOL, University Street, W C 1
10 15 A M Dr D A Pond Acute Psychiatric Emergencies in General Practice (Clinical demonstration)

Monday, 6th

MARLBOROUGH DAY HOSPITAL, 38, Marlborough Place, N W 8
8 15 P M Dr G D Fraser Steele Psychotherapy in Mental Hospital Practice—Its Instruments and Aims

Tuesday, 7th

ROYAL COLLEGE OF SURGEONS OF ENGLAND Lincoln s Inn Fields, W C 2
3 45 P M Dr R McP Livingston The Placenta (Arnott demonstration)
ROYAL SOCIETY OF MEDICINE, 1 Wimpole Street, W 1
8 30 P M *Orthopædics* Mr G K McKee, Mr John Charnley, Mr J H Hicks, Mr J M Zarek, PH D *Use of Metal in Bone Surgery*
INSTITUTE OF DERMATOLOGY Lisle Street, W C 2
5 30 P M Dr R H Meara Xanthomatoses
LONDON HOSPITAL MEDICAL COLLEGE, Turner Street, E 1
5 30 P M *Dr S Udenfriend* Pharmacological Studies Relating to Serotonin
UNIVERSITY OF BIRMINGHAM
4 P M (Medical School) Prof Rustin McIntosh (New York) Growth and Development (First of two Leonard Parsons lectures)

Wednesday, 8th

ROYAL COLLEGE OF SURGEONS OF ENGLAND
5 P M Dr D J Lyle (Cincinnati) Causes and Treatment of Exophthalmos (Moynihan lecture)
ROYAL SOCIETY OF MEDICINE
5 P M *Experimental Medicine* Dr R G White, Prof E Witebsky *(Buffalo), Dr Deborah Doniach,* Dr I M Roitt, Dr W R Trotter, Dr George Belyavin *Dr* A Waddams Auto immunity and Thyroiditis
POSTGRADUATE MEDICAL SCHOOL OF LONDON, Ducane Road, W 12
2 P M Dr D A Long Relationship of the Hæmolytic Streptococcus to Rheumatic Fever
INSTITUTE OF DERMATOLOGY
5 30 P M Dr Henry Haber Eosinophilic Granulomas of the Skin
INSTITUTE OF DISEASES OF THE CHEST, Brompton, S W 3
5 P M Dr R. W Riddell Fungous Infections of the Lungs
SOCIETY FOR ENDOCRINOLOGY
5 30 P M (26, Portland Place, W 1) Prof C de Duve (Louvain) Present Status of Glucagon
UNIVERSITY OF OXFORD
5 P M (Radcliffe Infirmary) Mr I Simson Hall Histopathology of the Temporal Bone (Litchfield lecture)
UNIVERSITY OF BIRMINGHAM
4 P M (Medical School) *Professor* McIntosh Growth and Development (Second of two Leonard Parsons lectures)
MANCHESTER MEDICAL SOCIETY
4 30 P M (University of Manchester) *Pathology* Dr J Ball, Dr E G Wade Unexplained Pulmonary Hypertension
ROYAL FACULTY OF PHYSICIANS AND SURGEONS OF GLASGOW, 242, St Vincent Street Glasgow
5 P M Dr Henry Doubilet (New York) Pathology and Treatment of Pancreatitis

Thursday, 9th

ROYAL COLLEGE OF SURGEONS OF ENGLAND
5 P M Mr A C McEachern Evolution of Safety in Prostatectomy (Hunterian lecture)
ROYAL SOCIETY OF MEDICINE
5 P M *Ophthalmology* Dr Lyle Arteriosclerotic Optic Atrophy
POSTGRADUATE MEDICAL SCHOOL OF LONDON
2 P M Prof T Pomfret Kilner Investigation of Defective Speech with special reference to Cleft Palate Conditions
INSTITUTE OF DERMATOLOGY
5 30 P M Dr O L S Scott Inherited Abnormalities of the Skin
HONYMAN GILLESPIE LECTURE
5 P M (University New Buildings Teviot *Place Edinburgh.)* Prof W I C Morris Obstetrical Hæmorrhage in Relation to Impaired Blood-clotting
UNIVERSITY OF ST ANDREWS Queen s College, Small's Wynd, Dundee
5 P M Prof J H Biggart Pathology of the Hypothalamus.

Friday, 10th

INSTITUTE OF CHILD HEALTH Hospital for Sick Children, Great Ormond Street W C 1
5 P M Professor McIntosh Meconium Ileus
ST MARY'S HOSPITAL MEDICAL SCHOOL Paddington W 2
5 P M Mr Jack Suchet Rupture of the Uterus in Pregnancy and Labour
POSTGRADUATE MEDICAL SCHOOL OF LONDON
4 P M Dr W C Cockburn Provocation Poliomyelitis
INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330, Gray's Inn Road W C 1
3 30 P M Miss Edith Whetnall Care and Training of Deaf Children
ROYAL COLLEGE OF SURGEONS OF EDINBURGH Nicolson Street, Edinburgh 8
3 P M Prof M F A Woodruff The Surgery of Replacement

Notes and News

APARTHEID IN MEDICAL EDUCATION AND NURSING

LAST week we summarised a statement by vice-chancellors and principals of universities and university colleges in this country expressing concern at recent developments in South Africa Similar concern, grave enough to override personal political convictions, is seen in a unanimous resolution of the South African Medical Council [1] This council, which was not consulted about the proposed transfer of the Durban Medical School from Natal University to State control, has unanimously adopted a resolution which says

> "It has been brought to the notice of the Council that a new method of control of education is envisaged for the Durban Medical School and that there is a possibility that this may lead to a new pattern which may not be acceptable to the Council for purposes of training of medical practitioners
>
> "As a statutory body the Council has grave responsibilities in regard to medical education In order to obviate unforeseen difficulties which may arise at some future date when the standards are to be considered and the facilities, School and examinations inspected, the Council respectfully suggest to the Minister of Education and of Health to take the necessary steps prior to enacting the legislation now before Parliament to have the implications as they affect the responsibilities of the South African Medical and Dental Council further investigated and reported upon"

Under the government's Nursing Bill [2] the Nursing Council of South Africa would be an all white body, separate races would have separate sections in the Nursing Association, and separate registers would be kept A fine of up to £200 is prescribed for anyone allowing a white nurse to work under a non white person in any hospital or similar institution or training school

CLERKS IN THE WARDS

LAST autumn four part-time clerks were appointed at the Ipswich and East Suffolk Hospital to relieve the ward sisters of clerical work and allow them more time for other duties The Ipswich hospital management committee reports [3] that the first six months of the experiment have been successful The ward sisters say that the clerks have been of "enormous help" and the matron thinks that the sisters are 'working under less strain"

CEREBRAL PALSY

LAST October, the British Council for the Welfare of Spastics held a conference at Birmingham on cerebral palsy, presided over by Prof J M Smellie A booklet combines the four admirable addresses then given [4]

It is hard to imagine a better account of the clinical picture than that given by Prof R S Illingworth He mentions the dangers of large doses of vitamin K in the newborn through hæmolysis leading to kernicterus, and this subject was among the many dealt with in Dr Frances Braid's talk on the ætiology of cerebral palsy Dr H M Cohen surveyed the scholastic needs of affected children, with illustrations from the practice in Birmingham, and Mr A Innes, F.R C.S, spoke on their management He emphasised how gross are the cerebral lesions in many cases, and discussed methods of treatment including physiotherapy and orthopædic and neurological surgery

HEALTH EDUCATION

A Ministry of Education publication,[5] modestly styled a "pamphlet," contains much good matter, excellently expressed, on the subject of health education. The anonymous author adds knowledge of English literature to that of his subject, and sympathy and imagination to both The result is stimulating instructive and pleasant to read The main thesis is that health education should arise from and be a part of almost all school subjects—history, geography and literature no less than the sciences, that ad hoc detailed and dogmatic "health instruction" is of limited usefulness and that example and practice are as important as precept Part 1 expounds this theme, and part 2 deals with the hygiene of body and mind and the prevention of preventible diseases An admirable chapter on normal development, from the report of the committee on maladjusted children forms an appendix

Flaws are few, but might not the young be dissuaded from smoking in terms more vigorous than those of the late Minister of Health ? Ought not all little girls to have rubella and why does choral singing find no mention as an unrivalled exercise for the spirit, the intellect, and the respiratory organs ?

RADIOLOGICAL UNITS AND MEASUREMENTS

THE 1956 recommendations of the International Commission on Radiological Units and Measurements have been published as a handbook [1] and replace the Commission's 1953 report [2] The new report includes basic information and data necessary to make radiation-dose measurements in energy units (rads), and to convert data expressed in röntgens to the equivalent in energy units

The comprehensive account of radiological quantities, units, and symbols includes a discussion of the parameters involved in the various definitions Guidance is given on the clinical application and physical aspects of absorbed dose measurements—for example, methods of calculating absorbed dose from measured ionisation The results of several recent international comparisons relating to both X rays and radioactivity are described A suggested outline of an international treatment summary form is given in one of the appendices

University of Durham

The honorary degree of D C L is to be conferred on Sir John Stopford, F.R S

At a special congregation to be held during the meeting of the British Medical Association in Newcastle upon Tyne the honorary degree of D C.L is to be conferred on Dr A H. Hall and Dr S Wand of D SC on Prof G W Pickering and of M.D on Dr Mona Macnaughton

University of Glasgow

On April 27 the following degrees were conferred

M.D—A. S Douglas (with honours)
M.S—J W Sutherland (with honours)

On June 19 the honorary degree of LL.D will be conferred on Brigadier J S K Boyd, F R.S, and Sir James Paterson Ross

Society of Apothecaries of London

Sir Henry Dale, O M, F.R S, will deliver the Gideon de Laune lecture on Tuesday, May 14, at 5 30 P M at the hall of this society, Black Friars Lane, E C 4 His subject will be Medicinal Treatment—its Aims and Results

At recent examinations the following were successful

L M.S.S.A—D L Oldfield J L. Currah W A Garson, S H. Thomas M L A. B Bancilhon M J Allan A F Broad, R E Owen A T Darko R C Snelling J H Kendall A G Snart C Bell G A Robson R J L Potts K C Kewish R Owen

D.I.H—D E Marchant C C Molloy, F H Pratt J D Walters

British Society for Immunology

A meeting of this society will be held at the Westminster Medical School, Horseferry Road, London, S W 1, on Friday and Saturday, May 10 and 11, starting at 10 30 A M The programme includes a symposium on non specific immunity, when Prof A A Miles will take the chair

Calouste Gulbenkian Foundation

In this Foundation's first list of grants it is announced that Dr H L Glyn Hughes, retiring senior administrative medical officer of the South East Metropolitan Regional Hospital Board, has been invited to survey the needs of homes for the dying in Great Britain It is explained that these homes, most of which are religious foundations, provide for a need, spiritual as well as medical, not always adequately met by hospitals of the National Health Service

Rockefeller Foundation Grants

During the first quarter of 1957 the Foundation distributed $2 700 000 Grants for medical education and public health amounted to $550,000, and for biological and medical research to $810,000 The grants include

> $36 000 to the University of Cambridge for research equipment for the school of biochemistry £10 000 (over the next two years) to the University of London in support of Prof J Z Young's research at University College on the structure and functioning of the brain and $12 000 (over the next three years) to University College Dublin to help Prof E J Conway to continue his research into the process of accumulation and exchange of inorganic ions in cells and tissues

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[1] Medical Proceedings March 30 1957 p 163
[2] Times April 18 1957
[3] East Anglian Times April 22 1957
[4] Four Addresses on Cerebral Palsy Pp 40 3s 6d Obtainable from the British Council for the Welfare of Spastics 13 Suffolk Street Haymarket London S W 1
[5] Health Education Ministry of Education Pamphlet no 31 London H M Stationery Office 1957 Pp 153 4s

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[1] National Bureau of Standards Handbook 62 Obtainable from the Superintendent of Documents U S Government Printing Office Washington 25 D C at a price of 40 cents
[2] Amer J Roentgenol 1954, 71, 139

Royal College of Physicians of London

At a comitia held on April 25, with Dr Robert Platt, the president, in the chair, the following were elected to the fellowship

M M SUZMAN Johannesburg, J L H EASTON, Bedford, P C C DE SILVA, Colombo, CHISHOLM MCDOWELL, Remuera New Zealand, A B STOKES, Toronto, MARTIN HYNES, London, OSWALD SAVAGE, London E C O JEWESBURY, London, F J W MILLER, Newcastle upon Tyne G W BODEN London, ARTHUR LEESE, Leeds, J N MORRIS London J H BOLTON, Melbourne, W R S DOLL, London G M KOMROWER, Manchester, I M ANDERSON, London, R B EVANS, Cardiff, J C GILSON, Penarth, Glam, P L MOLLISON, London, WALTER SOMERVILLE, London, C D NEEDHAM, Aberdeen, J M MALINS, Birmingham, N D COMPSTON London, J F GOODWIN London A G LEATHAM, London, W D BRINTON, Winchester, Hon D A P ANDERSON, Reading, E J MOYNAHAN, London, J M LEDINGHAM, London J A SCOTT, London, P M F BISHOP, London, J H BIGGART, Belfast, R F LOEB, New York, J R PAUL, South Carolina

The following having satisfied the censors' board were elected to the membership

L J H Arthur, M B Camb, J H Baron B M Oxfd, N M Bleehen, B M Oxfd, D R Coles, M B Brist J M Duggan, M B Sydney, Howard Duncan, M B Sydney, D A W Edwards, M D Camb, J S Garfield, M B Camb, J M Greenaway, M B Sydney, Laurence Henry, M B Birm, T H Hughes Davies B M Oxfd, Marcel Kinsbourne, B M Oxfd, Joyce J P Lomas, M D Lond, P J Maloney, M B Sydney I D Melville M B Glasg, Paul Mestitz, M B Lond, Marion B Morton M B Sydney, I B Munro, M B Glasg Abul Khayer Muhammad Nawab Ali, M B Calcutta, J R Officer, M B Melb, A M Parfitt M B Camb, Jane Platnauer, M B Lond, Stanley Shaldon, M B Camb, D H Trapnell, M B Camb, Mary P Wilkinson, M B Lond, R T Williams, M B Camb, B W Windeyer, M B Sydney

Licences to practise were conferred on the following 165 candidates who have passed the final examination of the Conjoint Board

Peter Abraham, Leslie Adamson, Mary M Adlington D R Amies, R St J Angel, J R Anthony G J L Ardouin, B R Baker, M A Barraclough, Gerald Bevan, D P Birkett, B D Birt, Sybil Birtwistle J L Booth, Anne Bromley Godfrey Brooke, R J A Brown, J A W Buckley, T M Bull, P G Burles, J L Canter, P B Carpenter Margaret T Challis, J A Chalmers, Zoe D Chamberlain, T D Cochrane, Joan R Colston, Christina M Comty, Phoebe M Cotes D R Couchman, J M R Cox, Dorothy Cullen D W Davies Patricia W R Daymond, J M Dunison, D M Dingle, B C Dixon Warren, A B Dunderdale M J Dyer, Joan M Edwards, P J Edwards, B J Ellam M K El D H El Rifi Pauline M Feavers, J S Ferguson, Ann L M Field, Elizabeth C Finn, P S Firth, G N Flaherty, Evelyn C Foot, J A Fox G G Francis P I Frank, R G G Gain, Ann F Gamble, R D Gardner, J C Garnham, W H S George, Jeremy Goodchild, Pamela J H Goodwill, M S Gottlieb J H C Gough Judith F Gould, J N Graham Evans, June S Grant David Greenwood, Olive M Grundy, Jack Hajioff, Ahmed Hakki J G Hall, T J Hall James Halls D L Hamblen, V J Hartfield Sally Haynes, M R Heal, R C Hicks, L M Hillman L J Hobbs, Margaret B Howell, P J W Howes, S W Hyams E E Inyang, J D Jowitt A C Kaeser, B R Kesby, M S Kessel, K C Kewish, D W Keys, R M Kinsey J O Knowles, M I Lander, M J Lavine, D J Lawson, D H Lawton J K Lawton F I Lee, Eva H Letchner, G C Liddle, Helen A Linn, D B Longson Mary K Lucas Gillian B McCullagh, M J McLoughlin, B C Mallaband, E C Marsh, Nancy E V Matthews, P A Mead, Katherine M Moore, R V Morris, K A A Mourin, R C Mulholland Elizabeth M Nicholson, K F O'Sullivan D W Owen, R E Owen, D W Patient, Sylvia J Pinder, M A Pratelli, V J Pratt, V M Rakoff, Rudra Rasaretnam, Savino Ravetto, R L Raymakers, P R Riddle, E O Roberts, Michael Roburn Marita R Rodan Christine A Rodgers H D Rogers, J E Rogers Muriel E Rolfe, K W Rowden, D H R Salter, Marie Luise B Seidler, H G S Sergeant, Mary Sibellas, S H Simonian, G B Smith J L Storey, P E N Suter, A R Taylor, M F Terry, C R Thomas Edith H Thomas, C D Thompson D F J Thompson I G Thomson, Janet E Timberlake J A D Walkden M P Walsh, R R Watkin, D M Wayte Felice M Weber, G T Whitfield William Whitrow, Anne M Wigley, F R Wilkes, R P Williams, Wadad Williams, Anne M Wilson, E H Wisely B E M Wright, Margaret E G Wright, G B Wyatt

The following diplomas and those mentioned in our issue of April 20 (p 846) were conferred jointly with the Royal College of Surgeons

D C H—B K North, J N Rea

Endocrine Aspects of Breast Cancer

The University of Glasgow is holding a conference on this subject from July 8 to 10 The topics chosen for discussion include the endocrine ablations and their effects, endocrine aspects of experimental breast tumours and hormone dependence in human breast cancer

Natural Childbirth Association of Great Britain

This association, lately formed with a lay committee, wishes to get in touch with pædiatricians, pathologists, and obstetricians who are interested in natural childbirth and who may be able to undertake research into the causes of stillbirth and infantile mortality and morbidity The association's offices at 44, Great Russell Street, London W C 1

National Birthday Trust Fund

Prof Stanley Walton is to speak at the annual meeting of this fund at the Royal College of Surgeons, Lincoln's Inn Fields, London, W C 2, on Tuesday, May 7, at 3 30 P M

International Congress on Proctology

The Argentinian Society of Proctology is organising this congress, which will be held at Mar del Plata from Dec. 1 to 8 The speakers will include Mr W B Gabriel and Mr Rodney Maingot

Hospital Authorities and Staff Management

The Royal Institute of Public Administration will hold a conference on this subject at the Royal Empire Society, Craven Street, London, W C 2, from May 20 to 22 Further particulars may be had from the director of the institute, 67A, New Cavendish Street, W 1

British Dietetic Association

The dinner of this association, with the Nutrition Society, will be held at the Royal College of Surgeons, Lincoln's Inn Fields, London, W C 2, at 7 15 P M on Friday, May 3 On Saturday, May 4, a scientific meeting will be held at Queen Elizabeth College, Campden Hill Road, W 8, at 9 30 A M, to mark the 21st anniversary of the foundation of the association Dr B Bronte Stewart will speak on natural and processed vegetable fats and their effects on health, and Prof R E Tunbridge on diabetes mellitus

Club for Disabled Children

The Wingfield Music Club was formed in Walthamstow, London, two years ago to help disabled children by teaching them music Among their members they have children with poliomyelitis, spastics, and amputees The club is entirely voluntary, and the teachers try to interest children in instruments best suited to their disability Thus a child who can raise its hands above its head can be taught the violin, one who cannot will be taught a wind instrument Three of the children have taken the second and third examinations of the Associated Board of the Royal School of Music The club has now an orchestra of thirty, which has given two public concerts and is holding a third on Sunday, May 19, at Lloyd Park, Forest Road, E 17, at 3 30 P M Further information may be had from the secretary of the club, 50, Belle Vue Road, E 17

Dr Leonard Browne has been elected vice chairman of the London County Council

Mr Hermon Taylor is to visit the United States this month to speak at the annual meeting of the American Gastro enterological Association in Denver, Colorado He will also address the American Gastroscopic Society who have given him the Schindler award

Appointments

CLARK, G O, M B Aberd F R C S E, D L O part-time consultant E N T surgeon, Wolverhampton, Dudley, and Stourbridge H M C s

DAWKINS, JOAN M ST V, M B Lond, D P H, D C H M O H, *Daventry, Northamptonshire*

DEARING RUTH M, M D Durh assistant pathologist (S H M O) regional cancer service, Newcastle upon Tyne

HALL J M M B Lond F F A R C S D A consultant anæsthetist, Guy's Hospital, London

O'NEILL D W J, M B assistant divisional M O, Lancashire

ORAM, E G, M B Glasg, registrar in psychiatry Fulbourn and Addenbrooke's Hospitals, Cambridge

RAHILL, M A, L R C P I, D P M senior assistant psychiatrist Carlton Hayes Hospital Narborough, Leicester

URQUHART D R M B Lond F R C S surgeon to the orthopædic department St Thomas's Hospital, London

WALKER J K M D Leeds D M R D consultant radiologist Hexham and Newcastle group of hospitals

Colonial Appointments

BRUN, M P C, M S, F R C S surgeon specialist Mauritius

DAVIES A G M, M B Brist, D M R D specialist radiologist Uganda

HUTTON P W M D Camb, M R C P, D T M & H *senior specialist, Uganda*

LOVITT, W C D O B E M D Lond, D P H, D T M & H senior M O Tanganyika

NAUTH MISIR R C M B Lond D P H venereal diseases and dermatologist British Guiana

POTTER, M R M B Leeds M O, Federation of Nigeria

WOLLENDEN, GORDON M B Belf M O, *Kenya*

THE INFLUENCE OF DIETARY FATS ON SERUM-LIPID LEVELS IN MAN

EDWARD H AHRENS, JUN
M D.

JULES HIRSCH
M.D

WILLIAM INSULL, JUN
M.D

THEODORE T TSALTAS *
M D

ROLF BLOMSTRAND †
M D

MALCOLM L PETERSON
M.D

From the Rockefeller Institute, New York, N Y

THE rôle of unsaturated fatty acids in human nutrition is a topic of rapidly increasing popularity in both scientific and lay publications It has been claimed that ingestion of this group of fatty acids decreases the concentration of lipids in the serum and that an inadequate intake of these acids may be the cause of the high serum-lipid levels so prevalent in Western civilisation Since these high levels are allegedly involved in the pathogenesis of arteriosclerosis and coronary disease, it has been tempting to implicate lowered intakes of unsaturated fatty acids in the rising incidence of these diseases Although existing experimental data do not as yet warrant such conclusions, there is mounting evidence that the precise chemical composition of ingested fatty acids, in particular the degree of saturation, may have considerable significance in both health and disease (Sinclair 1956)

A number of experimental observations indicate that saturated and unsaturated acids are not metabolically equivalent, as previously assumed

1 Burr and Burr (1929) demonstrated that certain polyunsaturated acids cannot be synthesised by rats, and that diets devoid of these acids produce a distinctive deficiency syndrome Since then it has been shown that linoleic, arachidonic, and other acids are essential for many species (Holman 1956) The complete deficiency syndrome is produced only by exclusion of these acids from the diet of growing animals, thus, it is hardly surprising that this deficiency state has never been clearly demonstrated in man

2 The turnover-rate of unsaturated acids is slower than that of saturated acids in rat liver and rat carcass (Pihl et al 1950), suggesting differences in the metabolic pathways of these two groups of acids

3 Studies of the structure of natural lecithins show unsaturated acids to be preferentially esterified at the alpha carbon of glycerol (Hanahan 1954), whereas most triglycerides are built with these acids esterified in the beta position (Mattson, personal communication) Such structural differences indicate different metabolic pathways

4 Enzymatic esterification of cholesterol in the intestinal lumen is more rapid with unsaturated fatty acids than with saturated acids (Swell and Treadwell 1955) Another relationship of essential fatty acids to cholesterol metabolism has recently been pointed out (Alfin-Slater et al 1954)—i e, that in the rat deficient in essential fatty acids the content of cholesterol esters in the liver is greatly elevated but serum-levels are decreased Peifer and Holman (1955) have shown that this deficiency state in rats can be accelerated by feeding cholesterol in the fat-free diet Since the cholesterol of serum is preferentially esterified with highly unsaturated acids (Clément et al 1955), this mechanism may remove these acids from sites where they exert their essential quality (Klein and Johnson 1954)

The most recent stimulus to study in this field comes from clinical investigations which suggest that levels of serum lipids may be related to the dietary intake of unsaturated fatty acids Kinsell and Michaels (1955) found that the feeding of coconut oil (a highly saturated fat) produced higher levels than the feeding of a highly unsaturated oil, soybean oil Long-term feeding tests in this laboratory (Ahrens et al 1955) indicated that serum levels of cholesterol and phospholipids varied inversely with the iodine number of six different dietary fats The findings of these two laboratories were greatly extended in the detailed report by Bronte-Stewart et al (1956) and also were confirmed by the experiments of Beveridge et al (1956)

None of the experiments known to us has proven conclusively that the effect on serum-lipids of these dietary fats is due to the double-bond structure of their fatty acids Nevertheless, there has been widespread acceptance of this hypothesis by workers in human nutrition, and broad applications of the hypothesis have already been made Since we think these extensions premature, it seems appropriate for us to set forth in some detail the studies carried out by us over the past 3 years which bear upon the important questions at issue The unique design of these studies was based on the belief that nutritional experiments can be carried out as precisely in man as in animals In view of numerous well-known differences in species response to nutritional variation, such an approach seemed essential All recognised extra-dietary factors influencing serum-lipid levels were kept to a minimum Patients were carefully selected and then observed within the closely supervised environment of the metabolic ward for periods long enough to assure establishment of equilibrium states Dietary intakes were simplified and rigidly standardised, even the variable of cooking was eliminated Yet all known requirements for essential foodstuffs, minerals, and vitamins were generously supplied Medical and hospital care were provided to the patients without charge, and constant attention was paid to socio-economic factors which might disrupt their adjustment to the study situation Under these circumstances the data obtained have quantitative as well as qualitative usefulness

Methods of Present Studies

In our previous studies (Ahrens et al 1954a) six obese but otherwise normal subjects were fed diets containing 12% of calories as protein and 50% as fat Solid foods made up a large part of the dietary intake At intervals of 6 to 8 weeks, vegetable and dairy fats were exchanged isocalorically without altering other variables Clear-cut decreases in serum-lipid levels were produced when the vegetable fats were fed These findings confirmed and extended the original report of Kinsell et al (1952)

To investigate this effect it was evident that more precise control of the diet was required Accordingly, a technique of oral feeding of liquid formulas was developed (Ahrens et al. 1954b) and has been used almost exclusively in all feeding experiments since 1953 With this method patients were maintained at constant body-weight by suitable adjustment of caloric intake, the proportions of foodstuffs remaining unchanged Changes in body-weight rarely exceeded 1 kg The basic formula consisted of protein 15%, fat 40%, and carbohydrate 45% of total calories There was no source of calories other than the formula Formula feeding has been used uninterruptedly for 36 months in one patient without recognised ill effect, however, in most of the experiments discussed below the feeding tests lasted 4 to 6 months Thirty-eight of forty patients were observed continuously under strict metabolic-ward conditions, four of the forty were sufficiently motivated and intelligent to follow the regimen at home Iodised salt (2 g sodium chloride with 200 µg potassium iodide),‡ 2 multivitamin capsules, and ferrous gluconate (0·3 g.) were given daily as supplements. The entire protein intake was derived from milk proteins; the intake of nitrogen and pattern of amino acid intake were considered completely adequate for adult men and women (Rose et al. 1955).

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‡ We are indebted to Dr Clayton Rich Rockefeller Institute Hospital, for demonstrating a requirement for supplemental iodine in our patients maintained solely by oral formula feeding Unpublished serial radioactive iodine studies showed significant increases in uptake in some patients in less than one month.

The subjects of these studies were hypercholesteræmic or hyperlipæmic patients (some with clinical evidence of arteriosclerosis and xanthomatosis) and normocholesteræmic patients with arteriosclerotic heart-disease. Table I lists the pertinent clinical data. All patients were free from conditions which might complicate the interpretation of long-term metabolic studies, such as renal, hepatic, endocrine, or infectious disease, or nutritional deficiencies. All were ambulatory. Patients with cardiac decompensation were considered ineligible for these studies because of our dependence on daily measurements of body-weight as an index of energy balance.

In addition to routine clinical tests, weekly measurements were made of total and free serum-cholesterol (Sperry and Webb 1950), total serum-lipid phosphorus (Stewart and Hendry 1935), and total serum lipids (Ahrens et al. 1954a). Cholesterol esters and serum triglycerides were calculated from these basic data; generally accepted mean molecular weights for the cholesterol esters (645) and phospholipids (775) were used in these calculations. Rapid determinations of total cholesterol (Abell et al. 1952) made each week checked (within 5%) with the Sperry-Webb values. Studies of lipoprotein changes will be presented elsewhere.

Base-line Levels on Corn-oil Formula

Fig. 1 is a graphic demonstration of the data of a typical feeding experiment. For the first 8 weeks the patient ate ad libitum. After relatively constant levels of serum-lipids had been achieved, formula feeding was begun. In the three succeeding periods, all dietary fat was derived from corn oil, coconut oil, and corn oil, respectively. There were striking decreases in all serum-lipid components during the two corn-oil periods and rises in all except triglycerides when coconut oil was fed. After each change of formula, lipid levels shifted upward or downward in an orderly manner through a 3-week transition phase. This was followed by a new steady state, a plateau of levels marked by only minor fluctuations. Body-weight remained unchanged in all periods.

Not all patients responded to the corn oil formula in the same measure, and only occasional patients with high serum cholesterol achieved normal levels. To compare responses to various dietary fats in different patients, it was necessary to establish in each individual a base line of serum-lipids attained on corn oil feeding. Then, when other fats were substituted isocalorically for corn oil in the basic formula, the serum lipid data obtained during successive steady states could be related to the corn oil base line. Thus, in fig. 1, the level of total cholesterol on the coconut-oil diet was 40% higher than that on corn oil.

Measurements during transitions were, of course, omitted in these calculations. The length of each transition phase was determined on an individual basis by inspection of the assembled data. Transitions varying from 3 days to 8 weeks have been encountered, but, usually, transitions were completed in 2 to 3 weeks. Consequently, with each change in formula at least the first 2 weeks' determinations were discarded; when selecting data for comparative calculations, when transitions were slower, more data were discarded.

It is relevant to define the extent of variation of week-to-week values during that terminal portion of each feeding period designated as the steady state. The duration of the steady state was at least 3 weeks and usually 4 or more. During the steady state the standard deviation of the mean level of total cholesterol, as well as of phospholipids, was less than ±20 mg. per 100 ml. serum in all cases except patient 3, and the pooled variation of the 120 steady states reported in this paper

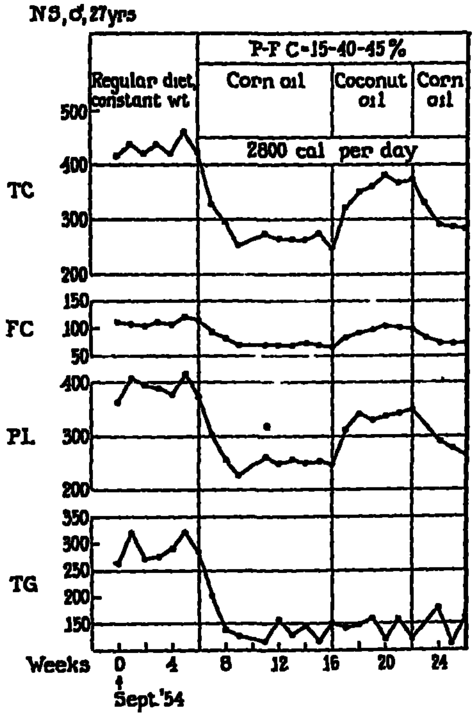

Fig. 1—26 week study of serum-lipids of patient 9, maintained at constant body weight on ad-lib feeding, then by oral formula feeding exclusively.

TC=total cholesterol, FC=free cholesterol, PL=phospholipids, TG=triglycerides—all in mg. per 100 ml. serum. P-F C=dietary proteins, fats, and carbohydrates, as percentages of total calories.

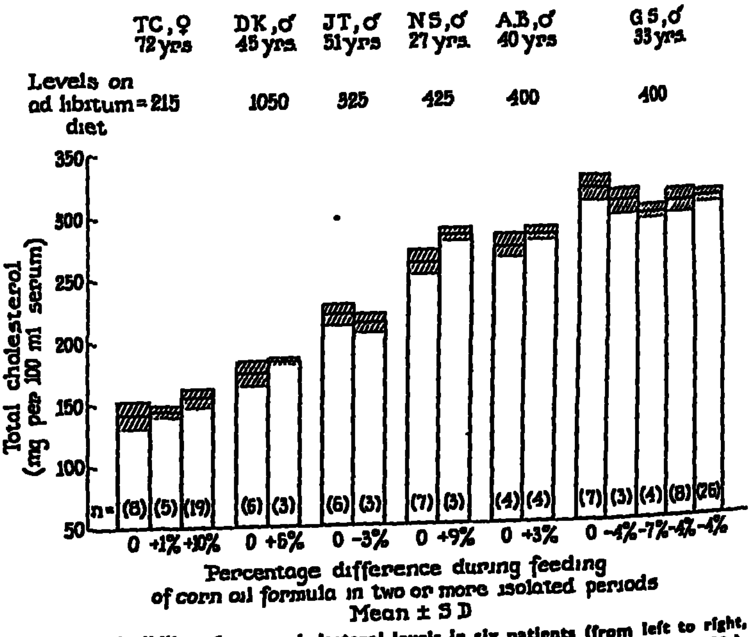

Fig. 2—Reproducibility of serum-cholesterol levels in six patients (from left to right, patients 34, 1, 27, 9, 12, and 13) retested on basic corn oil formula (P-F C=15-40-45%), with other regimens in intervening periods.

Bars show mean levels during steady states, hatched area one S.D. n=number of weekly data during each steady state. Percentage differences along base line calculated with reference to mean levels of first feeding periods.

TABLE I—CLINICAL DATA AND TOTAL SERUM-CHOLESTEROL LEVELS OF PATIENTS SUBJECTED TO BASIC CORN-OIL FORMULA

(Mean cholesterol levels are shown, ± one standard deviation Values in parentheses = number of determinations All formula feeding experiments conducted in metabolic ward, except for those marked *)

Patient		Clinical diagnosis	Total serum cholesterol (mg per 100 ml)						Percentage decrease on formula after ad lib diet
No	Sex Age (yr) (initials)		Ad lib diet (outpatient)		Corn oil formula (inpatient)		Total vegetarian diet (no formula) (outpatient)		
1	M 45 (D K)	Hl Xs	1089 ±59	(4)	*175 ±10	(6)	277 ±18	(5)	84
2	M 42 (H S)	Hl Xs	898 895	(2)	471 ±21	(7)			47
3	M, 40 (I N)	Hc, Xs Xt, Ashd	787 ±87	(9)	387 ±16	(5)			51
4	F 50 (E M)	Hc Mx Xt Xs Ashd Pm	625, 625	(2)	206 ±16	(3)			67
5	F 51 (D K)	Hc Xt Ashd Pm	533 ±12	(3)	425 ±20	(23)			20
6	F 50 (F R)	Hc, Xt Ashd, MI, Pm	502, 502	(2)	325 ±16	(6)			35
7	F 39 (F G)	Hc Xt, Xs	530 ±16	(6)	362 360	(2)			31
8	M 34 (V F)	Hc Xt Xs Ashd	436 ±24	(11)	*345 ±12	(7)			21
9	M 27 (N S)	Hc	430 ±16	(7)	*263 ±10	(7)			42
10	F 51 (E L)	Hc Xt, Pm	429 ±30	(9)	306 ±5	(3)			28
11	M, 50 (A O)	Hc Xt, Xs Ashd MI	413 ±29	(6)	192 ±10	(4)	290 ±19	(7)	53
12	M 40 (A B)	Hc, Xt, Xs	400 ±28	(9)	274 ±9	(4)	313 ±16	(13)	31
13	M, 34 (G S)	Hc Xt, Ashd, MI	400	(1)	*321 ±12	(7)			20
14	M 37 (B H)	Hc Xt, Xs	390 411	(2)	189 ±5	(4)			53
15	M 29 (I P)	Hc, Xt Ashd MI	386 345	(2)	363 ±3	(3)			0
16	M, 13 (R G)	Hc	363 ±27	(7)	195 ±7	(8)	289 ±25	(18)	46
17	F 26 (B W)	Hc, Xt Xs	370 340	(2)	185 ±6	(5)			47
18	M, 51 (W J)	Hc Ashd, MI	358 331	(2)	185 ±13	(4)	218 ±7	(4)	46
19	F 37 (N W)	Hl	323 ±20	(3)	180 ±7	(4)			44
20	M, 50 (J R.)	Hl Ashd MI	347	(1)	200 ±10	(5)			40
21	M 67 (M I)	Hc Ashd	301, 292	(2)	180 ±8	(5)			40
22	M 41 (W K)	Hc Ashd	300 294	(2)	191 ±8	(8)			36
23	M 61 (H K)	Hc, Ashd MI	298, 294	(3)	209 ±6	(4)	259 ±14	(24)	29
24	F, 36 (E C)	Hc Xs	295	(1)	156 ±7	(6)			47
25	M 40 (S E)	Hc, Ashd	302 261	(2)	198 ±11	(5)			26
26	F 62 (N I)	Hc, Ashd	275, 250	(2)	178 ±7	(6)			30
27	M 51 (J T)	Hc Ashd MI	259 245	(2)	222 ±9	(6)			12
28	M 52 (H J)	Ashd MI	267 224	(2)	156 ±8	(4)	221 ±10	(5)	37
29	M 55 (N P)	Ashd MI	244 ±16	(10)	161 ±7	(6)			34
30	F 46 (I T)	Cardiac neurosis	246 243	(2)	119 ±2	(4)			52
31	M 53 (O C)	Ashd	237 ±9	(3)	159 ±6	(5)	176 ±2	(3)	33
32	M 60 (L S)	Ashd MI	246 ±11	(4)	194 ±6	(5)			21
33	M 37 (L B)	Ashd	225 ±8	(3)	165 ±4	(4)			22
34	F 72 (T C)	Ashd MI Pm	208 ±7	(5)	142 ±11	(8)			32
35	F 52 (M W)	Treated thyrotoxicosis Ashd Pm	215 ±2	(3)	131 ±11	(8)			39
36	M 52 (E O)	Ashd	224 193	(2)	152 ±6	(3)			31
37	M 52 (J K)	Ashd	194 194	(2)	Experiment in progress				
38	M 32 (L R)	Ashd MI	186 170	(2)	105 ±5	(4)			41
39	F 46 (A H)	Sprue	152 ±16	(3)	99 ±7	(7)			35
40	F 34 (D B)	Sprue	125 117	(2)	79 ±6	(7)			35

M = male F = female Hl = hyperlipæmia Hc = hypercholesterolæmia Xs = xanthomatosis of skin (tuberous or planar, or xanthelasma) Xt = xanthomatosis of tendons Ashd = arteriosclerotic heart-disease MI = myocardial infarction, healed Mx = myxœdema Pm = postmenopausal

was ±9 9 mg for total cholesterol, ±4 2 mg for free cholesterol, and ±9 9 mg for phospholipids The deviations of each of these components were unrelated to their total mean concentration Both technical and true biological variations (Watkin et al 1954) of triglycerides were greater than in the case of cholesterol and phospholipids In 95 out of 100 steady states, standard deviations of mean triglyceride levels were less than ±60 mg per 100 ml serum, the pooled variation in these 100 periods was ±31 mg The deviations of triglycerides were larger at higher concentrations of this lipid component, as would be expected from the method of measurement Independent tests showed that about one-third of the total variation of each lipid level could be ascribed to methodological error Differences in mean cholesterol or phospholipid levels of 25 mg per 100 ml of serum are statistically significant at the 1% level, when 4 data are collected in each of 2 steady states under comparison and standard deviations of mean levels are ±10 mg

It is central to the issue under discussion that the concentration of a serum lipid during ingestion of corn oil be a reproducible constant for a given subject The similarity of these levels in re-test periods is shown in fig 2, in which data from six re-tested patients are graphed It is seen that mean concentrations of serum-cholesterol varied by no more than 10% from one corn-oil period to another In the same patients phospholipid levels varied by 7% or less from period to period, but the range of triglyceride fluctuations was as great as 50% In patients 33 and 13 there was no drift of levels during administration of the corn oil formula for 19 and 26 weeks, respectively, as shown by the small standard deviations of values from the mean of these periods Thus, for the period set as a minimum in all our studies (4 to 5 months) the corn-oil base-line remained fixed and showed no "escape"

In view of the fact that serum-lipid levels can be made to vary so strikingly by simple dietary manipulations, little is gained by analysing data obtained during ad-libitum feeding when dietary intakes vary in a complex manner Although data gathered during ad libitum feeding periods are obviously the net result of many undefinable and conflicting dietary forces, such levels are termed "normal" when gathered from patients without manifest illness We made no effort to collect large numbers of such data, although a few determinations of serum-lipids were made during the preliminary work-up of each case Table I compares total serum-cholesterol levels on ad-libitum diets and during maintenance of body-weight on the basic corn-oil formula Decreases of 20% or more were produced in thirty-six of thirty-nine patients during corn oil formula feeding In patient 1 a decrease of 84% was achieved, while a 12% decrease was seen in patient 27, and in patient 15 the corn-oil formula produced no change Excepting these three cases, the percentage decreases ranged from 20–67% (mean 37%, standard deviation ±11%) These data show clearly the unpredictability of response of individual patients to a given dietary fat intake

The Responsible Factors in Corn Oil

Experiments such as that shown in fig 1 suggested that certain factors in the diet raised the levels of serum-lipids, and others depressed them When corn oil was

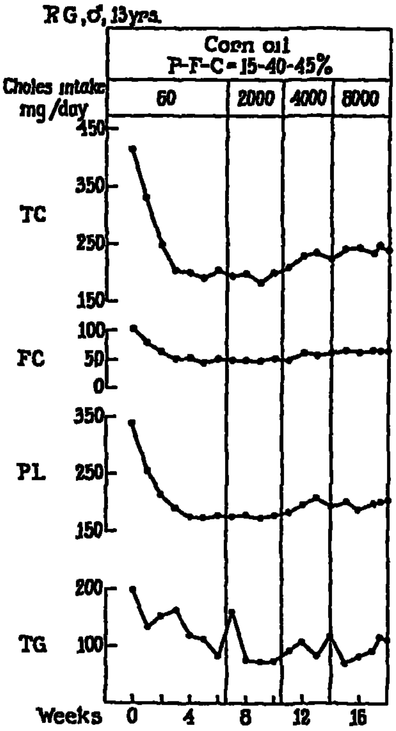

Fig 3—Effect on serum-lipids of additions of cholesterol to the basic corn-oil formula (patient 16) Crystalline cholesterol was dissolved in warm corn oil and homogenised in the formula Increases in cholesterol and phospholipid levels on intakes of 4 and 8 g per day were significantly higher (p< 0 01) than on 0 06 and 2 g per day, but differences were small

fed as the sole source of dietary fat, the lowered levels could have been due to an absence of elevating factors, or to a presence or dominance of depressing factors Since the protein and carbohydrate portions of these formulas were identical, and the total quantity of fat remained constant, the factors in question resided in the qualitative differences between dietary fats

An obvious difference between fats of animal and vegetable origin is the presence of cholesterol in the former and of poorly absorbed plant sterols in the latter However, experiments of the type shown in fig 3 convinced us that the depressions of serum lipid levels during feeding of the corn oil formula were not due to the absence of cholesterol from that formula Similar experiments have been carried out with a lard formula (patient 11), the ingestion of cholesterol (0 6 g per day) with lard produced no higher levels of serum-lipids than lard alone

Corn oil contains 2% or less of its weight as non saponifiable material (sterols, tocopherols, carotenes, hydrocarbons, waxes, phosphatides) About half of this small fraction is mixed sitosterols Therefore, a 65 kg adult maintained on the basic corn oil formula ingests a maximum of 1 g of corn sitosterols per day Experiments were carried out in six patients to whom large supplements of beta sitosterol § (18 g a day) were administered in conjunction with totally vegetarian diets of solid foods In all cases serum-lipid levels were very much higher than when the corn-oil formula was fed These studies indicated that the beta-sitosterol content of corn oil is not chiefly responsible for the depressing effect of this oil on serum-lipid levels

Other feeding experiments were made with oils freed of the major portion of the non saponifiable fraction by both physical and chemical procedures In the first, refined corn-oil was subjected to molecular distillation ‖ A 50 50 cut resulted in threefold enrichment of the non saponifiable material in the distillate fraction and a threefold decrease of this material in the residue Each fraction was fed in the basic formula at 40% of calories, as was the original undistilled oil Serum-lipid levels remained unchanged from period to period in this 17 week test (fig 4), despite a sixfold difference in non saponifiable content in the two distillation fractions Similar studies undertaken by Beveridge et al (1957b) also showed no significant difference in the effects of undistilled corn oil and various cuts of corn oil obtained by molecular

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§ Generously furnished by Eli Lilly & Co, Dr R E Shipley

‖ Molecular distillations of oils were carried out through the coöperation of Distillation Products Industries, Dr P L Harris

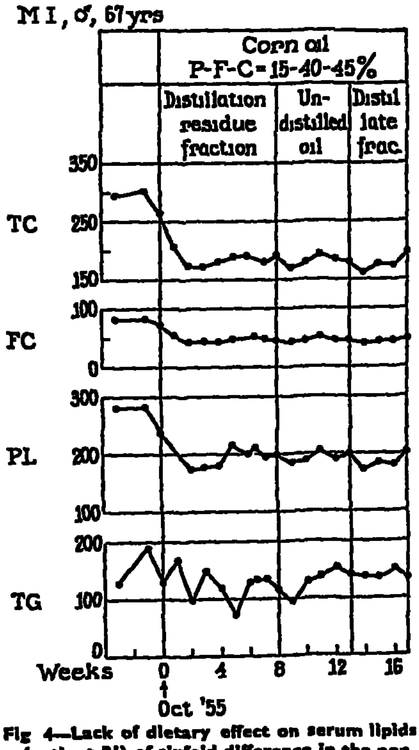

Fig 4—Lack of dietary effect on serum lipids (patient 21) of sixfold difference in the non saponifiable elements of corn oil produced by molecular distillation

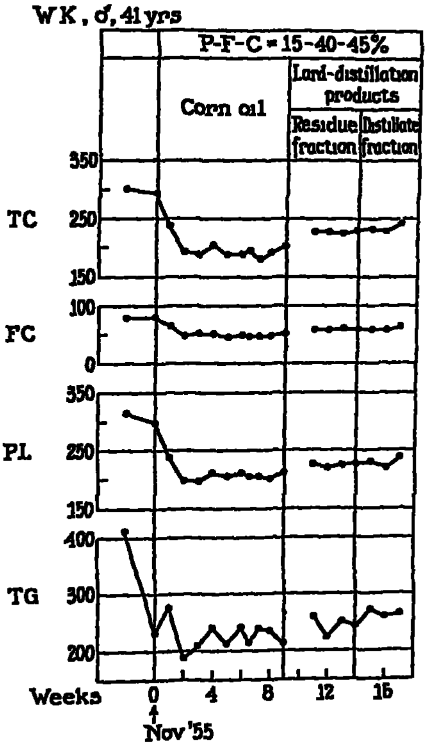

Fig 5—Lack of dietary effect on serum-lipids (patient 22) of threefold difference in non saponifiable elements of lard produced by molecular distillation Levels during second and third test periods were the same, but both were higher than during corn-oil ingestion

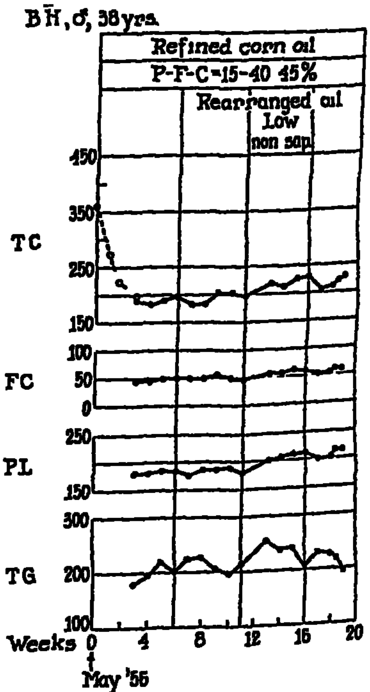

Fig 6—Lack of effect on serum lipids (patient 14) of sixfold difference in non-saponifiable elements of corn oil produced by chemical extraction Comparison of first and second periods shows that random rearrangement of corn-oil fatty acids produced no significant changes

TABLE II—COMPOSITION DATA ON FATS AND OILS USED IN FORMULA-FEEDING EXPERIMENTS

Fatty acid compositions listed as percentages of total fatty acids Data derived from spectrophotometric analysis after alkali isomerisation and from iodine values *Trans* acids obtained by infra-red analysis Analyses performed as follows GM = General Mills, Inc (D H Wheeler), EURB = Eastern Utilisation Research Branch, U S Department of Agriculture (R W Riemenschneider), DPI = Distillation Products Industries (P L Harris), P & G = Procter & Gamble (F H Mattson)

No	Oil or fat	Description and origin	Analysis by	Iodine value	% Saturated acids	% Oleic	% Linoleic	% n s	% *trans* monoethenoid	% *trans* diethenoid	% Conjugated diene	Melting point
1	Beef tallow	Oleo oil, Cudahy	GM	46 8	47 6	50 1	2 3					
			GM	47 6	45 2	49 2	2 3					
2	Butter oil	University of Wisconsin Agricultural College (H C Jackson)	GM	39 5	57 8	38 3	3 9					
3	Chicken fat	Ocoma Foods Co	GM	86 5	23 4	52 9	23 7					
4	Cocoa butter	Tower Brand	GM	36 6	60 1	37 0	2 9					
5	Coconut oil	E F Drew & Co	GM	9 7	90 7	7 3	2 0					
6	Corn oil	C P, winterised	GM	126 8	8 8	35 5	55 7					
7	Corn oil	C P, hydrogenated	EURB	79 8	18 0	48 9	6 2	1 22	21 1	4 7		34–35°C
8	Corn oil	C P, hydrogenated	EURB	57 7	34 4	33 1	0 0	1 16	31 4	0 8		44–47°C
9	Corn oil	C P, m d distillate	DPI	123 2				1 91				
10	Corn oil	C P, m d residue	DPI	129 0				0 32				
11	Corn oil	E F Drew & Co	GM	125 9	9 0	36 1	54 9	1 2	4			-
12	Corn oil	E F Drew & Co random rearranged	GM	124 1	10 6	35 3	54 1		4			-
13	Corn oil	E F Drew & Co rearranged, low n s	GM	119 6	12 6	36 1	51 3	0 2	7		10	-
14	Cottonseed oil	Procter & Gamble	P & G	105 8	26 7	25 4	47 5	0 42				
15	Cottonseed oil	Procter & Gamble, hydrogenated	P & G	68 1	25 5	70 2	4 6	0 59	32			29–36°C
			EURB	67 4	26 4	69 1	4 3					
16	Lard	Cudahy prime steam	GM	70 0	33 1	52 9	13 5					
17	Lard	Cudahy m d-distillate	P & G	67 4	36 1	51 3	12 2	0 20			0 2	
18	Lard	Cudahy m d residue	P & G	68 2	33 2	55 1	8 9	0 07			2 3	
19	Lard	R I	EURB	89 4	30 3	37 8	30 5	0 12				
20	Lard	R I	EURB	51 5	42 8	55 0	1 8	0 20				
21	Lard	Procter & Gamble	P & G	66 5	37 7	49 4	12 3	0 28	0 7		0 2	-
22	Lard	P & G random rearranged	P & G	66 7	37 3	50 5	11 3	0 78	0 6		0 2	-
23	Lard	P & G, directed interesterification	P & G	94 5	9 5	71 3	18 0	1 8	0 9		0 6	-
24	Olive oil	Ehmann Olive Co	GM	89 7	2 9	89 5	7 6				-	-
25	Palm oil	Durkee Famous Foods	EURB	53 1	50 1	39 1	9 9				-	
		Borden Co	CM	53 6	47 3	42 9	9 8					-
26	Peanut oil	Planters (A C Eaton)	GM	93 0	17 7	56 5	25 8					
27	Safflower seed oil	E F Drew & Co	GM	144 3	5 7	21 7	72 6					
28	Sesame oil	Welch Holme, & Clark	GM	113 0	11 8	45 4	42 8					

C P = Corn Products R I = Rockefeller Institute n s = non saponifiable fraction. m d = molecular distillation

distillation A second experiment was conducted with two fractions obtained in a 50 50 cut of lard by molecular distillation In an 18-week test the lowest lipid levels were reached on formulas containing corn oil (fig 5) Higher levels were found when the two lard fractions were fed (see below), but the feeding of residue and distillate fractions produced no significant differences in levels despite threefold differences in their contents of non-saponifiable materials

The chemical procedure consisted of saponification of the refined corn oil, formation of the insoluble barium soaps, and extraction of these soaps with ethylene dichloride four times to concentrate the non saponifiable materials in the extract ¶ The acids were regenerated and re esterified with glycerol Excess acids and catalysts were washed out before final deodorisation In this process the content of non saponifiable material was reduced from 1 2 to 0 2% Since the reconstructed oil consisted of corn-oil fatty acids arranged at random on the glycerol base, it was necessary as a preliminary control step to show that randomisation of fatty acids did not produce a different effect on serum lipids from that of the naturally constituted corn oil glycerides Therefore, in a 20-week test (fig 6) a patient was fed refined corn oil in the first period, then the same oil after random rearrangement in the second and fourth periods, and the rearranged corn oil poor in non saponifiables in the third period It is seen that the effectiveness of corn oil was not significantly changed by chemical removal of a large portion of the non saponifiable material The lack of effect of randomisation is hardly surprising in the light of previous experiments on digestion and absorption in man (Ahrens and Borgstrom 1956)

Thus, three lines of investigation failed to show that the factors responsible for depressing serum-lipid levels reside in the non saponifiable, non-glyceride portion of corn oil On the contrary, the various lines of evidence suggested that the glycerides themselves contained the sought-for factors Further experiments using fats and oils which varied in fatty-acid composition were carried out in order to test this conclusion

Variations in Fatty-acid Composition

A number of informative tests has been carried out by substituting various natural fats and oils for corn oil in the basic formula These fats were chosen to obtain wide variations in fatty-acid composition The chemical characteristics of the fats used are shown in table II ** Except in the cases of butter and coconut oil, all fats fed were composed of fatty acids of similar chain length (predominantly C_{16} to C_{18}) To simplify the interpretation of such experiments, oils rich in trienes were purposely avoided (soybean, linseed oils)

The levels of serum-lipids produced by the feeding of each of these fats are set forth in table III Calculations were made of the absolute and percentage differences of these levels from the base line levels reached during the feeding of corn oil The results were related to a number of characteristics of natural fats—iodine number, linoleic-acid content, and biological activity in rats deficient in

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¶ Chemical purifications of corn oil were generously accomplished by F F Drew & Co Dr V K Babayan

** We are greatly indebted to Dr Donald H Wheeler General Mills Inc to Dr Roy W Riemenschneider and Dr Waldo C Ault Eastern Utilisation Research Branch, U S Department of Agriculture and to Dr Fred Mattson Procter & Gamble Co, for numerous analyses and for their helpful advice on matters of fat technology essential fatty acids †† Absolute differences in lipid levels failed to correlate with any of these parameters However, a roughly linear relationship was obtained by relating percentage differences in cholesterol or phospholipid levels to the iodine values of the fed fats This analysis is shown in fig 7 The use of fats with iodine values below 90 produced levels of cholesterol significantly higher than the corn-oil base line (P<0 01) *in 23 of 26* tests However, fats with iodine values over 100 all produced equally low levels of cholesterol, suggesting a limit to the effect produced by the ingestion of unsaturated fats With the feeding of fats with iodine values below 90, the cholesterol content of the serum increased as the saturation of the dietary fat increased The plot of the phospholipid data showed the same type of correlation with a somewhat smaller dispersion of data In the case of the triglycerides there was no correlation with iodine value, all percentage differences falling within the ±25% limits of reproducibility noted above in the analysis of the corn-oil refeeding tests

Statistical analysis showed a significant correlation between P (the percentage decrease of total-cholesterol or phospholipid levels with a given dietary fat, relative to the corn-oil base-line) and the total iodine values of the fats fed An equally good correlation was found between P and the expression total saturated acids minus linoleic acid (S − L) Since our studies were performed with fats consisting almost exclusively of saturated (S), oleic (O), and linoleic (L) acids, it was simple to calculate that the iodine values of these fats are functions of any of the following expressions (S − L), (2S + O), or (2L + O) Thus I_T (total iodine value) = 90 − 0 9 (S − L), and (S − L) = 10 − 1 11 (I_T) With the natural fats available for feeding tests the variable (2S − L) also is practically a linear function of iodine value

Now, if our data can be correlated with iodine value they will *also be correlated with any of the* four alternative expressions To conclude that dietary oleic acid is neutral *or lacking in effect simply because the cholesterol data* can be correlated with some function of (S − L) or (2S − L) is no more correct than to imply that linoleic is unimportant because the data can be correlated with the expression (2 S + O) Correlations which utilise any of these modes of expression are no more meaningful *than an iodine*-value correlation

An analysis of variance was carried out to assess the relative importance of total unsaturation and the linoleic acid content of the various fats The linear regression of *P on total iodine* value of the dietary fats (I_T) was $P = -0\ 37\ I_T + 44$ The multiple regression of P on I_T and on linoleic acid, expressed in iodine-value equivalents ($I_L = L \times 1\ 8$) was $P = 0\ 14\ I_L - 0\ 49\ I_T + 47$ Comparison of residual variances showed that the multiple regression gave no better fit to the experimental data than the simple regression on total iodine value The simple regression of P on I_L gave a poorer fit than either of these (*P<0 05*)

It is noted that the butter and coconut oil data contribute heavily to the values of the regression coefficients Since it will be shown below that these fats may cause unusual effects on serum-cholesterol, perhaps due to their high *content of short-chain fatty acids*, it may be questioned whether it is permissible to include these *data in the mathematical analysis* Indeed, if they are excluded, the following regressions are calculated $P = -0\ 21\ I_L + 0\ 08\ I_T + 13$, $P = -0\ 16\ I_T + 24$, $P = -0\ 15\ I_L + 17$ No significant differences were found between the residual variances of these three regressions (F test) Comparison of these formulas with those given in the preceding paragraph suggests that the assembled data fall along *two* curves, a steep one in which the major factor is correlated with mean unsaturation, and a flat curve in which the content of short chain saturated fatty acids may be the dominant factor

It is a matter of great practical and theoretical interest to learn whether the observed effects of dietary fats on serum-lipids are caused by mean unsaturation, or by the content of a specific unsaturated acid such as linoleic acid, but it is clear that this issue cannot be resolved by tests *made* with commonly occurring natural fats The fatty-acid compositions of these fats are so constituted that there is great interdependence between I_T and L In fact, the coefficient of correlation (r) between I_T and L of all fats used in this study, excluding butter and coconut oil, is 0 88 ± 0 09 (P<0 01) When butter and coconut oil are included, r = *0 79 ± 0 12* (P<0 01), also a high degree of correlation If I_T and L are to be separately evaluated, it is obvious that tests must be

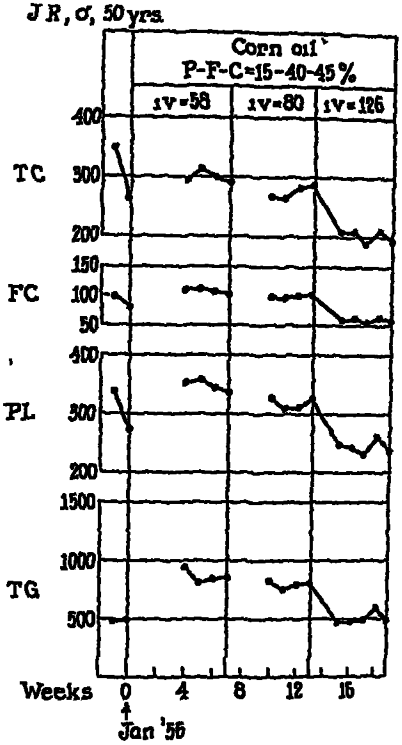

Fig 8—Effect in patient 20 of ingestion of corn oil hydrogenated to iodine values of 58 and 80, compared to unhydrogenated oil Levels of lipids significantly different (P<0 01), in three test periods

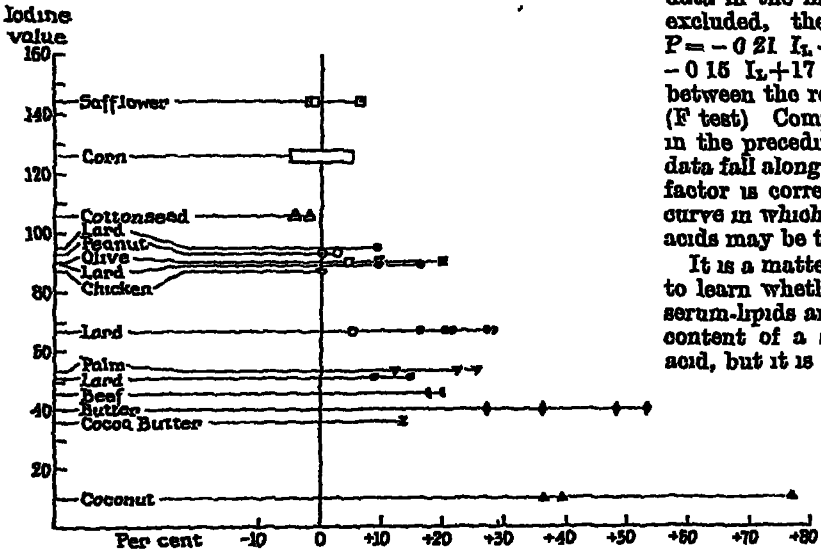

Fig 7—Relationship between iodine values of dietary fats and serum cholesterol levels, *expressed as percentage differences from base-lines established during ingestion of corn oil*

Iodine values of fats listed along vertical axis Open bar at I V 126 = estimated reproducibility of corn oil base line (fig 2) Open symbols represent results not significantly different from base line, solid symbols different at level of P<0 01, hatched symbols different at level of P<0 05 made with fats synthesised from pure acids The hypotheses suggested by our calculations can be critically evaluated only when I_T is held constant and L varies maximally, and vice versa It is idle at this time to carry the interpretations of the present data further than to state that the effect on serum-cholesterol and phospholipid levels is strongly correlated with the iodine value of dietary fat

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†† A number of bio assays on fats used in these tests were generously performed by *Dr H J Thomasson, Unilever Research Laboratory*, Holland, by the methods described in *Internat Rev Vitamin Research*, 1953, 25, 62

Hydrogenated Fats

If unsaturation of fatty acids is responsible for the effects under study, the obliteration of double bonds by hydrogenation would be expected to mitigate the depressing action of these acids Complete hydrogenation of such long-chain fatty-acid oils as corn or cottonseed produces triglycerides composed of palmitic and stearic acids—fats with high melting-points which are poorly absorbed by the small intestine (Deuel 1954) To insure complete absorption of the fed fat the investigator is forced to use partially hydrogenated oils with melting-points below 50°C Partial hydrogenation is, however, not a simple process, and isomers are formed as well as simple hydrogen addition products (Sreenivasan and Brown 1956) The nutritional effects of partially hydrogenated oils have received extensive study (Deuel 1954), and in terms of growth, maturation, and reproduction such fats are equivalent to their natural precursors However, in terms of the parameters under study here the effects of these complicated mixtures are unknown Since *trans* acids do not replace *cis* acids in remedying essential-fatty-acid deficiency (Holman 1951, Privett et al 1955) it seems probable that the isomers found in partially hydrogenated fats are metabolised through different pathways

Three feeding tests were carried out with partially hydrogenated oils, fed in the basic formula as 40% of calories The most clear-cut response was shown by patient 20 (fig 8) in whom the feeding of corn oils hydrogenated to iodine values of 80 and 58 in a moderately selective process, produced progressively higher levels of cholesterol and phospholipids in the serum In patient 30, however, the ingestion of corn-oil, hydrogenated to an iodine value of 80, produced no higher levels of serum-lipids than the unhydrogenated oil In patient 18, serum-lipids were equally depressed on unhydrogenated corn and cottonseed oils, but the subsequent feeding of cottonseed oil, hydrogenated to an iodine value of 68 in a selective manner, produced a small but significant rise ($P<0{\cdot}01$) in cholesterol and phospholipid levels The compositions of these products are listed in table II, and the serum-lipid data in table III It is worth emphasising that in these 3 patients the entire fat intake consisted of fats hydrogenated more heavily than in the case of the margarines and shortenings commonly marketed in the United States (Sreenivasan and Brown 1956), yet in two of three cases serum-lipid levels were not so high as those found during ad-libitum feeding

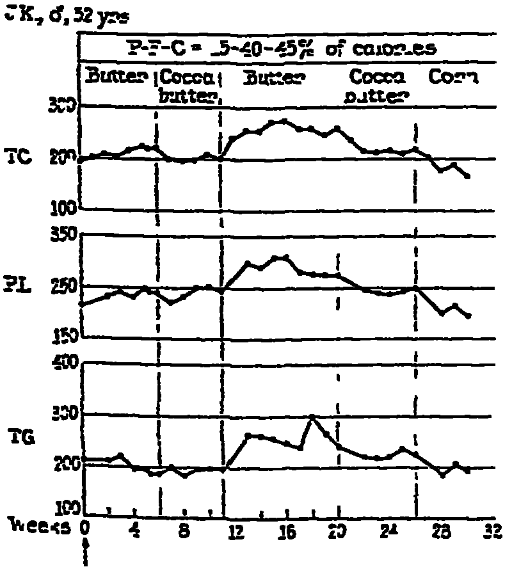

Fig 9—Feeding tests in patient 37 comparing butter and cocoa butter (experiment still in progress) These two fats have similar contents of saturated oleic, and linoleic acids (table II fig 11) but butter is rich in C_4-C_{14} fatty acids

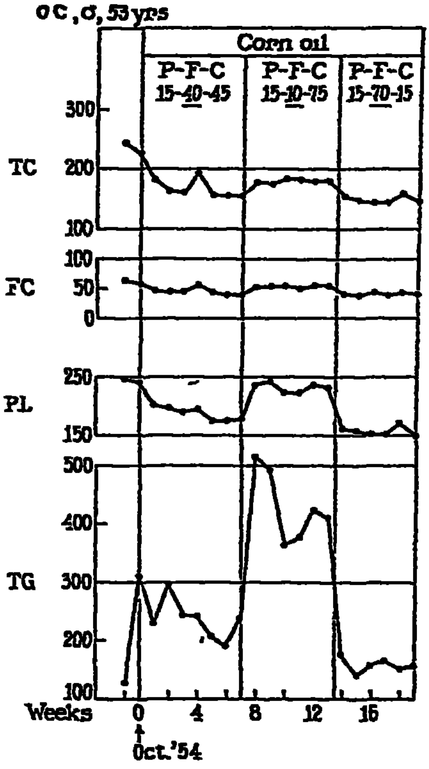

Fig 10—Effect on serum-lipids (patient 31) of varying the proportions of fat and carbohydrate calories reciprocally, keeping total calories, protein, and body-weight constant Major changes in triglycerides, smaller differences in phospholipids, and least striking effects on cholesterol Lowest serum lipids on highest intake of corn oil highest levels on lowest intake

Variations in Length of Fatty-acid Chains

The highest lipid levels encountered in our tests were produced by the feeding of butter and coconut oil (fig 7) While these oils were the most saturated of the dietary fats tested, it must be stressed that they were also the only fats which contained a high content of fatty acids with chain lengths less than C_{16} 25% of butter fatty acids have chain lengths of C_4 to C_{14}, while 60% of coconut-oil fatty acids have chain lengths of C_8 to C_{14} Thus, it is possible that the effectiveness of these fats in raising serum-lipid levels is due in part to the low content of unsaturated acids but also to the presence of short-chain acids

Experiments have been completed in patients 26 and 37 which were designed to test the importance of chain length as a variable In these tests butter was compared with cocoa-butter These fats are almost identical in iodine value and in percentage composition of saturated oleic, and linoleic acids (table II) However, the saturated acids of cocoa-butter are predominantly C_{16} and C_{18} acids, whereas 40% of the saturated acids of butter are C_4 to C_{14} acids Serum-cholesterol and phospholipid levels were significantly higher ($P<0{\cdot}01$) during butter-feeding periods in both patients (fig 9) The fats were apparently equally well absorbed, as evidenced by the constancy of body-weights over the many weeks of these tests when the formulas were isocalorically exchanged.

These results are interpreted as presumptive evidence that fatty acids of short and intermediate chain length cause higher lipid levels in the serum than do the long-chain saturated acids The short term feeding tests carried out by Beveridge et al (1957b) with fractions of butter prepared by molecular distillation seem to confirm this postulate Their highest cholesterol levels were produced by the fractions of butter containing the shortest and most saturated fatty acids However, in both laboratories' experiments the non-glyceride portions of the test fats also differed Therefore, final proof of this point awaits use of fats synthesised from pure fatty acids It seems clear that butter and coconut oil are not ideal prototypes of highly saturated fats for our experiments because of inhomogeneity in chain length of their fatty acids

Variations in Caloric Mixture

The response of patients to any given dietary fat is influenced not only by the chemical structure of the fat but also by the proportional contribution of fat to the total caloric intake These relationships are complex (fig 10) When only 10% of total calories was fed as corn oil, serum-lipid levels were significantly higher in all categories than when 40% or 70% of calories were derived from corn oil In fact, the lowest serum levels were attained on the highest fat intake Similar findings were made in three other patients This may be related to the presence in corn oil of factors which depress serum lipid levels, but clearly the proportions of non-fatty elements in the diet also may play an important modifying rôle It is important to note that the substitution of carbohydrate for fat calories produced major changes in the serum triglyceride levels, other lipids increasing less strikingly The regularity and dominance of this triglyceride response in all four patients contrasts with the lack of orderly change in this fraction in experiments where metabolic mixtures were held fixed while fats of varying fatty-acid composition were exchanged

Discussion

The results discussed above favour the hypothesis that serum lipids can be lowered by ingestion of highly

TABLE III—SERUM-LIPID DATA DURING STEADY STATES ON INGESTION OF VARIOUS DIETARY FATS

(Patient numbers refer to list in table I All food intake by method of oral formula feeding In all cases, just enough calories were fed to maintain constant body weight Protein calories were uniformly 15% of the total, fat and carbohydrate calories varying reciprocally as designated in third column Means, ±1 standard deviation, are shown in all cases)

Patient no	Dietary fat	% of calories	n	Steady state data (mg per 100 ml serum)			
				Total cholesterol	Free cholesterol	Phospholipids	Triglycerides
1	Corn	40	6	175 ±10 2	47 ± 3 2	215 ± 8 0	306 ±45
	Corn	40	3	185 ± 2 0	53 ± 2 0	214 ± 3 0	267 ±25
2 †	Butter	40	5	719 ±29 0	285 ±11 8	655 ±25 2	2968 ±131
	Corn	40	7	471 ±21 2	197 ± 9 6	495 ±21 7	2403 ±206
3	Corn	40	5	387 ±16 2	136 ± 8 4	383 ±24 3	722 ±80
	Safflower seed	40	3	377 ±29	131 ± 9 0	355 ±29	707 ±107
5 †	Olive	40	4	530 ± 6 7		400 ±13 5	427 ±36
	Corn	40	23	425 ±19 8		358 ±18 9	341 ±26
6	Corn	40	6	325 ±15 7	82 ± 6 6	260 ±11 5	166 ±16 3
	Palm	40	4	406 ± 6 9		316 ± 2 1	192 ±19 4
	Lard	40	5	417 ± 8 9		341 ± 7 4	185 ±24 5
	Palm	40	3	396 ± 3 8		330 ± 8 0	207 ±14 5
9	Corn	40	7	263 ± 9 8	69 ± 2 0	249 ±10 2	143 ±30 2
	Coconut	40	5	367 ±12 6	98 ± 4 0	340 ± 7 1	142 ±18 7
	Corn	40	3	286 ± 4 1	72 ± 0 7	278 ±12 0	151 ±35
11	Corn	40	4	192 ±10 2	18 ± 4 0	200 ± 8 9	258 ±19 9
	* { Corn +cholesterol	40	6	198 ±13 3	45 ± 3 9	200 ±14 1	268 ±26
	Lard +cholesterol	40	4	261 ±11 4	73 ± 5 0	251 ± 9 2	307 ±18 2
	Lard +egg yolk	40	4	278 ±13 7	76 ± 8 0	257 ±11 7	287 ±32
	Lard	40	4	248 ± 4 6	70 ± 2 4	240 ±15 6	272 ±22 0
12	Corn	40	4	274 ± 9 1	69 ± 3 6	219 ± 7 0	102 ± 9 0
	Olive	40	3	327 ± 5 0	86 ± 4 1	267 ± 6 5	104 ±21 8
	Corn	40	4	285 ± 4 7	77 ± 2 2	230 ± 4 2	126 ± 8 6
13 †	Corn	40	7	321 ±11 5	70 ± 4 4	260 ±16 8	238 ±28
	Corn	70	7	314 ± 8 7	76 ± 7 0	259 ± 7 4	187 ±17 7
	Corn	40	3	309 ±13 3	72 ± 4 1	263 ±13 7	178 ±14 7
	Corn	10	7	298 ±12 3	76 ± 5 2	272 ± 9 0	228 ±28
	Corn	70	7	303 ±15 4	73 ± 3 4	258 ±10 0	189 ±10 2
	Corn	40	4	298 ± 5 5	73 ± 1 9	260 ±10 0	220 ±35
	Corn	40	8	307 ±10 2	74 ± 2 9	263 ± 7 7	216 ±27
	Corn	40	26	308 ± 6 9	75 ± 5 4	254 ± 8 1	232 ±28
	Safflower seed	40	7	319 ± 7 6		261 ±10 7	251 ±39
	Corn	40	7	307 ± 8 8		259 ± 7 1	222 ±19 7
	Cottonseed	40	7	314 ±10 2		261 ± 8 0	266 ±65
14	Corn	40	4	189 ± 5 3	46 ± 2 1	180 ± 2 1	199 ±15 8
	Corn (rearranged)	40	4	197 ±10 0	49 ± 4 0	185 ± 3 3	210 ±12 4
	Corn (rearranged—low n s)	40	4	220 ± 7 2	67 ± 2 6	207 ± 5 2	224 ±19 7
	Corn (rearranged)	40	5	219 ± 6 4	57 ± 3 0	210 ± 6 5	210 ±14 0
15	Chicken	40	4	366 ± 7 5		288 ± 4 7	233 ±22 0
	Olive	40	4	379 ± 4 4		320 ±10 7	279 ±34
	Corn	40	3	368 ± 3 0		304 ± 4 0	235 ±22 1
16	Corn	40	8	195 ± 6 6	48 ± 3 1	177 ± 5 6	105 ±38
	Corn +4 g cholesterol daily	40	3	226 ± 5 0	57 ± 2 0	199 ± 8 2	102 ±16 9
	Corn +8 g cholesterol daily	40	4	238 ± 6 3	62 ± 1 4	197 ± 6 3	100 ±15 8
17	Lard	40	3	214 ±16 7	56 ± 1 5	237 ±11 6	141 ± 3 5
	Corn	40	[illegible]	185 ± 5 7	15 ± 1 8	200 ± 1 5	119 ±14 3
18	Corn	40	4	185 ±12 9	50 ± 3 3	191 ± 8 5	139 ±18 5
	Cottonseed (I V 106)	40	4	177 ±11 2	45 ± 2 5	182 ±12 2	148 ±13 4
	Cottonseed (I V 68)	40	5	217 ± 7 6	57 ± 3 4	203 ± 7 2	147 ±13 1
19	Corn	40	4	180 ± 6 8	43 ± 1 0	195 ± 6 6	192 ±17 6
	Palm	40	3	201 ± 8 0	51 ± 1 0	205 ± 3 5	171 ±10 0
	Lard	40	3	189 ± 6 5	48 ± 2 1	195 ±13 3	220 ±33
20	Corn (I V 58)	40	4	298 ±10 0	105 ± 3 6	345 ± 9 5	853 ±57
	Corn (I V 80)	10	4	273 ± 1 4	97 ± 2 2	315 ± 9 1	781 ±31
	Corn (I V 126)	40	5	200 ± 9 6	59 ± 1 6	243 ±11 4	504 ±49

unsaturated oils. The salient points supporting this contention are:

(1) Feeding-tests with dietary fats rectified in various ways suggest that the major influence on serum-lipid levels is exerted by the glycerides, not the non-saponifiable fraction.

(2) The lowest serum-lipid levels were seen when corn oil, safflower-seed oil, or cottonseed oil constituted the sole dietary fats. Higher levels were found with all other fats tested. The differences in these levels are directly related to the degree of saturation of the glyceride fatty acids as measured by the iodine value of the fat.

(3) Use of hydrogenated corn and cottonseed oils as sole dietary fats resulted in higher serum lipid levels than when the corresponding unhydrogenated oils were fed.

The experiments of Kinsell and Michaels (1955), Bronte Stewart et al. (1956), and Beveridge et al. (1956) produced qualitative data which accord with this hypothesis. It is noteworthy that, despite major differences in experimental design, the investigations of four groups led to the same tentative conclusions. Thus, the same type of response in serum-cholesterol levels was obtained when unsaturated fats were substituted for saturated fats in the diets of young normocholesteræmic medical students, vitamin- and protein-deficient normocholesteræmic Bantus, and Americans with and without high serum-cholesterol levels and arteriosclerotic heart-disease. Three groups kept caloric intakes and proportions of foodstuffs in the diet unchanged in comparative feeding periods; the South African experiments yielded qualitatively similar results even though these controls were lacking.

In our investigations the number of patients studied was limited by the long duration of the feeding tests, but

TABLE III—SERUM-LIPID DATA DURING STEADY STATES ON INGESTION OF VARIOUS DIETARY FATS—*continued*

Patient no.	Dietary fat	% of calories	n	Steady state data (mg. per 100 ml. serum)			
				Total cholesterol	Free cholesterol	Phospholipids	Triglycerides
21	Corn (D.P.I. residue)	40	8	185±14·1	47±3·2	194±15·5	119±21·1
	Corn	40	5	180±8·2	46±5·8	193±7·7	130±16·0
	Corn (D.P.I. distillate)	40	4	175±14·8	44±4·2	185±12·2	139±7·6
22	Corn	40	8	191±7·7	49±2·4	203±5·2	224±14·6
	Lard (D.P.I. residue)	40	4	226±9·1	58±1·0	222±4·5	244±15·5
	Lard (D.P.I. distillate)	40	3	233±7·8	59±3·0	227±9·0	265±5·7
24	Egg yolk, butter (1:2)	40	6	286±16·1	78±6·3	262±11·9	202±33
	Corn	40	6	156±7·4	40±4·8	165±6·9	170±19·1
26†	Corn	40	6	178±7·3	45±4·8	202±14·7	368±34
	Cocoa butter	40	4	202±8·7	55±4·9	241±5·8	420±61
	Butter	40	5	242±7·9		247±9·1	363±15·5
	Corn	40	5	200±4·5		206±4·6	257±34
	Butter	40	5	262±11·2		256±9·7	308±26
27	Corn	40	6	222±8·9	62±3·7	222±10·6	300±42
	Lard (R.I.) (I.V. 89)	40	4	240±4·6	67±2·5	248±4·5	369±19·4
	Lard (R.I.) (I.V. 52)	40	4	251±9·9	75±5·1	264±7·6	411±76
	Corn	40	3	216±8·2	63±4·9	237±4·7	416±3·6
28	Coconut	40	4	213±13·7	52±2·8	209±5·9	177±21·9
	Corn	40	4	156±7·9	37±2·5	168±9·3	218±32
29	Beef tallow	40	8	189±8·6	46±2·7	219±3·5	215±49
	Corn	40	6	161±6·6	39±2·7	185±4·0	196±22·9
30	Corn (I.V. 126)	40	4	119±1·5	27±0·8	164±6·5	107±2·2
	Corn (I.V. 80)	40	4	125±11·5	29±2·0	172±5·0	118±27
31	Corn	40	3	155±0	39±3·1	175±2·4	212±24·2
	Corn	10	5	178±2·8	51±2·1	230±8·6	393±29
	Corn	70	5	146±5·9	38±2·1	155±8·5	154±9·2
32	Lard (R.I.) (I.V. 52)	40	4	209±9·9	58±3·9	230±14·2	279±56
	Lard (R.I.) (I.V. 89)	40	5	225±7·8	60±2·1	241±13·8	272±13·9
	Corn	40	5	194±6·0	50±2·4	213±12·1	285±21·2
	Corn	70	4	185±8·6	46±3·1	180±7·6	202±15·2
33	Lard (P & G)	40	4	199±6·0	198±5·5	208±28	
	Lard (P & G) (randomised)	40	3	197±3·1	206±7·6	210±34	
	Lard (P & G) (directed interesterified)	40	4	179±6·9	193±10·9	222±42	
	Corn	40	4	165±4·4	179±6·6	201±20	
34†	Corn	40	8	142±11·3	38±2·5	198±10·3	335±38
	Peanut	40	4	126±5·8	32±4·1	190±4·5	344±34
	Corn	40	5	144±3·6	38±1·5	211±10·9	395±52
	Butter	40	6	188±7·6	54±2·8	241±8·5	402±31
	Corn	40	19	157±8·3	42±2·5	196±16·2	319±39
	No fat (P 15%, C 85%)	0	5	177±11·0	61±3·9	277±17·8	760±82
	Corn	10	7	159±4·2	49±2·2	249±9·1	584±48
	Corn	10	5	153±6·1	49±2·3	237±9·4	561±66
	Corn	70	11	186±10·8	49±3·9	189±7·7	204±28
35	Beef tallow	40	9	157±7·8	43±3·2	207±23·3	199±36
	Corn	40	8	131±10·6		168±14·4	153±23
36	Peanut	40	6	156±5·4	34±1·4	161±3·5	174±5·8
	Olive	40	5	166±7·0	35±3·1	174±6·9	167±11·9
	Corn	40	3	152±5·8	33±2·6	167±7·5	177±31
37†	Butter	40	4	219±2·5		241±8·4	191±5·0
	Cocoa butter	40	4	200±7·8		243±8·6	194±6·6
	Butter	40	7	259±9·8		287±17·8	259±21
	Cocoa butter	40	5	211±2·5		244±3·6	225±5·7
38	Corn	40	4	105±4·9	23±3·0	138±7·6	129±14·7
	Coconut	40	[illegible]	156±10·1	42±2·9	200±11·8	132±39
	Safflowerseed	40	4	111±8·6	22±3·4	144±7·3	129±46
40	Corn	20	4	91±9·3			
	Corn	40	7	79±5·9	20±2·1	119±4·9	137±23·7

* Daily cholesterol intake = 600 mg. † = Experiment still in progress. n = number of weekly data during steady state. N.S. = non-saponifiable content. D.P.I. = molecularly distilled oil [illegible] cut.

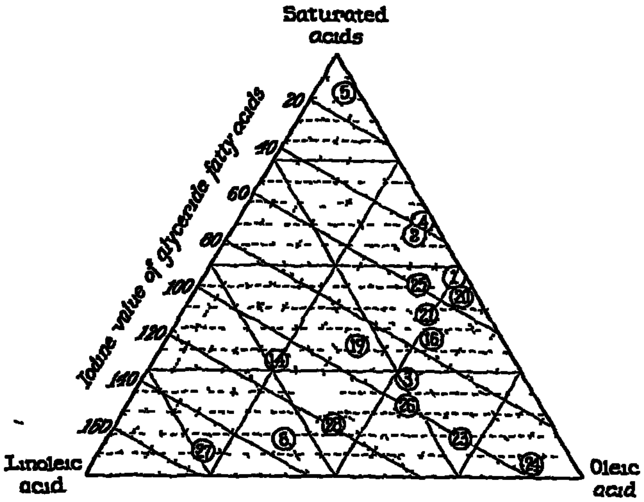

Fig 11—Triangular plot of fatty acid compositions of fats used in present studies

Corners represent 100% of linoleic, oleic, and total saturated acids, respectively, while sides represent 0% of the component in the opposite corner *Fatty acid mixtures having the same* iodine value are joined in a series of parallel lines, iodine values of the glycerides composed of these acids are about 5% *lower than those shown* Numbers in circles refer to fats listed in table II

our design allowed a quantitative comparison of the effects of various dietary fats Minimum feeding-periods of 5 weeks for each diet made possible the accumulation of serum-lipid data after steady states were reached, and minimum study-periods of 4 months provided data from several steady states in each patient During these periods all the major lipid classes in serum were measured at weekly intervals, affording for the first time a total analysis of the serum lipid picture The base line data obtained during the feeding of the corn-oil formula served as a common denominator when it was desired to compare quantitatively the varying responses of *patients to other dietary fats* The *use of this common* denominator was validated by the finding that patients' lipid levels returned to the same point whenever they ingested this oil It is probable that any dietary fat may serve the same purpose, for in a limited number of refeeding trials *other fats* and *oils* also have evoked serum-lipid responses which were reproducibly characteristic of the fat fed

This quantitative technique has provided evidence which strongly suggests that the effect of dietary fats on serum-cholesterol and phospholipid levels is a function of their iodine value *It cannot be stated at present if* this effect is more dependent on mean unsaturation of the fed fat than on its content of a specific unsaturated acid, such as linoleic, this issue remains to be clarified *in future experiments* Whether linseed oil (rich in triethenoid C_{18} acids) or fish oils (rich in tetraene, pentaene and hexaene acids of C_{20} to C_{22} chain length) will produce effects as great as, or greater than, the oils so far tested has not been investigated under our experimental conditions *For* the present it is profitable to analyse the response obtained in terms of the three major constituents of the fats used, namely, the total saturated fatty acids, the monoethenoid acid, and the diethenoid acids All the fats discussed in this report were composed of only these three components, if for the moment the nonsaponifiable material in these fats is disregarded There fore, it is possible to compare their composition graphically in a triangular diagram Fig *11 presents the data of* table II in this form This manner of representation has proved exceedingly useful to us in planning critical experiments Thus, to define the effect of iodine number while holding linoleic-acid content fixed, the investigator selects fats which lie on the same linoleic acid line (e g, olive oil and palm oil), but which vary maximally in iodine number (92 and 57, respectively) because of reciprocal variations in saturated and oleic acids Experiments designed to weigh the relative effects of the three postulated variables will be reported later

It has been of interest to us that all reported analyses of natural fats made up only of these three groups of acids spread across the triangle in an arc from linoleic toward oleic and then upward to the saturated corner Thus, a large portion of the triangle is unoccupied, representing an absence in Nature of fats rich in linoleic and saturated acids but poor in oleic acid The oleo margarines produced in the 1930s before the development of partial-hydrogenation procedures were blended mixtures of unhydrogenated with completely hydrogenated oils Such blended fats would lie in the portion of the triangle not occupied by any of the natural fats Materials of this type, which may become of interest once again as margarines and *shortenings, are currently being evaluated* in our programme

Over each locus on the triangular plot a vertical bar can be erected, the height of which is proportional to the degree of response of a serum-lipid to ingestion of that *particular fat* In *fig 12, serum cholesterol responses* are related to the compositions of the various fats and oils shown in fig 11 The shortest bars depict the lowest cholesterol levels, the longest bars the highest levels Each bar denotes a single feeding-test The average heights of the bars at each locus suggest a second surface with a contour which sweeps from the lower left corner upward *to the right* and then *still higher to the* upper corner It will be of interest to define the shape of this contour more exactly

Our present line of *investigation* has aimed at defining the specific dietary factors which cause the rises and falls in serum-lipid levels demonstrated above An understanding of the mechanisms involved in these changes clearly demands a thorough preliminary exploration of *food factors* *If it is finally established that the* phenomena under study are in fact due to the nature of the fed

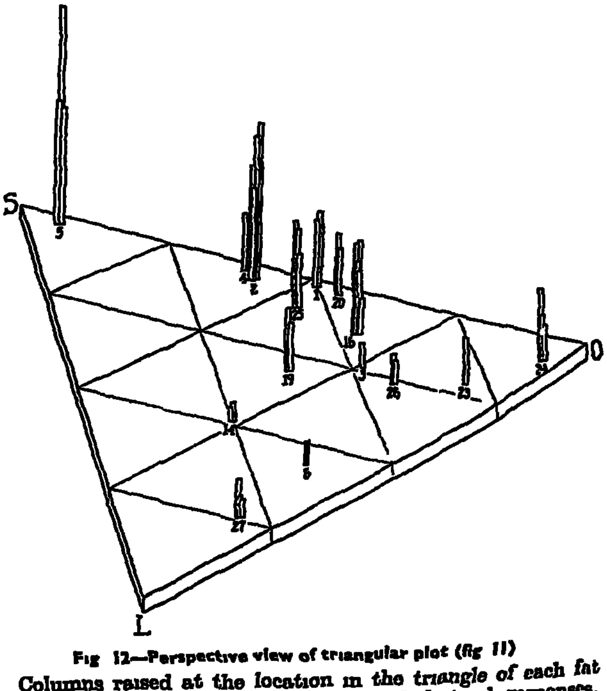

Fig 12—Perspective view of triangular plot (fig 11)

Columns raised at the location in the *triangle of each fat* are proportional in height to serum cholesterol responses, expressed as percentage differences from corn oil base lines Each column represents an individual *feeding experiment* A second contour surface is suggested fatty acids and not to trace components in the oils so far tested, it may be profitable at this point to enumerate some of the questions which will require answers If unsaturated acids cause lower lipid levels, is this due simply to the number of double bonds per unit weight of *methylene groups, as our data suggest at present*, or is the effect caused by certain unsaturated fatty acids and not by others ? Do the monoenes have half the potency of the dienes ? Are trienes more effective than dienes ? Are conjugated double bonds as effective as non conjugated ? Do saturated acids, per se, cause higher serum lipid levels, and if so, do all chain lengths have the same effect ? What is the effect of ingestion of the fatty acid isomers produced by hydrogenation processes ?

Assuming that the net effect of ingestion of a mixture of various fatty acids can be defined at one caloric level, what changes will be produced when the proportions of fat, carbohydrate, and protein are varied ? It was stressed that this manipulation of dietary intakes had its major effect on the serum triglycerides, other serum-lipids varying in parallel but to a smaller degree There have been many proponents of the low-fat diet, but few have measured the triglyceride response to this metabolic mixture Hatch et al (1955) studied the serum-lipid spectrum in forty-four patients subjected to a strict rice diet They noted that in one-fifth of these patients visible lipæmia developed with a marked rise in triglycerides, in addition, ultracentrifugal patterns of the lipoproteins showed rising concentrations of S_f20–100 species in all eleven patients so tested Comparable trends were observed in our four patients who were given varying ratios of carbohydrate and fat calories In the one patient so tested there was a dramatic rise in alpha$_2$-lipoproteins and in $S_f > 20$ species on low-fat regimens, and a reversion to normal on the 70% fat intake We recognise that high levels of cholesterol and phospholipids on ad libitum diets may be reduced on a low-fat regimen, at least temporarily, but in our experience a high intake of unsaturated fat leads to even more striking decreases in these serum components and in addition avoids increases in triglycerides

Our readiness to accept the unsaturation hypothesis as firmly proven has been tempered by the realisation that none of the experiments performed here or elsewhere has ruled out the possibility that the factors sought may lie in the non-glyceride portion of the fed fats In fact, in a recent abstract Beveridge et al (1957a) concluded that the "plasma cholesterol depressant effect of corn oil depends to a large extent upon its sterol content" Our tests with molecularly distilled corn oils and with reconstituted corn oil glycerides containing small amounts of non saponifiable material suggest that, if a trace factor is involved, it must be active in extremely low concentration By chemical processes on a pilot plant scale it was possible to reduce sixfold the content of non saponifiable material in corn oil The same order of magnitude of change in intake of non-saponifiable material was also achieved by reducing the intake of whole corn oil from 70% to 10% of calories In the latter experiment (fig 10) the depressing effect of corn oil on serum-lipid was lost, yet after a sixfold decrease in non saponifiable material by chemical treatment, the depressing effect was not lost (fig 6) Clearly, the resolution of this issue awaits completion of feeding tests with glycerides synthesised from pure fatty acids The great cost of producing sufficient amounts of pure acids has delayed the accomplishment of these critical experiments

It is often asked whether patients are clinically improved when their serum lipids are held continuously at a lower level by the regimens discussed in this report On the whole, our patients have shown considerable subjective improvement while under our care But we believe that this is primarily due to daily medical attention, to prolonged restriction of physical activity under pleasant hospital circumstances, and to our continual efforts to educate them about their disease Patients who have gained the most reassurance have unquestionably benefited the most Because so many non-specific factors have profoundly affected our patients' clinical status, it is impossible at this time to attribute to our dietary management any specific therapeutic merit In fact, we consider hazardous any short-term evaluation of a therapeutic regimen in patients with coronary-artery disease Until it becomes possible to assess the progress of the atheromatous process during life, it will be exceedingly difficult to determine whether a therapeutic measure is effective It has been gratifying to observe the disappearance of skin xanthomata in patients with hyperlipæmia or hypercholesteræmia, but we have seen no changes in tendon xanthomata despite marked decreases in serum-cholesterol levels for as long as 2 years It is an open question whether atheromata respond to this regimen as do skin xanthomata, or fail to be appreciably influenced like tendon xanthomata

It is our present conclusion that recommendations for radical changes in food habits, even by those populations most seriously threatened by atherosclerosis, should await a clearer definition of the specific food factors which control serum-lipid levels It is entirely possible that an understanding of the mechanisms evoked by these factors will lead to practical measures for control of serum-lipid concentrations Only then can large-scale epidemiological experiments be planned to determine whether the incidence of atherosclerosis and its complications in the human species will be affected by decreasing the levels of lipids in the serum

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NEONATAL DEATH AND ELECTIVE CÆSAREAN SECTION

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THE death of a newborn infant after cæsarean section is particularly disturbing because the operation is usually performed to save the infant's life. The decision to use this method of delivery has been made more difficult in recent years by the recurring suggestion that cæsarean section itself carries special and serious hazards for the infant.

Potter (1943) and Potter and Rosenbaum (1943) described a fatal syndrome preceded by mounting respiratory distress which was regarded as due to cæsarean section. This has been called the "cæsarean section syndrome" and has been regarded as a direct effect of the operation (Bloxsom 1942, Williams 1950, Simpson and Geppert 1951, Smith 1953).

Our attention was first drawn to this question in 1951, when, by agreement with our obstetric colleagues, pædiatric care in this hospital was extended to include resuscitation of the newborn. This required attendance of a pædiatrician at every abnormal delivery, including cæsarean section. We were anxious to establish whether the operation carried a special risk for the baby, and, if it did, to discover whether any modifications in our method of resuscitation were necessary.

At first sight the published figures for neonatal deaths after cæsarean section supported the view that it carried a high risk for the baby.

Marshall and Cox (1949) reported a neonatal death rate of 5·2% in a study combining the results of many centres. It was clear, however, that their material included many serious obstetric emergencies which exposed the baby to risks quite apart from those of cæsarean section.

Similarly, reports describing the "cæsarean section syndrome" included examples in which placenta prævia and rupture of the uterus were indications for the section (Potter and Rosenbaum 1943, Williams 1950).

Scope of Inquiry

As we considered these reports, it seemed clear that an assessment of the effect of cæsarean section on the baby could be made only in cases free from complications which were injurious in themselves. The maternal and neonatal case records of all cæsarean sections performed in this hospital in 1946–50 were therefore examined, but consideration was confined to those in which the reason for the cæsarean section was disproportion or uncomplicated pre-eclampsia before the onset of labour.

In this study (Strang 1953) all the deaths except one could be adequately explained on the grounds of malformation, prematurity, or hæmolytic disease. The exception, that of a mature baby, was due to a sudden massive pulmonary hæmorrhage on the fourth post-operative day. As this was the only unexplained death, we concluded that we had no convincing evidence that cæsarean section harmed the mature baby.

The numbers of premature babies available for study were too small to measure the effects in their case. We were encouraged to continue our observations, however, by the report of Hamilton et al. (1949), which suggested that cæsarean section is more favourable than surgical induction and vaginal delivery for the small premature babies of toxæmic mothers.

In the following five years (1951–55) we continued our study of babies delivered by cæsarean section. During this time several reports have appeared which include data supporting the view that elective cæsarean section does not carry a special risk for the baby.

Landsman (1951), after allowing for congenital malformations, had a neonatal mortality of 0·4% in 534 cæsarean sections for disproportion, and he concluded that the high overall mortality of cæsarean section was related to the indication rather than to the operation, and that cæsarean section for disproportion is no greater risk to the infant than spontaneous vertex delivery.

Williams and Hollenbeck (1952) reported, in 148 repeat cæsarean sections, 5 neonatal deaths, of which 2 were due to hæmolytic disease of the newborn and 1 to congenital malformation.

Carey (1955) had only 2 deaths in 679 "elective" cæsarean sections which could not be explained on grounds of blood disorder, congenital malformation, or prematurity.

In 321 "elective" cæsarean sections Posner et al. (1954) reported only 2 deaths, 1 from congenital heart disease and 1 from pneumonia.

A division of opinion on this question persists. Thus Montgomery et al. (1956), introducing important work on the blood oxygen saturation after vaginal and cæsarean delivery, said: "It is a generally accepted observation in obstetric and pædiatric circles that babies born by Caesarean Section do not do as well as those born by vaginal delivery." Because of this divided opinion we have decided to review our experience and to present our findings for the whole ten years *1946–55*. We have done this from our initial premisses: (1) that an assessment of the effects of cæsarean section on the baby is possible only in absence of *other obvious risks*; and (2) that mature and premature babies require separate consideration. During the second five years we made personal observations on the immediate newborn period, noting particularly the time taken to establish regular respiration.

Methods

The maternal and neonatal records for all cæsarean sections in the Princess Mary Maternity Hospital for 1946–55 were examined. *Stillbirths were excluded* because the issue concerned the influence of cæsarean section on the baby after delivery. The remaining records were divided into "elective" and "not elective".

Elective.—Cases in which a decision was made during the antenatal period to perform a cæsarean section and in which it was carried out before or within a few hours of *the onset* of labour. These included cases of disproportion from any cause and some cases of pre-eclampsia terminated by cæsarean section.

Not elective.—All other cæsarean sections, including emergencies of all kinds and cæsarean section terminating trial of labour. Included also were cases of hæmolytic disease of the newborn and maternal complications such as diabetes mellitus, heart disease, ante-partum hæmorrhage, and eclampsia.

Pre-eclampsia was included in the elective group on the basis of Drillien's (1947) *finding that*, in comparable weight groups, the infants of toxæmic mothers have survival-rates as good as those of infants of mothers without toxæmia. *In 27 of 36 premature cæsarean sections* the indication was the termination of severe pre-eclampsia. In some mature cases a mild pre-eclampsia coexisted but was not itself the indication for cæsarean section.

The fate of the babies in these two groups was determined by examining their neonatal records, and a note was made of any respiratory illness in the survivors and of any resuscitation required. In the deaths, the necropsy records, and where possible the histological sections, were examined.

Results

Mortality

Table I sets out the mortality after elective cæsarean section as defined above The corrected mortality after removal of deaths due to congenital malformation is also shown Of 251 mature babies 5 died The details of these are

TABLE I—NEONATAL MORTALITY IN ELECTIVE CÆSAREAN SECTION

—	Total	Deaths	"Corrected" deaths
Mature	251	5 (2 0%)	2 (0 8%)
Premature	36	9 (25%)	7 (19%)

Case 1 —Birth weight 6 lb 2 oz Infant became cyanosed at twenty four hours and died at forty-two hours Necropsy revealed dilated bladder with congenital atresia of urethra Lungs showed pulmonary hyaline membranes [1946 B 2162]

Case 2 —Birth-weight 5 lb 11 oz. Intestinal obstruction, operation at seventy-eight hours Obstruction due to extensive adhesions could not be relieved. [1947 B 1283]

Case 3 —Birth-weight 6 lb 2 oz This infant was observed with particular care and was quite normal until eighty-five hours. She then suddenly became cyanosed, with lung crepitations and a gush of blood from the mouth, and died at sixty-three hours. Necropsy revealed massive pulmonary hæmorrhage and pulmonary hyaline membranes [1948 B 1482]

Case 4 —Birth-weight 6 lb 8 oz. Died at forty minutes Necropsy revealed congenital laryngeal stenosis admitting only a fine probe [1947 B 1712]

Case 5 —Birth-weight 5 lb 15 oz Apparently normal until fifty five hours, when baby became suddenly ill, with gush of blood from mouth, and died at sixty-three hours Necropsy revealed massive pulmonary hæmorrhage, no hyaline membranes [1953. B 450]

The 3 deaths due to congenital malformations cannot be put down to cæsarean section The 2 deaths in mature babies with massive pulmonary hæmorrhage are a strange and unexplained finding but we have no good reason for attributing them to cæsarean section They are quite different from the "cæsarean-section syndrome" which has been described. Nevertheless we cannot deny that cæsarean section might have played a part in these deaths If massive pulmonary hæmorrhage is to be regarded as a possible complication of elective cæsarean section it has an incidence of 0 8% in this material

Premature Babies

The results for premature babies (table I) are more difficult to assess The numbers are too small to permit a statistical comparison with normal vaginal deliveries in comparable weight-groups It can be shown however, that the mortality after "elective" cæsarean section is of the same order as for the whole group of premature babies The results for all premature deliveries in this hospital for 1946–55 are given by weight-groups in table II, and in table III the results for cæsarean sections are compared with "expected" figures for these numbers on the basis of the figures in table II The total mortalities compared in this way appear to be similar

Necropsy was performed in 8 out of 9 premature deaths and the causes of death were severe congenital malformations, 2, massive pulmonary hæmorrhage 2, pulmonary hyaline membranes 3, and cerebral œdema only 1 In these deaths there was no unusual preponderance of pulmonary hyaline membranes, which Smith (1953) has regarded as the basis of the "cæsarean-section syndrome."

TABLE II—MORTALITY OF PREMATURE BABIES AFTER ALL FORMS OF DELIVERY (1946–55)

Birth weight	Total	Deaths
<2 lb 9 oz	98	91 (93%)
2 lb 9 oz.–3 lb 8 oz.	224	104 (46%)
3 lb 9 oz.–4 lb 8 oz	485	68 (14%)
4 lb 9 oz.–5 lb 8 oz.	1236	79 (6%)
Total	2043	342 (17%)

Morbidity in Surviving Babies Delivered by Cæsarean Section

During the ten-year period records were kept of every type of illness in all babies, and for 1951–55 records were also available of the time taken to establish regular respiration 1 mature and 2 premature babies developed an episode of respiratory distress requiring oxygen and lasting twelve to twenty-four hours All recovered completely 1 mature baby developed a mild irritability requiring sedation but also recovered satisfactorily There was no other illness in survivors In 113 babies the time taken to establish regular respiration (one to thirteen minutes mean, five minutes) was longer than after vaginal delivery This delay was probably due to the maternal anæsthetic and no harm was noted

Resuscitation of Newborn after Cæsarean Section

Some workers who have accepted the idea of a "cæsarean-section syndrome" have advanced explanations and advocated preventive measures based on these theories Potter and Rosenbaum (1943) associated the syndrome with the necropsy finding of excess cerebrospinal fluid in the subarachnoid space, and Bloxsom (1942 1953) recommended that labour should be allowed to start and progress for a few hours before any cæsarean section, in order to subject the fœtal head to compression Landau et al (1950) have suggested that the cæsarean baby is deprived of a normal transfusion from the placenta during labour and that the "cæsarean section syndrome" is due to partial exsanguination and consequent shock These workers recommend that after delivery the placenta, still attached to the baby, should be suspended until all its blood has drained into the baby's circulation Smith (1953) equates the "cæsarean-section syndrome" with pulmonary hyaline membranes and regards the increased liability to this as due to the inhalation of liquor, which has been shown to be present in excess in the stomachs of cæsarean babies (Gellis et al. 1949)

TABLE III—MORTALITY OF PREMATURE BABIES AFTER ELECTIVE CÆSAREAN SECTION COMPARED WITH "EXPECTED" MORTALITY

Birth weight	Total	Deaths	"Expected" deaths
<2 lb 9 oz	2	2	2
2 lb 9 oz –3 lb 8 oz	7	4	3
3 lb 9 oz.–4 lb 8 oz	12	1	2
4 lb 9 oz –5 lb 8 oz.	15	2	1
Total	36	9	8

Though we cannot accept the idea of a "cæsarean-section syndrome" we believe that the cæsarean baby requires special care after delivery The baby is usually anæsthetised and may be unable to cough clear any obstructing mucus, and large volumes of liquor may drain from its stomach Recent studies suggest that the full oxygenation of the blood may be delayed (Montgomery et al 1956) and that the blood-pressure may be lower initially than after vaginal delivery (Holland and Young 1956)

Our practice is as follows The obstetrician allows the cord to empty before it is divided The baby is then handed to the pediatrician, who normally performs a rapid laryngoscopy and removes by suction any obstructing mucus and then places the baby head-down in oxygen, the liquor being allowed to drain from the mouth If the onset of respiration is delayed beyond five minutes, the stomach is emptied by suction, and intragastric oxygen is given

In 1951–55 records of resuscitation were available for 91 mature and 22 premature babies delivered by elective cæsarean section Thick mucus requiring aspiration was found in 7 mature and 1 premature infants Intragastric oxygen was given to 1 mature and 2 premature infants As stated above, there was 1 unexplained death in mature babies in the five years before our resuscitation routine was started, and 1 similar death since it has been practised It is evident that we cannot expect to see any obvious benefits from these measures in terms of reduced mortality, but it is also clear that it would be unwise to omit them

Discussion

Because cæsarean section is so often the method of delivery when a serious obstetric complication is present, more babies die after it than after normal delivery The allegation that the operation introduces a further substantial hazard has not in our view been proved We believe that a misconception has arisen because attention has been focused on the whole group of cæsarean section, whereas a true assessment of the effects of the operation is possible only in cases free from all other risks

Our results for mature babies leave little doubt that the risk for them in elective cæsarean delivery is small In our material unexplained pulmonary hæmorrhage had an incidence of 0 8%, and we think it unlikely that the risk is higher than this Similar unexpected death after perfectly normal vaginal delivery is by no means unknown in our experience Because of our small numbers a definite statement on the delivery of premature babies by elective cæsarean section cannot be made, and it is arguable that larger numbers might demonstrate a definite hazard However, the evidence of Hamilton et al (1949) is against this

The amount of respiratory illness observed in survivors was *trifling*—only 1 mature and 2 premature babies were involved Although the onset of regular respiration was delayed, there is no evidence that this was harmful or due to anything other than the effects of the maternal anæsthetic We believe, however, that the anæsthetised state of the baby is a sufficient reason for practising a simple routine of resuscitation designed to maintain a clear airway

Although, in assessing the effect of the operation on the baby, we have regarded it as essential to consider only cæsarean sections free from complications, in these cases there is usually no alternative method of delivery The choice of method usually has to be decided in situations complicated by adverse factors If we accept that cæsarean *section* carries very little risk in the simple cases which we have termed "elective," we might reasonably argue that it does not add to the hazards of the complex cases in which a decision is really important The choice often involves the delivery of a premature baby, and we therefore hope that it will be possible in future to build up a larger experience of the behaviour of premature babies after elective cæsarean section

Summary

A "cæsarean section syndrome" has previously been described in which the death of the infant with respiratory distress has been attributed to the operation

The maternal and neonatal records were examined of 287 cases (251 mature infants and 36 premature) in which there was no complication of pregnancy or labour other than disproportion or pre eclampsia

In the 251 mature infants there were 5 neonatal deaths —3 from congenital malformations and 2 from massive pulmonary hæmorrhage

The results for 36 premature infants were of the same order as for the whole group of premature babies in this hospital, and an unduly high incidence of hyaline membranes was not detected

Only 3 of the surviving infants had an episode of respiratory distress

It is suggested that, though the infant who has been delivered by cæsarean section will benefit from close attention in the immediate neonatal period, cæsarean section does not carry an appreciable extra risk for the baby

We wish to thank Prof Donald Court, Prof H Harvey Evers, and Dr G A Neligan for their helpful criticism

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OUTPATIENT BRONCHODILATOR THERAPY

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THE importance of the chronic or recurrent wheezing which occurs in association with several pulmonary disorders lies in the fact that it is potentially reversible Whereas wheezing can almost always be controlled when the patient is in hospital, its treatment in ambulant patients is considerably less satisfactory and considerably more difficult to assess We have tried to assess the effects of five drugs, four of which are *known* to have a bronchodilator effect under controlled conditions, when each was given for a week in commonly used dosages under conditions approximating to those of ordinary outpatient practice In a pilot trial no objective benefit was demonstrable with oral ephedrine (Hume and Gandevia 1957a)

Plan of Investigation

The four bronchodilator drugs tested, with their dosages, were as follows

(1) 'Theodrox' *one* tablet three times daily, each tablet containing aminophylline gr 3 and dried aluminium hydroxide gr 4

(2) Aminophylline suppositories *one* three times daily, each containing aminophylline gr 4

(3) Choline theophyllinate one tablet (200 mg) three times a day

(4) Isoprenaline one tablet (10 mg) three times a day *sublingually*, increasing to two tablets three times a day or until side effects became unpleasant

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Aminophylline, choline theophyllinate, and isoprenaline have all been shown, by us and other investigators, to have an unequivocal bronchodilator action in short-term experiments. The theophylline content of aminophylline is 75–82% and of choline theophyllinate 64·4%.

For purposes of comparison phenobarbitone gr. $^1/_2$ twice daily, increasing to three times a day after five days, and a placebo composed of calcium carbonate and a trace of quinine sulphate one tablet three times a day were also included in the trial. In several patients we were unable to demonstrate a bronchodilator effect of phenobarbitone after a single dose of gr. 1. The dosages of all the drugs were the largest we were prepared to use in an experiment on volunteers, in whom it was desirable to keep side effects to a minimum.

The design of the experiment took the form of latin squares, whereby all the drugs were in use throughout the trial, each patient taking a different drug each week. There were six groups of 3 patients, each group being allotted a different drug weekly according to a predetermined plan. A design of this type ensures that the overall comparisons between drugs are not affected by temporal differences in, for example, climatic conditions or by the order in which the drugs are taken. The default of several patients made formal statistical analysis of this design impracticable but did not detract greatly from its basic advantages. The data were finally analysed as a simple randomised block design.

18 patients were selected from among 40 volunteer patients attending the physiotherapy department of the Brompton Hospital. The remaining 22 patients were excluded because they did not show at least a 10% improvement in either vital capacity or in the volume of air expired in the first second of a forced expiration following the inhalation of a 1% isoprenaline aerosol. The plan of the experiment and the necessity for full coöperation over the whole six weeks were explained to all the patients individually. We have every reason to believe that they adhered faithfully to instructions, probably more so than any unselected series of out-patients.

At the time of the investigation, in the summer of 1956, all the selected patients had wheezing as a prominent symptom and rhonchi as a physical sign. All complained of cough with some sputum, which had been yellow at some time in all but 1 patient. The diagnoses recorded in the case-notes, made on clinical and radiological grounds, were as follows: asthma (2), chronic bronchitis (2), asthma and bronchitis or asthmatic bronchitis (6), bronchitis and emphysema (8). 6 of the patients were women. The ages ranged from 25 to 69, and 15 patients were aged more than 40. Their clinical status is reflected in the proportion of the *forced vital capacity* (F.V.C.) which is expelled in the first second; this is called the *forced expiratory volume at one second* (F.E.V.$_{1.0}$). The word forced indicates that the vital capacity breath is expelled as rapidly as possible. Normally the F.E.V. is 75–85% of the F.V.C.; in our series of patients this proportion averaged 51% (37–68%).

All but 3 of the patients completed the trial. These 3 may be regarded as not having entered it, for they had to be withdrawn within the first few days for reasons unrelated to the experiment. Of the remaining 15 patients 2 stayed away on one occasion each.

1 woman was confined to bed by a severe exacerbation of her asthma (the only patient to suffer this in the six weeks of the trial) while taking isoprenaline tablets (this compound was subsequently found to have given no definite benefit in the remaining patients), and 1 man, taking choline theophyllinate missed the final assessment because of a miscalculation of his holiday dates. Both these patients' opinions (see below) of the two drugs they were taking at these times are available.

With the coöperation of the physicians and general practitioners concerned all other regular bronchodilator therapy was discontinued, the proviso being made that an exacerbation was to be treated as the general practitioner thought fit. The patients were allowed to continue with any sprays or tablets which they were taking only intermittently "when necessary," but each week they were asked to take into consideration the amounts which they had required when making their assessments of the value of the current trial drug.

The male and female patients were separately allocated at random into the required six groups, one for each drug. At each weekly visit each group obtained a supply of the drug to be taken for the following week. Until after the results had been collated and a preliminary analysis completed, the drugs were known to us only by their allotted code names.

Progress was assessed weekly in two complementary ways:

(1) The patient's opinion of each drug, based on his own assessment of his clinical condition over the appropriate week, was obtained by means of a questionnaire filled in at each visit. Several preliminary questions relating to the dosage of the trial drug taken, the time of the last dose, side effects, and the amount of other intermittent medication taken ensured that the patient gave careful thought to his condition before expressing his opinions. He was then required to select the most appropriate of four statements, corresponding to "worse,"[‡] "the same," "slightly better," and "much better," relative to his usual state, for which a point score of – 1, 0, 1, and 2 was made accordingly.

(2) The second method of assessment was objective—the measurement of the volume of air expired in the first second of a forced maximal expiration after a full inspiration (F.E.V.$_{1.0}$). This test is quicker and less distressing than the maximal breathing capacity test. The two are comparable in their sensitivity to the influence of a bronchodilator drug, both being more sensitive than the forced vital capacity (Hume and Gandevia 1957a). It is also more sensitive than the two-second volume (unpublished data confirmed for the present series of patients by analysis of the effects of inhaled isoprenaline), and it is generally regarded as a more repeatable measure than the forced vital capacity. The F.E.V.$_{1.0}$ was measured on a spirogram obtained from a spirometer of the type described by Bernstein et al. (1952), a peripheral drum speed of 16 mm. per second being used. The highest value derived from three satisfactory tracings was used; no correction for either temperature or pressure was applied. The tests were made with the patient seated and were supervised throughout by the same observer. The patients attended at the same time on the same afternoon of each week, the tests being made at the same time (between one and three hours) after the last dose of the drug under trial. A learning effect in the performance of the tests was not apparent, but the results of tests made in the preliminary examination and on the day of issue of the first series of drugs provided useful practice.

Each week half of the patients, always including the patients currently receiving the placebo, inhaled a mist of 1% isoprenaline administered with a Bright inhaler for one and a half minutes, after which the F.E.V.$_{1.0}$ was again measured. The chief purpose of this procedure was to provide a familiar standard—i.e., response to a commonly used aerosol—for comparison with the results obtained for the several trial compounds.

Results

We believe that the patients carried out the prescribed régime for each drug very well. No serious side-effects were observed. Only 1 patient (taking isoprenaline tablets) had a disabling exacerbation of asthma during the trial. The data for the objective assessment (F.E.V.$_{1.0}$), which it is convenient to consider first, were

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[‡] The statement "This treatment has not suited me at all" was used in preference to "This treatment has made me worse" to avoid the implication that bronchoconstricting agents had been deliberately included. Patients who were worse knew that this was the appropriate statement to mark as their opinion.

TABLE I—F E V$_{1 0}$ AT END OF TREATMENT WITH PLACEBO AND EACH DRUG AND PERCENTAGE CHANGE

Drug	Mean F E V$_{1 0}$ of 13 patients (c cm)	Mean percentage change on individual placebo values (standard deviation)
Placebo	1170	
Aminophylline suppositories	1350	+20 4 (35 8)
Choline theophyllinate	1310	+15 0 (15 7)
Theodrox	1220	+ 7 1 (8 8)
Sublingual isoprenaline	1210	+ 7 5 (26 7)
Phenobarbitone	1200	+ 4 5 (14 9)
Placebo plus isoprenaline aerosol	1180	+27 8 (13 1)

The results for the placebo plus isoprenaline aerosol are shown for comparison

analysed only for the 13 patients who were regularly assessed

The mean weekly F E V$_{1 0}$ of the 13 patients was the same throughout the experimental period, ranging only from 1210 to 1290 c cm This gratifying lack of variability with time in the series as a whole adds significance to the analysis in terms of the influence of the drugs

The mean F E V$_{1 0}$ after a week's treatment with the placebo and each of the drugs is set out in table I, together with the percentage change calculated from the values obtained for the placebo in each patient The percentage increase produced by administration of isoprenaline aerosol, in addition to the placebo, is also shown The table affords an easily appreciated comparison of the drugs, but detailed statistical examination was done after logarithmic transformation of the data to reduce the range of variation between patients or, more strictly, to validate certain assumptions implicit in making an analysis of variance

TABLE II—RESULTS OF ANALYSIS OF VARIANCE ON LOG F E V$_{1 0}$ VALUES FOR 13 PATIENTS TREATED WITH PLACEBO AND FIVE DRUGS

Source of variation	Sum of squares	Degrees of freedom	Mean squares	F ratio	Significance level
Patients	1 1463	12	0 1206	35 7	Highly significant
Placebo *v* drugs	0 0133	1	0 0133	3 93	$P = 1/20$
Between drugs	0 0267	4	0 0067	2 00	$P \simeq 1/10$
Residual	0 2029	60	0 00338		
Total	1 3892	77			

The results of an analysis of variance (table II) indicate that, though the patients were the major source of variation, the drugs (the four bronchodilator drugs plus phenobarbitone) exerted a significant influence on F E V$_{1 0}$ values, furthermore there is evidence that some drugs exerted a greater effect than others *This method of analysis* ignores the order in which the drugs were taken and the question of whether the influence of a given drug is in some way manifest for a week or more *after it has* been stopped We have assumed that these factors are unimportant

Table III shows the percentage changes in F E V$_{1 0}$ values for each drug in relation to the placebo values computed from the analysis of variance The upper and lower limits are shown between which the probability is 0 95 that the true percentage change lies The appearance of the geometric rather than the arithmetic mean is the result of logarithmic transformation of the data The procedure is an approximation, since same bias is involved in reverting from logarithmic values It may be concluded that, though the drugs in general seemed to have a slight favourable effect on the F E V$_{1 0}$ under the conditions of the experiment, only aminophylline suppositories and choline theophyllinate showed a demonstrable individual effect

In fig 1 the individual values for F E V$_{1 0}$ are shown for all the patients, the results being expressed as percentages of the values obtained after treatment with the placebo The influence of aminophylline suppositories and of choline theophyllinate is apparent The changes with sublingual isoprenaline *are inconsistent, but a small* and relatively consistent effect of theodrox is suggested The confidence limits cited in table III are based on the overall variation Since the variation is much less in the results for patients taking theodrox, it is likely that the confidence limits for this drug are somewhat narrower than those shown

The scores for each drug, based upon the patients' opinions, are set out in table IV Preliminary analysis showed no evidence that the scores were influenced by the order in which the drugs were taken The results indicate that the patients "identified" the placebo, and that their opinions were probably favourably influenced by all the drugs except isoprenaline *The outstanding* finding is the patients' appreciation of phenobarbitone, this was the only drug which no patient considered "did not suit him" and on which no patient felt he had deteriorated

TABLE III—PERCENTAGE INCREASE ON PLACEBO VALUES ABOUT GEOMETRIC MEAN *

Drug	*Mean*	95 % confidence limits	
		Upper	Lower
Aminophylline suppositories	+16	+29	+5
Choline theophyllinate	+13	+25	+2
Theodrox	+ 6	+16	−4
Sublingual isoprenaline	+ 5	+17	−5
Phenobarbitone	+ 3	+15	−7

* The use of the geometric mean is due to the logarithmic transformation

The relationship between the patients' opinions for each drug and changes in the values of F E V$_{1 0}$ is shown in fig 2 for the 13 patients for whom both sets of data were available The chief finding is that patients who felt greatly improved by any drug showed a mean increase of 32% in F E V$_{1 0}$ The patients tended to give lower

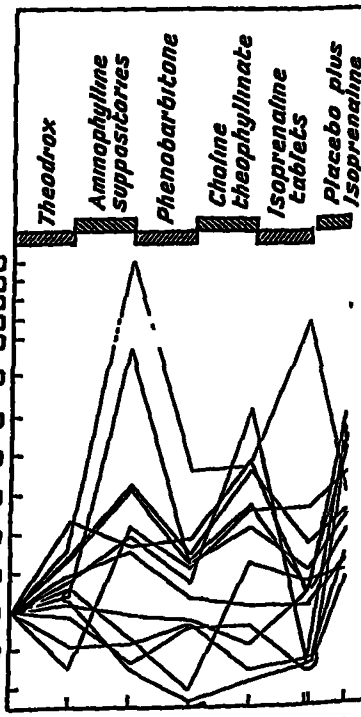

Fig 1—Changes in F E V$_{1 0}$ expressed as percentage of *placebo* value, at end of one week's *treatment* with each trial drug and, at extreme right, after inhalation of 1% isoprenaline during treatment with *placebo*

TABLE IV—PATIENTS' OPINIONS OF TRIAL DRUGS

Drug	Mean score	No. of patients having a score of			
		−1	0	+1	+2
Placebo	−0·07	4	8	3	0
Aminophylline suppositories	0·60	2	6	3	4
Choline theophyllinate	0·67	1	6	5	3
Theodrox	0·67	2	3	8	2
Sublingual isoprenaline	0·13	6	2	5	2
Phenobarbitone	0·73	0	6	7	2

The standard error of the difference between two means is 0·32, the calculation being based upon the residual mean square (0·786) of an analysis of variance.

scores for aminophylline suppositories than might have been anticipated from their improved F.E.V.$_{1\cdot 0}$ values. Our impression, based on their verbal comments and questionnaire replies, is that this was related to their dislike of the method of administration. Possibly the scores for isoprenaline tablets were influenced by the palpitations which sometimes developed. However, in one or two instances, the reason for lack of correlation between the patient's opinion and change in F.E.V.$_{1\cdot 0}$ was that the opinion was based on experience over a week, of which the F.E.V.$_{1\cdot 0}$ was not representative.

Discussion

In view of the finding that the response to inhaled isoprenaline is a complex function of the initial F.E.V.$_{1\cdot 0}$ (Hume and Gandevia 1957b) it is necessary to examine the validity of using changes in F.E.V.$_{1\cdot 0}$ to compare the effects of different drugs at different times. The relationship existing is such that, as the pre-inhalation values for F.E.V.$_{1\cdot 0}$ rise from the low levels associated with severe wheezing, so does the response to isoprenaline (both the initial level and the response being expressed in litres). There is a sharp peak of maximal response after which the response tends to decrease progressively, the post-inhalation value for F.E.V.$_{1\cdot 0}$ tending to remain constant. If a similar relationship exists for all bronchodilator drugs, irrespective of the route of administration, it may be unjust to compare the response to one drug on one day with the response to a second drug some time later. A spontaneous alteration in the initial level of the F.E.V.$_{1\cdot 0}$ in the group of patients studied may conceivably place one drug at a distinct disadvantage.

In the present investigation it is likely that the latin square design will have eliminated this factor as a cause of serious error. In any event the effect described would tend to blur the comparisons between drugs; yet we have been able to show significant differences between them.

The objective assessment provided by the F.E.V.$_{1\cdot 0}$ indicates that, under conditions of outpatient practice, choline theophyllinate and aminophylline suppositories are reasonably effective bronchodilators, the improvement produced being rather less than the immediate response to an isoprenaline aerosol. The possibility that some patients respond to one drug but not to another remains likely, but the effect of this in a small series is to diminish the chances of showing that any drug is effective at all. In so far as significance can be attached to the results in a single person, fig. 1 shows that 1 patient responded to choline theophyllinate but not to aminophylline suppositories, and 1 did the reverse. Fig. 1 also suggests that the trial series included 4 or 5 patients relatively unresponsive to all the antispasmodics tried, despite the fact that a prerequisite for inclusion in the trial was an improvement of more than 10% in F.E.V.$_{1\cdot 0}$ after an inhalation of 1% isoprenaline. 3 of these patients had been diagnosed as having emphysema, but the group showed no well defined distinguishing features clinically. Previous therapy with the trial drugs may have produced some drug resistance.

The patients' approval of phenobarbitone is of interest not only from the therapeutic point of view but also because of the light it throws upon the significance of the patients' opinions about their well-being. We believe that the search for objective methods of assessment has led to the patients' views being too often neglected and regarded as valueless. Phenobarbitone was deliberately included in the trial in an attempt to obtain, as it were, an objective assessment of the meaning of these opinions. Our results suggest that phenobarbitone is a satisfying drug for these patients, who probably tend to be anxious and introspective, in spite of its lack of definite effect on ventilatory capacity. It follows that, in assessing their own progress, these patients are influenced by sensations other than those of wheezing and dyspnœa, even when they know that their ability to breathe is the subject of a special study. That their opinions are also related to changes in their ability to breathe is indicated by the high values found for F.E.V.$_{1\cdot 0}$ when they were feeling "much better." From the present figures and from other observations it seems possible that an improvement of more than about 10% in F.E.V.$_{1\cdot 0}$ over a week can be reflected in a patient's opinion, but only if the drug used has no undesirable properties; an increase of this order is certainly appreciated when it is produced over a few minutes with a suitable aerosol.

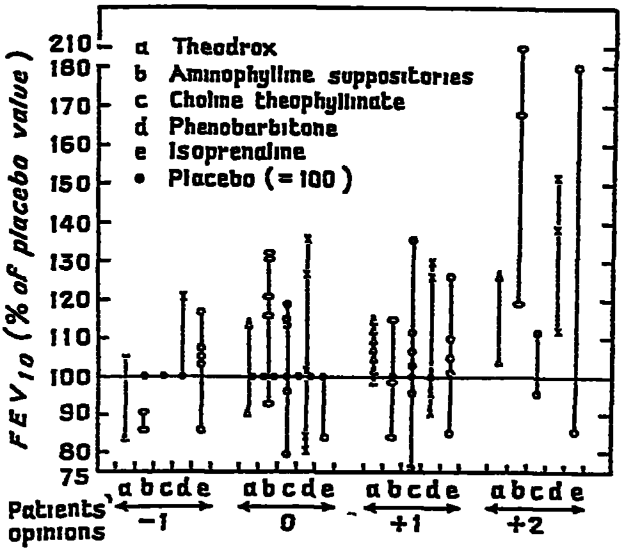

Fig. 2—Relationship between F.E.V.$_{1\cdot 0}$, expressed as a percentage of placebo value, and patient's opinion of his progress expressed in grades (−1 to +2: see text).

The influence of personality on a patient's opinion about his progress is well known.

Although we made no deliberate study of this factor, it was well illustrated by 1 patient, a most coöperative but uncommunicative, almost morose, man, who felt that four of the six treatments made no difference and two made him worse. One of the latter was associated with an increase of 20% in F.E.V.$_{1\cdot 0}$ and two of the former with an increase of over 30%; on these occasions clinical improvement was obvious at a glance.

More or less systematic errors of opinion are not important in comparative trials of this type. More important are those who are bad observers, suggested by the variability of their opinions. The existence of this group determines the necessity for relatively large series to obtain significant results. The observer conducting the tests gained the impression in conversation that the knowledge that they were taking part in an experiment made the patients more frankly critical of the drugs than were patients attending a routine clinic. This is of no significance in the circumstances of the trial but may be relevant in relating our findings to clinical practice.

In summary it is clear, from the present study of 15 patients, that not only are the patients' opinions complementary to objective methods but also the patients are successful in distinguishing between treatments The opinions of somewhat larger groups can achieve the more difficult feat of discriminating between two forms of breathing exercises, their distinction being supported by such objective assessments as were made (Bolton et al 1956)

Conclusion

The conclusion reached from this investigation is that, excluding hormonal therapy and under conditions of outpatient practice, the most satisfactory symptomatic treatment of wheezing dyspnœa at present available is likely to be a combination of one of the more effective bronchodilators with small daily doses of phenobarbitone The need for dual therapy in some form is emphasised when the effective drug is likely to be unpopular for any reason

Summary

On a latin-square experimental design four commonly prescribed bronchodilators, phenobarbitone, and a placebo were given for a week each to 15 patients complaining of wheezing dyspnœa associated with asthma, bronchitis, or bronchitis and emphysema The effects of these drugs were assessed in terms of the patients' opinions and the forced expiratory volume at one second

The patients' opinions distinguished the placebo and were favourably influenced by phenobarbitone and three of the bronchodilators

The changes in forced expiratory volume at one second showed that, though the drugs in general were producing a favourable response, only aminophylline suppositories and oral choline theophyllinate appeared reasonably reliable and effective in the dosages used

The significance of the patients' opinions is discussed in the light of these findings, and the complementary nature of the subjective and objective assessments is emphasised

We are indebted to Dr J G Scadding and to members of the consultant staff of the Brompton Hospital for permission to study their patients, and to the patients and their general practitioners for their willing coöperation Our thanks are also due to Dr P Armitage, in particular, for statistical advice and assistance, and to Mr S Powlson, chief pharmacist, for his help in distributing the drugs

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PLANTS AS ÆTIOLOGICAL FACTOR IN VENO-OCCLUSIVE DISEASE OF THE LIVER

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A PARTICULAR form of infantile cirrhosis of the liver reported from Jamaica (McFarlane and Branday 1945, Hill 1951, Hill et al 1953) differs in several respects from the mild hepatic injury seen in kwashiorkor The morphological picture in this infantile cirrhosis is dominated by an obliterating lesion—veno occlusive disease (Bras et al 1954)—of the medium sized and smaller ramifications of the hepatic veins with non portal cirrhosis as the ultimate result The essential pathology of veno occlusive disease was described in this journal by Bras and Hill (1956)

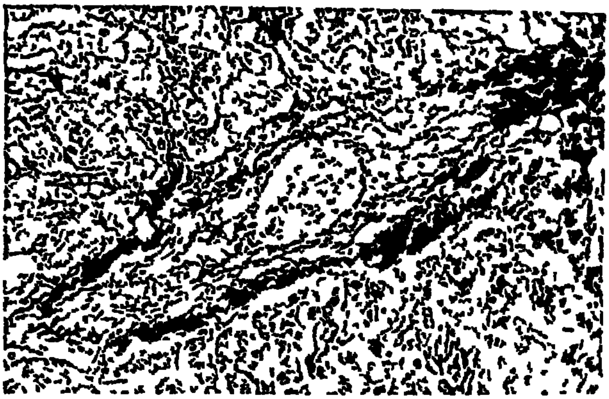

Fig 1—Occlusive lesion in branch of hepatic vein in cow dead from veno occlusive disease (Mallory trichrome stain ×107)

The toxic origin of veno-occlusive disease was originally suspected by McFarlane and Branday (1945) The practice of making a decoction of the leaves of various plants and consuming the resultant liquids (bush tea) is well established in Jamaica and neighbouring islands as a remedy for ailments and otherwise

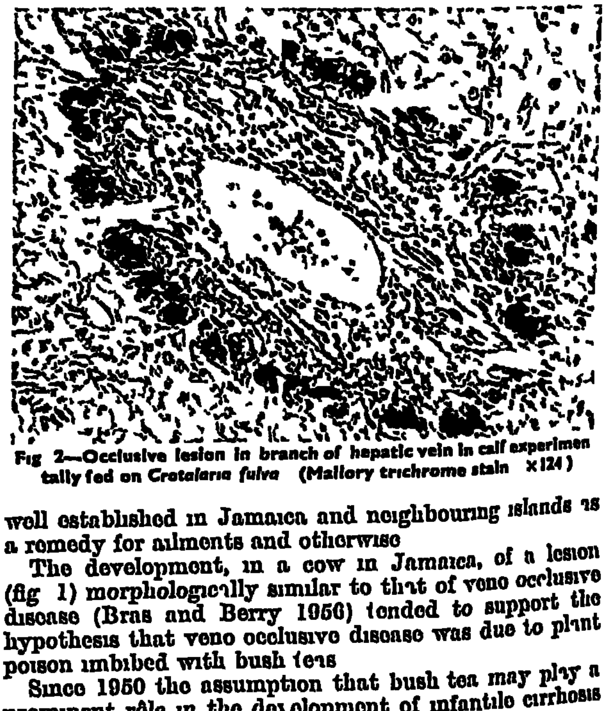

Fig 2—Occlusive lesion in branch of hepatic vein in calf experimentally fed on *Crotalaria fulva* (Mallory trichrome stain ×124)

The development, in a cow in Jamaica, of a lesion (fig 1) morphologically similar to that of veno occlusive disease (Bras and Berry 1956) tended to support the hypothesis that veno occlusive disease was due to plant poison imbibed with bush teas

Since 1950 the assumption that bush tea may play a prominent rôle in the development of infantile cirrhosis seen in Jamaica has been tested extensively in experiments on white rats under varying conditions * More recently we have experimented on calves †

It has been known for a considerable time (see Theiler 1920) that senecio (ragwort) is poisonous to horses and cattle and can produce a disease of the liver leading to fibrosis and cirrhosis Willmot and Robertson (1920) and Selzer and Parker (1951) focused our attention on these

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* These experiments were made in the laboratory of one of us (P G) as part of a collaborative study of the research groups at the University College of the West Indies and the University of Pennsylvania These investigations including those reported here were supported by grants of the Nutrition Foundation and the Josiah Macy jun , Foundation New York

† This part was done in Jamaica and made possible through facilities put at our disposal by Reynolds Jamaica Mines

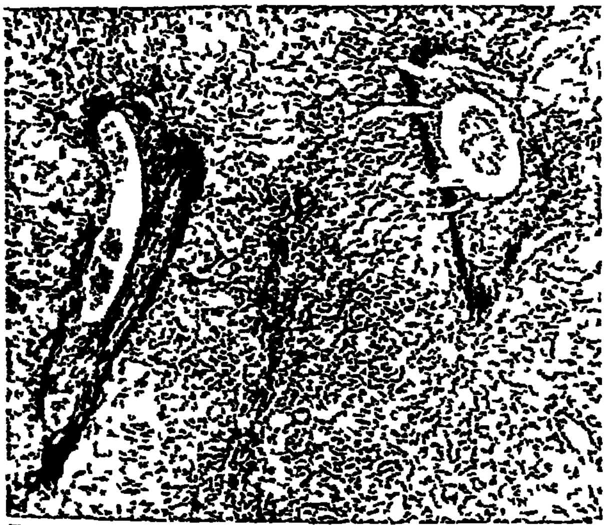

Fig 3—Occlusive lesions in branches of hepatic vein in horse with clinical crotalaria poisoning (Mallory trichrome stain ×47.)

plants, especially since, in the case reported by Selzer and Parker, a pathological lesion was observed in the branches of the hepatic vein. Betty and Markson (1954) and Cockburn et al (1955) have described poisoning with senecio in animals.

On the other hand, observations on veno-occlusive disease in man in Barbados implicated crotalaria (rattlebox) (Stuart and Bras 1956). In the veterinary literature crotalaria poisoning has been described since 1884 (Bessey and Stalker 1884) and has been associated with parenchymatous hepatitis in horses and cattle since 1920 (Theiler 1920). Reports of the toxicity of crotalaria and the incidence of poisoning by it in cattle (Becker et al 1935, Sanders et al 1936), swine (Emmel et al 1935), chickens (Neal and Becker 1933, Thomas 1934), quail and doves (Thomas 1934), and horses and goats (Emmel and Sanders 1942) came from America and from South Africa, India, and Australia (L B Bull, personal communication). Further reports on the toxicity of these plants were given by Piercy and Rusoff (1946) and Gibbons et al (1950). Intensive experimental studies with one of the hepatotoxic pyrrolizidine alkaloids, monocrotaline, present in crotalaria, were made by Ratnoff and Mirick (1948, 1949). Chemically monocrotaline is closely related to a similar pyrrolizidine alkaloid retrorsine, contained in senecio (Adams and Rogers 1939). We are not aware of previous reports of crotalaria poisoning in man.

Material

We report here our findings in a calf fed experimentally on *Crotalaria fulva* and our observations on material kindly sent to us by other investigators working on crotalaria and senecio poisoning. All the animals had obliterative lesions of the hepatic vein similar to those observed in veno-occlusive disease in man.

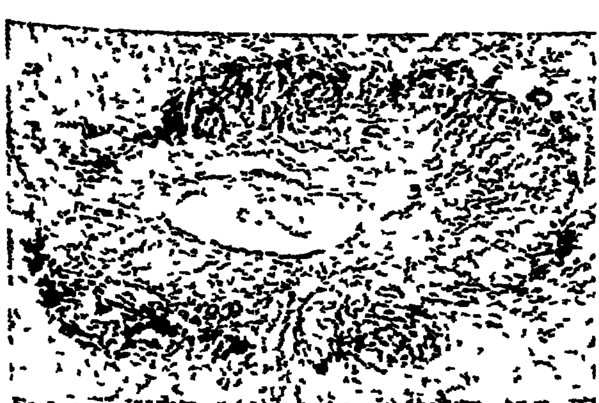

Fig 5—Occlusive lesion in branch of hepatic vein in cow dead from accidental senecio poisoning (Mallory trichrome stain ×87.)

Crotalaria

In 5 calves experimentally fed on *Crotalaria fulva* serial liver biopsies were made at monthly intervals. 4 of these calves died without remarkable histopathological changes in their livers. The 5th calf developed, after six months, an obliterative hepatovenous lesion (fig 2). 5 control calves remained free from change up till eight months after the beginning of the experiment, which was then terminated.

Dr. W J Gibbons kindly sent us material from horses with clinical crotalaria poisoning in which we observed lesions like that shown in fig 3.

Dr L B Bull's material from a horse dead from accidental crotalaria poisoning showed lesions like that depicted in fig 4.

Senecio

Material kindly put at our disposal by Dr L M Markson and obtained from cattle with accidental senecio poisoning displayed vascular lesions perfectly matching those of veno-occlusive disease in man (fig 5). Fig 6 shows a lesion in a horse fed experimentally on senecio by Dr. J Vanek.

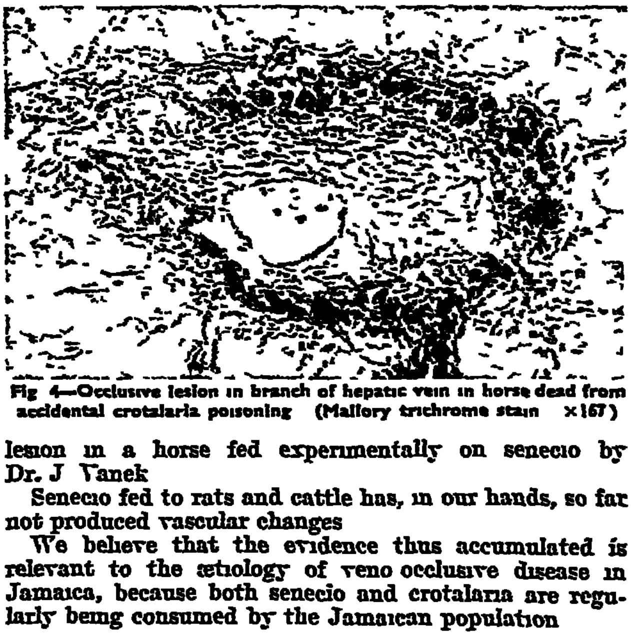

Fig 4—Occlusive lesion in branch of hepatic vein in horse dead from accidental crotalaria poisoning (Mallory trichrome stain ×167.)

Senecio fed to rats and cattle has, in our hands, so far not produced vascular changes.

We believe that the evidence thus accumulated is relevant to the ætiology of veno occlusive disease in Jamaica, because both senecio and crotalaria are regularly being consumed by the Jamaican population.

Discussion

Senecio and crotalaria, both in our hands and in the hands of others, have produced in rats, cattle, and horses

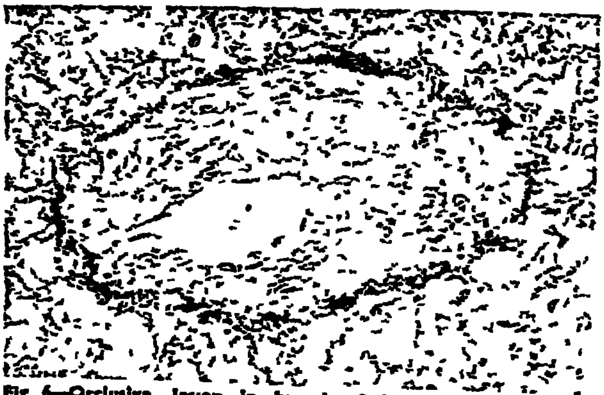

Fig 6—Occlusive lesion in branch of hepatic vein in horse experimentally fed on *Senecio erraticus barbaræfolius* (Mallory trichrome stain ×173.)

much hepatocellular damage The only convincing vascular lesions—i e, obliterating lesions of the branches of the hepatic veins—that we have been able to find published were those pictured by Davidson (1935) after the administration of retrorsine to rats and by Vanek (1956) A comprehensive report by Bull et al (1957) on crotalaria poisoning in horses in Northern Australia gives histopathological observations, including some hepatovenous changes Blood lagoons, with intralobular hæmorrhage and massive central necrosis in the liver lobules, have been described in animals with crotalaria poisoning (Emmel et al 1935, Harris et al 1942, O D Ratnoff personal communication), but no vascular changes

Senecio and crotalaria have pyrrolizidine alkaloids in common, and extensive work on this has been done in Australia (Bull et al 1956) and elsewhere (see Schoental and Head 1955), the damage to the liver being reported as hepatocellular

In our hands *Crotalaria fulva* has produced veno occlusive disease (fig 2), and in material sent to us by other investigators both senecio and crotalaria had produced obliterating lesions of the hepatic veins The importance of the obliterating lesion and its rôle in the production of hepatocellular damage with subsequent fibrosis need further study

In view of the seemingly independent and/or concurrent appearance of hepatocellular damage, on the one hand, and obliterating vascular lesions of the hepatic veins, on the other, we are exploring the possibility that more than one toxin may be responsible for this, each with a different target area The different poisonous substances may well be unequal in concentration and in toxicity and may differ in various parts of the plants and at various times of the plant's life

Summary

It is postulated, on the evidence of experiments with *Crotalaria fulva* on cattle in Jamaica, that herbal infusions made from crotalaria and taken by the Jamaican population for medicinal and other purposes constitute (one of) the ætiological factor(s) in veno occlusive disease of the liver

It appears that a similar rôle is played by senecio

All plants were collected by the Department of Botany, University College of the West Indies, and we are extremely grateful to Prof G F Asprey, Dr J H Palmer, and Prof A D Skelding for their cooperation

We are greatly indebted to Dr W J Gibbons, of the School of Veterinary Medicine, Auburn, Alabama, U S A, Dr L B Bull, of the Commonwealth Scientific and Industrial Research Organisation, Australia, Dr L M Markson, of the Ministry of Agriculture, Fisheries and Food, Veterinary Laboratory, England, and Dr J Vanek of the Karlovy University, Prague, for supplying material

We also thank the Josiah Macy, jun, Foundation, Reynolds Jamaica Mines, the Colonial Medical Research Committee, and the Government of Jamaica for providing facilities for this experimental work

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L-NORADRENALINE THERAPY IN ACUTE RENAL FAILURE

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The use of L-noradrenaline in the treatment of hypotensive states was inaugurated by Goldenberg et al (1949) and its successful use has often been reported since The physiological aspects of using noradrenaline as a vasopressor drug have been fully discussed by Von Euler (1955) He laid stress on the importance of starting treatment early, in view of the increasing refractoriness of the blood-vessels to the action of physiologically released or exogenously added noradrenaline during prolonged hypotension 'Levophed,' a solution of L noradrenaline bitartrate, contains 1 mg of active base to each millilitre and is usually diluted with 5% dextrose and given by continuous intravenous infusion

The term "peripheral circulatory failure" has come into use to describe the clinical picture of prolonged hypotension associated with a sluggish peripheral circulation and patchy cyanosis of the extremities It may arise when no blood has been lost, or after apparently adequate restoration of blood-volume when this has been reduced by hæmorrhage or severe dehydration Peripheral circulatory failure has been observed in patients with fulminating infections, intestinal strangulation, acute pancreatitis, coronary thrombosis, pulmonary embolism, chemical pneumonitis, diabetic ketosis, acute adrenal failure, and barbiturate poisoning, and after operations When acute renal failure is already present, or develops as a result of prolonged hypotension, the effect of noradrenaline on the kidneys has to be considered

Nickel et al (1954) and others have shown that in normal people noradrenaline, in doses large enough to raise the systolic blood-pressure by 25–50 mm Hg, produces a reduction in renal blood flow with an increase in urine-flow and in tubular reabsorption of sodium and potassium Nickel et al suggested that at least some of these effects were due to intrarenal vasoconstriction and relative tubular ischæmia Lathem (1956) demonstrated similar results in patients with chronic renal disease These results might suggest that noradrenaline should not be used in hypotensive patients with severe oliguria or anuria, because of the danger of increasing already existing tubular damage On the other hand, restoration of the systolic pressure to normal levels by noradrenaline will increase the renal blood-flow and may well outweigh the local vasoconstrictor effect on the renal vessels In the two cases reported here treatment with noradrenaline led to satisfactory recovery

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TABLE I—LABORATORY FINDINGS IN CASE 1

—	Normal range	Oliguric phase									Diuretic phase							
Postoperative day		2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	19	22
Hb (%)		88			93		88									77		
Blood urea (mg per 100 ml)	20–40	162	214	194	276	260	288	324	304	320	292	212	204	136	102	69	65	35
Plasma-sodium (m.eq per litre)	138–148	131		152	153	146	142	147	141	149	136	137	140	130	132	133		
Plasma potassium (m.eq per litre)	3·5–5·5	5·4		3·2	3·6	4·4	4·8	5·6	4·9	4·8	4·2	4·2	5·4	4·9	5·3	4·7		
Plasma-chloride (m.eq per litre)	96–106	85		106	100	95	91	99	94	96	88	88	96	96	96	100		
Plasma bicarbonate (m.eq per litre)	25–30	21·4		15·6	21·4	19·6	17·9	17·0	17·9		19·7	19·7	19·7		21·4	21·4		

Methods

All blood samples were collected from a vein. The analytical methods were as follows: sodium and potassium, flame-photometer (Evans Electro selenium Ltd.); chloride, method of Schales and Schales (King 1946); bicarbonate, titration method (Lehmann 1951); urea, urease nesslerisation method (King 1946). All urine samples were collected by an indwelling Foley's self-retaining catheter during the period of oliguria.

Case-reports

FIRST CASE

A woman, aged 63, with no history of renal disease and in otherwise good health, had a vaginal hysterectomy on account of complete procidentia on Nov. 24, 1955. Her preoperative blood-pressure (B.P.) was 170/90 mm. Hg. There was some blood loss at operation, but this was replaced by 2 pints of compatible whole blood at the time and her hæmoglobin next day was 92%.

1st postoperative day.—No urine was passed all day, and she started vomiting during the afternoon. Her daily fluid intake was restricted to 1 litre of distilled water containing 400 g. of dextrose by intragastric drip.

2nd day.—A further litre of the dextrose solution was given during the 24 hours. No fat was included in the drip because it increased the nausea and vomiting. Only 350 ml. of urine was collected by catheter. Blood was taken daily from now on for electrolyte and blood-urea estimations (table I). The patient was nursed in isolation and started on a single daily injection of a million units of crystalline penicillin. Parenteral ascorbic acid and vitamin-B complex were also given.

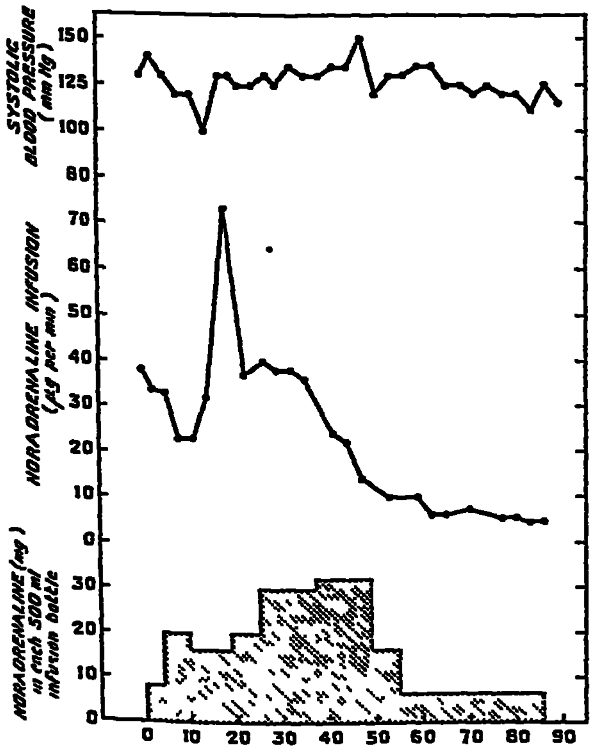

Fig. 1—Case 1: systolic blood-pressure; rates of infusion of noradrenaline; and amounts of noradrenaline in each 500-ml. infusion bottle.

3rd day.—During the night profuse watery diarrhœa developed. Her fluid intake was increased, but she continued to pass a lot of fluid per rectum and by the afternoon was in peripheral circulatory failure with an unrecordable B.P. She was now clinically dehydrated, but the rapid intravenous infusion of 2 litres of physiological saline solution and 2 pints of plasma had no effect on her B.P. Intravenous methylamphetamine hydrochloride ('Methedrine') 25 mg. was also without effect, and, as the patient was now moribund, noradrenaline (levophed) was added to the infusion fluid producing a rapid rise in her systolic pressure to 130 mm. Hg. The blood-pressure was maintained about this level, by adjusting the drip and altering the amount of noradrenaline in the infusion bottles, for several days (fig. 1). Through another vein a further 2 pints of compatible whole blood was given. She was now anuric again with a blood urea of 215 mg. per 100 ml.

4th day.—The intragastric drip was continued, but with a reduced dextrose content of only 100 g. per litre, for it was found that higher concentrations caused vomiting and diarrhœa. Fluid balance was difficult to estimate, for an unknown quantity of fluid—probably several litres—had been lost per rectum. Since this loss had now stopped, and she was no longer clinically dehydrated, the daily fluid intake was restricted to 1 litre by intragastric drip and intravenous infusion. In addition, water and later very weak tea were given by mouth equal in amount to her urinary output of the previous 24 hours (fig. 2). It was thought that the patient might be deficient in potassium because of the diarrhœa, and this was confirmed by a plasma level of 3·2 m.eq. per litre and also suggested by an electrocardiogram, the QT_c interval being prolonged to 0·48 sec. About 50 m.eq. of potassium, in a mixture of potassium salts, was added daily to the intragastric

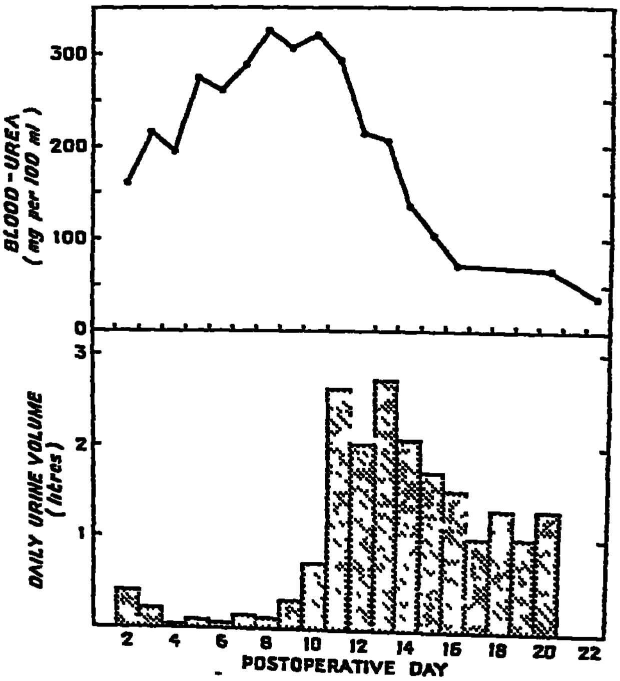

Fig. 2—Case 1: blood-urea levels and daily urine output (urine collections after the 14th day incomplete).

drip Her general condition had improved, but her temperature had risen to 101°F and fæcal culture had produced a strong growth of *Staphylococcus aureus* She was therefore given oral erythromycin 400 mg 6 hourly, since it was suspected, and later confirmed, that this organism might be resistant to other antibiotics Her fever settled in a few hours The amount of noradrenaline required to maintain her B P, which had risen to 73 µg per min, now began to fall

5th and 6th days —Oliguria persisted and the urine contained many red and white blood cells A strong growth of *Staph aureus* was obtained on culture, though by now fæcal swabs were sterile and the temperature normal The blood urea rose to 260 mg per 100 ml, but the nausea and vomiting had ceased The patient was very drowsy, sleeping most of the day The plasma potassium level was now within the normal range

7th day —The noradrenaline infusion was stopped when the infusion rate had fallen to 4 µg per min It had run for 86 hours without complications or obvious side effects, and through the same vein for over 80 hours

8th to 22nd days —The erythromycin was discontinued after a total dose of 5 6 g Fluids were restricted until diuresis started on the 11th day, adequate amounts were then given to compensate for the increasing urinary losses A low-protein, high-carbohydrate diet, with additional sodium and potassium, was then started and steadily increased to a normal ward diet by the 22nd day No renal function tests were carried out, but proteinuria persisted for some weeks afterwards

SECOND CASE

An obese man, aged 49, developed polyuria and polydypsia, and lost two stone in weight in 6 weeks He was admitted in a drowsy, confused state with diabetic ketosis and a blood-sugar of 800 mg per 100 ml Despite massive doses of insulin and intravenous saline, he became oliguric and pulseless, his blood urea rising to 160 mg per 100 ml A noradrenaline drip was started and the systolic pressure rose rapidly to 130 mm Hg, where it was maintained by a concentration of about 20 µg per min His urine output increased and he recovered completely after receiving 3200 units of soluble insulin and 12 litres of intravenous fluids during the first 12 hours of treatment

Discussion

The first patient did not become dehydrated until after the profuse diarrhœa on the 3rd postoperative day, this cannot have been the cause of the previous oliguria and raised blood-urea, though it may have contributed to the renal damage (Oliver et al 1951) Treatment was based on restriction of fluid and electrolyte intake until diuresis started (Bull 1955), and, apart from giving oral potassium when the serum level fell to 3 2 m eq per litre, the temptation to try to adjust the serum electrolyte levels towards normality was resisted during the oliguric phase The minimum 1600 calories a day was not achieved because the patient could not tolerate the high concentrations of intragastric dextrose and peanut oil to provide this For several days she did not receive more than 400 calories a day A direct infusion of a concentrated dextrose solution into the inferior vena cava (via a femoral vein) was thought to be contra indicated because of severe *Staph aureus* infection Peripheral circulatory failure developed at the onset of the fulminating staphylococcal enteritis The enteritis responded slowly to oral erythromycin Intravenous methylamphetamine failed to raise the B P, as Downie (1954) found when treating a patient with postoperative peripheral circulatory failure Similar negative results have been reported with dexamphetamine sulphate Methylamphetamine raises the B P by increasing the cardiac output, at the same time lowering the peripheral resistance (Churchill Davidson 1951), it would therefore not be expected to be effective in the treatment of peripheral circulatory failure On the other hand, noradrenaline produced an immediate rise in the systolic pressure, which was maintained by a continuous intravenous infusion Therapy was complicated by the need to restrict the total fluid intake to about a litre a day The infusion ran for 86 hours without any complications or side effects Diuresis started after 10 days of severe oliguria (fig 2)

In the second patient noradrenaline produced an immediate rise in B P, followed by a considerable increase in the urine output Noradrenaline produces a fall in renal blood-flow and an increased urinary output in normal people (Nickel et al 1954), but it seems more likely that the increased urinary flow in this patient was primarily due to restoration of the B P to normal levels Oliguria is not uncommon in hypotensive states, and a similar restoration of normal urinary flow was seen in two cases of barbiturate poisoning treated with noradrenaline (Mattingly 1955) It is impossible to prove that noradrenaline had no deleterious effect on these patients' kidneys, but it is equally certain that without it neither would have survived The theoretical dangers and toxic effects of L noradrenaline infusions have been surveyed by Ritchie (1956) In a small series of cases the only "toxic" effect observed was excessive sweating, which appeared only with high concentrations Local tissue necrosis was avoided in the first case by inserting a 'Polythene' tube several inches up an ankle vein and tying it in, this vein was used continuously for over 80 hours, watch was kept for the bluish discoloration of the overlying skin which is the first sign of impending trouble The second patient received an infusion through a needle in a superficial arm vein After some hours bluish discoloration developed, with obvious leakage into the surrounding tissues Fortunately it was possible to discontinue the noradrenaline at this point and there was no sloughing

Dosage

Little guidance is given in the literature as to the dosage of noradrenaline required to restore the blood pressure to normal levels in patients with peripheral circulatory failure

The dosage depends on the amount of noradrenaline in the infused solution and on the drip rate Ritchie (1956) states that the correct dosage is that which raises the pressure to the desired level and maintains it there There is, however, considerable difference of opinion as to what are desirable levels It seems reasonable to suspect peripheral circulatory failure if the systolic pressure falls below 100 mm Hg (Downie 1954), and to aim at raising it to about 130 mm Hg The amount of noradrenaline needed to achieve this varies widely from patient to patient Nickel et al (1954) used 12-15 µg per min in normal people to raise the systolic pressure by 25-50 mm Hg, and Lathem (1956) found that similar amounts were necessary in patients with chronic renal disease Much larger amounts—up to 72 µg per min —were required in some cases

For hypotensive states Goldenberg et al (1949) recommended not more than 0 36 µg per kg body weight per min, and Martindale (1952) suggests 6-8 µg per min administered in 1 5-2 0 ml per min In the present case 1, who required nearly 40 µg per min initially, such a dilution would have involved infusing 10 ml per min, or 600 ml an hour, and gross over hydration would have resulted De Swiet (1955) found it necessary to increase the dosage to 150 µg per min over two periods of 8 hours when treating a patient with pulmonary embolism There is no evidence that such a high dosage is dangerous provided the blood pressure is watched

Von Euler (1955) reports a case of phæochromocytoma in which as much as 9000 µg per 24 hours was excreted, probably corresponding to a release into the circulation of about 200 mg, or 140 µg per min In the average case of peripheral circulatory failure the initial dosage of noradrenaline required will range from 10 to 30 µg per min, but larger amounts may be needed, particularly if treatment is delayed and the vessels become increasingly refractory

The only real criterion of effective dosage is the fairly rapid rise of the systolic pressure, within a few minutes to about 130 mm Hg If no response is obtained the concentration of noradrenaline in the infused solution should be doubled or trebled to avoid overhydration

The management of these cases, once it has been decided to administer noradrenaline depends on two factors.

(1) The amount of intravenous fluid that can safely be given. Table II shows the relationship between drip rate and daily fluid intake. Not more than 0.6 ml per min should be given if the patient is anuric. For simplicity 20 drops has been taken to equal 1.0 ml, which is approximately correct for most drip sets. A more accurate relationship can be established by dripping the infusion solution into the barrel of a 2 or 5 ml syringe.

TABLE II—SUGGESTED RATE OF INFUSION, DEPENDING ON CLINICAL STATE OF PATIENT

Clinical state	Litres per 24 hr	Ml per min	Drops per min
Anuria, heart failure	0.8	0.6	12
Hydrated, normal renal function	2.4	1.8	36

(2) The initial concentration of noradrenaline to restore the blood pressure must be assessed beforehand. Table III provides a rough guide which has proved useful in practice.

TABLE III—SUGGESTED RATE OF ADMINISTRATION OF NORADRENALINE WHEN STARTING INFUSION

Clinical state	Systolic B.P. (mm Hg)	Noradrenaline (µg per min)
Early circulatory failure	More than 60	10
Severe protracted hypotension	Less than 60	20
Pulseless	Unrecordable	30

Only when these two factors have been decided is it possible to calculate the amount of noradrenaline to add to the infusion bottles.

For example, an anuric, pulseless patient will probably need 30 µg per minute in not more than 0.6 ml of fluid. It will be necessary to add 24 mg of noradrenaline to 500 ml of 5% dextrose to achieve this dosage at this drip rate.

To facilitate these calculations the noradrenaline dosage chart shown in fig. 3 was devised. The diagonal lines represent the amount of noradrenaline in mg which must be added to 500 ml of intravenous fluid at varying noradrenaline concentrations and drip-rates. They are spaced at 2 or 4 mg intervals, these being the contents of the ampoules supplied. Once the systolic pressure has been raised to about 130 mm Hg, and maintained there by adjusting the drip-rate, the actual rate at which noradrenaline is being given can be read off the chart. This enables future requirements to be assessed. If the drip-rate and systolic pressure are recorded by the nurses at half-hourly intervals once the systolic pressure has settled, it is possible to calculate the changing dosages of noradrenaline being used and prepare the next bottle well in advance. When the dosage has fallen to about 5 µg per min the drip can be discontinued to see if the blood-pressure is maintained spontaneously.

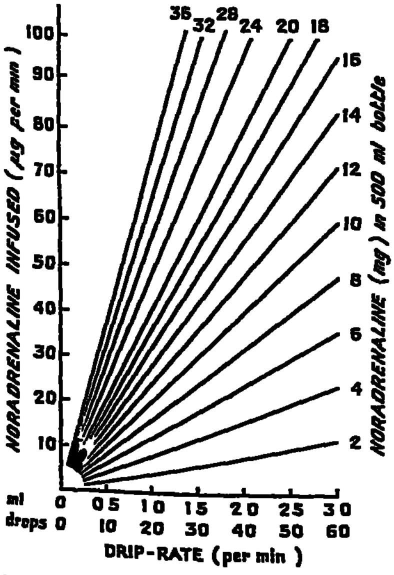

Fig. 3—Noradrenaline dosage chart. Diagonal lines represent millilitres of levophed in each half litre bottle since each millilitre contains 1 mg of active noradrenaline base. Using the appropriate line, the rate at which noradrenaline is being used can be read off the graph, provided the drip-rate is known.

Fluid Vehicle

Because L-noradrenaline breaks down in an alkaline medium, it should be given in 5% dextrose (West 1952) or dextrose saline. If intravenous physiological saline, blood, plasma, or antibiotics are to be given it is probably wise to give these into another vein, despite the added discomfort to the patient (Ritchie 1956). If this is impossible, the two infusion sets can be linked by a glass Y-piece near the vein. It is important to adjust the relative heights of the infusion bottles to prevent reflux of one solution up the other tube. Alternatively, the L-noradrenaline can be introduced into the other drip tube through an intramuscular needle inserted near the entry into the vein.

Steroid Therapy

Peripheral circulatory failure in patients in addisonian crisis, hypopituitary coma, or myxœdema coma may respond to intravenous hydrocortisone alone. If, however, hypotension persists, it seems reasonable to use noradrenaline as well.

Ramey et al. (1951) have shown that adrenal cortical extracts potentiate the blood-pressure response of adrenalectomised dogs to noradrenaline, and Fritz and Levine (1951) have shown that, in adrenalectomised rats, the refractoriness of the blood vessels of the mesoappendix to noradrenaline is abolished by adrenal cortical extracts, but not by deoxycortone. In man, Howland et al. (1956) have treated hypotension during operation with intravenous hydrocortisone and restored the blood pressure to near normal levels. They believe that prolonged hypotension which fails to respond to vasopressor drugs is a sign of adrenal cortical insufficiency. But only one of the seven patients reported was given noradrenaline, and it is doubtful if the dosage was adequate.

If patients fail to respond to a reasonable concentration of noradrenaline, or become refractory to it later, it would seem logical to assume that adrenal insufficiency has supervened and to try to restore the responsiveness of the vessels by steroid therapy. This can be done most rapidly by infusing 100 mg of hydrocortisone in 500 ml of 5% dextrose, following this with further cortisone by mouth or intramuscularly. Steroid therapy should be continued until the patient has been weaned off noradrenaline, and then slowly withdrawn.

Summary

Two cases of peripheral circulatory failure with impaired renal function are reported. Both patients recovered after hypotension had been treated with noradrenaline.

It is suggested that with administration of noradrenaline the increased renal blood-flow following restoration of normal blood-pressure more than compensates for the local vasoconstrictor action of this drug on the renal vessels.

I thank Mr P. M. G. Russell for permission to report the first case, and Dr C. M. Seward for permission to report the second case and for advice and criticism, Miss M. M. McCready for all the biochemical estimations, and the nurses of the Royal Devon and Exeter Hospital for their coöperation in treating these patients.

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MASSIVE HÆMORRHAGE IN CHRONIC CONGESTIVE HEART-FAILURE FOLLOWED BY SODIUM DEPLETION

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M B , B Sc Birm
MEDICAL REGISTRAR

Molly Hill*
M B Birm
LATE HOUSE PHYSICIAN

QUEEN ELIZABETH HOSPITAL, BIRMINGHAM

A patient with congestive cardiac failure had a massive hæmorrhage into her right pleural cavity after a thoracentesis Transfusion, with an amount of blood calculated to be about equal to that shed into the chest, was not followed by clinical improvement Cortisone was given and later salt The patient recovered, but died six weeks later from a pulmonary embolus

Case-report

A woman, aged 49, had an attack of rheumatic fever at the age of 7 years, after which she was well and led a normal active life until 1945, when her ankles began swelling and she was becoming rather tired Intermittently thereafter her ankles became swollen, and in 1947–48 she was becoming short of breath on exertion This gradually increased, and she was first seen as an outpatient in 1950, since when she had been taking digitalis At that time she was diagnosed as having mitral stenosis and incompetence and aortic incompetence with auricular fibrillation

She had been admitted to hospital in November, 1953, in congestive cardiac failure and with a right pleural effusion In the next two years she was in hospital seven times, and on each occasion she was in congestive failure with distended neck veins, œdema, and a massive right pleural effusion On the last three admissions she also had ascites Both pleural and ascitic fluids were tapped on each occasion, sometimes more than once Over this period 43 1 litres of fluid was removed

Since 1951 the patient had been given regular injections of a mercurial diuretic and since 1954 ammonium chloride 1 g three times daily

In March, 1955, her total exchangeable body potassium was estimated by using the radioactive isotope ^{42}K (Flear et al 1957) and found to be significantly lowered, and since then she had been receiving potassium chloride 1 g by mouth three times daily In view of the protein loss incurred by the recurrent tapping of effusions (more than 840 g) the patient was given ' Casilan ' and advised to take one or two eggs each day in addition to her meals She was finally admitted on Jan 26, 1956, because of congestive cardiac failure with considerable ascites, right pleural effusion, and œdema of the legs and the sacral regions Her neck veins were distended to the level of the angle of the jaw when she sat up

On admission her hæmoglobin was 11 4 g per 100 ml , serum urea 48 mg per 100 ml , serum sodium, serum potassium, and serum chloride 134 0, 4 6, and 99 0 m eq per litre respectively, serum albumin 4 2 g per 100 ml , and serum-globulin 1 8 g per 100 ml Electrocardiography confirmed the presence of auricular fibrillation, rate about 90 a minute, and showed depression of the S–T segment in leads 2, 3, VF, and V4–6 Chest radiography showed a massive right pleural effusion occupying most of the right hemithorax, displacing the heart to the left, and almost completely obscuring the underlying lung

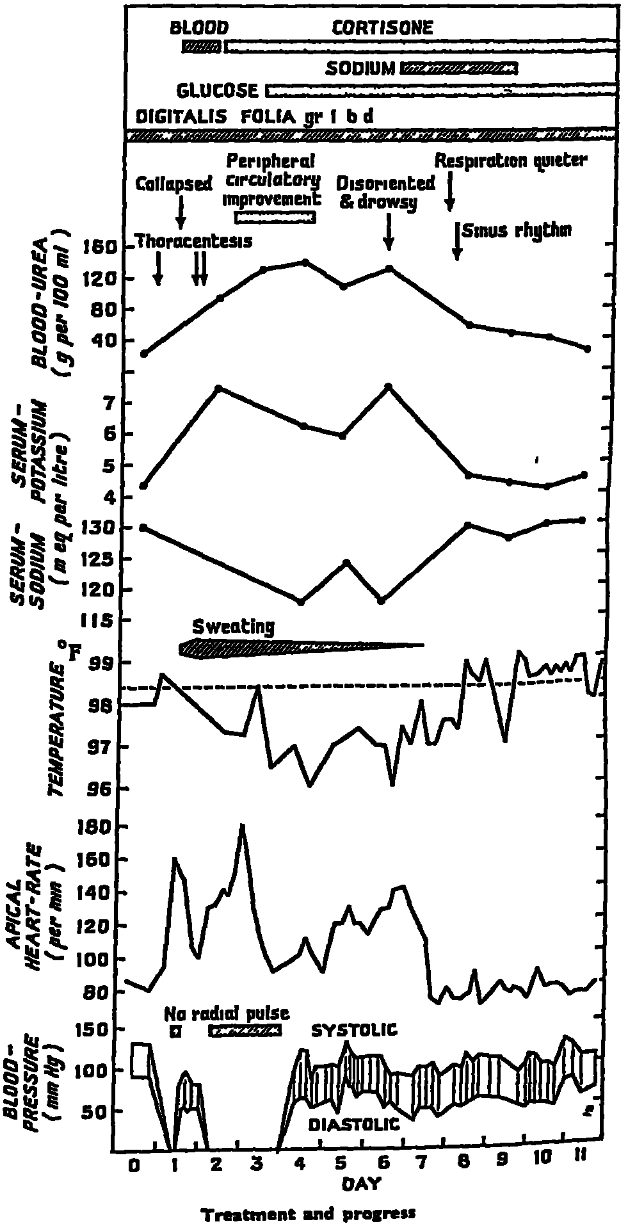
Treatment

As on her previous admissions she was given anticoagulant therapy During the seventeen days following her admission three thoracenteses and one abdominal paracentesis were done, 13 7 litres of fluid being withdrawn in this way, 8 5 litres of it from the chest During this period her weight decreased by 21 lb

After the third thoracentesis a considerable pleural effusion still showed on radiography of the chest , so a fourth thoracentesis was done at 4 P M on Feb 12 (day 0 in the accompanying table and figure) Towards the end of the aspiration the fluid was bloodstained

Progress

Her pulse rate and blood pressure remained steady over the next six hours Next morning, eighteen hours later (at 10 A M on day 1), she collapsed She had not been too well during the night, and her pulse had been a little weaker than usual at 7 A M and again at 9 A M She was sweating profusely and was extremely pale She was cold, her blood pressure was unrecordable, and her radial pulses were impalpable Her heart rate, counted at the apex, was 160 a minute Her peripheral veins were collapsed and did not fill easily when obstructed by digital pressure, and her respirations were rapid She was, however, fully conscious and coöpera-



Treatment and progress

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FLUID INTAKE, URINARY EXCRETION, HÆMOGLOBIN, AND CORTISONE TREATMENT

Day no	Fluid intake (ml.)	Urine							Hb (g. per 100 ml.)	Endogenous creatinine clearance (ml. per min.)	Cortisone (mg.)
		Volume (ml.)	Sp. gr.	Total osmolarity (m. osmol per litre)	Sodium (m.eq.)	Potassium (m.eq.)	Chloride (m.eq.)	Urea (g.)			
0*	2040	850			5.2	6.1			10.5		
1	1445	350							6.7		
2	2195	80							20.1		200
3	2200	261	1.013	360	0.8	14.4	8.0	1.8	17.9		200
4	2255	688	1.014–1.022	390–505	1.4	35.4	5.0	9.0	16.7		200
5	1660	629	1.011–1.028	510–610†	0.8	18.6	6.3	13.8	17.3	35	150
6	1520	649	1.010	470	0.8	17.0	11.9	10.6	14.6		150
7	3348	636	1.013–1.021	560–590	1.9	24.0	10.6	12.5			75
8	3701	898	1.012–1.015	440	2.9	35.5	10.9	17.8	14.0		50
9	2343	836	1.020–1.022	580	2.5	37.3	16.1	20.9	14.6		75
10	2938	620	1.020–1.024	610	3.2	29.8	22.0	12.3	14.6		50
11	2151	586	1.015–1.022	610	2.7	27.7	23.9	14.7	14.2	55	50
12	2125	789	1.012–1.021	570	2.8	28.4	24.6	15.8	14.0		
13	2615	1186	1.014–1.016	610	41.0	81.8	142.0	13.1	13.3		

* Day of thoracentesis.
† Serum total osmolarity = 305 m. osmol per litre.
Sugar was absent from all urine passed.
Occasional red cells were seen in urine passed on day 3 only; casts in urine passed on days 3 and 4.
Albumin +– in some of the urine passed on days 3, 4, and 5, and + on days 6, 7, 8, and 9.

tive. Her right chest was dull to percussion all over, and it was obvious that she had bled into the pleural cavity. Her hæmoglobin had decreased to 6.7 g. per 100 ml., and her prothrombin activity was 33%. Intravenous vitamin K_1 10 mg. was given, followed by intramuscular vitamin K_1 10 mg. t.i.d., and a blood transfusion was started with some difficulty through two drips with pumps attached to each. Owing to venous constriction it took twelve hours to give the first 8 pints. At first the patient responded well, her colour began to improve, her pulse became palpable at the wrists, and her blood-pressure rose to 80/50 mm. Hg. Her heart rate fell to about 95 a minute. She relapsed in the early hours of day 2, when her trachea was displaced to the left and her breathing was more difficult. She was also somewhat cyanotic, and her heart rate was 130 a minute. Thoracentesis was done and 1.5 litres of fluid, containing hæmoglobin 7.2 g. per 100 ml. was withdrawn. This was followed by improvement in her general condition, and a further 1.5 litres was withdrawn later in the day.

By 9 A.M. on Feb. 14 (day 2) twelve bottles of blood had been transfused, and she was being given her thirteenth; but she remained collapsed. Her face was still pale, though much less so than twenty-four hours previously, and her hands and feet were cold and cyanotic. She was still sweating profusely. Her neck veins were distended to the angle of the jaw on the right side but only half-way up her neck on the left (the level to which they had been before Feb. 12 (day 0)). She appeared moribund though still fully conscious and oriented. Her radial pulses were again impalpable, and her blood-pressure could not be determined. Her heart rate was 130 a minute. No more blood was transfused, because it was thought that the blood lost into the chest had been replaced. Her hæmoglobin was 17.5 g. per 100 ml. in venous blood and 20.1 g. per 100 ml. in capillary blood. She was given cortisone 200 mg. a day by mouth, and this was followed, during the next six hours, by improvement in her clinical condition and peripheral circulation.

Further improvement took place over the next seventeen hours, particularly in the circulation to the extremities; but, by 10 A.M. on day 3 it was still impossible to record her blood-pressure and to detect her radial pulses. Her hands were now warmer and pinker, and there was a quick return of blood to areas blanched by pressure.

Her radial pulses, which had been absent for fifty-six hours, returned by 9 A.M. on day 4, when her blood-pressure, unrecordable up to then, was 90/55 mm. Hg. By this time her twenty-four-hour urinary output, which had been poor, had returned to volumes similar to those before the bleeding. The table records data relevant to kidney function. The heart rate was then 90 a minute. Later on day 4 and on day 5, however, her heart rate rose to 120 a minute. The serum-sodium level on day 4 was low (118 m.eq. per litre) and serum-urea level 138 mg. per 100 ml.

On days 5 and 6 her heart rate increased and her general condition deteriorated, and on day 6 she had mental confusion and drowsiness and felt weaker. It was estimated (Black 1953) at this stage that she had a sodium deficit of about 670 m.eq., and 178 m.eq. of sodium was given as sodium bicarbonate orally on the night of day 6. Her condition improved, and she was given the remainder of the calculated deficit early on day 7. During day 7 her heart was regular at a rate of 85 a minute. Her serum-sodium level rose to 130 m.eq. per litre and her blood-urea level fell to 34 mg. per 100 ml. During the subsequent days she progressively became much less tired and began to read and to take an interest in her surroundings. The administration of further sodium had no effect on her serum-sodium level or her clinical condition. Her renal function improved (see table), and her general condition nine days after collapsing was better than before her thoracentesis.

Her subsequent course was very good until, six weeks later, she died suddenly after an attack of pain in her chest. No necropsy was done, but she was thought to have had a large pulmonary embolus.

Discussion

It has been routine practice for many years in this ward to maintain all patients with congestive failure on anticoagulant therapy. Many such patients have had repeated aspirations of fluid from accumulations in chest and abdomen, and in none previously has there been any significant bleeding.

In this patient the extent of the bleeding was not recognised until she collapsed, because much of the bleeding took place overnight. Her hæmoglobin at the time of collapse was 6.7 g. per 100 ml., compared with 10.5 g. per 100 ml. the day before (see table), suggesting that there had been considerable hæmodilution. The patient received 13 pints of cross-matched blood, and it is unlikely that the blood lost into her right hemithorax could have been much more than this. After aspiration of about six pints from the thorax there was still obviously much more remaining. More was not aspirated because by then her respirations were not being embarrassed by the effusion, and as it was felt that further aspiration might precipitate further bleeding.

Despite adequate replacement of blood, however, initial improvement was not maintained, and the patient was moribund and pulseless, with unrecordable blood-pressure and pronounced peripheral vasodilatation. Her condition called to mind the picture of experimental "irreversible shock" in animals (Wiggers 1950) which supervenes on blood loss of some duration. Lasche et al. (1951) have reported adrenal insufficiency in chronic heart failure, and it was thought that acute prolonged oligæmia, superimposed on the "stress" of heart failure, might have led to exhaustion of the suprarenal glands. This condition is associated with peripheral vasodilatation (Remington 1951) and hypotension unresponsive to the usual forms of therapy (Steenburg and Moore 1955). Cortisone was given and there did appear to be a general improvement Noradrenaline was not given to raise the blood-pressure, because blood-vessels lose their responsiveness to it in the absence of corticosteroids (Ramey et al 1951, Fritz and Levine 1951, Zweifach et al 1953), which appear to play a permissive rôle in the maintenance of vascular tone (Williams et al 1954) Moreover noradrenaline decreases renal blood flow, which was to be avoided

This patient appeared to have developed, by the fourth to sixth day after bleeding, a true depletion of sodium even though she was in congestive failure with systemic œdema She was sweating profusely for six days and had been taking water by mouth but no significant amounts of sodium In heavy sweating a person may lose several litres a day containing as much as 40–50 m eq of sodium per litre Although the daily urinary excretion of sodium decreased during the period of profuse sweating, a considerable amount of sodium must have been lost Cort and Matthews (1954) have warned that giving sodium to hyponatræmic patients who are in congestive heart-failure and not excreting sodium, and in whom there is already some œdema, may do little more than increase the œdema, as Elkinton et al (1952) found in some patients, although other patients improved with salt, and their œdema did not increase Black and Litchfield (1951) gave salt to patients who had been admitted with congestive failure and in whom œdema had subsided but who had deteriorated clinically and showed low serum sodium levels There was resulting improvement without return of œdema

Accordingly caution was exercised in giving sodium It was, however, followed by clinical improvement in well-being, mental function, and heart rate The serum potassium and serum urea levels fell, and the serum-sodium level rose There was no detectable further increase in œdema, the distension of the neck veins did not increase, and the lung base remained clear

The sodium depletion was probably only relative because, with a similar degree of œdema a year previously, the patient's total exchangeable mass of sodium had been about 360% of the mean normal value (Flear et al 1957) In the presence of œdema and with a serum-sodium level of 118 m eq per litre the body sodium is unlikely to be less than normal The depletion is therefore regarded as an acute lowering of the serum sodium level from the loss of sodium

For a time (days 1–3) the patient passed very little urine in spite of an unrestricted intake of fluids by mouth This was probably partly due to heavy sweating, but some renal damage may have resulted from the early period of oligæmia on day 1, when her blood-pressure was unrecordable for four hours A lowered filtration pressure in the glomeruli may also have been a contributory factor At this stage the blood-urea level was 90 mg per 100 ml and the serum-potassium level 7 5 m eq per litre

Despite the absence of recordable blood-pressure for about sixty hours there was little evidence of any significant damage to the kidneys Thus casts, red blood-cells, and albumin were present in the urine for only a few days The kidneys continued to deal with the electrolytes differentially, and their concentrating power also appeared satisfactory Presumably, in the absence of oligæmia, the renal blood flow, when the blood-pressure was unrecordable, was sufficient to prevent damage from anoxia, just as the cerebral circulation was sufficient to keep the patient conscious, rational, and cooperative

This case draws attention to some of the consequences of delay in replacing lost blood Chronic congestive failure is not a contra-indication to the rapid and complete replacement of blood after hæmorrhage, and in this patient there was never any evidence of a rise in venous pressure or of pulmonary œdema Sodium depletion resulted from excessive sweating, and a full recovery was not made until sodium had been replaced adequately as well as blood

We wish to record our appreciation of the help afforded by Sister V J Humphries and her staff in the care and study of this patient, who was in the care of Dr O Brenner, consultant physician to Queen Elizabeth Hospital, to whom we are indebted for permission to publish and for advice in presentation Dr H J Yardley, late of the department of experimental pathology in the University of Birmingham, kindly undertook estimations of osmolarity Other investigations were made by the departments of biochemistry and hæmatology at the hospital

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POTT'S PARAPLEGIA OF FIFTY YEARS' DURATION

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THE outlook for a patient with unrelieved Pott's paraplegia is poor at the present time , fifty years ago many would have considered it hopeless The following case is therefore of interest

Case-report

History

Born in 1899, the patient was a normal child until he was 3 years old • But at 3 years 8 months he attended the Royal National Orthopædic Hospital because of weakness of his leg and a feeling of "sand in his shoes" The hospital wished to admit him but his mother could not afford it Instead he was placed on a Bradford frame on which he lay at home for about a year

At the end of this time he could walk a few steps and was sent to a convalescent home He lay there for many weeks in a special box He was very miserable and received no teaching, and returned home about a year later, incontinent and dirty His mother then nursed him until he was 7, when he was admitted to St Thomas's Hospital Two operations for a paravertebral abscess were performed (details not available) The wounds had not fully healed when he went home some months later and he still had paraplegia

In August, 1907, at the age of 8, he was admitted to Cheyne Walk Hospital for Sick and Incurable Children, and for seven years he lay there flat on his back, with weights on his legs and a bottle between them His education was entirely fortuitous, depending on Society ladies who, out of charity, adopted his cot and taught him to read, write, and crochet He still, fifty years later, corresponds with his benefactors

In 1914, after a change of staff in the hospital, he got up in a jacket and gradually became mobilised in a wheel chair This mobilisation, after seven years on his back, took three years, and he was discharged at the age of 18 Three months' convalescence was paid for by his self appointed guardians who also sent a wheel chair By much determination he was able to get around the meadows and keep himself clean He kept careful watch on his bowels and regulated them by noticing the action of his diet, much as a patient with a colostomy controls its action He had a slight warning before defæcation

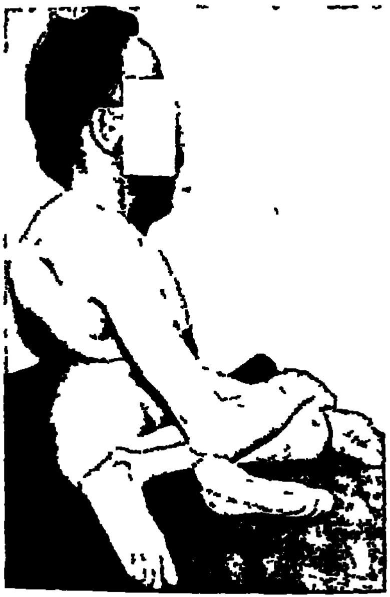
Fig 1—Present condition showing old operation scar over dorsal kyphus and typical posture adopted at rest. The wasting and deformity of the lower limbs contrast with well-developed upper trunk and arms

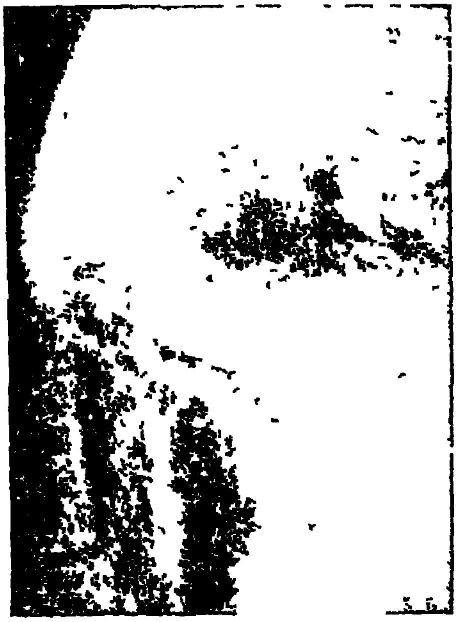
Fig 2—Radiographs of spine Old tuberculous caries of lower dorsal spine and almost complete destruction of T6–12, with marked angular kyphus and an old calcified paravertebral abscess at this level

He returned home in 1917 and remained with his mother till her death in 1952 He was given a typewriter by his sponsors, and taught himself to type with the aid of an instruction book He gradually began to make an income by typing, knitting, and crochet work His health remained fairly satisfactory except for occasions when he was troubled by episodes of loin pain and shivering attacks For these he took aspirin and hexamine tablets, prescribed by his doctor

Some time in 1931, his pain and fever became more severe and his urine cloudy On his own initiative he bought a catheter, carefully cleaned it, lubricated it with soft paraffin carbolic vaseline, and passed it on himself, copying the action he had seen many years before when he had been in hospital Filthy urine escaped, and he was so amazed at the relief that he decided to continue the practice He found that, if he did this night and morning, he was dry between catheterisations and need no long carry a bottle around He continued this until July, 1955, when he was unable to pass his catheter If the bladder was allowed to get over distended, he had flexor spasms of his legs, sweating, and general discomfort This provided some warning but the spasms made catheterisation harder A no 8 catheter was normally used, a no 7 being kept in reserve for difficult occasions

Since 1933, he has led an active life, using a 'Merlin' chair indoors and a wheel chair outside He usually wears a plastic spinal support Since the death of his mother in 1952 he has lived with his brother He has a separate upstairs room and conducts his own affairs He types sections for the *Encyclopædia Britannica* and is secretary of a Bible reading class

He was admitted to the West Middlesex Hospital in July, 1955, with retention of urine after he had failed to pass a catheter

Examination

He was a small, alert, cheerful man in good general health, with a rather pigeon shaped chest but no evidence of pulmonary disease (fig 1)

Spine and upper limbs—He had severe kyphosis in the region of the sixth to tenth thoracic vertebræ, and an irregular linear scar about 6 in long over this region (presumably the site of operations for paravertebral abscess) The upper limbs were well developed

Pelvis and lower limbs—The paralysed lower limbs and buttocks were grossly wasted An irregular scar overlay the left greater trochanter, the site of previous pressure sores The right hip was dislocated with 2 in shortening of the right leg Both hips had 50° fixed flexion deformity, but full

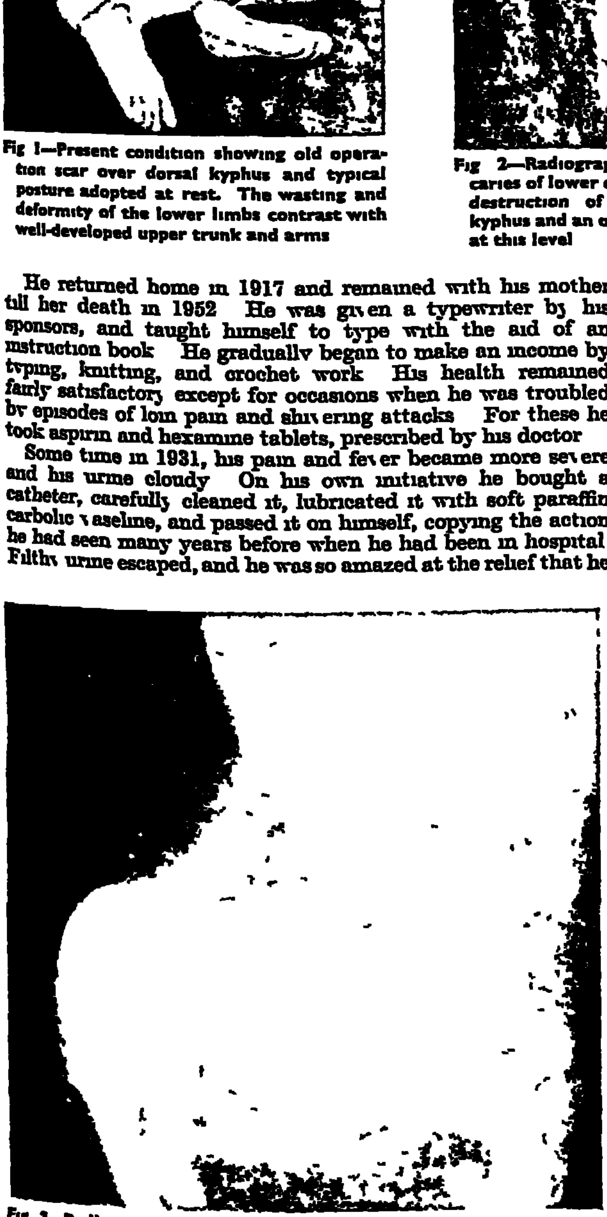
Fig 3—Radiograph of lumbar spine and pelvis The lumbar spine is unaffected but the right sacro-iliac joint shows evidence of old tuberculous disease The dislocated right hip prostatic calculi, and calcified mesenteric glands are clearly shown but no opaque renal calculi

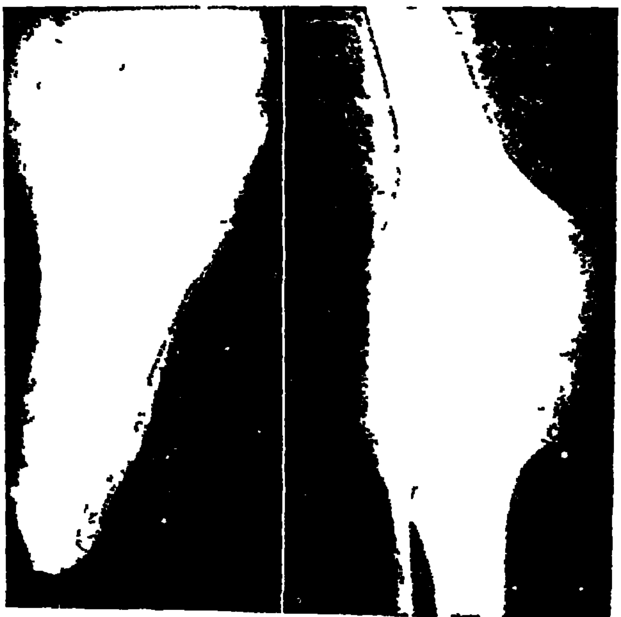
a   b

Fig 4—Radiographs of foot and knee. Note, *in the foot (a)*, the small size and the gross subluxation at mid tarsal joints and in the knee (*b*), the distribution of osteoporosis and Harris's lines

passive flexion was possible There was also 20° fixed adduction and internal rotation of the right hip, but almost full adduction and 20° abduction were possible in the left hip Both knees had flexion contractures, the right 50° and the left 40° Full passive flexion was possible The feet were both very small and were dislocated at the subtalar joint with 90° inversion The feet were 7½ in long and the tibiæ 6 in long—measurements similar to those of a child aged 6

Neurological examination revealed complete paraplegia at the *neurological level of* *T7, with no abnormality above this* level Below it there was complete loss of sensation to pinprick, posture, and vibration. Pinprick in the lower limbs produced a cross extensor response by which the patient knew that something was happening

The reflexes were normal in the arms, and the knee jerks were brisk and equal The ankle jerks and abdominal reflexes were absent, and the plantar responses doubtful There was a slow response in the sphincteric reflex

Obvious muscle wasting accompanied complete paralysis of all muscles below the level of sensory change The excellent function of his upper limbs, however, enabled him to move the matchstick lower limbs into a suitable position with a quick flick of the wrist and to move about with great agility

Investigations

Culture of the urine produced a heavy growth of *Streptococcus fæcalis* The blood-urea was 25 mg per 100 ml and the hæmoglobin 13 0 g per 100 ml

A plain X-ray film of the abdomen showed prostatic but no renal calculi Radiological features are illustrated in figs 2–4

Course

Bougies were passed, with some difficulty owing to a tight posterior stricture, and a Foley catheter left in for seven days A course of sulphafurazole (‘ Gantrisin ’) tablets was followed by aureomycin for five days

Further investigations were felt unjustifiable in a patient who was able to look after himself so satisfactorily After some difficulty on the first two or three occasions, he was able to re establish his catheterisation routine and was discharged home

Discussion

Among the unusual features of this case are

1 Survival despite inadequate treatment and a very poor prognosis

2 Absence of renal calculi or gross urinary infection despite many years' recumbency, and self catheterisation for twenty years

3 Paralytic dislocation of the right hip

4 Deformities and absence of growth of the lower limbs associated with paralysis and disuse

5 Rehabilitation to a self-supporting cheerful existence

Prognosis of the paraplegia—The complete flaccid paralysis, the sphincter disturbance, and the loss of vibration sense gave a poor prognosis for neurological recovery

Prognosis for life—The mortality-rate in various series of cases of Pott's paraplegia is given as 21% (Butler 1935, Seddon 1935), 25% (Dobson 1951), and 28% (Girdlestone 1940), in the series reported by Bosworth et al (1953) there were many advanced cases and the mortality-rate was over 60%

Urinary infection and stones—Guttman (1953) states that 22% of paraplegic patients develop renal calculi, and it is remarkable that our patient, during several years' recumbency, did not do so Occasional attacks of pain are probably due to mild recurrent urinary infection but up till his recent admission no long courses of antibiotics had been given That careful daily catheterisation can be so innocuous corroborates statements by Girdlestone and Somerville (1952) In this case no satisfactory automatic bladder was developed

Paralytic dislocation of the right hip—It seems likely that the dislocation of the right hip was a result of paraplegia Blundell Jones (1954) records such a dislocation in children with flaccid or spastic paraplegia It is usually accompanied by a valgus deformity of the femoral neck and is more common in children paralysed before the age of 2 It is attributed to lack of the moulding forces in the bone which are produced by normal muscle tone on weight-bearing

Deformities of the lower limbs are caused by osteoporosis, lack of growth, and muscle imbalance

Abramson and Kamberg (1949) attributed the bone changes to osteoporosis—i e, disturbance of the laying down of the bony matrix, rather than an alteration in the calcium deposition in bone, but they found that osteoporosis was commonly associated with soft tissue calcification and formation of renal stones These changes were largely prevented by ambulation within two years of injury Lack of growth is probably due to epiphyseal arrest, which is another result of long continued immobilisation (Gill 1944, Sissons 1952)

The feet also show changes resulting from osteoporosis, lack of growth, and muscle imbalance The adduction and inversion deformity is probably the result of prolonged invalid posture It causes little inconvenience since the legs are no longer used

Rehabilitation—Special hospitals have provided new hope for paraplegic patients This case illustrates how much can be done by simple determination alone, and provides many useful reflections for those confronted with such extreme disability

I should like to thank Mr W J Ferguson, M S, of the West Middlesex Hospital, for permission to publish this case, and Mr J I P James, M S, of the Royal National Orthopædic Hospital, for his helpful criticism

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Medical Societies

ROYAL SOCIETY OF MEDICINE

Aortic Stenosis

A MEETING of the society's section of medicine on April 18, with Dr G E BEAUMONT in the chair, discussed aortic stenosis

Dealing with the medical aspects, Dr RAYMOND DALEY said there was a history of rheumatic fever in more than half his cases and a predominance of males Death occurred between one and two years after the onset of symptoms He emphasised the frequency of sudden death, presumably from ventricular fibrillation He thought that the finding of a thrill in the neck was much more important than that of a thrill in the aortic area The largest group of patients lay between the ages of 40 and 59 years, and of 23 patients in this group 18 had calcification of the aortic valve He had studied the brachial artery pressure pulse and while prolongation of the upstroke time was a good indication of aortic stenosis, there were many other factors to be taken into account such as the dynamics of the left ventricle and the characteristics of the recording system Using Mr Ian McMillan's system of taking cine photographs of the aortic valve, as well as other hæmodynamic data, they had come to the conclusion that the critical orifice size was 0 5 sq cm Dr Daley divided cases of aortic stenosis into four groups depending on severity In the first group the orifice was greater than 0 5 sq cm and there were no hæmodynamic effects In the second group the orifice was less than 0 5 sq cm , there were no symptoms, and there were no changes in hæmodynamics, except following effort, when the end diastolic pressure rose in the left ventricle In the third group there were symptoms, and in the fourth group there was failure of both left and right ventricles

Mr **Andrew Logan** discussed the surgical treatment of aortic stenosis He had performed an aortic valvulotomy, as he called it, in 31 cases In 7 he believed the condition was congenital, and in 17 acquired , in 7 the aortic stenosis was accompanied by mitral stenosis In 6 of the 7 congenital cases subaortic stenosis was thought to have been excluded by angiocardiography , in 5 of them aortic incompetence was produced or increased, but all had improved for the duration of the follow-up period (at least three years) In 1 patient there was gross dilatation of the heart in the immediate postoperative period, but it later returned to its preoperative size The indication for operation in this group had been evidence of extreme left ventricular hypertrophy on the electrocardiogram In the 7th patient unfortunately no angiocardiogram had been performed, subaortic stenosis was found at operation, and sudden death occurred five hours later In the 17 patients with acquired pure aortic stenosis the symptoms were such that none of them were expected to survive more than eighteen months without the aid of surgery 15 out of the 17 had calcified aortic valves, 9 had died, 4 in the immediate postoperative period or during the operation Of the 8 survivors all had some increase in aortic regurgitation, but 5 had improved from the symptomatic point of view and 1 had lost all symptoms although he had been in heart failure with angina before the operation Of the 7 patients with aortic stenosis and mitral stenosis there was improvement in all

Mr Logan said that he had been criticised as deducting a few months of life from one case of aortic stenosis to add it on to another by his surgical efforts, but he felt that the results in the surgery of aortic stenosis were not intolerable to any surgeon brought up on cancer In order to get better results he would like to operate earlier, but since the prognosis was uncertain until late it would be necessary at this stage to make a series of those with a pressure gradient across the aortic valve of, say, 50 mm Hg, and use alternate cases as controls Describing his technique Mr Logan said he incised the anterior wall of the left ventricle and introduced and opened a dilator in the aortic valve while the head vessels were clamped He thought this was better than the use of a sharp instrument because it tended to select the commissures more accurately He was impressed, however, with McMillan's work showing that if the aortic cusps were malformed valvotomy was useless He noted that ventricular fibrillation was common and that cardiac massage was difficult because of the great thickness of the left ventricular wall Immediate electric defibrillation was necessary He concluded by saying that he felt that blind dilatation of the aortic valve produced as good results as any operative technique yet devised, including open surgery under hypothermia

Dr **J F Goodwin** discussed work done with his colleagues at the Postgraduate Medical School, Dr Abdin, Dr Nielson, and Dr Doyle The cardiogram in severe aortic stenosis showed deeper T-wave inversion (due to myocardial ischæmia) than in hypertension and coarctation A deep s wave in lead V5 indicated additional right ventricular hypertrophy In severe stenosis the systolic upstroke time of the arterial pulse varied directly with the pulse pressure, but this was not true for mild stenosis or incompetence Measurement of systolic upstroke time in relation to the pulse pressure in a number of beats during the Valsalva manœuvre was a better guide to the severity of stenosis than examination of the resting pulse wave

Mr **W P Cleland** said he had performed an aortic valvotomy on 15 patients In 1 the ætiology was believed to be congenital, in 9 there was pure calcific aortic stenosis, and in 5 there was additional mitral stenosis 3 patients had died and in the remainder the longest follow-up period was three years All patients were in Dr Daley's third group, and he disagreed that they should have been in the second group He was fairly optimistic about the results; all the patients were holding their own The pressure gradients across the aortic valve varied between 50 and 150 mm Hg, and he was content with a 50% reduction in the gradient, since it was dangerous to go too far in these cases He thought that the trans-ventricular approach with a blind operation was satisfactory, but he hoped in the future to have a bloodless field and a still heart

Dr **Ronald Gibson** said that at the Brompton Hospital and at Guy's Hospital direct puncture of the left ventricle had been performed in 60 patients The procedure was simple and safe, but the systolic pressure gradient across the aortic valve obtained by this method must be interpreted with caution [1] The pressure gradient depended not only on the size of the orifice but also on the stroke volume, which was related to cardiac output heart-rate, and the degree of aortic regurgitation A gradient of up to 100 mm Hg had been found with dominant aortic regurgitation There was little correlation between the size of the pressure gradient for the ejection period and the surgeon's estimate of valve size This was due to differences in stroke volume There was a good correlation between the calculated aortic valve area and the prolongation of corrected arterial upstroke time with estimated valve size

Mr **Ian Hill** had operated on 2 patients with isolated aortic stenosis and 10 with aortic stenosis and mitral stenosis He had found it difficult to assess the severity of the aortic stenosis by manometry at operation because of the varying cardiac output, and he now passed a sound in order to assess the size of the orifice

Mr **D N Ross** said that Sir Russell Brock had now performed 100 aortic valvotomies using the transventricular approach [2] He agreed with Mr Cleland that one must not persist in trying to abolish the pressure gradient, because of the danger of ventricular fibrillation He did not know the exact mortality figures but they were about 10% They had used direct vision with hypothermia in about 15 cases of congenital aortic stenosis, and they had found a surprisingly high incidence of subaortic stenosis (11 cases out of 100) Calcification-of-valve stenosis was so common that if calcium was absent in a patient more than 30 years old, the stenosis was probably subvalvular, and this could be confirmed by taking withdrawal pressure tracings across the aortic valve on the operating-table Subaortic stenosis was treated by splitting from below, using the transventricular route

Mr **B B Milstein** noted the high mortality in the early cases and attributed it to their advanced nature (they were mainly in Dr Daley's group 4) He did not now operate on patients with heart failure unless this had been treated successfully for three months Angina and syncope were usually relieved by valvotomy, but dyspnœa often remained and was attributed to fibrotic changes in the myocardium

Dr **C J Gavey** emphasised the importance of the symptom of weakness in bad cases of aortic stenosis it usually indicated a poor prognosis

Mr **Ian McMillan** was asked about the varieties of abnormalities of the aortic valve as shown by his method of cinephotography he replied that fusion of one commissure producing the fish-mouth type of stenosis was the most common and had been found in 28 out of 47 cases

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[1] Fleming P Gibson R *Thorax* 1957 12 37

[2] Brock R C *Brit med J* May 4 1957 p 1019

ASSOCIATION OF CLINICAL PATHOLOGISTS

THE 58th *general meeting of the association* was held at Torquay on April 11

Radioactive Materials and the Pathologist

Introducing a symposium on this subject, Prof D H COLLINS (Sheffield) said that where possible the pathologist should collaborate with a team of medical scientists and physicists, but the use of isotopes would undoubtedly become wider and every pathologist should know about them To enable him to assess the risks the pathologist must be informed of the radiation history of every piece of potentially radioactive tissue, cadaver, or other biological material coming into his department The purpose of the symposium was to arouse the interest of clinical pathologists so that they might play their full and proper part in the coming era of radiation medicine

Discussing the injurious biological effects of radiation Dr R H MOLE (Harwell) said that interference with the processes of repair was a characteristic feature, and one basic problem was whether malignancy was a sequel to prolonged and inadequate repair or whether it was due to some sub microscopic cellular change such as "mutation" Another characteristic feature was the time required *for* biological damage to show itself The time scale was even more drawn out in man than in animals, so that the sperm count might be at a minimum six to ten months after a sublethal exposure A limited exposure to radiation in early adult life might shorten the life span In fact the sequels of low level irradiation might conveniently, if not very illuminatingly, be described as premature ageing Experience had shown that 1 µg of radium in the body might cause bone tumours Thus 0 1 µg was taken as the body burden which would not do harm—i e, the maximum permissible level (M.P L) for occupational exposure The M P L for other radioactive materials—e g, radioactive strontium—was based on this and took into account the amount of radiation energy absorbed in tissue, differences from radium in degree of uniformity of deposition, and metabolic differences in excretion and in uptake from food and water

Dr R C CURRAN (Sheffield) said that many of the radioactive isotopes in use in hospitals were given in trace doses, and though it was always wise to avoid all unnecessary radiation in view of the lack of knowledge of the effects on man of even a small increase over his "normal" radiation background, the hazard from handling these was comparatively slight Some isotopes, however, including ^{131}I, ^{198}Au, and ^{90}y, were given in far greater doses for therapeutic purposes When the pathologist was asked to examine a surgical specimen or perform a necropsy on a body containing such large quantities of radioactive material, it was essential for him to have all relevant information The hospital physicist should determine the residual radioactivity After dissection of a highly radioactive specimen, all appropriate areas of these departments should be monitored by the physicist, who would detect any persistent foci of radioactivity that must be eliminated

Control of the Hypothermic State

Dr P I REED (London) described investigations carried out in the department of neurosurgery of the Maida Vale Hospital on 31 patients undergoing craniotomy under hypothermia for vascular abnormalities The study was designed to demonstrate possible differences in biochemical findings compared with cardiac surgery, and to show what screening tests, if any, were of value in anticipating any of the recognised or theoretical complications of hypothermia Significant changes were found in the serum bicarbonate, blood sugar, and blood urea levels, the bicarbonate decreasing from 28 0 m eq per litre preoperatively to 24 2 at 27 5°C and 24 4 postoperatively, the blood sugar rose from 107 mg per 100 ml to 207 at 27 5°C and 148 postoperatively, and blood urea from 25 mg per 100 ml to 30 and 40 respectively Changes in sodium, potassium, calcium, chloride, prothrombin fibrinogen, coagulation time, and platelet count were not significant Neurosurgical patients were much less prone to acid base imbalance than those who had undergone cardiac surgery stimulating ventricular fibrillation, and they were less likely to develop liver damage and in consequence less prone to abnormal bleeding The following tests were therefore worth carrying out serum potassium and bicarbonate before and during hypothermia (as a guide to correcting acidosis) and blood sugar and urea (to exclude diabetes and early uremia respectively) Other tests were indicated only when complications, unassociated with hypothermia were suspected There was at present no way in which the laboratory could anticipate any danger due to hypothermia itself, apart from helping to exclude those patients in whom hypothermia was contra indicated

Tryptophan Metabolism in Phenylketonuria

Dr C M B PARE, Dr M SANDLER, and Dr R S STACEY (London) presented evidence of a defect in the 5 hydroxyindole pathway of tryptophan metabolism in phenylketonuric patients They showed that there was a significant decrease in serum 5 hydroxytryptamine (5 H T) levels and urinary excretion of 5 hydroxyindoleacetic acid compared with control groups Surprisingly high levels of serum 5 H T were found in some mentally defective children in the control group The low levels of circulating 5 H T might be related to mental deficiency in phenylketonurics, for certain evidence suggested that 5 H T was functionally important in the central nervous system The improvement in mental function in some phenylketonurics on a low phenylalanine diet might be related to the rise in circulating 5 H T which had been observed in a small number of patients undergoing this form of treatment A possible form of treatment was the administration of 5 hydroxytryptophan, which passes the blood brain barrier and is metabolised to 5 H T in the central nervous system As a working hypothesis to explain the 5 H T deficiency, it was suggested that the defect in hydroxylation of phenylalanine may affect hydroxylation of tryptophan, either by providing competition for a limited hydroxylating mechanism or by the inhibition of tryptophan hydroxylase by phenylalanine or one of its metabolites

Proteins of Normal Urine

In the technique of Grabar and Williams, proteins are first separated electrophoretically and then identified immunochemically by means of the precipitin reaction

Dr G H GRANT (Shrewsbury) had analysed in this way the urine proteins of a small number of normal men women, and children, using three rabbit antisera prepared against serum proteins, urinary tract proteins, and the Tamm Horsfall mucoprotein respectively Normal urine contained small quantities of a large variety of different proteins Many were electrophoretically and antigenically identical with the serum proteins The glomerular pores must be much larger than used to be supposed, but they were apparently not wide enough to let through the large β lipoprotein molecule There were probably at least 3 proteins in the urine unrelated to the serum proteins and so presumably arising from the urinary tract The principal one was the mucoprotein described by Tamm and Horsfall, which was precipitated from normal urine on increasing the concentration of NaCl The high proportion of "α globuline" found in normal urinary protein by moving boundary or paper electrophoresis was due *not to differential tubular reabsorption of* plasma proteins but to urinary-tract protein

Biochemical Treatment in Renal Failure

In the Glasgow Northern Hospital Group, in the past seven years, 12 obstetric cases out of 13 with acute renal failure have been successfully managed by conservative treatment Dr J W CHAMBERS (Glasgow) added that in the past three and a half years some 20 cases of uremia had been treated and had recovered, all had normal serum urea levels before discharge (except 2 with ureter transplanted to colon) Half these patients had acute renal failure, the others were mainly patients with renal insufficiency associated with severe electrolyte depletion or toxemia Maximum serum urea levels ranged from 100 to 500 mg per 100 ml Half the patients were semicomatose or confused, and a third had an episode of circulatory failure Treatment was guided by the principles and practice of Professor Bull, with special attention to rectification of electrolyte depletion as indicated by the history, clinical status, and biochemical findings In 75% of cases the prognosis at the outset was very bad 3 of the most severely ill patients were known to be well two and a half years later

Blood-loss Following Trauma

Dr ELIZABETH TOPLEY (*Birmingham*) said that comparison of different red cell volume techniques in parallel showed that equally accurate results were obtained using ^{51}Cr labelled patient s blood ^{51}Cr labelled bottled blood, and ^{32}P labelled patient's blood Comparison of clinical assessments of blood loss with red-cell volume studies had defined the common degree and timing of blood loss in a variety of injuries, and had demonstrated the limitations of clinical assessment Red-cell volume estimates in burns might be inaccurate if more than 20% of the body-surface was involved In spite of this, estimates six and twenty-four hours after injury had increased the usefulness of hourly hæmatocrits as a guide to plasma therapy during the shock stage in extensive burns Inspection of a blood-film taken on admission helped to decide whether red cell volume studies were necessary A loss of more than 25% of the normal red-cell volume had so far not occurred in patients showing less than 1% of microcytes (less than 3 µ) in the head of the blood-films

Complications After Valvotomy

Dr A **Dick** and Dr R **Mathieson** (Glasgow) discussed a series of 41 patients who were subjected to mitral valvotomy during the years 1952–56, 5 died within six months of operation Histological examination of the auricular appendages revealed evidence of rheumatic disease in all but of activity in only 1 of these 5 The necropsy findings indicated that 2 patients died of thrombotic lesions, 1 of cerebral emboli, and 2 of infection within three weeks of operation In 1 of the infective cases two varieties of penicillin-resistant coagulase positive staphylococci were isolated, one from the lung and pleural and pericardial cavities, and one from the blood This patient had profound toxæmia which failed to respond to antibiotics, and at necropsy there was a fibrinous pericarditis and pleurisy, but the classical features of acute infection were absent

Ulceration of the Œsophagus in the Newborn

Dr G R **Osborn** (Derby) said that ulceration of the œsophagus had not been observed in the embryo fœtus or in stillborn babies It was not a consequence of shock In babies born alive, ulceration was uncommon when they had not been intubated If intubation was intermittent or of short duration, little damage might be done to the œsophagus The incidence of ulceration in a nursing-home where intubation was often necessary was 12% when intubation was not undertaken to administer intragastric oxygen, 71% of babies treated with intragastric oxygen had ulceration of the œsophagus Intubation caused pressure atrophy of the epithelium progressing to total destruction Next, but very early, there was intense congestion, often associated with hæmorrhage into the muscularis mucosæ and main muscle coat Later, large bacterial masses might form on the eroded surface and the bacteria might invade the blood stream or become obvious in the gastric mucus Staphylococci were the most important

Venous Thrombosis and Bed Rest

Dr N M **Gibbs** (Derby) observed that venous thrombosis in hospital patients almost always involved the legs and it was decided to try to correlate the site and incidence of venous thrombosis in the legs at necropsy with the duration of bed rest in hospital The vessels of the legs were dissected in 239 cases in which the period of confinement to bed was accurately known 163 patients had died within two weeks of admission to hospital, and the duration of bed rest was assessed to within twenty four hours The incidence of venous thrombosis rose to a peak in patients dying after one to two weeks confinement to bed 76 patients died after from two to twelve weeks in bed, and the age of the thrombi corresponded to the duration of bed rest Venous stasis occurred in two distinct anatomical sites in the leg veins—the intramuscular veins, particularly those of the soleus muscle, and the common femoral vein and tributaries near the inguinal ligament Dr Gibbs concluded that the most important cause of venous thrombosis in the legs in hospital patients was venous stasis due to muscular inactivity Most fatal emboli arose from the common femoral vein and tributaries near the inguinal ligament Emboli detached from the legs were usually small and produced no symptoms

The Doubtful Lymph-node

Dr K R **Dempster** (London) said that lymph node biopsy sections from 102 patients, previously reported either as ' non specific chronic inflammation " or as doubtful ' in the sense that a malignant lymphoma could not be excluded had been re examined and the patients followed up 10 cases could be definitely diagnosed as malignant lymphoma (follicular lymphoma 3, Hodgkin s disease 4, lymphosarcoma 1, and reticulum cell sarcoma 2), unequivocal evidence of which was obtained by later biopsy splenectomy or necropsy Certain histological manifestations of chronic inflammation were particularly likely to cause confusion with malignant lymphoma Reactive follicular hyperplasia was often mistaken for follicular lymphoma but the uniform distribution of macrophages in the follicles and the presence of patent sinuses in the inflammatory condition were useful differential points Many microscopical features of Hodgkin's disease were mimicked by the multiple abscesses of cat-scratch disease and lympho-granuloma inguinale Sternberg-Reed cells were not found in inflamed glands and they indicated Hodgkin's disease

Carcinomatous Neuropathy

Dr A L **Woolf** (Smethwick) had studied intramuscular nerve endings by Coers s techniques in 2 cases of carcinoma In 1, there was collateral reinnervation of denervated muscle-fibres with diffusely swollen nerve-fibres "Strength-duration" curves indicated partial denervation of distal muscles of upper and lower limbs Necropsy showed a bronchial carcinoma with carcinomatous infiltration of cervical, lumbar, and sacral spinal roots between the arachnoidal cul de sac and the ganglion The cord (apart from wallerian degeneration from a metastasis in the pons), cauda equina, and dorsal-root ganglia were practically normal There were many necrotic cerebral metastases, one bordering on the ventricle The 2nd case presented as a predominantly sensory ' peripheral neuritis " Muscle biopsy showed collateral reinnervation, many slightly oval swellings with dark lilac central and paler outer zones (methylene blue) on the nerve fibres and reduction of some end plates to single approximately spherical masses An anaplastic carcinoma was found in the bifurcation lymph-node Plasma cells were mixed intimately with the tumour There was posterior-column degeneration and severe loss of nerve cells from the anterior horns. The medulla showed cellular nodules in the olives and other nuclei suggesting virus encephalitis, but further examination showed the nodules to consist of plasma cells developing Russell bodies and what were probably carcinoma cells The carcinoma cells appeared to have been surrounded by plasma cells from the tumour stroma, during their passage through the blood stream to the brain

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Reviews of Books

The Eye in General Practice

C R S **Jackson**, B M, F.R C S E, ophthalmic surgeon, Royal Infirmary, Edinburgh Edinburgh and London E & S Livingstone 1957 Pp 152 21s

The talent to set out a complicated subject clearly and briefly is rare, but Dr Jackson has succeeded almost completely in his attempt to discuss in 152 pages the aspects of ophthalmology relevant to general practice Little of importance has been omitted and much matter, dear to ophthalmologists but of little concern to other doctors, has been left out

In a preface he says his intention is to describe the common diseases of the eye, to show how to distinguish conditions which need hospital attention from those which can be safely treated by the family doctor, and to help the practitioner to interpret letters from a hospital eye clinic and be able to reassure his patients These aims have been well fulfilled

The book has three main sections In the first part, devoted to the diseases of the eye, an introductory account of examination is followed by chapters on each of the structures liable to disease and separate chapters on refractive error, squint, and glaucoma That on squint (a subject about which there is too much complacency) is of special merit Squint is not only a cosmetic problem which causes much needless emotional hardship to school children but also the commonest cause of the ' *lazy* " *eye—that* is, an eye which has usually lost all useful central visual acuity Dr Jackson emphasises how poor are the results when treatment is delayed and how good when it is early

Part II is devoted to ocular manifestations of cardiovascular endocrine, and metabolic diseases, and diseases of the brain, ear, nose, throat and skin Part III has two informative chapters on subjects about which there is much ignorance—the welfare of the blind and the ophthalmic side of the National Health Service

There is no section which sums up the indications for local cortisone in the eye Though very useful in many eye conditions, cortisone is potentially dangerous in the presence of infection, but this is not clearly stated Not all ophthalmologists will agree that cortisone is justified in the treatment of disciform keratitis, a virus infection of the cornea which, though usually self limiting, has no specific treatment Most of the coloured illustrations are good, but some could be improved by magnifying the view of the eye and eliminating the surrounding face

Though intended for general practitioners, the book should be more widely used Augmented by clinical teaching, it will provide almost all the medical student needs to know, and many consultants will find it useful as a basis for lectures to nurses

The Physician-Writer's Book

Tricks of the Trade of Medical Writing Richard M Hewitt, A M, M D, senior consultant, section of publications, Mayo Clinic, associate professor of medical literature, Mayo Foundation, Graduate School, University of Minnesota Philadelphia and London W B Saunders 1957 Pp 415 63*s*

Guide to Medical Writing

A Practical Manual for Physicians, Dentists, Nurses, Pharmacists Henry A Davidson, M D, editor, *Journal of the Medical Society of New Jersey* New York The Ronald Press Company 1957 Pp 338 $5 00

For books on medical writing we are largely dependent on America Fishbein's classic, *Medical Writing*, was followed a few years ago by the delightful work of Jordan and Shepard, ℞ *for Medical Writing* Our debt to America is now increased by two more works, as different as chalk and cheese, and each more comprehensive than the two earlier books

Dr Hewitt is a pupil of Fishbein and has spent all his life as a professional full-time editor He is soaked in Latin, Greek, and English, and his many references include Demetrius, Horace, Pascal, Boswell, and Hazlitt, this scholarly background explains his dominant interest in English composition and style

The book itself falls into seven parts the whole article or book, the paragraph, the sentence, words, tables and illustrations, preparation of manuscripts, and the ethics of writing The text is amplified and illustrated by 21 appendices, but the material in the appendices could readily have been incorporated in the text

The author's style is discursive and conversational and suggests tape recordings of his seminars His approach to any topic is oblique and full of personal reminiscence, so that it is far from easy to see what he is driving at The book has an unusually full table of contents and a good index

Dr Hewitt's vast experience would have made a more effective book if it had been brought into sharper focus

Dr Davidson—a practising psychiatrist—is a born journalist and his book a superb piece of concise exposition He is everywhere crystal-clear and he never wastes a word, though the style is sometimes slangy The reader is instructed in how to start and organise articles, select catchy titles, hook " reader-interest," and master the tactics of syntax Other sections deal with the treatment of names, numbers, and nomenclature, case-histories, and the writing of summaries and conclusions The most original chapter is *The View from Olympus*, which discloses one way in which editorials are conceived and written

Physiologie und Pathologie des Lymphkreislaufes

Prof István Rusznyák, Mihály Földi, dr med, György Szabó, dr med, I Medizinische Universitäts Klinik, Budapest Budapest Verlag der Ungarischen Akademie der Wissenschaften 1957 *Pp* 836

The pathology of the lymphatic circulation is a neglected subject Many points were elucidated by the work of Drinker and his associates, and this work was summarised in 1941 in Drinker and Yoffey's monograph Succeeding work has been scattered in a variety of journals, but Professor Rusznyak and his colleagues have now drawn it together admirably

After a historical introduction the book describes in detail the anatomy and physiology of lymphatics, with particular emphasis on œdema formation The work done since Starling's day is thoroughly reviewed, including the authors' own investigations and Eppinger's studies on capillary permeability Attention is directed to the importance of Haitinger's fluorochrome method in the study of capillary permeability in pathological conditions and under the influence of various drugs A few sections stained by this method are reproduced in colour photomicrography Finally, the authors discuss the lymphatic circulation and its pathological changes in individual organs There are about 2000 references, some in Hungarian or Russian and not easily accessible The paper, print, and illustrations are excellent

Both the publishers, the Hungarian Academy of Sciences, and Professor Rusznyák and his colleagues are to be congratulated on this addition to medical literature

Liver Structure and Function

Hans Popper, M D, PH D, professor of pathology, Northwestern University Medical School, Chicago, Fenton Schaffner M S, M D, co chairman, Dept of Medicine, Woodlawn Hospital, Chicago New York, Toronto, and London McGraw Hill 1957 Pp 777 $20 00

No doubt it is the new knowledge derived from experimental studies and the widespread use of aspiration biopsy that has led to the steady crop of books on the liver and its diseases The combination of functional and structural investigation has now reached the stage when the two can profitably be correlated in both the healthy and the diseased organ, and this attempt by Professor Popper and Dr Schaffner is extremely successful They have not only achieved their primary objective of correlation, but they have also produced an excellent textbook Its encyclopædic content and the omission of anything about treatment may make it unsuitable for the student reading for higher qualifications, but it will undoubtedly be the standard reference book of its subject for years to come The bibliography contains 3735 references and is supplemented by an appendix, a sort of " stop-press " news bringing each chapter up to date about six months before publication—a remarkable feat The publication and the lavish illustrations are of high quality

The senior author, a student of Eppinger, has shared in producing a worthy successor to Eppinger's famous book As the authors claim, it is " a complete source book on the liver in health and disease "

The Management of Abdominal Operations (2 vols 2nd ed London H K Lewis 1957 Pp 1326 160*s*)—With one exception the contributors to Mr Rodney Maingot's book are the same as in the first edition its character therefore remains unaltered, though its form has been improved by substituting two volumes for the original one, whose bulk sat uneasily in the lap Revision has been undertaken, and almost all sections are fully up to date But it is a pity that no mention is made in the chapter on chemotherapy and antibiotics of the dangers arising from the encouragement of insensitive staphylococci, though the subject is referred to briefly under complications of the wound The special value of erythromycin receives no more than a line under peritonitis, and pseudo membranous enterocolitis is listed under complications of gastric operations, but is not discussed Since the book is concerned essentially with management, operative technique could with advantage be excluded from certain chapters For the postgraduate surgical student, this book will remain a valued guide

The Neurohypophysis (London Butterworth's Scientific Publications 1957 Pp 275 30*s*)—The proceedings of the symposium on this subject held by the Colston Research Society in Bristol last year have been published under the editorship of Prof H Heller

Microbial Ecology (London Cambridge University Press 1957 Pp 388 32*s* 6*d*)—The 7th symposium of the Society for General Microbiology was held last month and microbiologists from Britain and the United States took part The papers, which are edited by Dr R E O Williams and Dr C C Spicer, chiefly discuss the relationships of micro organisms with their inanimate environment, with each other, and with higher forms

THE LANCET

LONDON SATURDAY, MAY 11, 1957

Relatives in Hospital

It may puzzle a future generation of doctors that the medical students of today, though encouraged to spend many an idle minute gossiping with their patients, often qualify without having listened to a devoted wife being told that her husband will be dead before next Christmas, without having seen new hope kindled in the eyes of a sick child's mother, and without having been startled as the cause of a perplexing intestinal disorder is laid bare in the natter of a nagging wife or the bluster of a tyrannical husband. Nor are they usually taught—and many never learn to appreciate—the profound effect visitors have on sick people in hospital. Most of them take infinite pains to spare their patients physical hardship and mental anguish; but between three and four in the afternoon any well-meaning friend can talk the convalescent case of coronary thrombosis into a heart-attack, and milk-drips can beat solemn time to tales of unrelieved gloom. But if the protective isolation of a hospital should give the housewife her first chance in years to sleep undisturbed, to eat well, and to talk in complete sentences, to the proud mother regular visitors with the family news are as vital as rest, good food, and shots of the latest wonder-drug; and to the gravely ill the quiet presence of a husband or mother, just sitting close to the bed, passing a drink or (in answer to a familiar flicker of the eyelid) adjusting a crumpled pillow, brings comfort and solace that the best nursing care can never replace. In his contribution to a well-conceived group of articles on this subject in the *University of Leeds Medical Journal*, HELLIER writes: "The psychological effect of a relative's visit will obviously depend on circumstances; and these should be carefully considered before encouraging or discouraging visitors. . . . A regular visitor who can bring a needle and cotton or a favourite bottle of eau-de-cologne gives the patient a feeling that she has access still to her possessions."[1]

Patients at either extreme of life offer a special challenge to doctors, nurses, and hospital administrators. Children require strong emotional support in an emergency; and HELLIER is in no doubt that against emotional stress "the mother is the most effective prophylactic." Like ILLINGWORTH and HOLT,[2] whose pioneering inquiry we published in 1955, he believes that the initial disturbance of daily visits soon passes off and that only such close contact can prevent "the psychological scars of prolonged hospitalisation in childhood" which he sees in many adults today. At St James's Hospital in Leeds accommodation is provided for mothers to be admitted with their ill children—a striking contrast to venerable institutions which still allow their visitors to queue up in the rain. At the other extreme of life fear from our hostile world torments no longer; it is the long-legged shadows of the next which begin to assemble around the bed. Some elderly sick take to solitude with calm serenity—it becomes to them the audience chamber of God—but to the majority it is hell let loose on earth. Relief from their agony calls for patient inquiry from nurse, almoner, and social worker (for there is often some trivial obstacle in the way of visiting), but the ultimate responsibility for their peace of mind rests with the doctor. Only he can impress on the reluctant relatives of a dying man that, however strained and perfunctory their visit may seem to them, it is that magical coin which he most desperately needs—just as the doctor alone can tactfully relieve a relative from the moral compulsion of sitting up night after night by the bedside of an unconscious patient in extremis.

On the mentally ill, even more than on children and the old, outside visits may have a dramatic effect. Recalling our earlier appeal for easier access to mental hospitals,[3] Professor MACCALMAN, in a posthumously published article,[4] reminds us that "we are all members of a group—the family—and small though it is, it provides a nucleus of security for which there is no substitute." Yet, at the critical moment when the patient "finds himself suddenly, and perhaps violently, uprooted from everyday life, and cast into the confusion and indignity of a mental-hospital ward—there to wage unequal combat with the unspoken suggestion that he has done something he ought not to have done,"[5] he is both spiritually and geographically isolated from this source of strength.

If scant attention is being paid to the effect of visitors on hospital patients, most doctors feel that the effect patients may have on their visitors hardly concerns them at all. Nothing can be more comforting to a child coming round from an anæsthetic (and more trouble-saving to the nursing staff) than the mother's smile; but mothers deserve a warning before being confronted with an unconscious child smeared with blood and vomit. Seriously ill patients can be so changed in appearance that relatives, seeing them thus for the first time, may be unnecessarily alarmed; and their alarm will often communicate itself to the patient. And children should not be allowed to see adults gravely ill—or even Granny's familiar face without her false teeth—except for some special reason. The difficulty of obtaining accurate information from hospitals still causes much animated correspondence in the lay press; and doctors who dismiss this as yet another unpleasant manifestation of the *Zeitgeist* should occasionally visit sick friends incognito. There is no doubt that parents are still being fed on junior nurses' garbled versions of their child's major illness; and few are the happy doctors who have not been summoned to family conclaves where worried relatives try to piece together dropped hints from sister-in a-hurry, conversational fragments from patients-in-the-know, and ambiguous statements from popular health manuals. The reason for this secretiveness is neither pressure of routine work, nor delight in conspiratorial hocus-pocus nor the callousness of youth. To interview relatives is a subtle and exacting art (far more complicated than interviewing patients) which should be taught to every medical student as assiduously as the examination of the chest. But because the young doctor has received no such education, he is oppressed by the fear that under the anxious scrutiny of relatives he will make a fool of himself. And in fact, when indignantly (for there is usually some more pressing and congenial task to hand) he faces his ordeal, his performance is thoroughly lamentable. It is difficult to decide which is worse—the cocky "just-leave-it-to-us-and-don't-you-worry" attitude of some, or the nervous diffidence of others—and hilarious stories about relatives overheard mispronouncing medical jargon cast a poor light on their learned source of origin. The losers in this cruel game are, of course, the doctors even more than the relatives. The wise clinician not only talks to the family, but also makes them talk to him, and he takes careful note of tell-tale gaps as well as of the tale they tell. All relatives when first seen are upset, and, not being under the special licence of the sick to unburden their souls without restraint, their conversation becomes a mixture of wishful thinking, morbid fantasy, and time-honoured euphemisms. "Many mothers . . . bringing children suffering from an obvious behaviour disorder are eager to tell us about the time when he fell out of the pram as an infant, and relatives of those with psychosomatic disorder descant about his physical infirmities to the exclusion of all else."[4] But misinterpretations can be as revealing as hard facts, and even the silences of the strong silent father or the meek masochistic mother can point to the need for treating the relatives as well as the patient. "This more than doubles our task, but without it all our efforts to *help the patient may be in vain*."[4] With predominantly hereditary or familial disorders the value of examining all members of the family is obvious, but careful inquiry into the family history may be equally important when patients are genetically predisposed to a disease but not yet affected by it, when, in fact, careful adjustment of their environment may still prevent its onset. It has recently been claimed that, not only do the children of diabetics run an increased risk of developing diabetes, but, before they do so, many show small reversible blood-vessel changes, and treatment of these might possibly prevent the diabetes. CARTER[6] believes that "this type of preventive approach will become increasingly important for many of the now common disorders."

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[1] Hellier, F. F. *Univ. Leeds med. J.* 1957, 6, 1.

[2] Illingworth, R. S., Holt, K. S. *Lancet*, 1955, ii, 1257.

[3] *Ibid*, 1956, i, 334.

[4] MacCalman, D. R. *Univ. Leeds med. J.* 1957, 6, 1.

[5] Woodley, H. G. *Lancet*, 1956, i, 338.

That relatives have a legal right to see the doctor during their visit to hospital is now accepted. (HELLIER[1] mentions a case where a relative slipped and broke a leg while trying to locate a house-physician, and for this accident the hospital was held responsible.) But surely from a humane profession they have a moral right to expect more than this. We should appreciate the immense nervous strain, and often the financial burden, that hospital visiting can entail, and hospital management committees, which justly pride themselves on providing all comfort for their patients, should look after visitors with equal consideration. Their difficulties may be great—they range from deterring visitors from collecting expensive souvenirs to providing lavatories—but these must be overcome. The good name of a hospital depends today—and it will depend even more in the future—on its cooperation with the families and friends of the sick as well as on its care of patients. These twin tasks are indeed already inseparable.

Wilson's Disease

IN the past decade much has been learnt about Wilson's disease (hepatolenticular degeneration). There can now be no doubt that disordered copper metabolism is the underlying cause. Urinary excretion of copper is increased[1] and the copper content of the brain and liver is also enhanced[2], but the serum-copper level is low.[3,4] The association of high tissue-copper levels with high urinary excretion of the metal suggested that too much copper may be absorbed from the alimentary canal, and that this is so was proved by ZIMDAHL et al.[5] who in careful balance studies showed that in a three day period healthy subjects retained 79–140 µg. of copper, whereas patients with *Wilson's disease retained* 1·6–1·8 mg. Possibly this excessive retention is due to failure of some mechanism in the alimentary mucosa which normally inhibits absorption of copper. (An alternative interpretation—that copper absorbed from the alimentary canal is not excreted, as it normally is, into the bile—seems to be excluded by the finding of approximately normal *levels of* biliary copper.)

Like most metals copper has an affinity for proteins, the positively charged metallic ions forming a loose complex with the negatively charged parts of the protein molecule. It might be expected *therefore* that copper would exist in serum in such a combination, but plasma-copper has been found to exist mostly as a much more firmly bound complex. This was isolated by HOLMBERG and LAURELL,[6] who named it cæruloplasmin because of its blue colour. SCHEINBERG and GITLIN[3] *found that* in patients with Wilson's disease the serum level of cæruloplasmin was much lower than in health. The slight reduction in serum-copper found by these workers bore no comparison with the almost complete absence of cæruloplasmin, and it was clear that the serum must contain much copper in an abnormal *form*. Studies with radioactive copper led to a similar conclusion. EARL et al.[7] showed that radioactive copper (^{64}Cu) given by mouth to healthy people is at first attached to the albumin fraction of the serum-protein as separated by ammonium sulphate, and the same is true of ^{64}Cu added to serum in vitro. But samples of blood taken twenty-four hours after administration of the copper showed that this had been transferred from the albumin to the globulin fraction, and presumably in the interval the ^{64}Cu had been incorporated into the cæruloplasmin molecule.

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[6] Carter, C. O. *Univ. Leeds med. J.* 1957, 6, 1.

[1] Mandelbrote, B. M., Stanier, M. W., Thompson, R. H. S., Thruston, R. M. *Brain*, 1948, 71, 212.
[2] Cumings, J. N. *Ibid*, 1948, 71, 410.
[3] Scheinberg, I. H., Gitlin, D. *Science*, 1952, 116, 481.
[4] Bearn, A. G. *Amer. J. Med.* 1953, 15, 443.
[5] Zimdahl, W. T., Hyman, I., Cook, D. *Neurology*, 1953, 3, 569.
[6] Holmberg, C. G., Laurell, C. B. *Acta chem. scand.* 1947, 1, 944.
[7] Earl, C. J., Moulton, M. J., Selverstone, B. *Amer. J. Med.* 1954, 17, 205.

On the other hand, in Wilson s disease this transfer of copper from albumin to globulin does not take place the radioactive copper remains associated with the albumin fraction These findings accord with the observation by **Scheinberg** and **Gitlin** that in this disease the plasma level of cæruloplasmin is low It seems that the low level is due to defective synthesis in the body, which leads to the presence in the serum of large amounts of copper bound to protein but not so firmly as it is in the cæruloplasmin molecule , and is presumably this copper which is deposited in the brain and liver and results in the clinical manifestations of the disease Why the copper is deposited in the brain and particularly in the basal ganglia is uncertain, but normally basal ganglia contain a large amount of copper and possibly there is a protein there with a high affinity for the metal **Porter** and **Folch**[8] examined the form in which copper is laid down in the brain and have found notable differences between healthy subjects and patients with hepatolenticular degeneration **Chalmers** et al[9] have now put forward the hypothesis backed by some experimental observations, that liver-protein from patients with this disease has a greater affinity for copper than has protein from normal liver They feel that the excessive deposition of copper may be related to this rather than to the abnormal circulating copper

Treatment of the condition with dimercaprol (**Bal**) was first reported in 1951[2,10] This drug forms a stable non-toxic complex with copper and causes it to be excreted in the urine in even larger amounts In some cases this drug improves the clinical state—which strengthens the supposition that excessive deposition of copper is the immediate cause of the disease Lately other methods of treatment have been used Oral administration of potassium sulphide regularly with meals diminishes the alimentary absorption of copper by forming insoluble copper sulphide **Walshe**[11] has found that penicillamine increases the excretion of copper Calcium disodium ethylenediamine tetra-acetate has also been used, but has the disadvantage that it must be given intravenously

The diagnosis of Wilson's disease by chemical methods depends on demonstrating excessive copper in the urine or a low serum level of cæruloplasmin Small amounts of copper are not easily estimated, and there is always a possibility of error from contamination of the specimen with extraneous copper For this reason the estimation of cæruloplasmin, particularly by the simplified method of **Ravin**,[12] is probably to be preferred Serum-cæruloplasmin can be estimated indirectly by measuring the rate of oxidation of paraphenylene diamine in the presence of the serum , the rate of oxidation is proportional to the level of cæruloplasmin From **Denny-Brown**'s work it is apparent that the success of treatment with dimercaprol depends a good deal on early diagnosis Clinically the diagnosis in the early stages may be extremely difficult or impossible , so such helpful chemical methods are highly important

Long-term Studies in Man

Atheroma is perhaps the most important unsolved problem in human pathology and certainly the most discussed In the welter of observations and speculations on the relation between coronary-artery disease and dietary fat, three facts now stand out beyond dispute First, coronary artery disease is closely associated with a disturbance of blood lipids and in particular with high levels of cholesterol in the serum Secondly, in countries and communities with a high prevalence of coronary-artery disease, the susceptible population have levels of serum cholesterol and intakes of dietary fat higher than are found in countries where the disease is less common (In these epidemiological studies **Ancel Keys** and his colleagues at the University of Minnesota have been pioneers) Thirdly, in people whose level of serum cholesterol is high it can be lowered by altering the quality of the fat in the diet The study of the effects of different dietary fats on serum-cholesterol levels which Dr **Ahrens** and his colleagues present at the front of this issue confirms and amplifies earlier reports from themselves and others The most sceptical critic cannot now dispute the fact that the quality of the dietary fat influences the levels of serum-lipids He must be strongly impressed, too, by the evidence that the ability of the fat to lower the level of serum-cholesterol is associated with its degree of unsaturation, though, as **Ahrens** points out, other chemical properties of the fat have not been completely ruled out. Of course other factors besides diet—e g , the constitutional make-up of the individual, hormonal activity, and perhaps the extent of physical activity—also determine in part the levels of serum lipids Nor is it satisfactorily established that patients are clinically improved, and the risk of cardiac infarction reduced, when the serum-lipids are held continuously at low levels by a dietary regime All this obviously needs further study Unfortunately few medical centres in the world have, as yet, the organisation necessary for experiments on man on the [illegible] required

Mankind owes a great debt to laboratory [illegible] and much help has been obtained from the [illegible] acquiring an understanding of the nature of [illegible] arising as a result of acute infections and [illegible] deficiencies But, whereas there is much patho[illegible] common between a guineapig and a man [illegible] from generalised tuberculosis, and also be[illegible] rabbit and a child blinded by keratomala[illegible] animal counterparts of the [illegible] diseases of man either do not exist, [illegible] to human disease Hence it is [illegible] examine the progress of diseas[illegible] mentally controlled conditio[illegible] colleagues say that "the un[illegible] studies "was based on the [illegible] experiments can be carried o[illegible] as in animals" In this belief [illegible] the fortitude of the 37 citizens [illegible] prepared to live for periods ra[illegible] months without eating any na[illegible] entirely on synthetic diets [illegible] able to do so and for the [illegible] improve in health on these a[illegible] tribute to the skill and sym[illegible]

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[8] Porter H Folch J *Arch Neurol Psychiat* 1957 77 8
[9] Chalmers T C Iber F L Uzman, L L *New Engl J Med* 1957 256 235
[10] Denny Brown D Porter H *Ibid* 1951 245 917
[11] Walshe J M *Lancet*, 1956 i 25
[12] Ravin H A *Ibid* p 726

Rockefeller Institute and also to the administrative arrangements.

Advancement of our understanding of several important pathological processes would be much accelerated by the study of patients under similarly controlled conditions for periods to be measured in months. But although some teaching hospitals in Britain have small metabolic wards, none are provided with the staff or equipment required for studies on such a scale over so long a time. To ensure both the physical and social well-being of experimental patients and the accurate collection and analyses of data a very large staff is needed, as well as floor space for laboratories and social amenities: to care for and investigate thoroughly 5 patients, a staff of 25 to 50 persons may be necessary. But the setting up of one or more such research centres in this country would have immense practical value. Properly safeguarded, *Homo sapiens* can be a very useful laboratory animal.

Annotations

RACIAL DISCRIMINATION IN MEDICINE

THE Natal Provincial Administration, noting that the salary scales in their hospitals have always distinguished between nurses and teachers of different races, decided recently to extend this principle to the eight non-European doctors working as interns at Edendale Hospital, Pietermaritzburg. These doctors have resigned in protest.

Since 1950 in South Africa graduates in medicine have had to hold house appointments for a year in an approved hospital before registering with the South African Medical and Dental Council. In 1950, though no Transvaal provincial hospitals would employ non-European doctors, the number of non-European medical graduates from Johannesburg was small enough for all to find posts in mission hospitals or in the British Protectorates. In July, 1951, however, three Indian graduates could not find a place; and apparently no one was responsible for finding them one. For several months they searched in vain for appointments; and it was not until their plight had been given publicity by various student and professional bodies that arrangements were made for them in a provincial hospital serving non-Europeans. The practical difficulty that had to be overcome was that white nursing sisters in South Africa could not be expected to "take orders" from non-white interns. (The seriousness of this difficulty is emphasised by the provision of the present Nursing Bill, which imposes a fine of up to £200 on anyone allowing a white nurse to work under a non-white person.) This obstacle was circumvented in the Transvaal provincial hospital by employing non-white sisters in units where non-white interns were placed. Like all other Transvaal provincial employees, however, these interns in Transvaal hospitals were paid at a lower rate because of their race—a state of affairs accepted by the profession, no doubt because of the urgent need to enable them to serve their statutory year. At that time the Natal Provincial Administration was not prepared to give appointments to non-European interns in any of its hospitals: even the 1500-bed non-European hospital in Durban did not have non-European interns, though its present connection with the medical school for non-Europeans has obviously changed the position. Influenced probably by a serious shortage of junior doctors, it later decided to appoint non-European interns at Edendale Hospital; and these are the appointments now made vacant by resignation.

In South African society, different rates of pay for European and non-European doctors will be regarded by many as logical and consistent. It is entrenched national policy in industry and agriculture, and in other professions such as nursing and teaching (although not in university lecturing). To the South African doctor, however, it does raise a new issue, since differential rates affect not only the economic but inevitably the professional status of all his colleagues. The events of recent years are a challenge to the standing of the South African medical profession of which it is well aware. The British Medical Association's cancellation of its proposed conference in South Africa, because satisfactory arrangements could not be made for all delegates regardless of race, was a grave blow. When the South African government decided that only white donors might give blood to white recipients and that blood bottles were to be labelled accordingly, many South African doctors felt this as a slur on the scientific reputation of their country—though the Medical Council thought it could not act in this "political" issue. The recent decision to impose apartheid in all universities and medical schools is considered a threat to the maintenance of equal professional standards for all graduates. Different status and different training for non-European nurses, now to be added to the already existing lower salary scales, will also have repercussions for the medical profession. Not long ago a South African local authority advertised in the *South African Medical Journal* for 15 "European" general practitioners to attend to its employees. The local branch of the Medical Association have published their emphatic opposition to the racial discrimination implied in the advertisement and have approached the authority with a view to its revision. They recognise the duty to resist discrimination against colleagues.

At its March meeting the South African Medical and Dental Council decided after debate that non-European interns, in accepting posts at different pay-rates from European interns, did not contravene its ethical rules. The executive regarded the matter of differential rates as one of public policy in which it was inappropriate to intervene. On the other hand, many members of the profession hold that, though the rules of the South African Medical and Dental Council may not have been contravened, such discrimination does not conform with Hippocratic ethics. The professional interests of South African doctors are threatened in many ways by this and the other developments in the medical schools and the nursing profession. Consistent ethical and professional standards, scientific freedom, and a ready exchange between nations are essential to the advance of modern medicine in all countries.

NEPHRITOGENIC STREPTOCOCCI

ALTHOUGH Bright[1] observed over a hundred years ago that renal disease with albuminuria may follow scarlatina, the significance of hæmolytic streptococcal infections in the pathogenesis of acute glomerulonephritis has been slow to emerge. Nowadays it is believed that infection with group A streptococci may result in at least two non-suppurative complications—rheumatic fever and acute nephritis—but while the link with rheumatic sequelæ is well substantiated, until recently the evidence for the link with glomerulonephritis has been patchy. Much of the earlier work establishing the streptococcal association of acute rheumatism was epidemiological, but with glomerulonephritis epidemiology reveals no discernible pattern. In patients with scarlet fever (when this disease was very common) the incidence of nephritis varied very widely,[2] both between epidemics and from year to year. Rammelkamp and his colleagues,[3] using

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Lancefield's precipitin method of typing group A streptococci to study the distribution of streptococcal types in nephritis, showed that among sporadic cases in Cleveland, Ohio, the majority were associated with type-12 infections, and some with type 4. This preponderance of type 12 among strains inducing acute nephritis has been confirmed by independent studies, including a small British series.[4]

Rammelkamp[5] now affirms that there is strong evidence of specifically "nephritogenic" strains of group-A streptococci; these commonly belong to type 12, to type 4, or to a new type—Red Lake—recently identified by Updyke et al[6] in an epidemic of scarlet fever and nephritis in an Indian reservation in Minnesota. There is evidence, too, that children who have recovered from acute glomerulonephritis usually exhibit type antibody to one of the nephritogenic types of streptococcus.[7] There is a strong contrast here with rheumatic fever, in which no particular types or strains of group A streptococci have been incriminated as "rheumatogenic," although such evidence has been much sought. (In the Red Lake outbreak the source of the preponderant type was often in skin lesions. Does rheumatic fever ever complicate streptococcal infections unless they involve the upper respiratory tract?)

A striking point in Rammelkamp's work is that many strains of streptococci of types 12, 4, and 25 (another occasionally nephritogenic type) undergo lysis after infection with a bacteriophage not usually lytic for other serological types. It is known[8] that bacteriophage may convert avirulent diphtheria bacilli to toxigenic mutants; and possibly, as Rammelkamp suggests, a similar phenomenon determines the pathogenesis of nephritis. But it is necessary to bear in mind Maxted's work[9] on streptococcal phages, which showed that the hyaluronic acid capsule of certain mucoid strains protects against phage action; and it should be noted that Rammelkamp's type 12 strains are described as non-mucoid. Further studies on lysis of these strains will be of great interest. What has been discovered so far seems to indicate that in the causation of acute glomerulonephritis the peculiarity lies largely in the organism: in rheumatic fever it may lie in the host.

DEVELOPMENTS IN CANADA

After thirty years' consideration, Canada has taken the first step towards a national health service with a hospital care insurance plan which is to come into action early in 1959. Six out of ten provinces, containing more than half the country's population, have signed agreements with the Dominion government to set up hospital insurance systems to be financed jointly by the Dominion and provincial governments. With six provinces participating, the cost to the Dominion will be $100 million a year, a sum expected to be doubled when all ten provinces join in. The proposed plan includes standard ward care in general hospitals, with some diagnostic service and treatment, and care for the chronically ill. Benefits will be unlimited and cover universal; but treatment in tuberculosis sanatoria and mental hospitals will be excluded.

At present, 9 million people—about two thirds of the population—have some form of pre-paid hospital insurance from a wide variety of sources. Two provinces (British Columbia and Saskatchewan) have a universal compulsory insurance system financed by premiums and sales taxes, while two others (Alberta and Newfoundland) have voluntary plans for certain areas. Five plans for pre-paid care, sponsored by hospital associations, give service benefits to participants, and many commercial insurance companies are also in the field, offering set cash indemnities against sickness and accident. But the non-governmental agencies provide only limited benefits; and, since their cover is directed mainly towards groups of employees, the rural population and the self-employed can gain protection only through the high premiums set for individuals.

Cover for medical and surgical care is even more diversified than for hospital care and much less adequate. Some provinces provide for the treatment of specific diseases, such as tuberculosis, cancer, poliomyelitis, venereal disease, and mental illness, free or on a means test, and some provide free medical care for pensioners and people receiving public assistance. On the prairies and in the maritimes, a number of municipalities have salaried community doctors, and a few industries have company doctors. Commercial companies also insure against medical costs. A million and a half people are enrolled in eight plans for prepaid medical care sponsored by doctors' associations as an alternative to State medicine. These latter plans are the most popular and give the most comprehensive benefits; but, like the plans operated by hospital associations, their cover is so far confined to groups of employees.

Since hospital expenses are usually the heaviest part of medical costs to the patient, the new hospital care insurance plan meets the strong demand for some provision against the risks of illness—and meets it in a politically safe area. The Dominion government has firmly stated that it will not control or interfere with the hospitals. Doctors, though opposed to any State plan for complete medical care, have generally approved pre-paid hospital care where it has been tried. The introduction of a comprehensive medical service is not, of course, prevented only by resistance from professional bodies. Under Canada's federal constitution, matters of health and welfare are a provincial responsibility; and, even with the Dominion government footing half the bill, the poorer provinces could not assume the tax burden of a complete health service.

THE HOSPITAL BED

Efficient use of hospital resources was never more necessary; and the means to this end were helpfully discussed by the Institute of Hospital Administrators[1] at Torquay last week. Dr G. E. Godber, deputy chief medical officer of the Ministry of Health, began by saying that, on the medical side, we must be sure that treatment really does require the use of a bed and cannot be undertaken satisfactorily by the family doctor or in the outpatient department. Once admitted, the patient's medical needs require that his stay in the bed should be for the shortest period compatible with adequate treatment, and he should never be kept in the hospital for investigations or forms of treatment which could equally well be carried out while he is living at home. Though the doctor and nurse are concerned with doing their best for the patient actually in the bed, some account must be taken of the queue of other patients, behind his shoulder, whose need may be no less great: at the end of 1955, for every bed allocated to general surgery there were nearly four patients awaiting admission, and in gynæcology and ophthalmology there were six. Though nobody should be hustled out of the hospital bed to his own disadvantage, the waiting-list is a valid reason for taking special care that no time is lost in returning a patient to his own home if treatment can be completed there. Commenting on the fallacies of "bed occupancy" as an index of efficiency, Dr Godber pointed out that

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[4] Wilmers, M. J., Cunliffe, A. C., Williams, R. E. O. *Lancet*, 1954, ii, 17.

[5] Rammelkamp, C. H. *J. chron. Dis.* 1957, 5, 28.

[6] Updyke, F. L., Moore, M. S., Conroy, F. *Science*, 1955, 121, 171.

[7] Rammelkamp, C. H. *Proc. Inst. Med. Chicago*, 1953, 19, 371.

[8] Freeman, V. J. *J. Bact.* 1951, 61, 675.

[9] Maxted, W. R. *Nature, Lond.* 1952, 170, 1020.

[1] Some of the opening addresses have been printed by the Institute, 75 Portland Place, W.1.

Rockefeller Institute and also to the administrative arrangements

Advancement of our understanding of several important pathological processes would be much accelerated by the study of patients under similarly controlled conditions for periods to be measured in months But although some teaching hospitals in Britain have small metabolic wards, none are provided with the staff or equipment required for studies on such a scale over so long a time To ensure both the physical and social well-being of experimental patients and the accurate collection and analyses of data a very large staff is needed, as well as floor space for laboratories and social amenities to care for and investigate thoroughly 5 patients, a staff of 25 to 50 persons may be necessary But the setting up of one or more such research centres in this country would have immense practical value Properly safeguarded, *Homo sapiens* can be a very useful laboratory animal

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Special Articles

PUBLIC REACTION TO THE CURRENT DISPUTE BETWEEN THE MEDICAL PROFESSION AND THE GOVERNMENT *

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THIS is a preliminary account of the findings of a public opinion survey carried out in Edinburgh and London between March 11 and March 20, 1957 The survey was designed to assess the extent of the public's information concerning the remuneration of general practitioners, the size of general practitioners' lists, and the finances of the National Health Service, to obtain judgments of the adequacy or otherwise of the income of general practitioners and on the relations between these incomes and those prevailing in other professions, to ascertain what course of action was expected as a result of the current dispute; and to elicit some more general attitudes relating to the N H S and to the place of general practice within it

The interviews were conducted in their own homes with persons whose names had been drawn systematically from the electoral registers In Edinburgh two local-government wards were selected, and 100 names were drawn in each ward, one of the wards (Gorgie-Dalry) was known to house a predominantly working-class population, while the other (Corstorphine) was thought to have a fairly high proportion of middle-class inhabitants In London a sample of 200 was drawn in a single ward, known to be socially heterogeneous, in the Parliamentary constituency of North Kensington When the addresses were visited, it was found that 32 of the people on the London list and 15 of those whose names had been drawn in Edinburgh, had moved from their addresses, in each area 2 had since died Of the remaining 349 individuals, 273 (78%) were successfully interviewed The balance was made up of persons who refused to collaborate (7%), persons who in spite of repeated calls could not be found at home (8%), 3% who were in hospital or too ill to be interviewed and 4% who were temporarily away from home All interviews were carried out with a standard questionnaire, and all had been completed before the British Medical Association recommended a programme of phased withdrawal from the National Health Service

TABLE I *—SOME ASPECTS OF PUBLIC KNOWLEDGE

—	School leaving age of subjects	
	14	15 +
	%	%
Earnings of general practitioners		
Average earnings correctly estimated	21	24
underestimated	54	60
overestimated	3	2
Extent of increase claimed		
Percentage increase correctly estimated	12	16
" " underestimated	44	39
" " overestimated	4	5
Size of general practitioners' lists		
Average size correctly estimated	27	30
" " underestimated	49	47
" " overestimated	6	9
Basis of general practitioners' remuneration		
Known to be based on capitation fee	67	81
Source of N H S finances		
Known to be mainly from taxation	21	35
Believed to be mainly from National Insurance	57	44
Relative costs of G.P. and hospital services		
Hospital service known to be costlier	85	80
G P service believed to be costlier	5	11
N (=100%)	136	132

* Persons whose educational level was uncertain are omitted from this and subsequent tables

Public Knowledge

We may begin by considering how well informed is the general public on some relevant matters of fact The justification for dealing first with this question lies less in its intrinsic importance—though this is not inconsiderable—than in its value in providing a background against which judgments and attitudes can be evaluated

The principal findings under this heading are summarised in table I In this, as in most subsequent tables, the results of the two areas have been combined, and redivided so as to show the influence of educational level on attitude, opinions, and standards of information Only a simple dichotomy is employed, subjects who left school at the age of 14 being contrasted with those whose education lasted until the age of 15 or later †

The general level of public information is clearly unimpressive,‡ and not very heavily influenced by education When asked what was the average income of a general practitioner, after allowing for expenses and before deduction of income-tax, fewer than one in four of the persons interviewed gave an approximately correct answer There was a marked tendency to underestimate the general practitioner's earnings Well over half of all persons interviewed placed the average below £2000 and one in three thought it was less than £1500 By contrast only 6 out of a total of 268 substantially overestimated the average, suggesting that it exceeded £2500 Those subjects who had remained at school until the age of 15 or later were less ready to plead ignorance, but were in fact no better informed than those who had left school at the minimum age

About two in five of all persons interviewed admitted to having no knowledge of the size of the increase in remuneration which had been claimed from the Government, but in fact the extent of accurate knowledge was far smaller even than this would suggest Another two fifths of the sample underestimated the proposed percentage increase, and only 12% of those who had left school at 14 and 16% of the better-educated subjects, came close to an accurate answer The increase claimed was far more commonly believed to be of the order of 10% That the remuneration of general practitioners was based principally on a capitation fee was known to two thirds of the less well educated and to four fifths of the better educated group, about 8% believed that the general practitioner was paid on a fee-for-service basis, and another 3% imagined that he received a salary based on qualifications and experience There was, however, little knowledge of the average size of general practitioners' lists and again the general tendency was to underestimate rather than to exaggerate them Here again education it is better for the patient and the service that a bed should be empty than it should be needlessly occupied But there is every reason for avoiding waste of a bed even for a single day if it can be used The interval between admissions varies between specialties, but (excluding obstetric, chronic, and mental beds) the average in 1954 was 3 72 days Even allowing for the distorting effect of very long periods in a few specialties, this figure seems too high, and it is not falling as much as was hoped Admitting the many potential errors of calculations from national figures, "it is a reasonable proposition that improved admission procedures might save an appreciable amount of time that is now lost"

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* The London part of the inquiry was organised jointly by Mrs M Jefferys of the London School of Hygiene and Tropical Medicine, and by the Institute of Community Studies, Bethnal Green.

† It should be noted that the two groups are not strictly comparable in respect of age composition There are more young people in the group of subjects who left school at the age of 15 or later

‡ A very high proportion gave an initial "don't know" response to many of the questions and this was reduced by the interviewer who invited informants to choose one of a number of alternative answers

Much improvement has, of course, been made already Dr Godber said that between 1949 and 1955, with a rise of only 1 2% in the number of beds, discharges (including deaths) rose by almost 25% Part of the improvement was due to an increase of available staffed beds from 448,037 to 476,109, but there is no doubt that many hospitals have found it practicable both to shorten stay and to shorten the interval between admissions, and it is evident that "a substantial increase in work done in hospital beds can be achieved without any great increase in their number" In general, our lack is in quality and distribution rather than quantity of beds "We are more than keeping pace with demand and we may expect to reduce the deficit steadily" It is impossible to judge future requirements accurately, because we cannot say how many days of care would be needed if all our hospitals were modern well-planned units but it is significant that in class-I hospitals in New Zealand the treatment of acute medical and surgical conditions took a shorter time than it did in class-II hospitals, which are presumably less well equipped

Sir Harry Platt, P R C S, spoke more forcibly about the obsolescence of our hospitals, in both structure and equipment we are trying, he said, to practise 20th-century medicine in 19th-century buildings On the Continent, since the war, new hospitals—many with interesting features—have grown like mushrooms There developments have been financed by local loans, philanthropy, and central government grants, but with the emphasis on city and local loans In this country we must change the system by which hospital building is financed exclusively from central Government funds if people want the best hospital services, they must pay for them Urging that, in hospital design, account must be taken of changing techniques, Sir Harry mentioned new Canadian hospitals in which an acute unit—not just a few recovery beds—is attached to the operating theatre unit When patients return to the ward three or four days after operation they look after themselves, and the ward is designed so that they can do so

TUBERCULIN-TESTING

To be successful, an epidemiological survey must be simple to carry out, easy to explain to the populace, and capable of reproduction not only in the same country but also in other countries at the hands of other investigators These criteria can be fulfilled in surveys of tuberculin sensitivity by either the Mantoux or the Heaf method Yet little is known about the tuberculin sensitivity of the population of this and other countries, even though, as tuberculosis becomes less common, tuberculin sensitivity becomes more important

Nowadays the most widely accepted test is the intradermal Mantoux using 10 T U Minto [1] used this in 1954 and again in 1955 in his tuberculin surveys in Cumberland—a county with agriculture in the east and an industrial and once "depressed" area in the west In 1953 the death-rates from tuberculosis in these areas were 0 08 and 0 28 per 1000 respectively In that year a mass X-ray survey revealed 2 cases of active tuberculosis (0 07%) among 3015 school-children in the east, and 6 cases (0 35%) among 1692 children in the west In 1954, 73% of the 1102 children aged 5–6 years on the school rolls in east Cumberland were tested, and 7 1% of those tested had a positive reaction, while in the industrial west 69% of the 3177 children on the roll were tested and 10 8% of these were positive reactors In 1955 the tuberculin state of 13 year-old children was investigated Of the 2802 children of this age 78 5% were tested, and the proportions with positive reactions were 20 1% in the east and 36% in the west

Jarman [2] tested the tuberculin sensitivity of school children in the Rhondda Fach in 1950–51 and again in 1953, also taking samples, for use as controls, from a neighbouring valley The standardised percentage of positive reactors aged 5–14 years was 24 6 in the first Rhondda survey and 18 4 in the second, while the figures in the control valley were 20 2 and 18 2 respectively There is evidence that the fall in the Rhondda is unlikely to be due to chance Jarman also noted that the rate of tuberculin *reversion* was 13 4% in the Rhondda and only 2 2% in the control valley—suggesting that improved diagnosis and treatment in the Rhondda have decreased the chances of exposure An associated finding was that the morbidity-rates among children were 1 4% for those tuberculin-negative and X ray negative in 1951, and 4 3% for those tuberculin-positive and X-ray negative in the same year This finding is at variance with the conclusion of most observers—that the attack rate, judged radiologically, is higher among those previously Mantoux-negative than in those previously positive [3]

Bush [4] has shown that the proportion of positive reactors in children in the Los Angeles area rose from 1 1% in 1952 to 2 4% in 1954, though the case rate for all forms of tuberculosis in California fell This rise was attributed to more home treatment, which may allow closer family contacts with the children Furthermore, poorer patients may not be able to continue paying for drug treatment Tuberculin-testing of school children can be valuable not only in detecting unsuspected tuberculosis [5] but also in other ways—for example, by revealing a supply of tuberculous milk [6]

Dr Giannini and Dr Sloan [7] have lately reported from Glasgow that after the age of 34 in women and of 54 in men the proportion tuberculin negative increases with age In 1955, a combined mass radiography and tuberculin survey [8] was carried out in Blyth in Northumberland, and the persons radiographed were encouraged to read their own tuberculin test and report the result by post 20,900 persons were radiographed, representing 60% of the population over the age of 5 95% accepted the tuberculin test and 95% of these returned their cards In all, 40 cases of active tuberculosis were found The analysis of the tuberculin survey is not complete, but it can be expected to show areas where the proportion of people tuberculin positive is above the average, and here the search for source cases must be concentrated

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THE next session of the General Medical Council will open on Tuesday, May 28, at 2 15 P M, when Sir DAVID CAMPBELL, the president, will deliver an address The Medical Disciplinary Committee will meet on Wednesday, May 29, at 2 15 P M in each of these occupations, and then whether they thought they *should* earn more, less, or the same. A summary of findings is presented in table III. In general we may say that there is a conspicuous tendency to underestimate the incomes of general practitioners in relation to those of other professional groups, coupled with a strong belief that general practitioners deserved higher rewards than most of these other groups. Both belief and judgment are influenced by the level of education. Our better-educated subjects are a good deal less inclined to believe that family doctors receive relatively low incomes, and are also less prone to believe that doctors are entitled to exceptionally high rewards as compared with members of other professions.

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[1] Minto, W H P *Brit J Tuberc* 1957, 51, 60

[2] Jarman T F *Brit med J* 1955, ii, 1235

[3] Daniels, M Ridehalgh F Springett, V H Tuberculosis in Young Adults London, 1948

[4] Cited by Carson M J, Koch R *Calif Med* 1956 85 226

[5] MacDougall I A, Mikhail, J R, Tattersall, W H *Brit med J* 1953, i 64

[6] van Zwanenberg, D F, Stewart, C J Harding K M, Gray, S T G *Ibid* 1956 i, 1464

[7] Giannini D, Sloan, R S *Lancet*, March 9, 1957, p 524

[8] See *Ibid*, 1955, ii, 921

The only person on our list who is almost universally agreed both to receive and to merit a higher income than the general practitioner is the surgeon. The only other medical member of the list is in quite a different position. Only about 40% of our subjects believe that the school doctor earns less than the general practitioner, and slightly more of them agree that this is a desirable state of affairs. Judgments of the value of the surgeon may also be contrasted with those of the solicitor. Very few indeed of the people interviewed by us believed that general practitioners on the average received higher incomes than solicitors, but well over half of them thought that they were entitled to higher incomes. The tendency to underrate the value of the solicitor relative to the general practitioner was much less in the better-educated group, which may be presumed to have a clearer understanding of the functions and responsibilities of non-medical professions and a greater appreciation of their value. Again, only one subject in three believed that general practitioners earned more than bank managers, but twice as many believed that they should earn more; in this instance too the better-educated subjects were slightly less inclined to undervalue the non-medical profession. Two-thirds of the people in our sample who had left school at 14, and more than four-fifths of the others, recognised that general practitioners had higher incomes than grammar school headmasters; but while seven in ten of the former group believed this to be an appropriate state of affairs, those who had had a longer educational experience were more evenly divided in their opinions. General practitioners as a group were said to receive higher incomes than university professors by only 9% of subjects with minimal formal education, and by three times as many of the others. The number of subjects in the former group who believed that the family doctor should enjoy a higher income than the professor was nearly five times as great as the number who supposed that this was in fact the case, but in the better educated group the two percentages are very close together.

Perhaps the most striking feature in this list of occupations is the position of members of Parliament. Their standard income has been stationary for many years, and was, one would have imagined, well known to the general public. But among the people interviewed, only a quarter of those who had left school at 14, and less than half of those with a longer education to their credit, knew that general practitioners earned more than members of Parliament, while about two thirds of both groups believed that doctors were entitled to higher incomes than M.P.s. The relative poverty of the minister of religion in comparison with the general practitioner was recognised by almost all persons interviewed, and there were few who believed that the economic positions should be reversed. Only one manual occupation—that of coalminer—was included in our list. More than 70% of persons interviewed knew that general practitioners earned more than coalminers and an even higher proportion thought that they should earn more.

This section of our inquiry throws a useful light on the public's conceptions of the relative income-levels of general practitioners and members of some other professions. These conceptions are often erroneous, and consistently underestimate the doctor's relative remuneration. An analysis of public judgments of desirable relative income levels shows clearly that an extremely high value is placed on the general practitioner. We may recall here that all experimental studies of the prestige ranking of occupations agree in finding that the medical profession is among those accorded the highest degree of prestige. However, in this study the tendency to place general practitioners far ahead of other professions is a good deal less evident in the better-educated subjects.

The Expected Outcome of the Dispute

The high esteem in which the public holds its general practitioners is implicit not only in the economic value placed on their services relative to those of other professions but also in the expressed expectations of their behaviour in relation to the dispute over remuneration. When questioned as to the most likely outcome of the dispute, our subjects most frequently expressed the opinion that the Government would relent and meet the doctors' claim; this view was held by 42% of the sample, irrespective of level of education. But among those who thought this outcome unlikely, the view was not conversely held that the general practitioners would withdraw from the N.H.S. if the Government remained adamant. This belief was restricted to about one in nine of all persons questioned; and for every person subscribing to this view there were three who thought it more likely that the general practitioners would not carry out their threat to withdraw from the service.

TABLE IV—JUDGMENTS OF THE PROBABLE OUTCOME OF THE CURRENT *DISPUTE*

—	School leaving age of subjects	
	14	15+
	%	%
Expected outcome of current dispute		
Government will relent	42	42
G.P.s will withdraw	11	12
G.P.s will not withdraw	37	35
No opinion	10	11
Expected behaviour of G.P.s in event of withdrawal		
Not see any patients	1	1
See only seriously ill	11	14
See all patients, but charge	37	25
See all patients, but charge only some	37	43
See all patients without charge	7	5
No opinion	7	12
N (= 100%)	136	132

We went on to ask our subjects what course of action they thought that doctors would be likely to follow if they did in fact decide to withdraw, and listed a number of possibilities. It is a striking comment on the public conception of the doctor's rôle that of 268 people questioned, only 2 thought that in the event of a withdrawal general practitioners would refuse to see any patients. About one in eight thought that only patients who were seriously ill would be seen, but more than three quarters of our subjects believed that practitioners would continue to see all patients. These were divided, however, as to whether or not a charge would be made. A small proportion—about 6%—thought that a free service would be provided, but the remainder believed that general practitioners would charge some fee to their patients. The most common belief was that they would "charge only those who could afford it." In the better-educated group of subjects, this view was more widely seemed to have little influence on the level of information Slightly more than a quarter of all persons interviewed knew that the average size of list lay between 2000 and 3000 About half believed that the average was less than 2000, and only 7% thought that it exceeded 3000

The illusion that National Insurance contributions pay the greater part of the cost of the N H S was, as might have been expected, widespread, it was shared by more than half of those subjects who had received only minimum education, and by as many as 44% of the others Even in this better educated group only one person in three appreciated that the finances of the N H S were principally derived from general taxation However, few of the persons questioned were in doubt as to which was the more costly of the two major components of the health service, more than four-fifths of all subjects answered this question correctly

Supposed Adequacy of General Practitioners' Incomes

When our subjects were asked to estimate the average earnings of general practitioners, they were also requested to say whether they thought this average income—whatever they supposed it to be—was reasonable in relation to the services at present provided, or whether it was too little or too much As table II (i) shows, practically no-one, whatever his or her belief as to the average income of general practitioners, believed that this average was too high The belief that the average was too low went hand in hand with a tendency to underestimate that average Thus, of the subjects who believed the average annual income to be less than £1500, nearly 70% thought the average was inadequate The corresponding proportion falls to 39% among those whose estimated average was between £1500 and £2000, and to 30% among those whose answers were approximately correct At a later stage in the interview, the correct average was given by the interviewer, and the subjects whose earlier answers had been incorrect, or who had not ventured an opinion, were now asked to judge whether the actual average was reasonable Their answers are combined, in table II (ii), with those of the persons interviewed whose estimates had been correct at the first question We see from this table that only one person in four believed the average to be too low, while more than three in five thought it reasonable Differences in this respect between the different educational groups were almost non existent

TABLE II—JUDGMENTS OF THE ADEQUACY OF GENERAL PRACTITIONERS' INCOMES

(i) Supposed Average Income

Supposed average judged to be	Average income believed to be				
	Under 1000	£1000–1500	£1500–2000	£2000–2500	£2500–or more
	%	%	%	%	%
Reasonable	27	33	59	66	*
Too low	70	67	39	30	*
Too high				2	*
No opinion	3		2	2	*
N (=100%)	33	55	64	60	6

* Numbers too small to make an estimate

(ii) Actual Average Income

Actual average income of general practitioners,† after expenses but before taxes are deducted, judged to be

	%
Reasonable	62
Too low	24
Too high	6
No opinion	8
N (=100%)	268

† £2200 per annum

(iii) Extremes of Income

—	School leaving age of subjects	
	14	15+
	%	%
Incomes of £1000 believed to be		
Too low	79	82
Not too low	13	13
No opinion	8	5
Incomes of £3000 believed to be		
Reasonable	60	48
Too low	9	5
Too high	22	35
No opinion	9	12
N (=100%)	136	132

TABLE III—JUDGMENTS OF COMPARATIVE EARNINGS OF GENERAL PRACTITIONERS AND OTHER OCCUPATIONS

Occupations	Percentage believing G P s earn more		Percentage believing G P s should earn more	
	School leaving age of subjects		School leaving age of subjects	
	14	15+	14	15+
	%	%	%	%
Grammar school headmaster	66	84	71	57
Surgeon on hospital staff	10	8	7	7
University professor	9	28	42	33
Member of Parliament	24	44	71	64
School doctor	43	39	51	42
Bank manager	31	36	71	63
Solicitor	13	15	68	50
Minister of religion	79	87	74	76
Coalminer	70	74	78	86
N (=100%)	136	132	136	132

At this point in the interview the range of incomes as well as the average was considered The interviewers pointed out that some doctors with a small number of patients earned only £20 per week, while others with a large number might receive as much as £60 per week, were these incomes reasonable, too low, or too high? The evidence seems to suggest that public opinion as a whole favours a narrowing of the range of incomes of general practitioners That the doctor with a small list deserves a higher reward was agreed by four out of every five persons questioned, irrespective of their educational level So far as the practitioner with a large list is concerned, there seems to be less general agreement, and a greater divergence between educational groups 60% of those who had left school at the minimum age, and just under half of those with a longer educational experience, thought that the higher income was reasonable, but just under one in four of the former group, and slightly more than a third of the latter, considered it excessive

It seems likely that a move towards reducing the variation in general practitioners' incomes, especially by improving the lot of the doctor with a relatively small number of patients, would command considerable popular support In this context it is interesting to note that as many as 79% of all persons interviewed believed that "one general practitioner could not look after 3000 patients properly" Clearly, we cannot attach too much weight to this judgment, in view of the widespread misconception as to the number of patients the average family doctor does in fact look after But it does at least suggest that the balance of public sympathy lies with the practitioner with the small income

As a further step towards classifying public conceptions of the actual and the appropriate income levels of general practitioners, a short list of occupations (mainly professional) was prepared, and subjects were asked first whether they thought that general practitioners on the average earned more, less than, or the same as people in each of these occupations, and then whether they thought they *should* earn more, less, or the same A summary of findings is presented in table III In general, we may say that there is a conspicuous tendency to underestimate the incomes of general practitioners in relation to those of other professional groups, coupled with a strong belief that general practitioners deserved higher rewards than most of these other groups Both belief and judgment are influenced by the level of education Our better educated subjects are a good deal less inclined to believe that family doctors receive relatively low incomes, and are also less prone to believe that doctors are entitled to exceptionally high rewards as compared with members of other professions

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If a fee was to be charged for each consultation, how much was it likely to be? In respect of both surgery and home consultations there was a considerable difference of opinion between the two social groups, but it was the less well educated subjects, with their more modest estimations, who proved the more accurate prophets In this group, the most common estimates were *5s* for a surgery consultation, and *7s 6d* for a home visit, although at least a fifth underestimated both charges, while 15% expected that a surgery attendance would cost *10s* or more and as many as a quarter that the fee for a home visit would fall into this bracket In the group of subjects who had remained at school at least until the age of 15, 36% expected a surgery consultation to cost in the neighbourhood of *10s*, while only 30%, compared with half of the less well educated group, thought the fee was likely to be *5s* or less Again, 45% of the better educated group expected that the charge for a home visit would be *10s* or more, and two-thirds of these thought the fee was likely to be at least *15s*

So far as statements of intention provide a reliable guide, the imposition of a consultation fee seems likely to reduce the volume of the general practitioner's work, though not perhaps as heavily as some would suppose About a quarter of the less educated—and on the whole less well paid—subjects expected that if fees were introduced they would consult their doctors less frequently, this was also the belief of only one in eight of the better-educated subjects, in spite of the fact that they expected a higher scale of fees Another rather revealing finding of this section of our inquiry is that about 70% of our persons questioned did not believe that the introduction of fees would affect the quality of general practitioners' work The view that under such a system the general practitioner would take more time and trouble with his patients was held by only 27% of our subjects This view was slightly more commonly found among those with only minimum education, but even in this group it appears with less than half the frequency of the opposite view In general, the public is confident that the dispute with the Government will not affect the availability of general practitioners' services, and believes that the quality of this work does not depend upon the basis of remuneration

TABLE V—JUDGMENTS OF THE PROBABLE CONSEQUENCES OF WITHDRAWAL

—	School leaving age of subjects	
	14	15+
	%	%
Expected fee for surgery consultations		
Under 5s	21	10
5s to 6s	28	20
6s to 8s	18	21
8s and over	21	38
No opinion	12	11
Expected fee for home consultations		
Under 6s	20	10
6s to 8s	28	21
8s to 10s	13	9
10s to 15s	16	15
15s and over	10	30
No opinion	13	15
Expected effect of payment on use of G P s services		
Will use less frequently	27	13
Will not use less frequently	68	83
No opinion	5	4
Expected effect of payment on quality of service		
G P s will take more time and trouble	31	23
G P s will take same time and trouble	65	72
No opinion	4	5
N (= 100%)	136	132

TABLE VI—SOME VIEWS ON THE NATIONAL HEALTH SERVICE

—	School leaving age of subject	
	14	15+
	%	%
Effect of N H S on quality of medical care		
Has improved	20	10
Has deteriorated	16	18
Has not changed	51	49
No opinion	13	23
Most valuable part of N H S		
Access to G P s without charge	24	27
Access to hospitals without charge	59	65
Equal value	10	3
No opinion	7	5
Comparison of G P and hospital outpatients		
Hospital preferred	24	18
G P preferred	69	71
No opinion	7	11
Desire for N H S to continue		
Want N H S to continue	81	79
Would prefer to pay for treatment	15	19
No opinion	4	2
N (= 100%)	136	132

Some Views on the National Health Service

It is clear that there are no widespread public beliefs concerning the relation between the quality of medical care and the nature of its administrative and financial context This is indicated not only by the common view that a fee paying system would not improve the quality of general practice, but also by retrospective judgments of the effect of the N H S on medical care Half of all persons interviewed believed that there had been no significant change, while the remainder were more or less evenly divided between those who thought there had been an improvement, those who believed there had been a deterioration, and those who had no opinion It is perhaps significant that among those members of the sample who were less well educated—and on the average less well placed socially and economically—the view that the quality of medical care had improved since the introduction of the N H S was twice as common as in the other half of the sample The higher proportion of "no opinions" among the better educated subjects reflects the greater number of young people in this group who were not in a position to make any comparison

Asked which was the more valuable part of the N H S —the fact that all members of the community now had access to the services of a general practitioner without charge, or that everyone was entitled to free hospital treatment—a substantial *majority cast its* vote for the hospital This latter view was held by three fifths of the persons interviewed, as compared with about a quarter who believed that access to general practitioners, unrestricted by economic considerations, was the more valuable The question was framed in economic terms, and most of the replies were prompted by a consideration of the probable cost of hospital treatment But this should not be taken to mean that the hospital is in some sense preferred to the general practitioner Our subjects were asked whether, if they were to have a course of treatment which could be given either by their own general practitioner or at a hospital outpatient department, they would prefer one or the other In this context about 70% expressed a preference for their general practitioner, more than three times as many as preferred the hospital The former preference was sometimes explained in terms of convenience and proximity, and sometimes in terms of specific objections to the hospital, but far and away the commonest reason for preferring the general practitioner was that he had a personal knowledge of the patient and gave a closer personal attention to his needs; this was often contrasted with the anonymous and impersonal nature of the hospital situation.

Finally, we asked our subjects whether they wanted the National Health Service to continue as at present, or whether they would prefer to pay for their own medical care. Four-fifths of the people interviewed, irrespective of social level, wanted to see the service continue.

Summary

A brief account is presented of the results of 268 interviews with members of the general public on the subject of the remuneration of general practitioners and the current dispute between them and the Government. The names of the sample were drawn from electoral registers in Edinburgh and London, districts being selected so as to yield a final sample with a higher representation of middle-class groups than might be expected in a random sample of either city.

The level of public knowledge concerning some of the basic facts relevant to the dispute is unimpressive, and the better-educated members of the sample are not very much better informed. The errors are not random, however. The average earnings of general practitioners, the magnitude of the increase claimed by the medical profession, and the average size of the general practitioners' lists are consistently underestimated. The National Health Service is widely believed to be financed mainly from National Insurance contributions.

The average income-level of general practitioners is thought to be adequate by more than 60% of the sample, and to be too low by about a quarter. The incomes of doctors with small lists are almost unanimously agreed to be too low.

A comparison of the incomes of general practitioners with those prevailing in other professions shows a tendency for doctors' earnings to be underestimated relative to those of other groups and for their comparative economic worth to be very highly rated. Both these judgments were appreciably less common in the better-educated subjects.

Few thought it likely that general practitioners would withdraw from the National Health Service, and it was widely expected that one or the other side would relent. Opinion as to the most likely consequences of withdrawal was divided, but a large majority agreed that doctors would continue to see all their patients, and charge fees to either all or some of them. The better-educated members of the sample expected a higher scale of fees than did the other subjects, who were in fact more often accurate in their predictions. A substantial majority agreed that the introduction of fees would affect neither their own use of the general practitioner's services, nor the quality of those services.

There was no consensus of opinion as to the effect of the National Health Service on the quality of the medical services, about half our subjects supposing that there had been no significant change. The hospital service was considered, on economic grounds, to be the most valuable part of the service, but most people interviewed would prefer to be treated by their general practitioner rather than at hospitals. An overwhelming majority preferred a continuation of the National Health Service to a fee-paying system.

Our thanks are due to the Institute of Community Studies and Mrs M. Jefferys for their organisation of the London interviews, and to Mrs. Jefferys and Dr. Cecil Gordon for many valuable comments and suggestions.

CLINICAL RESEARCH

THE Ministry of Health has issued a memorandum[1] describing arrangements for coördinating and financing clinical research at hospitals in the National Health Service.

The Minister hopes that hospital authorities will do all that lies in their power to foster clinical research in their hospitals. But these authorities have research powers only under section 16 (2) of the National Health Service Act, 1946, and they have no power to assist by grants or otherwise any persons or body to carry out research which is not "conducted" by the board or committee.

> "The research can be carried out by the Board or Committee alone acting through their own officers, whether regular hospital staff or specially employed, or in conjunction with another body. The circumstances must be such that it can reasonably be said that the Board or Committee, alone or in conjunction with someone else, has promoted or sponsored the research project and has general control over its character and the carrying out of it. While, therefore, there are ample opportunities for Boards and Committees to combine with other bodies in research work, they cannot make grants to bodies in respect of research conducted solely by those bodies."

The Minister does not intend by his recommendations to limit the conduct of research by boards and committees at the cost of their non-Exchequer funds, but, having regard to the need for coordinated development, the hospital authority or the appropriate research committee should not hesitate to seek advice from the Clinical Research Board about schemes proposed to be financed from non-Exchequer funds.

CENTRALLY ORGANISED RESEARCH

One function of the Clinical Research Board is to help the Medical Research Council in organising major clinical research financed from Exchequer funds and to recommend to the Council any clinical research units—existing or proposed—for which the Council should be responsible. "Major research," says the memorandum, may be broadly defined from the white-paper[2] which led to the setting up of the Clinical Research Board. This said that hospital authorities should be debarred from paying salaries of whole-time research-workers above the grade of senior registrar, and a limit of £1000 annually should be placed on individual grants for assistance and expenses.

Following a review by the Clinical Research Board, major schemes that were being conducted by hospital authorities are being transferred to the Medical Research Council. "It is particularly requested," says the memorandum, "that all proposals for new major schemes to be financed from Exchequer funds should be referred to the Clinical Research Board and that no new commitments should be entered into in this field without prior consultation with that body."

When it is decided to establish new clinical research units at hospitals, it is for the M.R.C., advised by the Clinical Research Board, to make the necessary arrangements with the hospital authorities, including arrangements for consultation with the board or committee on the appointment of members of the unit. But "it does not follow that all major research schemes would be initiated by the central organisation. Many schemes start from proposals made by an individual clinician who may put proposals to a Hospital Board or Committee for submission to the Clinical Research Board or may apply direct to that Board."

Hospital authorities will be responsible for providing clinical facilities for the units of the central research organisation This will entail honorary contracts for those members of the research units who must have access to patients, and it may sometimes require strengthening of the *hospital* clinical staff Where a board or committee considers that extra clinical appointments are necessary to cope with the additional hospital work imposed by research requirements and, for example, where a highly specialised type of treatment attracts more patients to the hospital, the hospital authority will no doubt consult the M R C and where necessary make proposals to the Minister for an increase in establishment In small clinical research units the director alone will normally be eligible for the status of honorary consultant, but exceptionally a senior assistant may also qualify for this status, and in large units one or more of the senior workers may also qualify The grading of all honorary appointments should be decided in agreement with the M R C A research-worker with the status of honorary consultant will be eligible for a distinction award

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[1] H.M. (57)36.

[2] Clinical Research in Relation to the National Health Service. H.M. Stationery Office, 19 . See *Lancet*, 1953, ii, 123, 13

LOCALLY ORGANISED RESEARCH

In conducting locally organised research, hospital authorities should pay special regard to the recommendations in the 1953 white-paper that each regional board and each board of governors should set up a research committee, after consultation with the associated university or medical school, to advise on the spending of money from any source which the board has available for research, and that, where convenient, a regional board and a board of governors might set up a joint committee to serve them both Management committees which wish to undertake research, however financed, should put forward proposals to the regional board for consideration

Hospital boards are to receive from the Exchequer a specific annual allocation for locally organised research To enable the Minister to decide on an appropriate allocation for 1958–59 and subsequent years, boards are to submit annual reports on locally organised research undertaken at the expense of Exchequer funds These reports will be the subject of consultation with the Clinical Research Board, so that, in agreement with that body, the Minister may from time to time (generally at five-year intervals) reassess the annual allocations to ensure that they are directed to the hospitals where "the right men and facilities are available" In their reports boards should include information about research conducted by them from non-Exchequer funds in order to give a complete picture of the work in progress

Although a board should not find it necessary to employ clinicians above the level of senior registrar for the sole or primary purpose of research, there is no objection to its arranging for a consultant, S H M O, or S H D O to undertake research which is incidental to his clinical employment Where such a doctor or dentist is employed part time on his routine work, he should be remunerated for research by a lump sum payment, renewed if necessary at intervals

RESEARCH FROM NON EXCHEQUER FUNDS

The Ministry suggests that research paid for from non-Exchequer funds might be subjected to the following broad considerations which apply to research paid for by the Exchequer (1) advice from a joint research committee set up in agreement with a university or medical school, (2) an approved programme on broad lines in cases where lump sum grants are to be paid to research workers, (3) periodical progress reports to the body or bodies financing the research, and (4) inclusion of information about such research in reports to the Minister These suggestions are "not intended in any way as a measure of limitation or supervision of the powers of Boards and Committees to use non-Exchequer funds for research in accordance with the provisions of Section 16 (2) of the National Health Service Act"

OTHER ARRANGEMENTS

A part-time consultant, S H M O, or S H D O wishing to carry out research in his own time may, instead of seeking to make arrangements with his board, apply direct to the M R C for financial help or for a part time appointment on the Council's staff

Any suitably qualified person in the hospital service may apply to the M R C for a grant to cover the expenses or technical assistance required for a research project

FALLOUT FROM BOMB TESTS

In a paper to the American Physical Society on April 26, Dr WILLARD F LIBBY, commissioner of the United States Atomic Energy Commission, discussed in detail the present sum of knowledge about radioactive fallout and its effects From his assessment of the data so far collected, Dr Libby concluded that the risk from nuclear testing at the present rate was small

He said that the present body burden of strontium 90 in new bone in the United States from atomic tests corresponded to the increased dosage to the bones from cosmic rays which would result from an increase of some 400 feet in altitude, and the present vital statistics showed no observable effect on the occurrence of bone cancer or leukæmia of much larger changes in altitude The tolerance figure of 100 "sunshine" units (100 micromicro curies per g of body calcium) that was now recommended was about two hundred times the present level for new bone in the United States, and it would not be exceeded by fallout from weapon tests in any foreseeable circumstances

The effect of locality was important, particularly the effect of calcium deficiency in the soils Careful consideration of this question indicated that there would be very few individuals with a strontium-90 content which was strictly inversely proportional to the available calcium concentration of the soil in their region The explanation was that food distribution systems automatically averaged over a wide area and people assimilated their calcium slowly Most people drank milk and ate cheese and other calcium-bearing foods from a rather wide area, and this effect reduced by an estimated factor of ten the potential effect of calcium deficiency in the local soils

Laboratory experiments suggested that the human body concentration of strontium 90 at equilibrium would be between 13 and 30 times less than that in the top soil The present data indicated that the higher figure was closer to the truth, and a conservative estimate for this ratio would be 20 Therefore, the present burden of 50 sunshine units in the top soil of the United States may eventually lead to as much as 2 5 sunshine units in the human bones, but more probably it would lead to about 1 7

The strontium 90 still in the stratosphere would fall out, Dr Libby expected, at a rate which just about compensated for the decay of the material already deposited, so that no great additional increase from this source was to be expected from weapons fired in the past If the testing continued at about the same rate as it has averaged over the past five years, then an equilibrium rate of fallout would be reached after an infinite time, and that rate would be 8 times the present one In other words, in the United States something between 5 and 20 sunshine units would be the equilibrium concentration of human bones if testing continued indefinitely at the average rate of the past five years This level would be approached only after a few decades After 28 years the level would be half of this equilibrium value, and in the year 2008 three fourths of the equilibrium figures would have been reached Thus, somewhere between 4 and 15 sunshine units in human bones in the United States might result from the present type of testing being continued for the next fifty years

In those parts of the world where the soil was low in calcium, this level might increase by as much as five times At the present rate of testing it might indeed approach the figure of 100 sunshine units, the tolerance limit for large populations, at the beginning of the 21st century for these certain limited regions in the world But, Dr Libby added, the observed conditions in these regions could be relieved by fertilisation of the soil with calcium, either calcium nitrate or lime being used

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Conferences

DECISIONS DEFERRED

Special Representative Meeting of B M A

In its decisions about what course the remuneration dispute should take, the special representative meeting of the British Medical Association on May 1 was not as decisive as expected New developments were put before it, and, though some representatives were doubtful whether the situation was thereby changed, the meeting decided to defer a decision on the plan for progressive withdrawal of general practitioners from the National Health Service , and it also agreed to postpone the question of evidence or no evidence to the Royal Commission until the next representative meeting

Dr Solomon Wand, chairman of the council of the B M A , reviewing the events that had led to the present position, said that the profession's claim had been met by the appointment of a Royal Commission and two acts of dictation—the 5% and 10% interim awards An honourable profession had been treated with contempt and driven into a defensive action thoroughly distasteful to every one of them , but that action had been justified

NEW DEVELOPMENTS

In recent weeks Dr Wand had had talks with the Minister of Health and with the chairman of the Royal Commission, Sir Harry Pilkington, in an attempt to find a solution One outcome of these discussions was a letter dated April 26 from Mr Vosper to Dr Wand, and this letter, it seemed, was one of the main reasons why the B M A council withdrew its original recommendation to the meeting and substituted one which advised deferment of decisions on the Royal Commission and on withdrawal This letter, read as follows

> Dear Dr Wand,
>
> I was glad of the opportunity of a long talk with you yesterday and I hope you feel—as I do—that it is that kind of informal and personal discussion which does most to clear away misunderstandings
>
> First, let me confirm what I said to you when I assured you that, following the report of the Royal Commission, there will be full consultation with the profession before implementation of any of its findings and that such consultation could of course include any matters relevant to the report or the present dispute
>
> Second, you seemed to fear some inconsistency between the terms of reference of the Commission and the public statements issued by its Chairman I can certainly reassure you here too It is normal that the interpretation of the terms of reference of a Royal Commission should be a matter for its Chairman and the Commission, and you can certainly regard the public statements which have been issued as having full validity
>
> Finally, I have thought—as you asked—about the position of the public health medical officers I cannot add anything of substance to what I said in my letter of 17th April on this, but let me repeat that I am sure that any settlement for others, following the Commission's report, could not fail to be taken into account in considering the position of these officers and any claim through the normal machinery would of necessity be considered in the light of the report and of any settlement subsequent to it
>
> I do hope that these remarks, and our talk yesterday, will help to rid us of unnecessary apprehensions
>
> Yours sincerely,
> Dennis Vosper

Another development which had influenced the situation was an additional statement from Sir Harry Pilkington

> "That part of the Royal Commission's task that consists of considering what should be the proper current levels of remuneration of doctors and dentists will include hearing submissions from those professions as to the remuneration which they are now claiming."

At the same time the chairman had made it plain that the Commission did not and would not regard itself as an arbitrating or adjudicating body He had also said that if it became unlikely that a report could be published by Easter, 1958, he would so inform the Government and other interested parties

Discussing these events, Dr Wand said that, despite the facts that the claim had not been met and that Spens was in the melting-pot of the Royal Commission, the gains were not inconsiderable The terms of reference had been broadened (in a way that was probably unprecedented) , a time-limit had been set for the report , the validity of the chairman's statements had been confirmed , full consultation had been promised before implementation of the Commission's findings , and the Government had made interim awards

The present issue, to Dr Wand's mind, was "give evidence or withdraw" A third alternative—to do nothing—was not, he thought, in the minds of most of the profession Whatever decision the meeting took the struggle was not yet over and the need for closing the ranks of the profession was as great, or greater, than before

ROYAL COMMISSION

The council put before representatives the following recommendation

> That in the opinion of this meeting circumstances have so changed that the position has altered since the council issued its recommendation to the representative body not to give evidence to the Royal Commission, but, realising that divisions and the profession generally have not had an opportunity of considering the statements by the chairman of the Royal Commission or the letter (April 26, 1957) from the Minister of Health to the chairman of council, this special representative meeting defers a decision on the question of giving evidence to the Royal Commission until the next meeting of the representative body

But whether "circumstances have so changed" proved a point for much argument, and a move to delete any mention of change from the recommendation was widely supported, most forcibly perhaps by Dr B Burns (Sheffield) Conditions were not altered, he declared, by "a form of words" "Spens to be the basis of general practitioner remuneration" that had been a form of words "Negotiations on terms of service" that had been a form of words And forms of words had lured the profession into a "paradise" in which they were the doormats of the Welfare State If doctors cooperated with the Royal Commission they would have discussed an alternative to Spens—and that was where the politicians wanted to get them Dr O C Carter (Bournemouth) thought that one phased withdrawal was being replaced by another—withdrawal of the profession's resistance If doctors gave in now, they could never in the future resist unilateral action by the Government Dr F S Rickards (Lancaster) spoke of 5% and 10% gobstoppers to keep the profession quiet Doctors were proving tough and the

Government was beginning to respect them for it Dr H Guy Dain (Birmingham), however, was sure that things *had* changed the Royal Commission amounted to effective arbitration, he declared—but amid cries of dissent The move to modify the council's recommendation was defeated by 163 to 199

An amendment frankly in favour of cooperation with the Commission was then debated Dr A H Hall (Brighton), president of the B M A, said that the efforts of Dr Wand and others had narrowed the gap in the *dispute and he hoped that it could be narrowed still* further—but not, he was sure, without the aid of public opinion, which should not be ignored in the meeting's decisions

Dr Talbot Rogers (Bromley) confessed that he had had serious doubts about the Royal Commission because of the probable delay in the appearance of its findings and because of the difficulty of deploying the profession's arguments before it But these doubts had been completely resolved The doctors had got to give evidence some time and Dr Talbot Rogers hoped they would give it soon Dr A B Davies (Walsall and Lichfield), who succeeded Dr Talbot Rogers as chairman of the General Medical Services Committee, said it was highly desirable that the meeting's decision should accord with that of the Special Conference of Local Medical Committees held on the previous day[1] (the conference had decided to defer until June a decision on the Royal *Commission and on withdrawal*)

Prof H W Rogers (Belfast) said his division had instructed him to vote against cooperation, but his own feeling was that to give evidence would provide doctors with a much better opportunity of having their claim heard He thought it would be selfish, however, for some people who, like himself, were already getting an adequate salary, to claim a penny more Doctors should raise their eyes from the mire and bitterness and try to help the country as a whole

Mr T Holmes Sellors, chairman of the Central Consultants and Specialists Committee, said his committee had reversed a previous decision against cooperation, and the Joint Consultants and Specialists Committee had asked its constituent bodies to prepare evidence

Several speakers were concerned at the damage cooperation with the Royal Commission might do to the public health doctors Dr H D Chalke (London) recalled a unanimous decision, at the last representative meeting, to "stick together" Now the public-health doctors were in danger of being thrown to the wolves

Finally, the meeting decided to accept the council's recommendation without reservation or amendment

WITHDRAWAL

Moving the council's second recommendation—to defer a decision on withdrawal—Dr Wand emphasised that a date on which a decision *would* be taken had been deliberately omitted from the wording of the recommendation It was a strong resolution a date could easily be determined after consultations—or the breakdown of consultations—when the Royal Commission had reported Many amendments concerned with withdrawal on the original agenda were not discussed, but it was agreed to ask the Central Consultants and Specialists Committee "to take active steps towards a special levy in proportionate amount to help in the present remuneration crisis" And the B M A council was asked to use all its efforts to increase the Defence Trusts If any of the representatives had a mind to call for an immediate decision to withdraw, they kept it to themselves, and the meeting quickly approved the council's recommendation

A LEGAL FIGHT ?

Though the fire seemed to have gone out of the meeting, Dr J A Gorsky (Westminster) struck quite a spark with his robust plea for the institution of legal proceedings to establish whether the Spens reports constituted a legally implied contract The surrender of rights by doctors when they entered the National Health Service must, he claimed, have some significance in law, and he thought that the Spens report for the general practitioner constituted a legally valid contract The profession should ask the High Court for a declaratory judgment to that effect

Dr W N Leak (Mid-Cheshire) read to the meeting the much quoted paragraph 179 from the Ministry of Health *Handbook for General Medical Practitioners* This paragraph, according to Dr Gorsky, was admissible in a court of law

> "The Central Pool is now calculated on the basis of the estimated net remuneration appropriate for general practitioners in 1939 (as recommended by the Spens Committee in 1946) together with a betterment factor taking account of changes in the value of money since that time This amount is adjusted to take account of changes in the number of general practitioners participating in the Service, their estimated remuneration from other sources, and the superannuation contributions made by the Exchequer"

Dr Wand said that Dr Gorsky's points had been in the minds of the council in recent weeks Eminent legal opinion had been against going to court, but if another counsel were to be consulted and if he said that there was even a small reasonable chance of success, then it might be the thing to do If legal advice was against going to court, it would be foolish to do so The meeting was keen to see the prospects of legal action examined further, and Dr Gorsky's plan was referred to the council

Public Health

Adolescents

At the Royal Society of Health congress, held at Folkestone on April 30 to May 3, Mr W Emrys Davies, PH D, described how, with the forthright spirit of our times, he had challenged his teen-age pupils to uncover anonymously the pattern of their private lives, and with the trust and frankness of youth they had done so How far the children of a comprehensive school on a large Manchester housing estate are typical of youngsters in the rest of Britain is unknown, but there seems no reason to think that Wythenshawe's are any better or any worse than their contemporaries elsewhere Indeed it is popularly believed that children in the south of England reach social maturation and sophistication earlier than their northern brothers and sisters Whether that is so or not, Dr Davies's findings at least point to the broad trends in our social progress, and they are not without medical significance if we can bring ourselves to face realities

The home background of the youngsters was mainly in social classes III and IV, 82% of the fathers being skilled or partly skilled, and the age-groups questioned were the 13½–14½ or the 14½–15½ cohorts Most groups contained about 190 pupils, but some selective inquiries were much smaller On that account many of the results should perhaps be viewed with reserve

Dr Davies asked his 13½–14½-year olds how they spent their spare time, and what were their major interests outside school Physical activity in one form or another still held the interest of 60%, the other 40% had already acquired the more sedentary pursuits of British adult life today Television and cinemas attracted both sexes fairly equally, but while the rest of the girls were starting to look for boy-friends, or occasionally reading, their male contemporaries were consoling themselves by making things with their hands Reading anything more than comics featured little in their boyhood lives It was another year before the boys became more girl-conscious At $14^1/_2$-$15^1/_2$ years of age, 60% of boys and girls chose either companionship of the opposite sex or mixed parties

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[1] See *Lancet*, May 4 1957 p 927

It was found that a third of the $13^1/_2$–$14^1/_2$ age-group had nine or less hours' sleep, and Dr Davies suggested that this was too short a time for growing bodies and active minds Whether a child comes to terms with sleep requirements is the parents' responsibility, but it is the schoolmaster who gets the backwash Early to bed was never a popular cry, and perhaps less so nowadays when the hypnotic television screen stirs up sex and violence until nearly 11 P M

There is evidence of early recourse to sedatives 5% of the $13^1/_2$–$14^1/_2$-year-old group admitted taking sedative drugs regularly, and another 36% occasionally If that is what happens with the odd bottle of pills in the bathroom cupboard, what will happen when the flood tide of tranquillisers crosses the Atlantic? If smoking can be regarded as a sedative, and not merely a display of teen-age bravado, nearly half of the boys and a fifth of the girls in the $14^1/_2$–$15^1/_2$ group had acquired a taste for smoking, and indeed that taste might already have developed into a habit So much for the progress of the campaign against lung cancer Stimulation with alcohol had already started in the same age-group Of a sample 33 boys and 32 girls, 41% seldom had a drink, 32% admitted occasional indulgence, 15% drank regularly, and 5% did so both regularly and frequently

Answers on personal hygiene were illuminating 65% of the youngsters bathed only once a week. Hand-washing after toilet was practised always by 34%, usually by 55%, and seldom by 11% Teeth-cleaning was disappointing 39% brushed their teeth either occasionally or never, 35% did so once a day, and only 25% observed did so night and morning, 3% of the girls did so more than twice a day Sharing hair-combs was very prevalent in both sexes, but communal life no doubt encourages the practice of borrowing items of personal toilet

The answers to these questions may suggest fresh lines of approach We must recognise the earlier social maturation of our teenagers and realise that it is developing unevenly If heterosexual interests are being aroused earlier than in our own generation it is no use blinding ourselves to the fact Surely there is scope to play on the vanities of awakening consciousness to get across the basic points of personal hygiene and bodily health, this is no more than is done for the adult population by the advertisers of cosmetics, deodorants, drugs, and fancy foods If grown-ups are most easily taught through the medium of strip-cartoons, eye-catching posters, slogans, and television, why should children be fed with less exciting fare? We are still a long way behind commercial practice with our market research

It would be equally unrealistic to assume that youngsters know all the answers Dr Davies proved that they do not Outline anatomy of the human body was only hazily understood by most of the $14^1/_2$–$15^1/_2$ age group, and knowledge of basic physiology was even scantier In the $14^1/_2$–$15^1/_2$ age-group 75% of the boys and 94% of the girls registered a strong desire to learn more about the development and functioning of the human body No-one can blame them for their ignorance of this subject, and by their answers they threw the challenge squarely back to us

Scotland in 1956

Provisional statistics for last year have been issued by the Registrar-General for Scotland [1] The birth-rate was 18 5 per 1000 population, which was 0 5 above the rate for 1955 The stillbirth-rate was 24 per 1000 live and still births—1 less than that for 1955 The death-rate (12 0 per 1000 population) was the same as that for 1955 The infant-mortality rate was 29 per 1000 live births, which was the lowest ever recorded, and the neonatal-death rate was 19 per 1000—1 less than in 1955 The death-rate from tuberculosis was 16 (respiratory 14, non-respiratory 2) per 100,000 population

A Primer in Public Health

Dr A. R Southwood, director-general of public health in South Australia, has written a booklet [1] for the guidance of newly appointed medical officers of health It is in simple, at times breezy, language, and covers a wide field, with ample quotations from authors as various as Percival Pott, Charles Dickens, and J S Mill Some of the material has special application to South Australia, and some of the rest will be familiar to any doctor, but the medical officer of health in this country may find the clear presentation useful in his activities in health education

Infectious Diseases in England and Wales

Disease	Week ended April			
	6	13	20	27*
Diphtheria	9	3	7	7
Dysentery	1051	1171	875	570
Encephalitis				
Infective	4	4	4	2
Post infectious	1	4	6	2
Food poisoning	204	194	209	134
Measles, excluding rubella	25 280	27,276	21 857	26,960
Meningococcal infection	29	24	19	35
Ophthalmia neonatorum	32	27	31	21
Paratyphoid fever	3	3	4	2
Pneumonia primary or influenzal	466	497	386	425
Poliomyelitis				
Paralytic	17	22	26	44
Non-paralytic	20	15	16	19
Puerperal pyrexia	204	205	193	248
Scarlet fever	878	740	568	542
Smallpox				
Tuberculosis				
Respiratory	583	697	555	570
Meninges and C N S	10	10	9	9
Other	76	78	64	59
Typhoid fever	2	2	4	5
Whooping cough	2768	2616	1896	2237

* Not including late returns

Parliament

The National Health Service Contribution

As has already been announced, the Government proposes to introduce a Bill to institute a separate National Health Service contribution and to double the 10*d* which is at present allocated to the service from the present joint National Insurance contribution Since the proposals are an increase in amounts paid into the Exchequer the Bill has to be founded on a Ways and Means resolution, and in introducing this resolution on May 1 Mr J **Enoch Powell**, financial secretary to the Treasury, pointed out that the National Health Service element had always stood on a different footing from the rest of the combined payment Unlike the rest of the contribution, it was paid from the Fund, where the rest remained, into the Exchequer, it did not constitute a qualification for receiving benefit, and, finally, whereas the rest of the combined payment was designed to meet the whole cost of the insurance benefits, it was never contemplated that this element should represent more than a fraction of the cost of the National Health Service There had been a good deal of misunderstanding and misapprehension as to the nature, the amount, and the effect of the National Health Service element, and he thought it sensible that its entirely separate nature should be formally and explicitly recognised In his report in 1942 Lord Beveridge had written

> "There is no obvious reason apart from a desire to keep the insurance contribution as low as possible, why insured persons should be relieved of this burden wholly, in order that they may bear it as taxpayers If importance attaches to preserving the contributory principle for cash benefit it attaches also to contribution for medical treatment There appears to be a case for including part of the cost of domiciliary treatment in the insurance contribution."

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[1] Quarterly return of the Registrar General Scotland for the quarter ended Dec 31 1956 also preliminary return for 1956 H M Stationery Office Pp 40 2s 6d

[1] Southwood A R The Bases of Public Health Published by the Department of Public Health Adelaide 1957 Pp 84

Lord Beveridge had recommended that 10*d* should be included in the weekly contribution for the purposes of the National Health Service, and it had been expected that this contributory element of finance would represent about a quarter of the gross cost of the entire service. But the gross cost of the service had risen from £170 million to £690 million, so that the yield of the 10*d* today represented, not nearly a quarter, not something over 20% as was the intention of the 1946 Bill, but 5·8%. Mr. Powell agreed that when the increase in the gross national product was taken into account, the increase in real cost of the service was of course not so large as the gross figure suggested. But this did not affect the ratio of the gross cost which was financed by these contributions. It was, however, fair to take into account the charges now paid by patients. But even these payments and the contributions together only accounted for just over 11% of the gross cost of the health service, or scarcely more than half the amount which it was intended should be yielded by the contributory element. The increased contribution and the yield of the charges would still only represent some 17% of the gross cost.

The constitution of a separate National Health Service contribution, he added, would have an effect on the parts of the contribution eligible for taxation relief. Except for an employer engaged in trade or business, the National Health Service contribution would not in future rank as an allowance for tax purposes. In his view this change was logical because the benefits for which contributions were paid would be tax-free. Again if the N.H.S. contribution could count as an allowance it would mean that the higher taxation was, the more tax a person paid, and the higher his income was, the less he contributed towards the maintenance of the National Health Service.

Miss MARGARET HERBISON, who objected to the new contribution, pointed out that, though the gross cost of the National Health Service had risen, the proportion of the national income that went to it had fallen from 3·51% in 1948–49 to 3·24% in 1953–54. In the light of these figures it seemed to her that the Government had no case for raising the contribution. In particular, they had no case for imposing it on the low-wage earners, who would find it in the nature of a poll tax which they would be ill able to pay. Dame IRENE WARD seized the opportunity to ask what proportion of the new payment would come to her region—the Newcastle Regional Hospital Board—which when the N.H.S. started received a smaller share than more fortunate regions because it had fewer hospitals and fewer specialist services. Mr. ARTHUR BLENKINSOP, with local patriotism but little hope, supported her plea. The regional board was, in his view rightly, concerned that it had not been able to expand its specialist services. It had been restricted not only by the size of its allocation but also by the direct fiat of the Ministry of Health which was denying it opportunity to make appointments which, especially in the psychiatric service, were urgent. He feared that it was now the Government's object to finance the National Health Service in large part out of insurance contributions and charges. He believed that it was fairer to meet the undoubtedly heavy, but not unreasonable, cost of the service out of general national revenue. He feared that we were getting back to an insurance scheme, rather than maintaining the kind of National Health Service we had in mind in 1946.

Mr. RAYMOND GOWER thought that we were fortunate compared with countries which did not possess a health service, but we must be realistic. It would be dangerous if we got rid of our financial difficulties in financing the service by adding the cost to the general burden of taxation since we were so heavily taxed already.

Mr. DENNIS VOSPER, the Minister of Health, said that he did not wish to anticipate the speech he would make when introducing the Bill. But he reminded those who talked of hardship that between 1946, when the contribution was fixed at 10*d* and 1956 there had been an increase in wage-rates of 70% and in earnings of 99%. Today the increase was still greater, therefore it seemed reasonable that there should be an increase in the contribution. The Government were anxious to establish in the minds of the public the part of the contribution that went to the health service, and the stamp would, in some form as yet to be determined, make this clear. But this increase in the contribution was not an increase in the total National Health Service finance. The contribution, in fact, would be only sufficient to meet the estimates of regional hospital boards already approved by the Ministers.

In his view the Opposition must face the fact that, if they were not prepared to increase taxation to a considerable extent to finance the whole of the National Health Service, they might have to increase the charges to patients. It would be possible for the Opposition to propose a hospital boarding charge. Was that in their minds? The House had not heard the answer. The Government's policy was that the health service should be financed in part, but in part only, by direct contributions paid by those who were fit and at work, and he believed that that was something which commended itself to the great mass of opinion of this country.

Radioactivity and Food Contamination

In a debate on the adjournment on May 8 Mr. HECTOR HUGHES asked the Government what steps were being taken to preserve the world's food-supply from contamination by strontium 90 released by hydrogen bomb tests. Mr. J. B. GODBER, joint parliamentary secretary to the Ministry of Agriculture, Fisheries, and Food, said that research into non-medical biological hazards caused by radioactive substances was sponsored by a committee under the chairmanship of Lord Rothschild, the president of the Agricultural Research Council. The committee had been set up jointly by the A.R.C., the Medical Research Council, and the Development Commission, and its members included experts from these bodies and the Atomic Energy Authority.

Any danger from hydrogen-bomb tests, he said, resulted from the gradual radioactive fallout from the upper atmosphere. At present the danger of contamination of fish landed at our ports was negligible. The radioactive particles carried to the upper atmosphere by explosions in the Pacific and other distant areas drifted to all parts of the world before being deposited very gradually over a period of years on the earth's surface. In 1956 the A.R.C. embarked on a field trial at the Compton research station on the uptake of radiostrontium from the soil by barley, grass, and sugar beet. The actual form of radiostrontium used for these experiments was strontium 89, which had a half-life of 54 days compared with strontium 90, which had a half-life of 28 years. This reduced the hazard and ensured that the land would not be put out of use permanently for agricultural purposes. The effects were identical. This experiment would give fundamental knowledge for the guidance of farming practice in the event of agricultural land becoming contaminated either by fallout from nuclear attack or from an accident to an atomic power-station. The chance of such an accident was remote but we must be prepared. The results had not yet been published, but he could say that the uptake of radiostrontium by the plants grown was less than 1% of the amount put down.

The soil at the Compton station was chalk downland, and the results were to be checked this year in five other soils. The Atomic Energy Research Establishment at Harwell, in cooperation with his department, had for some years been carrying out long-term investigations designed to show the uptake of strontium 90, due to fallout from nuclear explosions, in the soil, vegetation, bones, and milk. Nine sampling sites had been chosen: 2 of them in Suffolk, 3 in Wales, and 1 each in Cambridge, Norfolk, Devon, and Durham. The sampling was done by the regional officers of his department and samples were taken of soil, grass, and animal bones—sheep bones in particular. Apart from those investigations, large quantities of milk had been taken for analysis from areas as far apart as Somerset and Northern Ireland. The results were being compared with the results of similar work in the United States, and in addition they had organised a supply of samples of soil, grass, and bones from Commonwealth countries

QUESTION TIME

Psychiatric Treatment for Prisoners

Sir LESLIE PLUMMER asked the Home Secretary how many prisoners sentenced to prison for sexual offences, and promised treatment for their abnormalities, in fact received such treatment —Mr J E SIMON replied Prisoners sentenced for sexual offences receive psychotherapy if they are found suitable for treatment and if the sentence is long enough to allow of it Particular attention is always paid to any recommendation by a court *In 1956, 60* men and boys sentenced for sexual offences received treatment by visiting psychotherapists, but I cannot say how many of these had been recommended for treatment by the court at the time of sentence Sir LESLIE PLUMMER Is it not clear that there is little validity in the statement made constantly by magistrates and judges to sexual offenders that when they go to prison they will receive the medical treatment which they should have for their abnormality ? Does not this mean that there must be a rapid extension of the very admirable psychiatric work now going on in Her Majesty's prisons ?—Mr SIMON We hope to extend that considerably when we get the new psychiatric institution at Grendon Underwood Mr ANTHONY GREENWOOD May we take it from the Under Secretary of State that he is not very happy about the facilities which are available ? Can he give a rather more definite idea to the House when he expects the facilities to be made adequate ?—Mr SIMON It would be very difficult to give a firm date for completion at Grendon Underwood, but a start is to be made this year

Use of Drugs

In the House of Lords the EARL of CRAVEN asked the Government whether they would consider, in the light of conditions arising out of Dr Adams's case, whether or not the time was appropriate for a review of the laws relating to the use of drugs for medical purposes —Lord STRATHCLYDE replied that the Government did not consider it appropriate to circumscribe the clinical freedom of doctors to treat their patients in accordance with their individual judgment except in so far as a doctor's authority to possess or prescribe dangerous drugs might be withdrawn, after conviction of an offence under the Dangerous Drugs Act The EARL of CRAVEN went on to ask if the Government were prepared to sanction euthanasia in any form. An answer to this question would give relief to a great many people in this country LORD STRATHCLYDE said that this was a completely different question, and he asked for notice before he answered it

Doctors for Colonial Territories

Mr DAVID JONES asked the Secretary of State for the Colonies to what extent there were still vacancies for doctors in the Colonial Territories, after the 300 applications which he received each year from qualified doctors already in the National Health Service in this country had been appointed to the Colonial Medical Service and allocated their posts —Mr A T LENNOX BOYD replied There are generally some 120 to 150 vacancies at any given time, recruitment being roughly balanced by normal wastage and, in some cases, by expansion in territorial establishments By no means all the 300 applicants take up appointments Mr JONES How many of the 300 applicants have their applications rejected ?—Mr LENNOX-BOYD Of the 300 applicants, approximately 45 are, on the average, rejected Of the remainder, about half withdraw their applications or decline offers of appointment Not all of these applicants are employed in the National Health Service

Mental Hospital Superintendents

Mr KENNETH ROBINSON asked the Minister of Health if he was aware of the increasing difficulty in obtaining suitable candidates for the post of physician superintendent in mental and *mental-deficiency* hospitals, owing to the lack of any financial inducement to compensate for the extra responsibilities, and whether he had considered the views of the Bradbeer and Guillebaud Committees on this subject —Mr VOSPER replied · I am aware of the difficulty and the views which have been expressed on the absence of inducement to consultants to take posts as medical superintendents at mental and mental deficiency hospitals The level of remuneration of these officers is within the terms of reference of the Royal Commission I do not feel able to comment further on it at present

In England Now

A Running Commentary by Peripatetic Correspondents

THOSE who switch off their light after getting into bed, knock their heads gently on the pillow 4, 6, or 8 times, and fall into a sound sleep until 4, 6, or 8 A M are envied by many But light sleepers who wake two or three times a night have learnt that even reduction of their sleep to five or six hours does not lead to ill health, and indeed may have compensations

When I put down my book, switch off my light, and turn on my side, my room seems very dark, but when I wake two or three hours later it is alive with a dim light This is caused by the projection, on floor, ceiling, and walls, of the distant street lights and the lights from neighbouring houses These are mostly dim, but after my sleep my eyes can appreciate them readily Sometimes a bright light suddenly appears and I know that one of my neighbours, too, is awake These lights always give me a sense of company during the night The large patch of sky which I see from my bed is rarely so dark that I cannot distinguish it from the house-tops, and it may be very light indeed when the moon is about on a clear night It also may be light when there are high clouds, which reflect the lights of London The planets, Jupiter, Mars, and, in the early morning, Venus, appear bright to my dark-attuned eyes A few months ago Jupiter and Mars were very close together I considered setting my alarm to see how close they would be the next night but decided to chance my luck I woke at the right time and found them so close that they seemed to touch, and the next night they had separated considerably I have also seen a planet nearly occulted by the moon in its last quarter When such sights are visible I lie in bed with my eyes open until I fall asleep

There are other pleasant sights and sounds On the Ides of March this year a blackbird, who prefers to nest among the chimney-pots instead of in the bushes on the other side of the house, began to sing at 5 36 A M Soon after dawn I may see the starlings flying up from their roosting-places in Trafalgar Square to their feeding-grounds in the country They differ in their habits from some of my colleagues who prefer to work in town and sleep in the country (These might be said to crawl there in comparison with the starlings) Later still come the pigeons and in the winter the gulls, which wheel above the house-tops until someone comes to feed them, when they sweep down in great circles Twice in twenty-two years I have seen a kestrel hovering over Great Portland Street (I have not had the good fortune of a colleague who once saw a peregrine falcon flying along the *Euston Road*)

All these sights and sounds add interest to the hours when I lie awake Provided I have had a pleasant day, recalling the events, say, of a game of golf, is a diversion But if the day has been difficult, my thoughts are sometimes too disturbing to let me sleep If so, I switch on my light and eat a digestive biscuit, which has the great merit that it crumbles easily against my almost toothless gums After various trials during the past forty-odd years I have decided that a drink of very hot water helps me more than any other drink I fill my 'Thermos' *on going to* bed and may eat and drink two or three times in the night As to reading, I may continue the book I was reading before I went to sleep, but if I am very restless I take a book which I can skim easily, dealing with "raw heads and bloody bones" *Kim* used to be a great standby and I could pick it up anywhere, but of late an old detective story may suffice Half an hour's reading is usually enough, but the process may have to be repeated more than once

I also use the night hours to thresh out my difficulties and often solve them When I *am writing* a paper I con the wording, or I think of a note such as this When I wake in the night I rarely feel *sleepy, but* at 8 A M I may be very sleepy *and loth to* get up When I was a busy house-physician I learnt to "go round" my wards, thinking *of the problems* of each patient, before I got up I still like to think over the problems of the day, while *still in bed*—though these, alas, are now chiefly committees To my mind those who sleep soundly miss many pleasant and interesting moments and the opportunity to solve some at least of their day-time problems. I have long ceased to envy them.

* * *

The other day, as I copied the names and addresses from the visiting-book in our surgery, I noticed that I accepted with sweet reasonableness a visit requested because of "spots," but "no better" or "getting giddy turns again" provoked irritation. My reactions made me wonder whether it might not be useful to insert in the appendix to all textbooks of medicine a Comparative Table of Disease and Doctor's Time. My own version would be something like this:

1 passport photo = 1 eye form = $^{1}/_{2}$ rubella.
2 rubella = 1 chickenpox.
3 chickenpox = 1 measles.
3 measles = 1 whooping cough.
17 whooping cough = 1 fat pink boy who's "had a cough for 3 years, doctor. Never sleeps a wink with it. Hasn't kept anything down for 2 years. Had whooping cough 8 times without the whoop, his last doctor said."
2 fat pink boys = 1 "only 94 and I don't seem to have any go in me, can't you give me a tonic?"
9 tired 94's = 1 chronic endogenous depression who has "seen most of the best psychiatrists in Europe and the last young specialist I saw said he couldn't give me the E.C.T. any stronger without stopping all the trains on the Inner Circle. But I'm no better and I'll pop round again tomorrow, doctor."

* * *

Restaurateurs' menus can be disturbing to the uninitiated, but my niece, aged 10, sees through them. Lately, she accompanied me to lunch at one of those small Belgravian restaurants where the décor is modern and the dishes recherché. She enjoyed an exotic preparation of "Filets de Sole à la Crème aux Champignons avec Sauce Mornay, les Petits Pois à la Nivernaise et les Pommes de Terre Dauphin." To her mother's inquiry later as to what she had had she replied without hesitation "fish and chips."

* * *

Away goes another illusion. That oft-quoted example of the perfect egalitarian community, the beehive, has let us down. It is indeed sad to learn that the famous waggle dance of the bee, far from being a conscious rallying effort for the good of the State, is but an elaboration of a primitive and innate reaction to a satisfactory meal.

An American biologist has shown that the common blowfly, a lone forager and confirmed individualist, can be made to perform a similar dance—with no audience—when its taste-organs are stimulated with a solution of sugar. This, he says, is simply an automatic reflex, whereby the fly hunts around hoping for more in the vicinity of the first find. Moreover, the complexity, duration, and extent of territory covered by the dance increases with the strength of the sugar solution, just as the vigour of the bees' dance is related to the concentration of the nectar collected. The bee apparently cannot even claim that its habit of regurgitating nectar from its honey sac on return to the hive is a desire to share with its fellows. The fly also regurgitates, and this we are told is in order to restimulate the taste-organs, and so reinforce the reflex and prolong the period and extent of the "food-searching" dance. Alas, it is for this purpose that bees, like the flies, gorge themselves to repletion when they chance on a food depot.

Thus the mystic "information" dance of the bee is but a delayed reponse to an effective taste stimulation, whose pattern and duration are controlled by the nasty habit of regurgitation of food from an overloaded stomach. According to the biologist, the complex and highly organised life of the hive has its origin in a primitive and wholly selfish individualistic rite.

* * *

Alas for the days when it was *de rigueur* for doctors to be properly dressed. The other day I went across to the ward to see a new patient. I was wearing a (slightly faded) black suit with striped trousers. The poor man was asleep when I approached, and got a terrible shock when he woke to find me standing by his bedside. He was sure I must be the undertaker.

Letters to the Editor

SENIOR REGISTRARS AND CONSULTANT APPOINTMENTS

SIR,—I write to support the letter of Dr. A. G. Freeman in your issue of April 27 and to congratulate you on the prominence which you gave to it. I find the Ministry's neglect of the senior registrars' problem as alarming for the future of medicine in this country as their refusal to negotiate in the matter of remuneration. When I stated, in a combined regional hospital board/board of governors medical committee the other day that there were too many senior registrar posts, a first-rate medical administrator retorted that the number had been fixed by the Ministry's statisticians—and, presumably, therefore we were intended to conclude that the number was right. From the figures in your table (April 13, p. 785) we may more correctly conclude that either the statisticians were wrong or they planned for an expansion of the consulting service which has not occurred.

I agree with Dr. Freeman that the appointment of senior registrars to non-teaching hospitals should be discontinued—at least in general medicine. It may be that in other specialties, such as general surgery and pathology, the non-teaching hospitals have more to offer the senior registrars. I am now convinced that in general medicine, although we may improve the experience of senior registrars, we do not promote their professional progress. Moreover, there is work waiting for consultants in non-teaching hospitals. In the group of hospitals which I serve we have an urgent need for another general physician and another general surgeon.

I do not agree with Dr. Freeman that these new consultants (again, at any rate in medicine) should be of assistant status. By the time a young physician has completed four years as senior registrar (doffing his cap and saying, "Sir, how splendid are your physicianly qualities and how unworthy am I, Sir, to take up your stethoscope") he should be independently fulfilling his own promise. This is the way of English medicine and it should not be lightly discarded.

Derby. DOUGLAS HUBBLE.

FATS AND DISEASE

SIR,—The question of the effects of dietary fats on serum cholesterol concentration, and the larger issue of the rôle of diet in the promotion of coronary heart disease, needs more facts and less argument. We do not propose to meet the letter from Dr. Kinsell and Dr. Sinclair in your issue of April 27 in a similar polemic defending one point of view and attacking all others, but your readers may be served by providing a few facts.

In the first place it is simply not true that in our experiments[1] "the actual qualitative and quantitative fatty-acid composition of the oils was completely unknown." The sardine oil used, prepared from *Sardinops cærulea*, the California sardine, was found to have an iodine value of 188 and saponification value of 174. We did not attempt a detailed analysis of the extremely complex lipids in this fish oil but for these purposes were content with the finding that this oil was, indeed, very highly unsaturated as is typical of the fish oils. And we noted that such fish oils have been universally found to be low in linoleic acid and to contain only very small amounts of arachidonic acid. Aliquots of the other oils were stored in full containers at –20°C and at the end of the experiments these were analysed blind by the research division of Procter & Gamble Co., with the following results for corn and sunflower seed oils respectively:

Iodine value: 123 and 140. Percentages of the fatty acids: saturated, 15·8 and 10·3; monoene, 26·2 and 18·2; diene, 56·6 and 70·8; triene, 0·7 and 0·1. Trans acids amounted to 0 7% and 1 3% respectively, while conjugated dienes were less than 0·6% in these oils

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[1] Keys, A., Anderson, J. T., Grande, F. *Lancet*, Jan. 12, 1957, p. 66.

Kinsell and Sinclair state that the efficiency of absorption of the oils in our experiments was "apparently unknown" We are unaware of any evidence that fresh oils such as we used are not well absorbed by man, and we do know that their ingestion by our subjects was not productive of any steatorrhœa or change in calorie equilibrium Since the test oils provided more than a fourth of the total calories in the diet, any significant failure of absorption would have caused a loss of body-weight

It may be that changes of 9 3 and 20 2 mg of cholesterol per 100 ml of serum "would be regarded as being within the range of spontaneous fluctuation" in the laboratories of Kinsell and Sinclair They are unaccustomed to studying groups of men in controlled cross-over experiments and so apparently pay no attention to statistical analyses or the significance of mean changes of 14 and 12 men, respectively, that are 3 3 and 5 4 times the standard error Incidentally, these changes are in the *opposite* direction to those expected if conformity existed with the hypothesis that either linoleic-acid content or degree of unsaturation were the controlling factor in such comparisons

Kinsell and Sinclair ask about comparison of olive oil with cotton-seed oil Such comparisons with 16 men subsisting for four weeks on each oil in a strictly controlled cross-over experiment, and with 12 men in a similar experiment with two-week cross-over periods, are provided in a paper currently in the press on the Effects of Different Food Fats on Serum Cholesterol Concentration in Man [2] No significant differences were found

We have been conducting experiments with safflower oil which is remarkable for its very high content of linoleic acid (70–80%) and correspondingly high iodine value The effect of safflower oil on serum-cholesterol in man is less than that of corn oil An interesting demonstration of this fact was made recently by the University of Minnesota Medical School class in physiological chemistry The serum-cholesterol response to the daily ingestion of 57 g of fat was studied in 141 students This admirable class exercise, under the guidance of Prof W D Armstrong, which is now ready for publication, showed lower serum-cholesterol levels on corn oil than on safflower oil, both by the students' analyses and by our own which were made ' blind" The oils used, analysed by Dr R T Holman of the Hormel Research Institute, proved to have, respectively, iodine values of 126 7 and 144 2, with linoleic acid comprising 57 5 % and 72 0% of the fats.

We should call attention, also, to the recent study of Beveridge, Connell, and Mayer,[3] from which they conclude, "The results demonstrated unequivocally that the plasma cholesterol depressant effect of corn oil depends to a large extent upon its sterol content"

Kinsell and Sinclair state "It is known that the feeding of a synthetic triglyceride containing unsaturated fatty acid is associated with a major decrease in serum-cholesterol as compared with the level existing during the ingestion of an equal amount of vegetable fat essentially devoid of unsaturated fatty acid," and they cite as evidence a letter to the editor of the *American Journal of Clinical Nutrition* [4] We should have thought it wiser to attempt to forget this little note but, since it is again seriously offered as evidence, it must be examined

The synthetic triglyceride was stated to have the following fatty-acid composition oleic acid, 74%, palmitic acid, 19%, stearic acid, 5%, linoleic acid, 2% Approximately 100 g of this fat was ingested daily by a single patient and "a prompt and profound decrease in plasma cholesterol occurred" If we were to credit this report, we must conclude that the linoleic-acid content of this fat could explain no part of the reported effect, since the synthetic triglyceride they used is as near to being devoid of linoleic acid as any natural fat or oil we know about The equivalent fatty-acid composition would be approached by beef tallow plus a little olive oil Natural (unhydrogenated) coconut oil contains about 2% linoleic acid while butter-fat and lard usually contain about twice and four or five times as much respectively If the "essential" fatty acid was the effective agent, butter-fat should have the same effect only much more so But, since this synthetic material was reported to cause a fall of around 100 mg of total cholesterol per 100 ml, to a value between 100 and 150 mg per 100 ml, perhaps it contained some remarkable factor not indicated by the fatty acid composition, and Kinsell and colleagues should make it available to the pharmaceutical trade

We should have thought it was clear enough in our letter of April 13 that we do not deny an important rôle of degree of fatty-acid saturation in the effect of dietary fats on serum-cholesterol Our evidence is that the saturated fats have a powerful cholesterol-raising effect, that the mono ethenoids (or more specifically, oleic acid) cannot be very influential, and that the poly-ethenoids have a cholesterol depressing effect which is considerably less powerful, per gramme, than the opposing action of the saturated fats Further, our evidence indicates that corn oil has an effect additional to that which may be ascribed to its fatty-acid content As of this date, we are unaware of any significant published data with which these conclusions are inconsistent

ANCEL KEYS
JOSEPH T ANDERSON
FRANCISCO GRANDE

Minneapolis Minnesota

PULMONARY COLLAPSE IN CHILDREN

SIR,—Your excellent annotation [1] was very stimulating. James et al [2] may indeed be congratulated on their presentation of the natural history of pulmonary collapse in childhood In their study of 5000 consecutive chest radiographs in children, 854 patients were diagnosed as having pulmonary collapse The follow-up study in 472 patients was completed and analysed ætiologically, but no mention is made of cystic fibrosis of the pancreas except for a passing reference in the miscellaneous group of 29 children—9 cases, all fatal

Our experience in the New England area shows that pulmonary collapse, lobar and segmental, transient and persistent, is not uncommonly a feature of cystic fibrosis of the pancreas The incidence of this disease is about 1 in 600 children, it forms 3–6% of all admissions in the large pædiatric hospitals, and causes about 5% of hospital deaths In this Center a study of some 600 cases of mucoviscidosis confirms the common association with pulmonary atelectasis and bronchiectasis (5–15%)

Of additional interest in the study by James et al is the anatomical distribution of lobar and segmental collapse As a whole, the right lung had a greater incidence of collapsed segments than the left, but of the lobes, the left lower had the greatest incidence and the right middle the next greatest Their explanation that collapse is due to the left lower lobe bronchus being obstructed by aspirated and secreted mucopus, and the right middle lobe bronchus becoming occluded by enlarged hilar glands with or without erosion may be true in many cases Di Sant Agnese's[3] and our observations, however, both suggest that the prevalence of collapse in the right lung (mostly right middle lobe) in many patients with cystic fibrosis of the pancreas is due to endobronchial obstruction with viscid, highly tenacious, bronchial secretion Our experience points to the fact that, for instance, many patients treated for asthma or some others suspected to have pulmonary tuberculosis have been proven in this Center to have cystic fibrosis of the pancreas with or without pancreatic enzyme deficiency

We have also studied 6 children with mucoviscidosis [4] having predominant respiratory difficulties in whom lobectomy was performed for persistent lobar or segmental collapse or bronchiectasis or both In 4 of them the diagnosis was made preoperatively, but in the other 2, aged 3 years and 8 years, the diagnosis was not made until six and twenty months respectively after operation, when the children were referred to the

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[2] Keys A Anderson J T Grande F J Nutrit (in the press)

[3] Beveridge J M R Connell W F Mayer G A *Fed Proc* 1957 16 11

[4] *Amer J clin Nutrit* 1956 4 285

[1] *Lancet* 1956 ii 1342

[2] James U Brimblecombe F S W Wells, J W *Quart J Med* 1956 25 121

[3] Di Sant Agnese P A *Pediatrics* 1953, 12 178

[4] Kulczycki L L Craig J M Shwachman H In the press

clinic In all 6 children the histopathological changes in the resected pulmonary segments were typical of or compatible with cystic fibrosis The recent introduction of a diagnostic chloride-imprint test [5] has made it possible to confirm this disease within a matter of minutes, and a large number of children can be screened within a short period

Pulmonary atelectasis may indicate cystic fibrosis of the pancreas, and *it is important not to overlook the* association Further, mucoviscidosis may also be responsible for occasional localised bronchiectatic changes or collapse and therefore should be considered in every case where a lobectomy is suggested

The Children's Medical Center,
Boston

LUCAS L KULCZYCKI

SALMONELLÆ IN REPTILES

SIR,—I refer to your annotation of March 23 In Cape Town there is a very high summer incidence of gastro-enteritis We have many flies but no reptiles in the urban area A colleague who had worked in Ibadan remarked recently that, despite the primitive sanitation, flies there were scarce and the incidence of gastro-enteritis was very low It was suggested that the abundance of lizards in that hot climate kept down the fly population, which was a prominent vector of salmonellæ If that is so, this observation suggests that reptilian excreta are not so dangerous as human

Salt River Cape Province

L RUSKIN

UTERINE ELECTROLYTES IN PREGNANCY AND LABOUR

SIR,—We were delighted to read the letter of Dr Hawkins and Professor Nixon (April 20) with its valuable criticism of our short communication and confirmation of the main clinical point raised—namely, that uterine inertia can be associated with a reduction of potassium in the myometrium

We quite agree that part of the "normal labour" group may have contained a number of cases of trial of labour which had gone on long enough to be on the borderline of uterine inertia, or which would have been uterine inertia had they been left This selection is in part necessitated by the very conservative approach to cæsarean section in Czechoslovakia There is a far smaller incidence than in England, and an elective cæsarean section is quite rare, except for cases of placenta prævia diagnosed beforehand, which is itself a rare occurrence Since a trial of labour is the rule, this limits the possibilities of selecting patients at various stages of labour, and since we are unwilling to biopsy a healthy uterus in a young woman of childbearing age to the extent required for muscle analysis, our selection of non-pregnant controls was also to some degree compromised—a necessary compromise we feel

Hormonal explanations are very much the vogue in dealing with electrolyte changes these days, but it is perhaps a mistake to neglect other factors Acidosis per se can lead to a loss of K from muscle cells, and a metabolic acidosis is often found during labour, particularly after the prolonged labour of uterine inertia Drs Vedra, Hoder, and Štenbera (to be published) in Prague have been following blood lactic acid levels and other effects of acidosis on carbohydrate metabolism during labour, and have found significant effects Moreover, the factor of local anoxia, which would lead to similar tissue changes, cannot be ruled out at present

We would ourselves be very hesitant about drawing conclusions from either the determined level of K concentration in the serum, or the calculated level of K concentration in myometrial, or any other, cells The correlation of serum K with cellular levels is seldom reliable except in extreme cases, and since one does not really know how much cell K or H_2O is bound, it is not very meaningful at present to speak of concentrations in the intracellular fluid under such conditions

We would finally broach the point that the borderline between a "physiological" K loss from cells and a "deficiency" is not necessarily an easy one to recognise, particularly since the latter word is a more general clinical term which should include some data on the total K balance in more quantitatively significant tissues than myometrium The word "physiological," when used in a clinical situation, should, we feel, connote whether a given process is advantageous to the patient or not, and we would ask whether any loss of K from the myometrium, whether covered by the term "physiological" or "deficiency," is advantageous or disadvantageous to the patient in labour

Prague, Czechoslovakia

R L CORT
J H CORT

ON THE UTILITY OF THE WORD *FÆX*

SIR,—There are, in the vernacular, two words which approximate in meaning to the commonly used *fæces* One is used exclusively as a substantive to denote a discrete mass of fæcal matter, the other as a verb or noun Their persistence through the centuries attests as well to their utilitarian as to their scatological value Physicians need an acceptable word which will permit the greater flexibility inherent in our Anglo Saxon heritage *Stool* does not meet this need, it lacks sharp definition and is employed variously—to go to stool, pass a stool, stool of such and such measurements, formed stool, watery stool, &c *Fæces*, a collective noun in plural form, also lacks precise meaning

It is the singular which we require, this will permit us to say, in one word, that unit of a formed stool delimited by two successive anal sphincteric contractions *Harper's Latin Dictionary* (1907, p 720) gives *fæx, fæcis* as this singular The diphthong suggests that the word be pronounced *feex* Some clumsy circumlocutions might be avoided by incorporating *fæx* into our medical vocabulary

New Orleans Louisiana

VINCENT J DERBES

THE LIVER IN HÆMOCHROMATOSIS

SIR,—In your leading article (Feb 23), you draw the conclusion that African studies support the view that the influence which leads to cirrhosis also leads to increased absorption of iron The facts available do not seem to support this view

Most abnormal livers in the South African Bantu, in whom siderosis is common, fall into two categories

(*a*) *Livers with a severe coarse cirrhosis*, the histological features of which (in most cases) suggest post necrotic origin [1] This type of cirrhosis is unrelated to the presence of siderosis

(*b*) *Livers with a fine portal fibrosis*, which develops into a true septal cirrhosis only occasionally The relationship of fibrosis to siderosis in this group is striking, and in some cases there is evidence of liver cell degeneration associated with hæmosiderin deposition

It is thus possible that, in the Bantu liver, iron pigment deposition may not be benign Further, the histological picture also suggests fibrosis secondary to iron pigment deposition, which is in contrast to experimental work, when, however, iron is almost invariably deposited in a healthy liver In these cases the iron storage pattern in the body is different from that seen in classical hæmochromatosis, and diabetes mellitus is not a feature

That the mechanism of iron absorption is abnormal in the African has yet to be proven Walker and Arvidsson [2] have brought forward considerable evidence that it is unnecessary to postulate such an abnormality to explain the widespread visceral siderosis found in the Bantu of

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[5] Shwachman, H Gahm N *New Engl J Med* 1956 255, 999

[1] Higginson J Grobbelaar B G, Walker, A R P *Amer J Path* 1957 33 29

[2] Walker A. R P Arvidsson, U B *Trans R Soc trop Med Hyg* 1953, 47 536

Southern Africa Moreover, Bothwell et al [3] were unable to demonstrate abnormal iron absorption in 4 patients with Bantu siderosis

The significance of diet in Bantu siderosis has yet to be established While it is true that diet has been shown to influence the absorption of iron in animals, this seems to be because conditions inside the bowel render the iron less easily available to the mucosa for absorption rather than because the mucosal barrier is damaged In rats fed a diet of maize, porridge, and sour milk supplemented by iron, I was unable to demonstrate increased iron deposition as compared to a control group on a stock diet

I would therefore subscribe to the view that as yet it cannot be stated that the factors causing siderosis and cirrhosis in the Bantu patient are the same, or that dietary pattern (apart from excessive iron intake) is a major factor in African siderosis and liver cirrhosis in this region

Geographical Pathology Unit
South African Institute for Medical Research Johannesburg

JOHN HIGGINSON

VACCINATION AND THE EPIDEMIOLOGY OF POLIOMYELITIS

SIR,—Your editorial of April 20 on formolised polio myelitis vaccine says "when children are vaccinated first, the young parents may for a time be more commonly exposed to the risk of paralytic infection as a result of inapparent infection by virulent virus in their children" This statement has already caused anxiety, which may be unjustified to parents about to have their children vaccinated With a properly prepared and tested vaccine no live virus is being introduced into the community which was not already circulating naturally The supposed risk to parents can thus arise only because they are being exposed to infection which they would avoid if they were able to recognise the illness in their children You cite evidence that in an unvaccinated population there may be 32–496 subclinical infections to every clinical case, so that at best it is possible for anybody to recognise no more than 3% of those who expose him to risk of infection

It is almost impossible to distinguish non-paralytic poliomyelitis from other forms of aseptic meningitis so quickly that the patient can be isolated before others are exposed to risk, while the appearance of paralysis which makes the diagnosis simpler is often too late to serve as a warning The recent studies of Littell and Smith [4] and of Spicer and McDonald [5] underline this by the demonstration that multiple cases in families are usually so close in time of onset that quarantine measures taken after the appearance of the first case would have little value It seems that vaccination might conceal a very small proportion of the infections which expose patients to risk, but that in any case the recognition of an infection in a child gives the parent very little opportunity of protecting himself

You further state "we do not know whether vaccination of children by existing methods will protect them until they have reached the young adult age, at which infection is more likely to cause severe paralytic disease" In this formolised poliomyelitis vaccine may well be no different from other immunising agents It is not apparent why prolonged immunity could not be as readily obtained by reinforcing doses of a formolised vaccine rather than by the use of live attenuated virus Indeed, the international requirements for vaccination against smallpox or with yellow-fever vaccine would seem to imply that the live virus vaccines do not always produce life long immunity Furthermore, the recent studies in Belfast suggest that with the use of live attenuated virus there may well be a risk to the parents of vaccinated children

London School of Hygiene and Tropical Medicine, W C 1

J KNOWELDEN

CLINICAL COMPARISON OF DIAMORPHINE AND PHOLCODINE

SIR,—In your issue of April 27 Dr Snell and Dr. Armitage introduced a very useful method of sequential analysis for the evaluation of clinical trials

I must, however, disagree with the title of the paper, "Clinical Comparison of Diamorphine and Pholcodine as Cough Suppressants," since the authors have compared 'Lipect' with diamorphine linctus *B.P C* the former containing, inter alia, antazoline and liquid extract of ipecacuanha, and the latter oxymel, all of which are far from being inactive ingredients

Dr Snell and Dr Armitage show that

(*a*) Lipect is superior to the placebo
(*b*) the placebo is inferior to diamorphine linctus , *but*
(*c*) "at the 5% level of significance there was no evidence of difference between the heroin and pholcodine preparations"

I submit that the latter conclusion really refers to diamorphine linctus and lipect and that, had the test been carried out with only one of each of the drugs under test in an inert base containing, perhaps, some flavour to mask the taste of pholcodine, then a truer evaluation of the effectiveness of the two drugs would be obtained

This is especially true in this case since the difference is only borderline at the 5% level and such a standardisation of vehicle for the drugs (and placebo) might tip the balance in favour of one or other of the drugs

School of Pharmacy
Brighton Technical College

JAMES C PARKINSON

GOVERNMENT AND PROFESSION

SIR—Dr McCallum (May 4) seems to take great exception to letter of "Blackleg" (April 27), but are there not several good points in it—particularly the last paragraph about negotiating terms of service instead of talking about principles ?

I wonder if Dr McCallum remembers a little booklet issued by the public relations department of the British Medical Association in 1948 ? It was called *The Doctors' Case* On p 6 is the following "The dispute is not about money The government has treated the profession fairly enough in its arrangements for deciding what doctors should be paid The issue is a matter of *principle*"

Dr McCallum says that to do everything by postal ballot would increase the subscription by at least one guinea Does he forget that, before the last election for the G M C, doctors were circularised with documents asking for the support of certain candidates ? This was done through the B M.A organisation but I have not heard yet that the action was as expensive as he suggests

Worthing

HAROLD LEESON

SIR,—Nothing could be more alarming than Dr Grant's suggestions (April 27) for revising the system of payments to practitioners

Rewards given to doctors for keeping their prescribing costs low, for reducing the certified days off work of patients on their lists, and for reducing the number of patients sent to hospital would mean quite simply, that a doctor would not be rewarded for good doctoring but for his part in promoting public economy Heaven knows what kind of desperate cut pricing competition this would lead us to

Apart from the objections I have mentioned, Dr Grant's system smacks too much of good marks for the good boys with yet more work for the bureaucrats and yet more control Better by far the present abuse, which has at least this to recommend it—that the patients do not suffer from cheese-paring physicians keen as governesses to pack them off to work after dispensing thrifty therapy Nor is their admission to hospital delayed in order to provide points for the good boy

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[3] Bothwell T H van Doorn Wittkampf H V Du Preez M L Alper T *J Lab clin Med* 1953 41 836
[4] Littell A S Smith G V *Amer J Hyg* 1955 61 302
[5] Spicer C C McDonald J C *Lancet* March 2 1957 p 470

Lancaster **FRANK S RICKARDS**

SURGEON'S "PRIVILEGE"

SIR,—It is with indignation that I hear that the legal question of surgeons' meals in hospital (referred to in Mr Capener's letter last week) has ever been raised

How mean can hospital administrators become? If they are really interested in the saving of a few shillings a week in hospital expenditure, they should first assess the cost and necessity of their own tea-breaks and luncheons during their short and regular working hours

It is the surgeon who sacrifices his night's rest, gastric mucosa, and blood-pressure in the interest of the patient In Mr Hamilton Bailey's words "To a patient stricken with a catastrophe necessitating an operation, the physical fitness and mental alertness of his surgeon are almost as important as the surgeon's training and experience" For this reason alone, the surgeon needs adequate nourishment between operating sessions

Who would grudge the hardworking surgeon his occasional frugal hospital meal? Certainly not the patient, or the nursing staff

Royal Aberdeen Hospital for
Sick Children, Aberdeen **BARBARA JUDGE**

INSULIN TREATMENT OF SCHIZOPHRENIA

SIR,—May I attempt a further defence of what appears to me an irrational but well-patronised remedy now being condemned on very slender evidence? It was unwise to get trapped by the irrelevant yardstick of discharge, but at least I seem to have been in the company of Dr Ackner and his colleagues

Consider their result in terms of clinical states Clearly there was no difference in recovery-rate in the insulin and control groups (9/24 and 10/25), but this means nothing unless the precision of this apparent absence of difference is considered Perhaps the best estimator in such a trial is the percentage difference between the recovery-rate in the two groups Let us consider a result of the form

	Insulin	*Control*
Recovered	a	b
Not recovered	c	d

This estimator will be $\left\{\left(\frac{a}{a+c}-\frac{b}{b+d}\right)\times 100\right\}$ % and will have a standard error of $\left\{\left(\sqrt{\frac{ac}{(a+c)^3}+\frac{bd}{(b+d)^3}}\right)\times 100\right\}$ %

In the trial considered this standard error is about 14%, so that the only statistical inference that can be made with reasonable safety is that insulin therapy would be unlikely to benefit more than 20% of patients

It would be interesting if exponents of this treatment would give their views on what percentage benefit should be expected Suppose it were 10% (and this would be a most important contribution to the therapy of a common disorder), then such a trial could reject this claim with reasonable provisional safety, on statistical grounds, only if the precision of their estimate were such that it had a standard error of less than 6% This would require well over 200 cases

With such low precision available from such an analysis of such a trial it seemed reasonable to question the assumption that more was gained than lost by leaving the bedside I did not intend to question the randomising of therapy

As the function $\left(\sqrt{\frac{ac}{(a+c)^3}+\frac{bd}{(b+d)^3}}\right)\times 100$ will usually approximate to $\frac{100}{\sqrt{N}}$ in a blind trial of N cases in which a single response, such as recovery, occurs in from one-third to two thirds of cases, this sets an absolute limit to the precision of a debunking trial of this type

Conventionally, using a one tail test at the usual level of significance, a claim that a worthless but harmless remedy has a benefit of p% will usually take more than $\left(\frac{165}{p}\right)^2$ cases to contradict on statistical grounds If a 5% benefit is regarded as of practical importance (and who would forgo a 1-in-20 chance of recovery?) exponents of therapies need not be intimidated if such trials show "no statistically significant differences" unless the numbers exceed at least a thousand

Birmingham **J H EDWARDS**

RELEASE OF HISTAMINE IN URTICARIA PIGMENTOSA

SIR,—The preliminary communication by Dr Hamrin from Lund University, in your issue of April 27, is most interesting Although patients with urticaria pigmentosa do not show intolerance to salicylates, those with chronic urticaria not infrequently do so There are genuine cases of urticaria and associated reactions which are manifestations of true allergic sensitivity to salicylates Their reaction occurs only in response to these drugs, and they would seem to have specific antibodies

But apart from such instances, there are patients with chronic urticaria who are made worse by taking salicylates, and who improve but do not clear up when the drug is stopped Their reaction does not appear to be a specific allergy That salicylate may act as a histamine liberator in such cases (as suggested by Dr Hamrin), and so aggravate the urticaria, would be an acceptable explanation

St John's Hospital for
Diseases of the Skin,
London, W C 2 **C D CALNAN**

THE ENANTHEM OF MONONUCLEOSIS

SIR,—Dr V G Letsou [1] has lately discussed credit for priority regarding the description of palatal eruptions in mononucleosis Dr A Holzel reported on this sign in *The Lancet* in 1954 [2] When I read Dr Holzel's article I intended to write to you, but procrastinated Earlier I had stated [3] that observation of a palatal enanthem was helpful in the diagnosis of mononucleosis, and, as far as I knew, Berberich and Thomas [4] were the first to describe this sign Perhaps this letter will serve to evoke responses disclosing that this important sign was described even earlier

U S Army Hospital
Fort Benning, Georgia **ROBERT J HOAGLAND**

ALLOXAN AS A POSSIBLE THERAPEUTIC AGENT IN CARCINOMA OF THE LIVER

SIR,—I was particularly interested in Professor Gillman's communication (Jan 12), for I myself have worked on this question for 22 years, and have applied alloxan therapy for several years

My communications include a paper on the clinical and biochemical opposition between malignant neoplasms and diabetes mellitus, read to the Société de Medecine de Paris on Oct 23, 1953, an article on diabetes and malignancy,[5] and a paper on alloxanic diabetotherapy and cancers, read to the Société de Pathologie Comparée on Jan 8, 1957 English, German, and Spanish translations of the latter will soon appear

I have treated many cancers of the liver with tangible results I use only 80 mg intramuscularly twice a week

Paris Ier ***PIERRE GROBON***

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1 Letsou, V G *J Amer med Ass* 1956, 162 1178
2 Holzel A *Lancet*, 1954, ii, 1054
3 Hoagland R J *Amer J Med* 1952, 13, 158
4 Berberich, W F, Thomas, F H *U S Naval med Bull* 1949, 49, 271
5 Grobon P *Santé publ* May 10 1955

TONSILLECTOMY

SIR,—Your annotation of April 20 was stimulated by my "Tonsils and Adenoids Evaluation of Removal in 50 Doctors' Children,"[1] and it seems *a little unfair*, in view of my carefully worded title, to complain that I did not have a control series or say how many doctors' children I had decided not to operate upon in the same period of time My belief that the operation was of great benefit for the conditions for which I undertook it was confirmed by my study of the results in these 50 doctors' children, and I would have felt a little unhappy and certainly not very helpful to my colleagues if I had refused to operate upon some of their children in order to use them as controls Many experienced general practitioners and pædiatric physicians believe as I do, and I wonder if you are justified in stating that "it is fairly well known that introduction of controls shows that the operation makes no impressive difference" That statement is based on a small series which you suggested[2] would have shown the same result whatever the number Comparable controls are very difficult to come by, and the numbers would have to be very large to equal out the variations If you had applied the same kindly thought, exercising unbiased editorial outlook, to my small series, I think you would have been getting nearer the truth

London, W 1 JAMES CROOKS

HAZARDS OF EPOXIDE RESINS

SIR,—Your annotation of April 20 in my opinion calls for comment A distinction should be drawn between the resin and the catalyst, as well as the finished polymerised resin product My experience with the amine catalysts over the past 9 years has shown that the amines are the most dangerous hazard and sensitisation to any one is liable to cause further sensitisation to others Boas Traube et al[3] and Dernehl[4] reported on the amines as skin poisons long enough ago to warn of the need for caution There is also the further problem of dangers arising from the partially polymerised final compound, which if drilled, sawn, or otherwise worked may give off a fine dust which is also a marked irritant when inhaled[5]

You state that "manufacturers of resins and hardeners are well aware of the hazards involved" If they are, then *it* appears to me that they could have done much more to prevent the trouble They have not been outstandingly cooperative, in fact it is known that one company in U S A had carried out considerable research on the toxicity of the glycidyl ethers, closely related *compounds*, and published its results in 1954 It is also known that another large producer in Europe has been investigating these compounds for some years without publishing data In spite of this, the information on prevention has not been passed on in a satisfactory manner to users It would *appear that question* of international patents complicates the *publishing of complete* data of the processes I am indebted to Mr W Whitby for clarifying the position he informs me that "in the U S the situation is quite different from that on the Continent of Europe because the U S Courts have forced the companies under the anti-trust laws, and also under the rulings re the Devoe and Raynolds patents, to form a patent pool This has *prevented* to some extent the hold that "X" has on some patent operations in Europe I discovered these various things in attempting to get information at an early date"

As far as prevention is concerned, *I do not* permit the use of gloves in the factories under my supervision The sticky compounds cause the fingers of the gloves to adhere to each other They dry and get hard, reducing manual dexterity considerably An adequate barrier-cream, good washing facilities, a "no-touch" technique, and reasonable engineering application have been adequate to prevent any cases The recent introduction of a resin-removing cream has eased the situation considerably This will remove even the hardened resin from the skin without damage to the epithelium

Unfortunately epoxide resins and amine catalysts are used in many small factories where no medical facilities are available and where the knowledge of protective *methods is practically non* existent

L B BOURNE

London N 5 Senior medical officer A C Cossor Limited

THIRTY-MINUTE SCREENING TEST FOR PHÆOCHROMOCYTOMA

SIR,—I wish to add my support to Dr Frazer's remarks (May 4) on this test

With this method, I too have recovered only about 30% of both noradrenaline and adrenaline added to urine, using either B D H alumina (prepared as described in the original paper) or Woelm acid alumina (L Light & Co Ltd)

Increasing the amount of alumina and eluting several times with acid did not increase the recoveries recoveries of catecholamines added to water were, however, quantitative

Pekkarinen[1] notes that there is a substance present in the eluate from urine which inhibits fluorescence This effect is neutralised by using high dilutions, but this requires a sensitive fluorimeter for measurement

Like Dr Frazer, I seem to be a slow worker requiring almost two hours for one estimation

Royal Sussex County Hospital
Brighton 7 CLIFFORD RILEY

SIR,—In reply to Dr Frazer's comments I should like to give the following information which, to save space, I omitted from the original paper

(1) In preliminary experiments using a fixed volume (200 ml) of urine it was found that recovery of added catechols varied greatly (as judged by fluorescences obtained), the recovery from more concentrated urines usually being obviously lower By using an aliquot ($^1/_{10}$) of a 24-hour collection diluted to 200 ml these variations in recovery were greatly reduced Since the standard is prepared always from a pooled urine specimen we are concerned only with variations in recovery *from urine* and comparison with pure noradrenaline standard is irrelevant

(2) Although visual comparison of fluorescence is sometimes difficult, the specificity of adsorption on aluminium oxide at pH 8 5 is such that few interfering substances are present and urines having 2 µg difference in added noradrenaline (equivalent to 20 µg per 24 hours) can be distinguished In one or two cases a blue fluorescence was seen and on these occasions or whenever a comparatively high fluorescence was obtained, the test was repeated including recovery estimations on the urine being tested

(3) The aluminium oxide used (Merck) was dried, after washing and filtering by suction, by spreading on large sheets of filter paper and leaving overnight in a warm room followed by heating in an oven at 100°C for one hour As the same batch of aluminium oxide (kept in a *stoppered bottle*) was always used for unknowns and corresponding standards, variations *in* adsorptive properties were of no consequence

The results given for urines tested were intended to represent only very approximately the levels of catechols present, the primary object of the test is to detect amounts in excess of 180 µg per 24 hours That it is capable of doing so can readily be shown by a few tests on normal urines with and without added noradrenaline

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[1] *Practitioner* 1957, 178 215
[2] *Lancet* 1955 ii 810
[3] Boas Traube S G Dressel E M, Dryden I G C *Nature, Lond* 1948 162 960
[4] Dernehl C V *Industr Med Surg* 1951 20 541
[5] Bourne L B International Congress of Industrial Medicine Naples 1954 *Trans Assoc industr med Off* 1956 6 94

[1] Pekkarinen, A, Pitkanen M E *Scand J med lab Invest* 1955, 7, 1

I fail to understand why any competent operator should require longer than half an hour to complete the test We often carry out the whole procedure (including a standard preparation) in less than 30 minutes Further, a modified form of the test (using $^1/_{50}$ of the 24-hour urine collection made up to 40 ml in a large test tube and centrifuging only at the final stage) can be completed in 15–20 minutes

Department of Biochemistry
and Pharmacology
University College Dublin D HINGERTY

CLINICAL THERMOMETERS

SIR,—Having been the victim of a pyrexial illness, I have been wondering why the so called half-minute clinical thermometer requires at least two minutes to record a correct reading, and why in domiciliary practice no adequate means of sterilisation has been devised to prevent the possibility of cross-infection

London W 2 F WIDLAKE

DEFINITION OF MENTAL DEFICIENCY

SIR,—The modern medical concept of mental deficiency is of social incapacity due to incompleteness of development of mind

Thus, we find detained on order under the Mental Deficiency Acts not only the obviously idiot, imbecile, and feebleminded, but patients who might equally well be regarded as aggressive psychopaths, habitual criminals, or merely members of the "social problem" group Whatever our professional concept may be, there is no doubt that in the public's mind mental deficiency is identified with low I Q I feel it is the interpretation of this concept to include a wide range of I Q s which gives rise to the recurring allegations of wrongful certification

It was repeatedly put to the Royal Commission on the Law relating to Mental Illness and Mental Deficiency that high grade patients should not be cared for in the same hospital as lower grade patients, and there is no doubt they resent being classified in the same way as patients in whom the defect is more obvious

Those of us concerned with the care of mental defectives have been at some pains in the past to avoid the acceptance of the I Q as a basis for diagnosing mental defect However, it seems to me that it would clarify the present position and ultimately improve the therapeutic possibilities if we limited the term "mental defect" to a condition of social incapacity with low I Q (below 70) and treated as a separate problem social incapacity with higher I Q s

Patients falling into the latter group are often more in need of psychotherapy than of the type of training given in most mental-deficiency hospitals, and if they are considered to require institutional care, I suggest this should be given outside the provisions of the Mental Deficiency Acts At present there is no other legislation to cover this group, apart from voluntary admission to a mental hospital Most of these patients are not suitable for admission to the ordinary mental hospital, and there seems to be a need for separate accommodation for them Where their voluntary admission was not considered appropriate, their admission could be obtained on magistrates' order after the presentation of a petition as under section 6 of the Mental Deficiency Act, such legislation should be incorporated in the Mental Treatment Acts

I am aware that there will always be borderline cases, which will give rise to difficulty, but the sooner we stop calling the socially inadequate group with "normal" I Q "mental defectives," the sooner we shall remove a powerful source of resentment among these patients, the greater will be our chance of obtaining their coöperation in psychotherapy, and the less frequently will we be accused of wrongful certification

Bristol W ALAN HEATON WARD

SERUM-CYANOCOBALAMIN LEVEL IN CHRONIC INTESTINAL DISORDERS

SIR,—Dr Meynell and his colleagues (May 4) fail to do justice to the pioneer work of Dr G I M Ross and Dr D L Mollin, at the Postgraduate Medical School of London, on the assay of vitamin B_{12} in human serum

Ross[1] was the first to adopt a microbiological assay of vitamin B_{12} (that of Hutner and co workers[2]) to the quantitative measurement of the vitamin in serum and other body-fluids, and to demonstrate that the serum B_{12} concentration was unusually low in pernicious anæmia In 1954, Mollin and Ross[3] gave details of serum assays in a variety of gastro intestinal types of megaloblastic anæmia included in this report were data obtained from 33 patients with idiopathic steatorrhœa, 13 of whom had low serum B_{12} concentrations

Neither of these papers are mentioned by Dr Meynell and his colleagues

Department of Pathology (Hæmatology)
Postgraduate Medical School of London J V DACIE

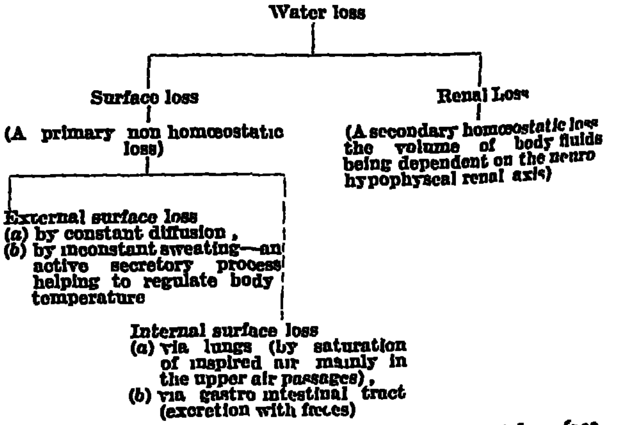
WATER-LOSS FROM THE BODY

SIR,—There is not, to my knowledge, any real justification for describing the combined water loss from skin and lungs as "insensible loss" Thus, Le Quesne in his excellent monograph[4] says

> Unfortunately there is no satisfactory term to describe this loss [entire losses from skin and lungs] There are cogent objections to the use of the three most obvious terms—namely "insensible loss," "inevitable loss," and "extrarenal loss"

The chief drawback of such terms is that they describe qualities of water loss which do not serve to illuminate our understanding of either their source or their nature It is perhaps impossible to coin an ideally all inclusive "blanket" term, but I suggest "surface loss" to replace the one most commonly used—"insensible loss"

At first glance this term might seem *as vague as* "extrarenal loss," but in the context of the classification given below I hope it may prove more accurate


Water loss
Surface loss
(A primary non homœostatic loss)
Renal Loss
(A secondary homœostatic loss the volume of body fluids being dependent on the neuro hypophyseal renal axis)
External surface loss
(a) by constant diffusion ,
(b) by inconstant sweating—an active secretory process helping to regulate body temperature
Internal surface loss
(a) via lungs (by saturation of inspired air mainly in the upper air passages) ,
(b) via gastro intestinal tract (excretion with fæces)

I use the word "surface" to express the *total* surface presented by *the body to* its environment, which is therefore external (mainly as skin) *and* internal (mainly as the lining of the gastro intestinal *tract* and lungs) The term "homœostatic" in the above classification is used in the specific sense of the body-fluid homœostasis and does not include thermal homœostasis A very small amount of water is lost via the secretions of the exocrine glands of lactation, salivation, lacrimation, and via the genital secretions This loss could be included in the surface loss

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[1] Ross, G I M *Nature, Lond* 1950, 166 270

[2] Hutner S H Provosoli L , Stokstad, E L R Hoffman, C F Belt M Franklin A L Jukes J H *Proc Soc exp Biol N Y* 1949 70 118

[3] Mollin D L Ross, G I M *Proc R Soc Med* 1954, 47, 428

[4] Le Quesne, L P Fluid Balance in Surgical Practice London 1955

Department of Pædiatrics,
Whipps Cross Hospital,
London, E 11
AYUB K OMMAYA

SUBUNGUAL HÆMATOMA

SIR,—May I add a simple method for the relief of pain in a subungual hæmatoma, which I have been practising for years? It is very quick and effective

An old pocket sized surgical knife with a very narrow blade is used The point has lost its sharpness and is more round The knife is placed perpendicularly on the nail, with its point resting over the centre of the hæmatoma It is rotated there and back with the thumb and index-finger exerting only light pressure After a few movements the nail is painlessly penetrated and a few drops of dark and thick blood appear These are wiped away and after a few more rotations with the knife all the blood of the hæmatoma is evacuated The hole made in the nail in this way allows an easy escape of the thick blood

Using a needle, safety-pin, or other similar pointed instrument, as advocated by some, is bound to cause pain, because it has to penetrate the nail enough before the blood begins to escape, the sharp point meanwhile pricking the sensitive subungual tissue Using the old knife without a sharp point makes the hole in the nail larger before touching the subungual tissue

London S E 25
A FRY

Obituary

GEORGE AUGUSTUS AUDEN

M.A , M D Camb , Ph D Birm , F R C.P , D.P H

Dr Auden, who died on May 3 at the age of 84, was Birmingham's first school medical officer When he was appointed in 1908 he was a consulting physician rather than a specialist in public health, but he was drawn to this comparatively new form of medical practice by his interest in education and children His wisdom as a physician was matched by his learning as a scholar and antiquarian, and in letters to our columns he would quote from Sanskrit writings as easily as from the *Saga of St Olav*

He was the son of the Rev John Auden, of Horninglow, Burton-on-Trent, and he was educated at Repton and Christ's College, Cambridge, where he was a Porteous medallist After taking a first-class in the natural sciences tripos in 1893 he continued his medical studies at St Bartholomew's Hospital where he won the Kirkes scholarship and medal and the Lawrence scholarship and medal Having qualified in 1896 he held house-appointments in London at Barts and at the General Lying-in Hospital Later he settled in practice in York and was appointed physician to the York County Hospital In 1908 his interest in education led him to apply for the new post of school medical officer at Birmingham There was strong competition for the appointment, but the committee was impressed by Auden s work for children at York County Hospital and his membership of the school board and education committee of the city

At first the work of his new department had to be directed to relieve disease, but even in those early days he showed that he was far sighted and broad-minded In his first annual report he stressed the need for psychological help in "the many problems which beset educational effort" Much later his own ability to assess the psychological needs of children was recognised by his appointment as honorary psychiatrist to the Birmingham Children's Hospital

During the 1914–18 war his work at Birmingham was interrupted by his service with the R.A M C in Egypt Gallipoli, and France On his return he quickly took up the threads of his growing department He was also "sanitary adviser" to the governors of Rugby School and demonstrator and later lecturer in public health in the University of Birmingham When he was elected F R C P in 1919 he was one of the first school medical officers to be admitted to the fellowship Meanwhile the emphasis of the work of his own service was happily shifting from treatment to prevention, and the chapters on nutrition and the milk-in-school scheme in his report for 1936 made clear that he recognised the school medical service's changing responsibilities The following year, in his last report, he urged the need to re-examine its functions in the light of changing social conditions

After he retired in 1937 he continued his work at the university, and in 1941 he was appointed to the chair of social medicine He also wrote effectively and widely on public health hygiene, psychology, and mental deficiency More than most men he had resources in interests outside his own profession, and his study of history and archæology made his local histories of York and Birmingham valuable and scholarly works His chief interest was the antiquities of the Scandinavian countries He had translated Rathgen's *Preservation of Antiquities* and the official guide to the prehistoric collections of the Danish national museum, and he was a foreign member of the Society of Northern Antiquaries of Copenhagen as well as of the Society of Antiquaries of London

A colleague writes

Dr Auden built up an excellent medical service for the schools in Birmingham by inspiring enthusiasm for a new development He was rather impatient and suffered at times because others could not see so far ahead as he did, but the recent *Report of the Committee on Maladjusted Children* paid tribute to his far seeing view His interest and knowledge of those who are now called the handicapped was wide and tribute was recently paid him by the Birmingham Education Committee who named a school for the partially sighted after him This month's *Public Health* also refers to his recommendations

Dr Auden was extremely popular with his staff, always thoughtful and kindly, unassuming in his manner, with a strong sense of humour He was extremely versatile with many interests His erudition weighed lightly upon him, and yet it was glimpsed at times when he spoke of calling on a medical officer in Iceland and discussing Homer with him Passing years did not diminish his many interests He continued to attend the meetings of the Midland branch of the Society of Medical Officers of Health of which he had been a president He was a successful wood worker He wrote articles on many subjects His last, only a few years ago at the time of the Boat race, was on the longevity of oarsmen He kept up a lively and knowledgeable correspondence to the end *Multis ille bonis flebilis occidit*

Dr Auden leaves three sons one of whom is W H Auden, professor of poetry in the University of Oxford

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Appointments

DUNCAN G D M B Aberd , D P H M O Leeds Regional Hospital Board headquarters

GORDON, N E M B Belf D P H M O H Todmorden, and divisional M O West Riding of Yorkshire

GREW SHEILA M E M R.C S assistant M O H and school M O Gloucestershire

HOWARTH E C M B Lond assistant M O Hertfordshire

LINDSAY G G M B Glasg , D P H depute M O West Lothian

LINTON J S A F R.C S consultant thoracic surgeon Nottingham City Hospital

MARTIN J R M M B Lond D M R.F assistant radiologist Royal Infirmary and General Hospital Leicester

MOORE, JEAN M , M B Lond assistant M O H and school M O , Gloucestershire

SEN S K M B Calcutta D G O registrar in obstetrics and gynæcology, West Norfolk and King s Lynn General Hospital

SHEARER A B M B Queensland medical registrar Ipswich and East Suffolk Hospital

WARD A J M B Durh assistant radiotherapist (S H M O) Leeds regional radiotherapy service and Bradford Radium Institute

Manchester Regional Hospital Board

MCHUGH JOHN M B Durh D P H deputy medical superintendent and assistant psychiatrist Brockhall Hospital Blackburn

PURSER D W M B Manc F R C S consultant traumatic and orthopædic surgeon Lancaster and Kendal hospitals

SIMS A J M B Lond F F A R.C S assistant anæsthetist Bury and Rossendale group of hospitals

Notes and News

THE INTERIM INCREASES IN REMUNERATION

SALARIES of hospital doctors and dentists up to and including the grade of senior registrar were raised by 10% from April 1 The corresponding increase for their seniors in the hospital service will be 5% from May 1 The new rates per annum for whole-time appointments (with the old rates in parentheses) are

CONSULTANTS

Appointed earlier than 31 —Starting salary £1890 (£1800)
Appointed at 31 —Starting salary £2047 10*s* (£1950)
Appointed at 32 or over —Starting salary £2205 × £131 5*s* to £3255 (£2100 × £125 to £3100)

The *maximum salary*, with the addition of the maximum distinction award, is now £5455, compared with £5300 previously

SENIOR HOSPITAL MEDICAL AND DENTAL OFFICERS

Appointed earlier than 31 —Starting salary £1548 15*s* (£1475)
Appointed at 31 —Starting salary £1601 5*s* (£1525)
Appointed at 32 or over —Starting salary £1653 15*s* × £52 10*s* to £2126 5*s* (£1575 × £50 to £2025)

As from May 1, 5% will be added to the aggregate net remuneration of general practitioners—i e , their remuneration after the deduction of practice expenses The Government propose that the method of distributing this extra money between individual doctors should be the subject of consultations with representatives of the profession The meeting of local medical committees last week recommended that the money should be accepted "without prejudice" and that negotiations should be entered into with the Ministry to decide the best method of distributing it

Dentists taking part in the general dental service will receive on average an increase of 5% on their net remuneration (before deduction of income tax) As practice expenses have to be taken into account, the actual increase will be 2 6% on the gross scale fees payable The increase will be payable on all payment schedules dated on or after May 1 For dentists working whole time at a health centre, the new scale will be

Grade I —£1575 × £52 10*s* to £2100 (£1500 × £50 to £2000)
Grade II —£1260 × £52 10*s* to £1575 (£1200 × £50 to £1500)
Grade III —£840 × £52 10*s* to £1207 10*s* (£800 × £50 to £1150)

Working in the National Health Service in Great Britain are over 10,000 senior hospital doctors and dentists, about 21,000 family doctors, and about 11,000 dentists The estimated cost of the two "interim adjustments" is nearly £6 million (senior hospital medical and dental staff, £1,200,000 , junior hospital medical and dental staff, £900,000 , general practitioners, £2,500,000 , dentists, £1,200,000)

EMPIRE RHEUMATISM COUNCIL

PRESENTING the report [1] of the Council for 1955–56, at the annual meeting held in the House of Lords on May 1, Dr W S C Copeman, the chairman, emphasised the importance of basic research in rheumatology lately reported It has, for instance, been shown by electron microscopy that there are many different varieties of muscle fibre , further research will be needed to decide whether this has a bearing on extra articular rheumatism

The report refers to work done by the Council's three fellows

Miss I H M Muir gives an account of the first isolation from cartilage of a complex of chondroitin sulphate and protein Small changes in its chemical structure lead to large physical changes, which may explain some of the changes in rheumatic conditions The linkage between carbohydrate and protein is probably an ester between the carboxyl group of a glycuronic acid and the hydroxyl group of serine An esterase, by disrupting such bonds, may lead to loss of elasticity and increase of permeability—an effect similar to that of hyaluronidase Miss Muir also reports the discovery of a new amino sugar (talosamine) in cartilage

Mr J K Norymberski, DR ING , reports biochemical studies of the steroid hormones—on the oxidation of corticosteroids with sodium bismuthate, the urinary excretion of cortico steroids in pregnancy, the ultraviolet absorption spectra of α ketols and the partial reduction of steroid hormones

Dr Madeline Keech has studied the structure of collagen and its possible relation to elastic fibres, and has been awarded the first prize in an international competition for the most outstanding contribution on the study of ageing

Other investigations referred to in the report include a controlled psychological comparison of patients with rheumatoid arthritis and their siblings , a study of antigen/antibody reactions , and a survey to find out the prevalence of rheumatic disease in Leigh, Lancashire, where a 4% sample of the population is having clinical and radiographic examinations and blood tests

The Council has launched an appeal for £250,000, in the hope that these promising lines of research can be followed up quickly and effectively

THE HEALTH OF EXECUTIVES

LAST year [1] Prof Alexander Kennedy gave an account of the hazards of being an executive (hazards both to himself and to his firm), and gave some guidance in the avoidance of breakdown in the "top management" of industry An essay on the Health of Executives by Dr V C Medvei [2] reminds us that many large organisations are coming to see the advantage of "treating their executives like expensive machinery"

Greater use of automatic control may tend to eliminate both the skilled craftsman and the worker at the moving belt , but the alphas (and probably the epsilons) of Aldous Huxley's brave new world will still be needed Even if the unpheavals and degradation are less than some people fear, the time when the top executive (Kennedy's "generaliser") is replaced by a robot is not to be foreseen On the contrary the current tendency to bigger and bigger organisations, which is creating Burnham's "managerial revolution," leads not only to an increase in the number of administrators but also perhaps to an increase in the sources of stress

Medvei regards "health" as signified by resilience, stamina, equanimity, and self reliance Many leading personalities possess these qualities , indeed the sickness rates are lower in persons with large responsibilities than in the multitude But even the higher resistance of these people may not suffice to protect them against breakdown if fatigue and stress are too severe Everybody has weak spots, such as a familial tendency to a certain illness, and the effect of the stresses to which executives are subject (such as anxiety, fear, worry and perhaps guilt , irregular timetables , and physical fatigue caused by travel, large meals, and alcohol) may act as triggers for illness Some cannot stand the pace and fall out , some can continue, but at the price of arterial disease or peptic ulcer , while a few seem constitutionally hardy, able to remain fit despite every strain Nothing can be done to give this hardiness to people who are not born with it , and the organisation which has them for its leaders is indeed lucky If the rest of the administrators are to avoid breakdowns, those who cannot stand the pace must be channelled into some backwater, and the middle group must be helped as much as possible

The wise organisation, Medvei says, will insist on its executives having enough leisure, holidays, secretarial help, and comfort in travel and at work (A New York textile firm has lately announced that its senior executives are to be given a week's holiday every seven weeks [3]) Thus hours and methods of work should be adapted to the individual one man will do as much in an hour (and be as exhausted at the end of it) as another in four hours , one works best at night, another in the morning Some firms have a scheme for regular medical examinations, even including X ray and laboratory tests But Medvei points to the danger of such overhauls on the one hand they make for a false sense of security, and on the other they make people conscious of their health and worried about it Moreover, an examination is not much use unless the physician is acquainted with the subject's background and the stresses he meets

The executive's life outside the office must be considered Here the social activities which are part of his work may be a burden These should be reduced to a minimum and perhaps shared by some of the juniors Board and committee meetings should be similarly pruned The executive should be warned against over exercise, and encouraged to relax (with an occasional sedative if need be) A change in surroundings and a hobby are both useful , a purposeful hobby that is not an obsession will give meaning to life after retirement

The head of an organisation, Medvei says, must be personally responsible for actively guarding the health of his colleagues , and a continuing partnership between physician and executive is needed to get the best results

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[1] Issued by the Council, Tavistock House North, Tavistock Square London, W C 1

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[1] Kennedy, A *Lancet* Feb 2, 1957 p 261
[2] Medvei V C *Public Administration*, Spring, 1957 *Obtainable* from the Royal Institute of Public Administration, 76A New Cavendish Street London, W 1
[3] *The Times* April 16, 1957

THE BRITISH HOSPITAL IN PARIS

The Hertford British Hospital in Paris was first opened in 1871, to provide medical and surgical care for indigent British residents Lack of money forced it to close in 1952, but it has been redecorated and re-equipped to serve a dual function—the treatment of British soldiers and their families and (in conformity with Sir Richard Wallace s original endowment) the treatment of British civilians, for whom 25 of the beds are reserved French doctors and the doctors and nurses of the Royal Army Medical Corps will share the care of the civilians who will pay for their treatment if they can. The needy will be provided for by the administrators of the original Hertford Hospital, they will not be a charge to public funds

The hospital in its new guise contains 60 beds (in wards of not more than 3) including maternity wards as well as 2 operating-theatres and an outpatient department It was opened on May 3 by Lady Alexander

A PASTORAL CLINICAL COURSE

For some time it has been felt that future clergymen some of whom will become hospital chaplains should during their training acquire some knowledge of conditions in hospitals, especially mental hospitals Accordingly in the second half of March, a pastoral clinical training-course was held at Deva Hospital, Chester, and attended by first-year and second-year theological students from St Michael s College, Llandaff, Cardiff

The programme included lectures on mental disorders nursing, and related topics, with a talk on the Church s Ministry to the Sick, demonstrations of physical treatments and electro-encephalography, and visits to wards, classes, and recreational functions The students lived in the hospital and were favourably impressed by the atmosphere there, and thought the course of great benefit Several intend to return during the long vacation and work in the wards

The chaplain at Deva Hospital is the Rev. N W J Autton

NUTRITION RESEARCH AT COONOOR

The latest annual report[1] from Coonoor shows that the Nutrition Research Laboratories continue to flourish with a graduate staff of more than 30 These can be roughly divided into three groups—biochemists, clinical scientists, and public-health field workers Biochemical studies include the following

The vitamin B_{12} activity of the fæces of rats was found to be almost as high when the diet contained only vegetable proteins as when skim milk was given

In the rat there is a critical level of dietary protein necessary for the synthesis of liver enzymes (succinic acid dehydrogenase and xanthine oxidase) This is about 10% of protein in the diet At this level an adaptive mechanism can come into play which delays the effects of protein deficiency but 7 5% protein is clearly inadequate

The citrogenase activity of epiphyseal cartilage from rachitic puppies has been shown to be much below normal and the old problem of how vitamin D deficiency affects tissue metabolism is being studied

There is also a brief account of the chemical nature of the fatty acids in butter and beef fat which is a continuation of earlier work started long before this subject became fashionable

The clinical scientists have been concerned mostly with protein malnutrition

The hæmatological picture including bone marrow biopsy has been studied in 18 patients with kwashiorkor In most there was macrocytic anæmia sometimes with a megaloblastic reaction Improvement was usually slow even after treatment with folic acid or vitamin B_{12}

The cystine content of the hair of children with kwashiorkor was found to be low but the level of other amino acids tested was normal It is suggested that the cystine content of the hair may be a better index of the severity of protein malnutrition than the hair discoloration

In monkeys kept on a low protein diet for two to three months diffuse interstitial myocardial fibrosis was found

The public health work has been concerned chiefly with problems of infant feeding in South India

Detailed information about the quantities of breast milk secreted by the mothers supplements a previous study on the quality of maternal milk

A group of breast fed infants received daily 2 0 g of protein per kg of body weight in the first two weeks of life This figure fell gradually to 1 4 g after eight weeks and 1 2 g after twenty weeks The babies grew satisfactorily and the generally accepted figure of 3 5 g per kg for the protein requirements of infancy may be an over-estimate

The attractive feature of this report is the obvious close coöperation between the biochemists clinical scientists and public-health workers who are all centred on the laboratories This is a fortunate juxtaposition seldom found elsewhere It is now the fashion for young British graduates wishing to study abroad to look Westwards Any unconventional young man or woman who decided to go East might be well advised to spend time at Coonoor He would find the intellectual atmosphere in the Nilgiri Hills like the climate —bracing

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[1] Nutritional Research Laboratories Coonoor South India annual report 1955–56

University of Oxford

To commemorate the work of the late Sir Hugh Cairns a fund for neurological research is to be established It will be administered by the Nuffield Committee for the Advancement of Medicine, and £2000 will be paid annually into the fund from the Nuffield medical benefaction to assist research in neurology and neurosurgery in the medical school

Royal College of Obstetricians and Gynæcologists

The following were successful in a recent examination for the diploma in obstetrics

D A Aitken, R W Allin, A A Allison, Andrew Armstrong G A E Baker, Vijayaratnam Balachandran Amarendra Banerjee, A F Barrett R W Beard Felicity M Bedford Kailash Bhalla J T Binless P M Binns G C Bird Sybil D Bonnini, W M S Boyd R T Boyle P V Briffa K G Buckler Mary E Budleigh, M F D Burton, Sheilah Caldwell D J C Cameron J J Camp H A Campbell P J S Cannon Gerald Caplan J M Carr B R T Carroll, Leila M Chacko J E Charlewood R R Charlwood Helen Clarke B J Clayton Payne D J Cliff D T Cousins A F Crowley G H C Daley S N Das D I Davies Edna L Davies, W F T Davies, Pauline M Dean, H V Z De Klerk L P De Souza Raymond Dingley, Pamela M Dodson Marion R H Donald, A M Donaldson B G Dooley K B Dorofaeff B J Drake, R E Dreaper Florence M Duckenfield G H H Dwyer Judith M Edmundson, P A E Edmundson P E Elwood, Michael Entwisle, J F Evans L W S Evans Edith Faierman David Fairbairn F G Feinstein Elizabeth A Fisher A F Floyd Beryl M Foley H K Ford E J H Foster James Frame A T R Fuller Richard Gardner Ethel F E Gelber Srisht Kumari Ghai Saroj Kumar Ghosh H R Gibson B B Giri S L Goodman C M Green Everel C Green W F Griffith Peter Griffiths D S Hamilton Julian Joseph Handler, D C Harris F A S Harris Rex Harrison D F Hawkins F S N Hazel Anne Heath Rita Henryk Gutt M D Heyman R F Heys E P Hilary-Jones J G Hill Molly Hill W G Holland J A Hopson J M Hughes Samuel Hyndman F L Johnstone Audrey Jones F W Jones R J B H Jones J A Kay Sylvia I Keet R M B Kerr P J King J A Kirkland Iris M Krass Dorothy K C Kwan Z K Langdana J F Lecton Penelope A Leighton W G H Leslie E H Loxton, A R Lyall, H D MacEwan I A W McKelvey Irene F McLaren Elizabeth M McNab I S McRobbie James Maguire Kissundath Mahabir Dorothy Mainwaring R B Malcolm Eric Mallett, Pauline A Manfield B H Markham Veronica Mercer G C Metcalfe J S B Meyer J G Millar H F Molloy P L C Monier-Williams R M A Moon Sheila M L Moore Thomas Moore J M Munn Mira Vinayak Muzumdar B E H Neal H I L Nicholls T M Nottbower F I O Connell Mary G Orrell S C Paget E G Palmer Ponniampalam Paramaswami D C Pearson L J T Pearson L G Pereira Frances K Philips A D Prowse P W Quinn, F A Raja G L S Rankin M A H Rayman Edward Redfearn K W Reed B F Reeves C B Rennick Hilary A Roach T H Roach T L Roberts Brian Robertson G F C Rosser A J Rowland Shefali Roy N D Royle M F Russell Betty V Scott I A Seddon M S Shalom C A Sharples A J Shaw James Smith R W G Stewart J S Sugden J F W Sutherland E P W Tatford G A Taylor M G Taylor M B Teal Ann Thomas D K M Thomas M C Thornton Martin Tobias Patricia A Topham Bhanumati Mrigendra Trivedi Roger Unwin Alice E M Van Waterschoodt James Vernon Parry A P Walker G P Walker Edgar Wallace P F Warnock J R Watson Marjory I K Watt John Whewell G T Whitaker Joan W Whitaker Margaret White Agnes F Whitter J D Wisdahl I T D Williams W A Williamson Mary Young

Royal Commission on Remuneration

The commission held a meeting in Edinburgh on May 2 for preliminary discussions with the Joint Consultants Committee (Scotland) and the Institute of Chartered Accountants in Scotland This meeting was the eighth held by the commission

Medico-legal Aspects of District Nursing Practice

The Queen s Institute of District Nursing is holding a conference on Wednesday, June 5 at 2 30 P.M at Church House Westminster S W 1 when Dr J A Gorsky will open a discussion on this subject Applications for tickets should reach the institute, 57, Lower Belgrave Street, S W 1, by May 20

Conference on Medical Records

The Association of Medical Records Officers is to hold a conference from May 16 to 19 in Brighton Speakers will include Mr L E C Norbury F.R.C.S Mr A M Michie and Dr M P Curwen Further information may be had from Mr B B Bonner 11, Queensway, Horsham, Sussex

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West Midlands Physicians Association

The spring meeting of this association will be held at Holme Lacy Hospital, Hereford, on Saturday, June 1, at 11 A M

Institute of Dermatology, London

A semi permanent exhibition on the xanthomatoses, by Dr R H Meara, will be available at this institute, Lisle Street, W C 2, from May 5 to 29

London Hospital Research Building

This building, described last week (p 928), was opened on May 1 by Mr Dennis Vosper, the Minister of Health It was on view to a large number of guests, who were received by Sir John Mann, chairman of the board of governors

The Dentists and the Royal Commission

The representative board of the British Dental Association at a meeting on May 4 decided that " it would be in the best interests of both the public and the profession that they should give evidence to the Royal Commission on remuneration of doctors and dentists "

Chelsea Clinical Society

The annual dinner of this society will be held at the Rembrandt Hotel, Thurloe Place, London, S W 7, on Tuesday, May 14, at 7 30 P M The guests will include Viscount Hailsham, Q C , and Judge H C Leon

United Hospitals Choir

This choir is to give a choral and orchestral concert in October, including works by Purcell, Schubert, and Handel Rehearsals are held on Thursdays (7 30 P M to 10 P M) at the Pulteney School, Peter Street, Soho, London, W 1 Further details may be had from the secretary, Miss J Magrath, 18, West Side, Clapham Common, S W 4

London Amateur Boxing Association

A meeting of the medical officers of this association (69, Victoria Street, S W 1) is to be held at the Great Northern Hotel, King's Cross, on Wednesday, May 29, at 8 P M , when Dr J H Taylor will speak on psychiatric aspects of head injuries

South East Metropolitan Regional Hospital Board

Dr J S S Fairley has been appointed senior administrative medical officer of the board in succession to Dr H L Glyn Hughes, who is retiring

Dr Fairley studied medicine at the University of Cambridge and qualified in 1928 taking his M B two years later After holding house appointments at the General Hospital, Birmingham, he settled in general practice in that city In 1938 he proceeded to the degree of M D As a territorial officer he was called up in 1939 and later in the war he served as D A D G , Army Medical Services, at the War Office In 1945 he was appointed assistant director of personnel to the Emergency Medical Service Since 1947 he has been deputy senior administrative medical officer in the South East Metropolitan region.

Mental Hospitals

At their eighth annual general meeting on April 27, the Friends of Menston Hospital (near Leeds) passed a resolution calling the attention of the Minister of Health to the following " appalling admission " in the Ministry's report for 1955 (p 123)

> For it may well be that the hospital system reinforced by some inevitable stagnation during the war years is responsible more than disease for the fact that many patients have become chronic and deteriorated

The resolution says that " many relatives and friends who are in the grievous position of helplessly observing their patients suffering from a gradual process of deterioration, have long suspected, with deep concern and indignation, that prevailing conditions in many mental hospitals are a major contributory factor in this process Whilst welcoming official recognition of a situation that can only be regarded as intolerable, this Association now demands an assurance from the Minister of Health that urgent steps will be taken to accelerate and extend, on a scale more commensurate with the gravity of the problem, such efforts as are at present being made for the improvement of our mental hospitals "

Sir Russell Brock Dr Paul Wood and Mr Rodney Maingot are attending the Middle East Medical Assembly in Beirut Lebanon, from May 10 to 12 under arrangements made through the British Council

Mr A S Parkes SC D F R S is visiting Yugoslavia from May 5 to 25 at the invitation of the Yugoslav national commission for UNESCO and the British Council to lecture on the work of the division of experimental biology of the National Institute for Medical Research

Diary of the Week

MAY 12 TO 18

Sunday, 12th

King's College Hospital Medical School, Denmark Hill, S E 5
10 30 A M Clinical meeting for general practitioners

Monday, 13th

University College London Gower Street W C 1
5 30 P M Prof J B S Haldane, F R S Karl Pearson centenary lecture

University of London
5 30 P M (London School of Hygiene and Tropical Medicine Keppel Street W C 1) Prof Charles Huggins (Chicago) Treatment of Mammary Cancer

Royal Institute of Public Health and Hygiene, 28, Portland Place, W 1
5 P M Prof Philip Drinker D SC (Harvard University) Air Pollution and the Public Health (First of three Harben lectures)

Tuesday, 14th

Royal College of Physicians of London, Pall Mall East, S W 1
5 P M Prof G W Pickering Regulation of Body temperature in Health and Disease (First of two Croonian lectures)

Royal College of Surgeons of England, Lincoln s Inn Fields W C 2
3 45 P M Prof Geoffrey Hadfield Application of Physiological Principles to Hormone dependent Human Breast Cancer (Imperial Cancer Research Fund lecture)

Society of Apothecaries of London, Black Friars Lane Queen Victoria Street, E C 4
5 30 P M Sir Henry Dale, O M , F R S Medicinal Treatment—Its Aims and Results (Gideon de Laune lecture)

Royal Society of Medicine, 1 Wimpole Street, W 1
8 P M *Psychiatry* Dr Richard D Hahn (Johns Hopkins Hospital) Treatment of General Paralysis of the Insane with Penicillin and with Penicillin Plus Malaria

Institute of Dermatology, Lisle Street, W C 2
5 30 P M Dr F A Whitlock Neurophysiology of Itching

Royal Institute of Public Health and Hygiene
5 P M Professor Drinker Air Pollution and the Public Health (Second of three Harben lectures)

West End Hospital for Neurology and Neurosurgery 91, Dean Street W 1
5 30 P M Dr D F Bosanquet Neuropathology

Wednesday, 15th

Royal Society of Medicine
5 P M *Comparative Medicine* Dr F Kingsley Sanders, Mr R F Sellers Mr T W F Pay Use of Tissue culture Methods in Virus Research
8 P M *General Practice* Dr Hugh Sinclair Physiology of Laughter

Postgraduate Medical School of London Ducane Road W 12
2 P M Sir Howard Florey, F R S Endothelium

Institute of Dermatology
5 30 P M Dr Henry Haber The Dyskeratoses

Institute of Diseases of the Chest Brompton S W 3
5 P M Mr C E Drew Experimental Studies of the Extra corporeal Circulation

Royal Institute of Public Health and Hygiene
5 P M Professor Drinker Air Pollution and the Public Health (Third of three Harben lectures)

Royal Microscopical Society Tavistock House South, Tavistock Square W C 1
5 30 P M Mr H E Huxley, PH D , Miss Jean Hanson PH D Studies on the Mechanism of Muscular Contraction

University of Liverpool
5 15 P M (Old Medical School Liverpool) Prof G Wald (Harvard University) Molecular Basis of Vision

Thursday, 16th

Royal College of Physicians of London
5 P M Professor Pickering Regulation of Body temperature in Health and Disease (Second of two Croonian lectures)

Royal College of Surgeons of England
3 45 P M Miss J Dobson Curiosities of Natural History (Arnott demonstration)

Institute of Neurology National Hospital, Queen Square W C 1
5 30 P M Dr Hahn Tabes Dorsalis, with special reference to Primary Optic Atrophy

Royal Society of Tropical Medicine and Hygiene 26 Portland Place, W 1
7 30 P M Dr C A Hoare Group Captain W P Stamm Dr R A Neal, Dr G Woolfe Laboratory Aspects of Amœbiasis

Alfred Adler Medical Society
8 P M (11 Chandos Street W 1) Dr A Spencer Paterson Psychopathology of Schizophrenia

British Institute of Radiology 32 Welbeck Street W 1
8 30 P M Mr I G Williams *Rôle of Surgery and Radiotherapy in the Treatment of Breast Cancer* (Presidential address)

Manchester Medical Society
8 P M (Staff House University of Manchester) *Anæsthetics* Dr M Johnstone Dr O W Suckling Dr J Raventos Development of Fluothane

Friday, 17th

St Mary's Hospital Medical School Paddington W 2
5 P M Mr J D S Flew Genital Prolapse

Postgraduate Medical School of London
10 A M Prof A M Boyd Management of Obliterative Arteriosclerosis of the Lower Extremity

University of Dublin
5 P M (Trinity College Dublin) Dr F B Walsh (Johns Hopkins University) Ocular Movements associated with Regeneration of the Third Nerve (Montgomery lecture)

DERMO-OPHTHALMOLOGY *

JAMES H DOGGART
M.A., M D Camb , F R C S

SURGEON TO MOORFIELDS, WESTMINSTER, AND CENTRAL EYE HOSPITAL, LONDON, OPHTHALMIC SURGEON TO THE HOSPITAL FOR SICK CHILDREN, GREAT ORMOND STREET, LONDON

THE dangers of over-specialisation in medicine and surgery have in recent years been stressed on both sides of the Atlantic Ocean, and we often hear people say that the great clinicians of the 19th century had far more bedside acumen than is evident in their successors today I suppose we would all agree that a firm background of general medicine is desirable for specialists On the other hand we have to sympathise with those who settle the medical curriculum, because nearly all specialists, including those who are most vocal concerning the dangers of over-specialisation, maintain that their *own* specialty should be allotted more space in the curriculum

Were those old physicians really so wise ? They had their fads, and many of the pronouncements which fell with such dogmatic emphasis from their lips would immediately have been disproved by a modern pathologist or biochemist Moreover their training, we are told, was much easier Surgery had a limited range, and the technique of special investigation was so simple For these and other reasons an attempt has been made to show that our distinguished forebears had feet of clay, and that they would not have achieved much in the present medical set-up

Shall we join in this debunking ? I would say "no" Some few of these former giants may perhaps have become prominent because of circumstances peculiar to their time, but the greater number, I feel sure, would have done great work at any epoch Addison and Osler could never have been insignificant in their profession Nor could Jonathan Hutchinson (1887), who said about dermatology seventy years ago that "beyond all others it offers attraction to the student of the laws of disease, and to the seeker after the causes which disturb health and local nutrition" He was quite right Some branches of modern medicine have little obvious relationship with each other, and only slender links with general health; but nobody can reasonably deny that the skin and the eyes can act as mirrors to each other and to the whole bodily state. Let us now inquire into the overlap

The Overlap between Dermatology and Ophthalmology

Bearing in mind that certain differentiated elements in the eye are derived from the embryonic ectoderm, we should naturally expect that some of the hereditary and environmental factors which help to determine the state of the skin should also influence the eye That expectation is abundantly fulfilled, because in fact we find innumerable instances of parallelism in dermal and ocular pathology Thus thyroid deficiency can bring cataract as well as alteration in the skin texture Another disease notorious for attacking eyes and skin is Boeck's sarcoidosis Fundus lesions may be associated with sebaceous adenoma of the face in epiloia Facial nævus can supply the clue to retinal angiomatosis in Hippel-Lindau syndrome Von Recklinghausen's disease also manifests itself in the eyes as well as in the skin.

Then again, the eyelids, which normally serve as eye-shields, can act as a bridge by which infection and other noxious agents travel from the skin to the eyes Therefore topical therapy of the facial skin must sometimes be modified *in order to avoid ocular damage*—and vice versa That is to say, various medicaments applied to the eyes have been known to set up a dermatitis not necessarily confined to the face Furthermore the lids themselves are a favourite site for basal celled carcinoma, and may be implicated in and distorted by facial lupus Xanthelasma, xeroderma pigmentosum, and psoriasis are among the many diseases that have occurred in the palpebral skin, and they can all produce consecutive changes in the eye A host of different organisms, including moulds and protozoa, has also been identified, so that the pathology of the eyelids, considered in relation to their size, is extraordinarily varied

Nearly all the acute infectious fevers that have been known for centuries are characterised by a rash, and many of them also provoke ocular complications In most countries syphilis has become so much less common than it was a generation or two ago that we often forget its existence nowadays, but in fact the spirochæte can still produce a wide range of skin and eye lesions, and occupies an important place in differential diagnosis Among the skin diseases which can create ocular havoc few can be more distressing than certain vesico-bullous outbreaks of obscure origin Pemphigus, which is their prototype, not *uncommonly destroys the sight of both* eyes

As the skin of the eyelids is more sensitive than any other part of the integument, it is commonly the first to become affected by noxious physical and chemical influences, and may also flare up in consequence of dermatitis beginning elsewhere Palpebral skin is also vulnerable to numerous nutritional defects, including shortage of vitamins Styes were often attributed in former times to refractive errors, ocular muscle imbalance, and other sources of eye-strain, but that explanation now seems doubtful. More probably styes are simply the expression of a temporarily lowered resistance to staphylococci, being analogous to boils in other parts of the skin

It would be easy to multiply instances of diseases in which the dermatologist and ophthalmologist are jointly concerned, but the reasons already given are enough to underline the need for coöperation between the specialties Before we go on to consider some of the relevant changes in exposed skin, I should like to say that I have always found skin physicians most helpful, and I am convinced that they can offer the ophthalmologist more than he is able to return

Significance of the Exposed Skin

Mistakes in diagnosis, and delay in arriving at a correct diagnosis, could often be prevented if we were to examine the whole body-surface For instance, I remember a case of orbital carcinomatosis being at first misinterpreted because the patient protested that she was and always had been perfectly well, apart from recent stiffness and hampered movement of her left eye She was afterwards found to be harbouring a scirrhus carcinoma of the breast This growth had started sixteen years before but she had steadfastly refrained from mentioning it to anybody. Returning to skin problems, we have all encountered or recently heard about women presenting themselves with blepharitis and not saying anything about the primary seat of trouble—e g , dermatitis of the thigh caused by a nickel containing suspender buckle

We could all recite a series of examples to show the practical value of a complete examination, but unfortunately time is fleeting, and few ophthalmologists could ever get through their work if they had to make every patient strip So much the more, then, should we strive to make use of the information vouchsafed by whatever skin is open to view. Clearly the face is the most important, but we should never neglect the head and neck, and even the hands can supply valuable pointers Not long ago a patient with failing vision presented me with an immediate clue in the form of fingers stained brownish-yellow. Detailed examination afterwards confirmed the "spot" diagnosis of tobacco amblyopia.

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* A lecture given on April 5, 1957, at the 30th annual spring congress of the Gill Memorial Eye, Ear, and Throat Hospital, Roanoke Virginia, U.S.A

Syphilitic stigmata of the face are less common than they were, but they furnish a good example of how skin changes can throw light upon associated eye trouble. Another obvious link is provided when iridocyclitis arises at the peak of a herpes zoster ophthalmicus rash, or scleritis as a sequel, by which time the characteristic pitted scars will be visible. Rosacea as a cause of conjunctivitis and keratitis is now so well known that we might be tempted to blame anyone for missing the facial signs. It is only fair to point out, however, that these signs can swiftly alter, and that the eyes may be severely involved without there being any conspicuous rash on the face.

Blepharitis is often an infection limited to the eyelids, and it can also be a form of allergic reaction; but sometimes it is merely part of a facial seborrhœa, and thus in its turn is typically associated with masses of dandruff. In such cases a spirit lotion to the scalp, together with facial treatment and regulation of diet, will often clear up the blepharitis even if little or no treatment be directly applied to the lids. Dryness and desquamation of the face arising for the first time in a middle-aged or elderly patient should make us think of diabetes. Pallor and fine parchment-like wrinkling of the facial skin has more than once been noted in patients suffering from pituitary growths. Pigmentation can appear for a multitude of reasons, including pregnancy, Addison's disease, systemically administered arsenic, and industrial exposure to silver nitrate. Two of the most interesting cases I ever examined were twin brothers in their early 30s. They both had swarthy faces and early bilateral cataract, and they died of hæmochromatosis within a few months of each other.

Enthusiastic physicians often combine amusement with the exercise of their skill by trying to diagnose the ailments of casual acquaintances or fellow-passengers. That is a fruitful pastime which many of us have tried, and it is astonishing how many vital facts can unobtrusively be gleaned. When we come to assess our own patients we start with the initial advantage of having heard their complaints and plied them with questions. Careful history-taking, together with alert preliminary inspection from a distance, will strongly indicate the diagnosis in a large proportion of cases, and the corollary is true: that is to say, we shall certainly commit unnecessary blunders if we plunge into direct ophthalmoscopy without first making a general survey.

Disturbance of the Palpebral Skin

The eyelids are a miniature museum of pathology. They can be the seat of various neoplasms, primary or secondary, and they often register events in remote parts of the body. For instance, a small hæmorrhage in one eyelid may be the first obvious sign of a medullary neuroblastoma; and suffusion of all four lids with blood is a classical sign of vitamin-C defect. Œdema can arise not only from infected meibomian cysts and other inflammatory lesions of the eyelids or eyes, but also in consequence of dental abscess, food-poisoning, or renal failure. Blepharochalasis is the name which Fuchs (1896) applied over sixty years ago to a so-called idiopathic form of palpebral œdema, intermittent at first, later becoming constant, and not attributable to any known local or systemic malady.

Dermatitis of the eyelids is perhaps the most important of all the subjects that jointly concern skin and eye specialists. There are many different ways in which lid eczema can be classified; but let us first consider, without any attempt at differentiation, what signs are relevant.

1. *Change of colour* is important because it can be recognised from afar in all but the slighter degrees. Acute dermatitis of recent onset often produces a pink flush, but brownish discoloration suggests longstanding trouble. In chronic marginal blepharitis the lids may turn dark red.

2. The *eyelashes* may be altered in colour or diminished in number. Crusts of dried secretion are sometimes found entangled, and the line of eyelash growth may be distorted.

3. The *skin surface* may show fine additional wrinkles, branny desquamation, fluid droplets, adherent crusts, or even *lichenification*. There may be fissures, especially at the outer canthus or underneath a redundant fold (cf., intertrigo beneath pendulous breasts).

Even if the causation of a patient's lid eczema is obscure at the original examination, we are more likely to track it down if we set out a written description of all these items straight away; and coloured photographs taken at intervals are particularly valuable in cases of lid eczema.

Psychosomatic Considerations

We sometimes hear people talk as though psychosomatic medicine were an entirely modern concept, but of course the notion of bodily states being produced or aggravated by stress of mind is as old as history. Jonathan Hutchinson (1876) was aware that severe cheiropompholyx is as a rule associated with a highly nervous temperament, and he said that this disease "must certainly be regarded as a neurosis." Psychosomatic medicine is no new thing, but it certainly looms much larger in medical thought than ever before, and some of its extremists have laid themselves open to ridicule.

The fact that the skin can in so many ways mirror the mental state does not mean that we should ignore other factors—e.g., heredity, infection, and allergic susceptibility—which help to produce dermatitis. We must also remember that skin lesions are in themselves a source of worry. Sensitive people with a pride in their appearance and the habit of personal cleanliness are naturally distressed by rashes or blisters on exposed areas of their skin. The friends who tactfully avert their gaze can embarrass such a patient almost as much as do those others who rake the blemish with an inquisitive stare—and the neurosis that ensues may be misinterpreted as the cause, not the effect, of the dermatitis.

Clearly some skin diseases, such as rosacea, are far more closely linked with an anxious state of mind than was formerly recognised, and at the other extreme are conditions mainly or exclusively due to material factors; but much of the ground is debatable. It is not always possible to say whether a given instance of skin trouble arises from mental disturbance. We know that, of two morphologically identical congenital defects, one may be truly hereditary and the other due to intra-uterine inflammation. Similarly neurodermatitis can imitate or be imitated by eczema of quite different origin. Great judgment is needed to apportion the relative responsibility of body and mind in skin upsets, and no man is wise enough to be right every time. How could he be, when the mind and body are so inextricably interwoven that "never the twain shall *separate*"?

Subject-matter of Dermo-ophthalmology

No comprehensive classification of dermo-ophthalmology will here be attempted, but let us now consider a few of the important groups encountered in practice.

1. *Dermatitis of the Eyelids*

We have already seen that lid eczema may be part of a widespread seborrhœic state. It is also a common manifestation of rosacea. Another potent source of trouble is neglected conjunctivitis, especially among children, who so often introduce staphylococci by plucking at the crusts entangled in their eyelashes. Unless we act quickly to remove the dried secretion and discourage the patients from touching their lids, severe

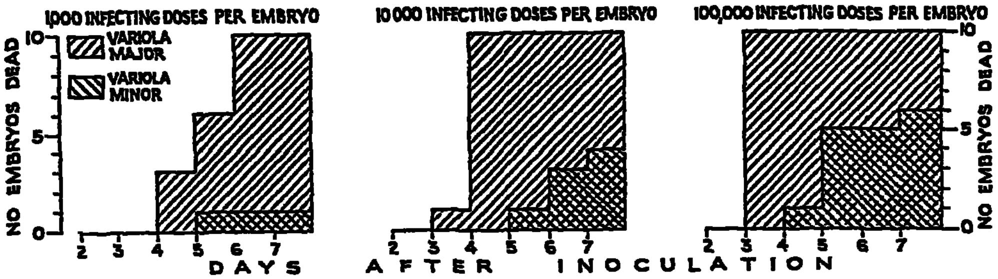

Fig 2—Cumulative deaths of chick embryos after inoculation of three different doses of variola major and variola-minor viruses on the chorio-allantois

(1) To determine the rate of growth of virus on the chorio-allantois the inoculum was about 150 pock-producing doses After one, two, and three days the eggs were opened and the chorio-allantois removed for estimation of the virus

(2) In the experiments designed to follow the rate of virus increase in the livers of chick embryos 10^4 infective doses of virus were used as inoculum on the chorio-allantois Each day thereafter two embryos of each series were examined, and their livers were removed with sterile precautions, weighed, and pooled Suspensions of chorio-allantois and of liver were made by shaking them mechanically in 'Universal' containers with glass beads and a known volume of 12% broth in distilled water with penicillin Debris was removed by low speed centrifugation, and the supernatant fluids were used for titration Pieces of liver were fixed with 10% formalin and stained with hæmatoxylin and eosin

(3) For a comparison of mortality-rates of chick embryos after inoculation of the chorio-allantoic membranes, three different doses of inoculum (approximately 10^3, 10^4, and 10^5 infective doses) were used Ten embryos were inoculated with each dose Eggs were candled daily and the number of dead embryos recorded up to seven days, when the observations were terminated

Titration of Virus

The virus content of suspensions was estimated from the number of specific lesions formed on the chorio-allantois three days after the inoculation of 0 1 ml volumes of serial dilutions The estimation of titre was made from membranes inoculated with that dilution which gave a mean count of 20–200 lesions For titration of the purified suspensions used as inoculum in various experiments tenfold dilutions were tested near the expected end-point, four eggs being used for each dilution For experiments in which the virus content of chorio-allantoic membranes or of livers was compared, the supernatant fluids from extracts were tested in tenfold dilutions, two eggs only being used for each dilution Though this method could not provide accurate estimates of the concentration of virus, the results proved adequate for comparing variola major and variola-minor strains of virus

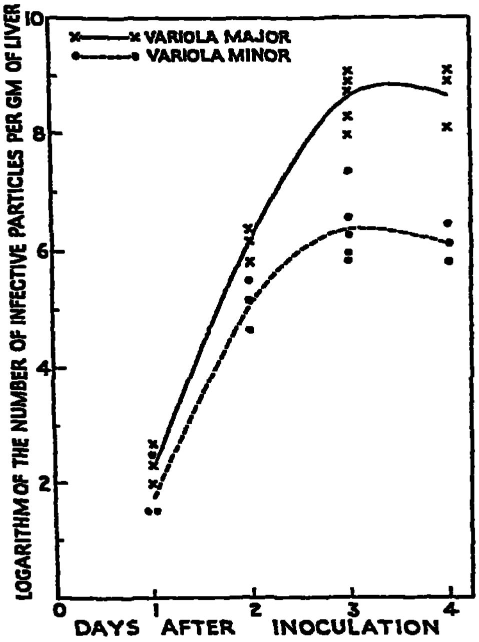

Fig 1—Amounts of virus recovered from chick-embryo livers infected with either variola major or variola minor strains

Results

Recovery of Virus from the Chorio allantois

Increasing amounts of virus were recovered from eighteen to seventy-two hours after inoculation, and the rate of increase was logarithmic for the first forty-eight hours On the second and third days after inoculation membranes infected with variola-major strains gave more virus than did those infected with variola-minor strains This difference was never greater than twofold but was constantly found with all pairs of virus strains tested

Recovery of Virus from Chick-embryo Livers

Virus was recovered from chick-embryo livers twenty-four hours after chorio allantoic inoculation, and there was a steady increase in the amount recovered during the following forty-eight hours Fig 1 shows the results obtained with the five pairs of virus strains tested From forty-eight hours after inoculation more virus was always recovered from embryos infected with the variola-major strains The livers of these embryos showed at least fifty, and usually several hundred, times as much virus as did those infected with the variola-minor strains

Histological changes in infected chick embryo livers—Fatty degeneration affected the livers of embryos inoculated with either virus but became more conspicuous in those infected with the variola-major strains On the second day after inoculation with variola-minor virus the livers showed mononuclear-cell infiltration, which later became very extensive Livers of embryos infected with comparable doses of variola-major virus, on the other hand, showed only slight mononuclear infiltration, which did not appear until the fourth day after inoculation, when many of the embryos were dead The more rapid rate of increase of variola-major virus, associated with a greater degree of hepatic degeneration, appeared to have impaired the defence mechanisms of the embryo

Mortality of Chick Embryos Inoculated with the Viruses of Variola Major and Variola Minor

Chick embryos were observed for a week following the inoculation of comparable doses of virus strains Four of the three hundred embryos inoculated died on the first day of the experiments and none on the second day Deaths taking place later than the second day were considered specific From the third day after inoculation the total mortality rate varied directly with the dose of virus, and the survival time increased as the dose became smaller

The mortality was greater and deaths took place earlier after the inoculation of variola major virus This difference was found with all the five pairs of virus strains tested Fig 2 shows the cumulative total numbers of embryos dead each day after inoculation with comparable doses of the first pair of virus strains listed in the table These experiments were not designed to measure statistically the dose of virus producing a 50% mortality-rate (L D 50), but with each pair of strains the approximate L D 50 of the variola-minor virus was at least ten times greater than that of the corresponding variola major strain

Discussion

The observations recorded here indicate that the five strains of variola major virus were more virulent for the chick embryo than were the five strains of variola-minor virus tested in parallel This difference in virulence is not apparent in the character of the lesions produced on the inoculated chorio allantois, on this tissue the naked-eye and histological appearances of the pocks produced by the two viruses are identical It is manifested after chorio-allantoic inoculation by the greater multiplication of the virus of variola major in the livers of the embryos and by the greater mortality when tests are made with approximately similar inocula of the two viruses The chick embryo has been used to elicit similar differences in virulence of other pox viruses—e g, between strains of ectromelia virus (Fenner 1948) and between cowpox virus and its white variant (Haddock 1952) The difference shown by Dinger (1956) between the survival of variola major and variola-minor strains on the chorio allantois may, in part, be consequent on greater multiplication of the major strains in the tissues of the chick embryo

Constant differences between the two kinds of smallpox virus were not found in our experiments with mice and rabbits, nor by F O MacCallum, in tests with suckling mice, suckling rats, or suckling hamsters As serological methods have not differentiated the viruses, the chick embryo seems to offer the best means of identifying the type of smallpox virus in the laboratory This may be important in isolated cases of smallpox or in outbreaks involving only one or two patients, when there may be no clear clinical indication of the identity of the infecting strain The laboratory investigation of such strains, however, would require about a fortnight to complete The tests would involve the comparison of the virulence of the fresh strain for chick embryos with those of known variola-major and variola minor viruses, using comparable infecting doses determined by preliminary titration of the viruses by the pock-counting technique on the chorio allantois

Summary

Five strains of variola-major virus were compared with five strains of variola-minor virus as regards their virulence for the chick embryo when inoculated on the chorio-allantois

With comparable infective doses the variola major strains constantly produced a much greater mortality in the chick embryos The greater virulence of these strains was associated with the presence of much more virus in the livers of the embryos from two to four days after inoculation

These findings indicate a method whereby the virus laboratory could assist in the differential diagnosis of variola major and variola minor

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ABSENCE OF RAYNAUD'S PHENOMENON IN WORKERS USING VIBRATORY TOOLS IN A WARM CLIMATE

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The Raynaud phenomenon is induced by exposure to cold (Hunt 1936a) and precipitated by the use of vibratory tools (Hunt 1936b) In cold weather people working with vibratory tools often display this phenomenon on their way to work, especially if they use a bicycle or a motor cycle, but symptoms may disappear during work when the body warms up (Marshall et al 1954)

Raynaud's phenomenon is unknown among men using vibratory tools in Singapore, and it was therefore of interest to find out whether it is either masked or prevented by a warm climate Singapore is within 1½° of the equator, and its climate is uniformly warm, the maximal limits of diurnal and seasonal variations being about 20–34°C (68–93°F), but the temperature very seldom falls below 22°C (72°F) or rises above 33°C (91°F)

Methods

31 dockyard workers, aged 24–53, using vibratory tools at H M Dockyard in Singapore were investigated at random 16 of them were Chinese, 10 Indians, and 5 Malays 28 had worked with vibratory tools for at least three years, and 10 of these for fifteen years or longer All riveters and caulkers had used vibratory tools for 80–120 hours a month during the past two years but the scalers used vibratory tools only for 120 hours each alternate month

3 controls were used A, a male Chinese clerk, aged 35, recovering from hæmatemesis, B, a male Chinese physician, aged 30, who had lived in Singapore since birth, and C, a European physician, aged about 45, in transit through Singapore In England on his way to work, in the winter he constantly suffered from Raynaud's phenomenon He had so suffered a few days before being tested on the spur of the moment, without preliminary general cooling All the controls had very little subcutaneous fat

All the tests were conducted in a temperature controlled room at 10 5°C (51°F) ±2°C The men wore tropical clothes but no shoes or socks, and they were tested in groups of 3 while lying still on stretchers of woven cane

The skin-temperature of the palmar surface of the distal phalanx of the little finger of both hands was recorded with a bare thermocouple (Glaser 1949), a 'Cambridge' vernier potentiometer, and a 'Cambridge' spot galvanometer A period of not less than 75 minutes was allowed to enable the men to complete immediate thermal and postural adjustments Previous evidence has shown that this length of time is adequate for the skin temperature to stabilise (Glaser and Newling 1955)

The blood pressure was recorded with a sphygmomanometer by auscultation of the brachial artery several times during this preliminary period After the preliminary period each man immersed his right hand and wrist in water at 10°C (50°F) for ten minutes. Anteroposterior radiographs of both hands and wrists were taken from the dockyard workers on a subsequent occasion. The European control was tested after only fifteen minutes in the cold room.

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Tools and Work

The vibratory tools were driven by compressed air. They were either riveting tools giving 1600 blows a minute or scaling, chipping, and caulking tools giving 1700–3050 (average 2100) blows a minute.

These tools and their methods of operating were the same as in British dockyards, except that the riveting machines were often supported by a sling. A common fault was that the riveting hammer was not always held close against the head of the rivet, causing frequent rebounds and breaks. The average number of rivets driven in was 100 daily, although up to 300 a day is not uncommon in England. Riveting hammers were held in the left hand and opposed by the right hand, but scaling and caulking machines were held in either hand.

Results†

One workman, aged 53, showed a rise of blood-pressure to 250/140 mm. Hg during the initial period of cooling and was not allowed to continue the experiments, leaving 30 dockyard workers to immerse their hands in cold water. Inspection of the hands before the tests showed no evidence of any of the small skin lesions associated with Raynaud's phenomenon.

During the preliminary period of cooling the finger-temperature of the dockyard workers invariably remained 2–8°C above the room-temperature, and there was only one instance in which the skin-temperature of one finger fell just below 14°C, which fact suggests that the resting circulation in the fingers of these workers was adequate. The skin temperature of the left hand was always lower than that of the right hand, and no satisfactory explanation can be advanced for this. There was no evidence either of cyanosis or of pallor of the fingers among the workers at any stage of the experiment, and none of the workmen complained of pain in the hands or of numbness in the fingers when their hands were not immersed in cold water. During immersion none of them considered the pain severe.

On radiological examination 6 of the 31 workers were found to have minimal cystic changes in the bones of the hand, and there was some suspicion of cystic changes in 1 other man. These findings were equally frequent in both hands and were not confined to those men who had used vibratory tools for the longest time, because 3 men who had used these tools for only 2–4 years showed such changes. 4 dockyard workers, including 2 without cystic changes, were reported to have mild osteo-arthritis of the wrists. In a control group of 36 Asian men (11 of whom were aged 25–39, 13 aged 40–49, and 12 aged 50–58) only 2 (aged 35 and 57) had minimal cystic changes, and 4 had early osteo-arthritis.

In control B, who was tested in exactly the same way as the dockyard workers, the finger temperature fell to within 1°C (2°F) of the room-temperature after an hour in the cold room. When his hand was immersed in water at 10°C (50°F) he developed cyanosis of the fingers and a severe and painful swelling in the dorsum and in all fingers of the immersed hand, followed by persistent swelling and pain after he had returned to a warm environment.

Control A had pain, and his fingers were pale, with purplish patches, after an hour in the cold room and before immersion of his hands in cold water. During immersion the pain became worse, but the fingers did not swell. Control C, who was tested without a preliminary period of cooling, did not develop any symptoms or signs of Raynaud's phenomenon.

Discussion

Hunter et al. (1945) had observed in England that 81% of riveters and 61% of caulkers in a large group had signs of Raynaud's phenomenon; even among those who had used vibratory tools for only two to five years about a third showed symptoms of this phenomenon. The absence of Raynaud's phenomenon among the dockyard workers taking part in the present investigation was therefore probably due to the fact that they were living in a warm climate. The method used in the present investigation was adequate, however, to produce symptoms of the Raynaud phenomenon in two controls (A and B). In control B symptoms and signs were severe; he had been frequently exposed to vibration and cooling because he rode a motor-cycle, and he spent much of his time in an air-conditioned theatre, where his hands were exposed to localised cooling by volatile anæsthetics and alcohol. This suggests that vibration produces symptoms of Raynaud's phenomenon only under conditions of intermittent cooling.

It is unlikely that the absence of Raynaud's phenomenon among dockyard workers in the present investigation was due to any other cause. Changes accompanying acclimatisation to heat could not have had a decisive protective effect, because such acclimatisation to heat was present in two controls (A and B), who displayed the phenomenon, and absent in the other control (C), known to show the Raynaud phenomenon.

The finding that control C, who had been inadequately cooled, did not develop Raynaud's phenomenon though he had suffered from it a few days earlier in England, conforms to findings of Hunt (1936a), who could not produce this phenomenon unless the whole body was cooled. This is further supported by evidence that the blood-flow to the skin depends not only on thermal impulses arising from the skin but also on the temperature of the deep tissues and on previous cooling or warming of the body (Glaser and Newling 1955, 1957). The fact that men in Singapore drive in fewer rivets a day than do workers in England could not explain the complete absence of the Raynaud phenomenon among Singapore workers; nor could the suspension of the riveting hammer by a sling provide complete protection, because such slings are sometimes used elsewhere.

The finding that cystic changes were present in nearly 20% of the workmen investigated, whereas Raynaud's phenomenon was completely absent, bears out a suggestion by Hunter et al. (1945) that cystic changes are not caused by vibratory tools but by repeated jarring. Such jarring was common among the dockyard workers in Singapore.

Conclusion

A reasonable conclusion is that an investigation on the lines of the present experiment, involving thorough cooling of the whole body as well as immersion of the hand, would show up potential sufferers from the Raynaud phenomenon.

If all those intending to use vibratory tools were tested in this way, it would be possible to classify Raynaud's phenomenon as an industrial disease and to eliminate the objection against such classification (Beney 1955).

Alternatively, thorough general warming of the body and hands before starting work in work places heated to relatively high environmental temperatures might be advantageous.

Summary

30 men using vibratory tools in an equatorial climate were tested in a cool environment by immersion of a hand in cold water, but none showed any signs of Raynaud's phenomenon.

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† Copies of a table setting out the results more fully may be had from THE LANCET office, 7, Adam Street, Adelphi, London W.C.2.

The evidence suggests that vibration induces the Raynaud phenomenon only if there is also intermittent cooling of the body and of the hands

The Raynaud phenomenon could be classified as an industrial disease if all those intending to use vibratory tools were suitably tested beforehand

We thank the Commodore Superintendent of H M Dockyard, Singapore, for permitting the experiments to be made, the Chief Contractor and his staff for their generous cooperation, and Dr A M Poutsma, of the General Hospital, Singapore, for reporting on the X-ray films and for advice

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A SERIOUS HEAD INJURY IN A PREGNANT WOMAN

TREATED BY HYPOTHERMIA

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B Sc Manc, F R C S
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On May 4, 1956, at 2 45 P M, Mrs Ellen Moore, aged 22, was walking along the pavement pushing her only child, aged 18 months, in a perambulator In the morning she had been to the antenatal clinic and had been told that she was about eight weeks' pregnant In the afternoon she was escorting her mother to the bus stop when a heavy tree trunk, 30 feet long, rolled off a lorry and knocked her head first into a wall Witnesses said that they found her lying on the ground as if dead She was admitted to the neurosurgical unit at 3 15 P M

Acute Phase

Examination

On examination she was in deep coma, without even the swallowing reflex She lay supine, with legs extended and stiff Her arms were stiff, straight, and pronated, her wrists and metacarpophalangeal joints were flexed and her fingers extended Both plantar reflexes were extensor Both pupils were widely dilated and did not react to bright light Her face had lost its expression her mouth was open, and her tongue had fallen backwards Breathing was light and rapid, 38 per min, the pulse rate was 100, the blood pressure 120/80 mm Hg, and the skin temperature 101°F

There was profuse bleeding from her left nostril and ear, and she had a large hæmatoma and a laceration on the left side of the head Her left eyelids were swollen and discoloured, and there were signs of a massive intraorbital hæmorrhage The bones of her limbs and neck were intact, no obvious thoracic or abdominal injury was detected

Radiography a fortnight later (May 17) showed a fissure fracture extending downwards from the parietal region through the squamous temporal bone into the floor of the middle fossa, probably on the left side

Diagnosis

The speed and depth of unconsciousness made it certain that her brain had been severely damaged Also, the nature of the injury made it likely that, apart from extensive neuronal paralysis, which might or might not be reversible, there were scattered contusions and possibly lacerations of the cerebral hemispheres, particularly the temporal lobes The decerebrate rigidity pointed strongly to damage in the upper part of the brain stem, though the exact nature of the damage must be conjectural

At this point it was impossible to know whether or not a surface blood clot was present, or forming, that could profitably be removed surgically There were no lateralising neurological signs Before a decision on whether to open the head was forced on us, and before we felt it necessary to do a lumbar puncture, the patient's temperature began to rise ominously, and we felt it imperative to resort to antipyretic therapy and to take a chance on possible compression of the brain This is the type of case that so commonly ends fatally within three days

At 2 A M on May 5 her condition was much the same except that the muscles of her limbs were a little less spastic, but, though excessive warmth had been deliberately avoided, her temperature began to rise By 10 A M the skin-temperature was 105 5°F and, judged by the slope of the rise, was still on the way up Past experience has proved that simple cold sponging and intravenous aspirin often fail to control malignant hyperpyrexia in cases such as this, and therefore we decided to try the new method of cooling

Hypothermia (K B)

The object of hypothermia in head injuries is twofold (1) to counteract hyperpyrexia resulting from disturbed function of the heat centre, and (2) to slow up excessive and harmful reaction to the injury, and to diminish metabolic requirements while the damage to the brain and other tissues is undergoing repair

May 5—An intravenous drip was set up at 11 A M, and a *solution of chlorpromazine* 25 mg, *promethazine* 25 mg, and pethidine 25 mg in 540 ml of physiological saline solution was given at the rate of 3 pints per day—i e, a daily dose of 75 mg of each drug Then the patient was completely stripped, and the overlying bed clothes were removed The patient was sponged with ice water, and her limbs, body, and head were packed about with ice bags, cold air was also blown across the bed

By 6 P M—i e, seven hours after the start of the drip—the rectal *temperature* had dropped by stages to 30°C By this time the depth of consciousness was still the same, but the hypertonic limbs had become flaccid, the respirations were 40 per min, the pulse rate 120–150, and the blood pressure 118/70

To prevent infection a course of intramuscular sulphadiazine was begun A stomach tube was passed with difficulty and *feeding started*

May 7—Though there was now evidence of return of the swallowing reflex, tube feeding was still necessary The pupils were less dilated and reacted faintly to light The muscles were regaining their tone from the secondary *state* of flaccidity into which they had passed on the institut*ion of* cooling Respirations 35 per min, pulse rate 120–150, blood pressure 90/50

May 8—There was some lightening of coma, and the patient *groaned and moved* when disturbed for nursing purposes She was, however, still deeply unconscious, and all the muscles of her limbs were spastic Respirations 18 *per* min, pulse rate 140–150, blood pressure 120/80

May 9—Coma was a little lighter, limbs were *spastic* At this stage the intravenous drip was taken down and the drugs were given per rectum chlorpromazine *100* mg, *promethazine* 100 mg, and pethidine *200 mg daily*

May 11—The patient was still deeply unconscious, and all her limbs were spastic Cooling was discontinued at 8 P M

During this period of seven days' cooling the rectal temperature was as low as 30°C and as high as 36°C Our design was to keep it between 30°C and 34°C, and during the period of cooling the mean lay somewhere between these figures *After the lowering of the* temperature to 30°C the ice bags were removed, and cooling was maintained mainly by keeping the patient unclothed and uncovered by bed clothes, with occasional damping with cold water, aided by potentiating drugs

The patient was fed with special protein and *vitamin* foods because even at a temperature of 30°C metabolism, though substantially damped, is still active The blood-pressure ranged between 96/58 and 120/80 mm Hg, and the pulse rate remained fast, but the respiration rate fell from 52 to 16 At no time was there any anxiety about the firm and regular action of the heart, though its rate of beat fluctuated considerably between 150 and 100 per minute Before cooling was started the muscles of the limbs were already becoming less spastic, but they became definitely flaccid in the cooling stages, later to become spastic What the effect of low temperatures may be on spasticity is still uncertain, but judged by other cases spasticity seems to lessen in lower temperature ranges, though associated drugs may contribute to this

At the end of the period of cooling the patient was dried with a towel, covered with one blanket, and allowed to warm up slowly as other coverings were slowly added to the bed Three days after cooling her temperature went up 1° above normal but it was soon lowered by simple sponging, and we never again had any anxiety about hyperpyrexia

Stage of Cerebral Irritation

On June 4 the patient became one of the most difficult problems that a medical service ever has to cope with

She scrambled and slithered about the bed, pulling and biting at the sheets until they were in ribbons, dozens of sheets were completely ruined For most of the time she was doubly incontinent Every few minutes, during the day and often through the night, she would let off a piercing wailing scream, rising to a crescendo and then fading out Early in this stage any approach by word or by touch, however gentle, would provoke outbursts of resistance and noise

During the long period of a hundred and thirty eight days, in spite of the patient's incessant restlessness and double incontinence, her skin remained healthy and intact This is a commentary on the devotion and pertinacity of the nurses There is little that militates more against recovery of damaged nervous tissue than infection, particularly that associated with decubitus ulceration and loss of serum-proteins

Gradually Mrs Moore became less restless and more purposive in her movements At times she would react favourably by gesture to the quietly spoken voice, when some kind of understanding or recognition would come into her eyes

As she slowly became more accessible and more amenable to examination we discovered that all her limbs were considerably paralysed and spastic, the left side being the worse The reflexes of all four limbs were those of an upper motor-neurone paralysis with hyperactive stretch reflexes and extensor plantar responses There was no evidence of a fracture dislocation of the cervical spine to explain the quadriplegia

On July 10 she was examined by Prof Martin Roth, who like us concluded that she was suffering not only from a brain-stem injury but also from hemispheral injuries He advised electro encephalography and this had to be done under anæsthesia (thiopentone because she was not yet sufficiently coöperative) Dr J N Walton and Miss B P Longley reported " intermittent but very prolonged discharges of high amplitude activity in all areas, these are sometimes more prominent on the right side The changes indicate a severe disturbance of the basal regulation mechanisms and are compatible with a lesion in the region of the upper mid brain or thalamus '

As the mental processes are awakening from injury, greater wisdom has to be shown in the exhibition of drugs for controlling restlessness, as a general rule the less given the better from the patient's point of view The months of August and September we regarded as constituting the transition stage between the phases of cerebral irritation and confusion

On Aug 10 the patient (cooperative but considerably confused) was examined for her pregnancy by Mr Linton Snaith, who estimated it at about 20 weeks Radiography on Aug 30 showed a fœtal skeleton of about 20-22 weeks Mr Snaith agreed that if possible the baby should be born by the natural route

At this stage, in August, the patient was doubly incontinent It was not until Oct 3 that she successfully used a bedpan and not until Oct 21 that she became completely continent of urine and fæces

During August she began definitely to speak, though she had uttered occasional words many weeks before this By the end of September she was repeatedly muttering short sentences such as " I love my Mummy " It is very doubtful whether, by the end of September, she was actually recognising her mother or her husband, who were constant visitors Perseveration of simple sentences spoken in a baby voice became an outstanding feature of the next weeks The perseveration possibly pointed to a lesion in the speech centre So far as we could judge, insight was very superficial during August and September, but in other ways there was definite improvement

Stage of Confusion

In October Mrs Moore unequivocably recognised her husband and gave him a proper kind of welcome

Formal psychometric testings were made on Nov 6, Jan 11, and March 1 by Mr R F Garside, of the department of psychological medicine in the University of Durham, using verbal tests, the picture completion test of the Wechsler Bellevue Scale, and Raven's Progressive Matrices On Nov 6 the patient had an I Q of 55 and a mental age of 6½ years, and on Jan 11 an I Q of 55 and a mental age of 7½ years During the early part of her pregnancy she had no insight into her condition Towards the end of gestation, however, she appeared to realise what was about to happen

Labour

On Nov 17 she went into labour and was transferred to the maternity department at 10 30 P M

By midnight definite contractions were evident, and thereafter she made rapid progress in the first stage of labour She proved to be most coöperative As soon as labour was well established, pethidine 100 mg was given to prevent undue excitement No other analgesic was necessary, and at no time did she manifest any real discomfort A healthy and perfectly formed boy was born at 4 A M on Nov 18

Mother and Child

Before the birth Mrs Moore kept asking when the baby would come When her newborn baby was handed to her, she immediately took hold of him with many expressions of delight She always held her baby in an experienced manner and looked forward to the times of breast feeding, which she managed perfectly

On Nov 26, while still in the maternity department, she had a generalised epileptiform convulsion and was unconscious for three minutes and deeply confused for half an hour There have been no further epileptic seizures She was sorry when the baby was sent to her aunt's in Leeds on Jan 1 but understood when it was explained that her mother, who lived in Newcastle, could only look after her son, aged 2, and it was necessary to get the child into the fresh air and away from a busy ward Mrs Moore is devoted to both children Her aunt writes regularly about the baby's progress, and Mrs Moore replies in her own handwriting and composition

Present State

Physical

Her general health is excellent Since her recovery from the acute stages of her illness she has virtually had no infection The contused contaminated wound on the left side of the scalp healed with hardly any inflammation Her smell, taste, hearing, and seeing are normal

Movements, tone, power, and coordination of her arms are normal, but both legs remain considerably paralysed Lying in bed she can lift each limb from the bed, bend the knee, and waggle the toes, but these movements are slow and tremulous With a walking cage she can support herself and make a few shuffling steps with each leg

Walking exercises were first started on Feb 11, each day there is some improvement, and with practice we expect further improvement because the difficulty in locomotion appears to be partly due to apraxia—i e, not knowing what to do—rather than entirely to paralysis and lack of coordination She can easily propel herself about the ward in a wheel chair

Mr J V Todd, our senior orthopædic surgeon, has supervised the problems arising from locomotion and lengthened the right tendo Achillis because of contraction

The patient's appearance is pleasant, and she keeps herself tidy and neat

Mental

Memory —Retrograde amnesia a few weeks ago was almost complete Today, March 25, 1957, there is definite evidence that glimmers of her earlier life are coming through, and we have, on this and past experience, reason to hope that the period of retrograde amnesia will substantially shorten Memory for present events is satisfactory, for example, Mrs Moore can remember what she had for breakfast, whether or not she bought a paper earlier in the day, and what transactions she had to make for it

If the temporal lobes of the brain are the chief site of memory, they must have been damaged but not irretrievably destroyed, because the patient can remember some things Without the background of the memory of previous experience the remaining intellect will be short of those ingredients of which depth of thinking is made The first indubitable sign of return of memory was a visual one—i e, recognition of a familiar face

Speech —Her ability to speak, though much impaired, is now approaching normal Her chief defect is a nominal aphasia—e g, she will recognise an apple, peel it, and eat it, but cannot easily find its name When the name is mentioned to her, she nods her head in assent and smiles She can read quite freely from a newspaper She can write a letter, but in the more involved parts of construction she needs help She writes accurately and quickly from dictation

One of the outstanding features nowadays is her tendency to go on repeating sentences such as "I love my baby," and often these are included in a wrong context Her word centre at one time was greatly disturbed, giving the impression that she was rather more severely demented than she actually was Of course, it has to be realised that intellect and speech are very closely interwoven She speaks in a high-pitched childish voice which in some ways gives the wrong impression and suggests that she is a little more simple than she really is The report of Miss M E Morley, our speech therapist, is as follows

" *Articulation* is normal There is no sign of any dysarthria or apraxia

" *Language* —When I first saw Mrs Moore on Dec 30, her language was childish and she used short phrases What she said was sensible, but there was a peculiar intonation in her speech resembling that of a spoilt child, and when she attempted to use longer phrases or became excited at all there was a clonic spasm, chiefly on the initial consonant in words involving a rapid repetition of the initial consonant sound Since then her language has continued to improve very slowly She uses longer phrases, but the stammer is still in evidence and now frequently involves the initial syllables in words At times there appears to be more tension in this spasm than there was initially This may be comparable to the transient stammer of childhood which she may outgrow, although it is possible that it may become worse if she becomes aware of it and attempts to inhibit it It may become increasingly worse as she uses longer phrases

Comprehension appears to be adequate There was no visual agnosia when I first saw her in December Auditory verbal comprehension was normal as were also oral reading and comprehension for reading, so far as I could assess it "

Accessibility —Within the limits of her immediate surroundings of time and space she is perfectly accessible Any faults that there may be are due to faults in memory

Awareness —She is perfectly aware of her surroundings She knows that she is in hospital is much interested in the activities of the ward speaks freely with the other patients, and knows the day of the week and the time of day She can add single figures, use money, and give change In the morning she buys her own papers and knick-knacks and carries out accurately the monetary details concerned

Insight —It is her insight that is superficial, indeed it is her mental shallowness that is her main incapacity at present She recognises her husband, mother, and eldest child (the baby is away in Leeds), but her reactions to them are entirely superficial She knows that she had an accident but does not appreciate its significance though here again a glimmer of comprehension is beginning to appear Her state is that commonly seen in the early stages after a fairly radical prefrontal leucotomy

Emotionally she is labile, extroverted, trusting, and affectionate She is not, however, without a sense of humour—when asked which was her weak leg she replied that she did not think much of either of them

Psychological report —On March 1 Mr Garside reported

" On this occasion I gave Form II of the Wechsler Bellevue Scale Her Verbal Scale I Q of 65 is slightly higher than that obtained before but her Performance Scale I Q of 66 is just about the same Her score was also the same on the Raven's Progressive Matrices Test

Her test scatter still suggests that her mental processes which involve knowledge and experience are more impaired than those which are concerned with the solution of new problems It therefore seems that her relearning might be helped by some kind of appropriate tuition "

Electro encephalographic report —A report on Feb 28 stated " The record is again within the limits of normal variation, and there is a stable alpha rhythm at 10–11 cycles per second "

Progress —Since the above summary was written further improvement has taken place, particularly as regards insight

Comments

Cooling

The value and the depths of cooling necessary for certain types of operation on the heart and head are now becoming known Less, however, is known about the optimum limits of depth and duration of cooling for direct therapeutic purposes When used therapeutically the objects of cooling are threefold

(1) *Antipyretic* —The object here is to combat excessive rises of temperature that are harmful and possibly lethal Our experiments have shown that lowered temperatures of 30–34°C can be safely maintained for seven days without inflicting serious damage on vital tissues

(2) *Protective* —The object in protective therapy is to tide tissues over from the deleterious effects of injury and infection and from excessive reactions of the body to the damaging agent while natural processes of repair or special medicaments—e g, antibiotics—have time to act We judge that, for protective purposes, the temperature will have to be 28–32°C How long such degrees of cooling can be maintained with safety we do not yet know On the other hand, experience gained at operation has shown that they can be maintained safely for twenty four hours

(3) *Curative* —Here the object is to lower a patient's temperature to such a degree that the injuring agent is destroyed while the normal cells of the body are left unharmed Such therapy may be the future means of destroying certain forms of bacteria and malignant cells This type of treatment will probably require temperatures well below the fairly safe figure of 28°C

Pregnancy

This is the first opportunity we have had in our Newcastle clinic of observing the effect of a head injury on a pregnancy established for 3 months or less

The fœtus continued to develop normally although much of the mother's nervous system was out of action while the fœtal brain was developing

No doubt the patterns of the future are laid down at the moment when the mother's ovum and father's spermatozoon unite and are little influenced by the mother's nervous system during growth The mother affords shelter and nutriment Any fault or disease in the maternal nutriment can, of course very seriously affect the child—e g, the toxæmia of rubella is likely to cause mental defect The effects, however, of injury to the head, or indeed the other parts of the mother's body, are not passed on to the child, and mothers can be firmly reassured on this point

Uterine injuries, of course, can harm the child directly, but this is a totally different matter

Seat of Unconsciousness

Because some of the evidence in the acute stages of injury pointed to damage of the upper brain-stem, it would be wrong to argue too closely that the clinical happenings described above were due to paralysis and gradual awakening of upper-brain-stem function Indeed, there is much to suggest that the post traumatic picture of the clinical improvement points more to recovery of hemispheral than of upper-brain stem function Indeed, the sparing of the arms and paralysis of the legs can be more easily explained on hemispheral than on upper-brain-stem damage, as can the dysphasia There is now some evidence forthcoming from the neurological world that the highest level of neural integration lies somewhere within the upper brain-stem area

None the less, should this hypothesis prove true, the integrative action of the brain stem must depend on information that comes to it from elsewhere It is likely that paralysis of the cerebral hemispheres will remove sources of information that are essential for proper functioning of processes of integration and give the erroneous impression that the brain-stem has been primarily concussed and not affected secondarily by paralysis of the cerebral hemispheres, as no doubt it commonly is We are far from convinced that the loss of consciousness in most head injuries is due to brain stem damage

It has been our experience that a head injury of the closed variety rarely leaves the patient seriously demented permanently No tissue in the body seems to react more wisely to injury or infection than does the brain tissue It is this knowledge that encouraged us from the outset in this difficult case

Finally, though the treatment of the patient with a serious head injury calls for many surgical disciplines, what success we have had in this case is due largely to the skill, devotion, and pertinacity of our nurses

Our thanks are due to Miss F E Shaw matron of the Newcastle General Hospital, Mr K C Booker, group secretary of Newcastle upon Tyne Hospital Management Committee, and Mr J B Duckworth our hospital secretary, for their continued help and encouragement

KERATO-ACANTHOMA OF LOWER-LIP RED MARGIN

C Howard Whittle
M A, M D Camb, F R C P
PHYSICIAN, SKIN DEPARTMENT, UNITED CAMBRIDGE HOSPITALS AND ASSOCIATE LECTURER, UNIVERSITY OF CAMBRIDGE

Roy A Davis
M B Lond
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Kerato acanthoma and molluscum sebaceum are the names given to a benign self healing tumour of the skin which grows rapidly for six weeks or more, reaches a maximum of 1-3 cm in diameter, and then slowly regresses, leaving after several weeks a flat atrophic area with a crinkled and slightly hypertrophic edge Without spontaneous regression the diagnosis remains in doubt While it is growing a kerato acanthoma so closely resembles a well differentiated squamous carcinoma, both clinically and histologically, that in the past many lesions have undoubtedly been diagnosed and treated as such

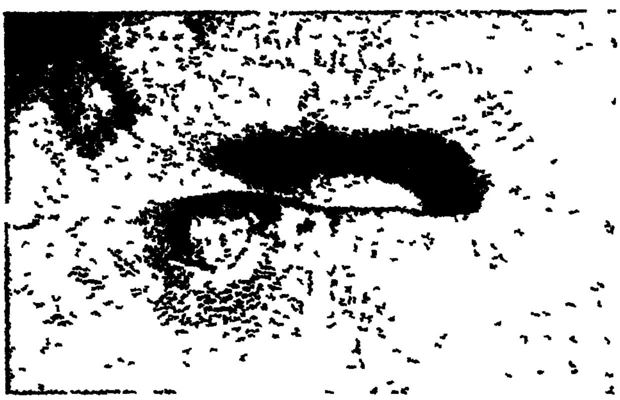

Fig 1—At 6 weeks

This benign tumour is fairly common, and occurs in Great Britain about half as frequently as squamous carcinoma (Rook 1956) MacCormac and Scarff (1936) were the first in this country to recognise and describe the lesion, which they called molluscum sebaceum Other names such as "molluscum pseudo carcinomatosum" (*Lancet* 1953) have been suggested Since Rook and Whimster (1950), at Dowling's suggestion, thoroughly investigated the condition, there have been many reports testifying to its widespread prevalence—e g, Baumann and Lennox (1954), Beare (1953), Binkley and Johnson (1955), Finley (1954), *Lancet* (1953), Levy et al (1954), Liban and Lennox (1955), Musso and Gordon (1950), Russell and Calnan (1952), Whittle and Lyell (1952), Wigley and Pettit (1952), and Zoon et al (1954)

The reason for publishing one case is that kerato-acanthoma on the red margin of the lip has not hitherto been seen, or at least *reported*, in Great Britain, and of 181 lesions described in the literature (Rook 1956) none started on the lip There have been one or two lesions on this site mentioned in foreign journals—e g, Ereaux et al (1955), Rabut and Hewitt (1954), and Spier and Thies (1956)—but this type of lip tumour has apparently been overlooked

We believe that a more general awareness among clinicians of its incidence will lead to the discovery of many such tumours on the lip, perhaps as many as on the rest of the skin Kerato acanthoma is rare on clothed parts—only 3% of the lesions recorded (Rook 1956)—and the same agents that affect the exposed skin also affect the lip Outdoor workers are those most likely to develop kerato acanthoma, especially if they have bright complexions and fair hair Such skins are readily irritated by strong sun and harsh weather and, after years of exposure, commonly show keratoses on the face and backs of the hands

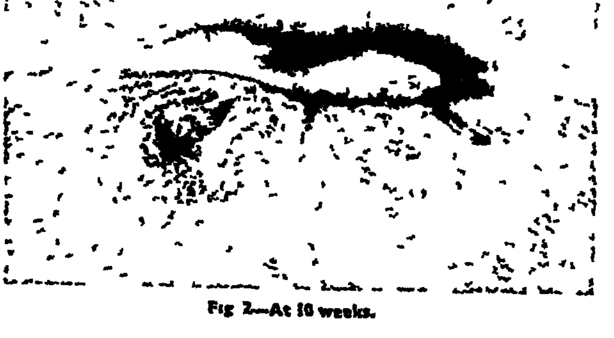

Fig 2—At 10 weeks.

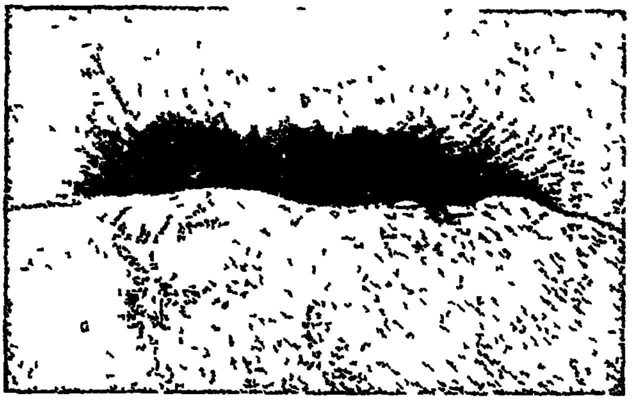

Fig 3—At 19 weeks

Case-report

A farm worker, aged 48, sandy-haired and ruddy, showed such keratoses In May, 1956, he noticed a spot on his lower lip, on the site of a "cold sore," which grew rapidly and presented after six weeks the button like tumour depicted, measuring 1 cm in diameter, with a large central keratotic plug (fig 1) Four weeks later it had flattened, and the centre plug had been shed, leaving a granulomatous crater (fig 2) At nineteen weeks from the onset the lesion had further flattened, the crater had healed and was hardly visible, and the infiltration had almost gone (fig 3) Diffuse roughening and scaling of the whole of the lower lip, also shown in the photograph, have been present for months At no stage has there been any palpable enlarged lymph node, and the only treatment was the local application of hydrocortisone ointment and antibiotics Biopsy at six weeks showed an appearance consistent with the diagnosis of kerato acanthoma, but the possibility of squamous carcinoma could not be excluded The subsequent course appears to have ruled out the more malignant alternative, but the patient is still under close supervision (Postscript, May, 1957 The lip is now normal)

Summary

Kerato-acanthoma on the red margin of the lip is apparently unknown in Great Britain

A case showing spontaneous regression is described

Awareness of its possibility and closer examination of lip tumours generally may well reveal a frequency on the lip comparable to the known frequency of kerato acanthoma on areas of skin exposed to light

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Preliminary Communication

CORRELATION OF SERUM-MAGNESIUM AND SERUM-CHOLESTEROL LEVELS IN SOUTH AFRICAN BANTU AND EUROPEAN SUBJECTS

IN a recent publication from this institute[1] it was shown that in many cases of coronary heart disease a dramatic clinical improvement followed parenteral administration of magnesium sulphate Two groups were treated

(*a*) Patients who were first seen during an acute attack of coronary thrombosis or coronary insufficiency

(*b*) Patients who had recently recovered from an attack of coronary thrombosis or who were suffering from angina of effort

Abnormal lipoprotein patterns rapidly reverted to normal in many of the cases

In those areas of Africa in which reliable information is available, coronary thrombosis is reported to be uncommon in Africans[2]

In Johannesburg the disease is very rare among the Bantu Thus Becker,[3] in 352 necropsies on predominantly Bantu people over the age of 50, attributed only 1 death to coronary thrombosis, and Higginson and Pepler,[4] in 523 unselected necropsies at a Johannesburg non European hospital, found an incidence of only 1 6% and 3 0% respectively of coronary occlusion in the 41–60 and 61–80 age groups These figures contrast with an incidence of 12 8% and 13 3% found in similar age groups by Gordon et al[5] in 3400 post mortems at the Massachusetts General Hospital

Serum cholesterol levels are lower in the African than in the European

The mean serum cholesterol level of newborn Bantu and European babies is virtually identical One of us found that, at the age of 21–30, 70 healthy South African Europeans of both sexes had a mean cholesterol level of 215 mg per 100 ml, whilst in 89 African nurses of a similar age group the corresponding level was 174 mg A group of male Bechuana Africans had a mean cholesterol level of 156 mg[6] Walker and Arvidsson[7] have shown that in the Bantu the rise of serum cholesterol levels with age is slight compared with the steep rise in Europeans

In view of our striking results with magnesium sulphate therapy in coronary thrombosis and the low cholesterol levels and low incidence of coronary occlusion in the Bantu, we decided to investigate the serum magnesium level in European and Bantu groups, and to find out whether it was correlated with the serum cholesterol level

Serum magnesium levels were estimated by the method of Orange and Rhein,[8] and cholesterol determinations were carried out by Sperry and Webb's modification of the Schoenheimer and Sperry technique[9]

Serum-magnesium levels were determined on 47 normal European and 53 normal Bantu (all 25–45 years) The results were

Subjects	*Serum magnesium level (mg per 100 ml)*
European	Range 1 52–2 50 Mean 1 82 (S D 0 15)
Bantu	Range 1 85–2 55 Mean 2 11 (S D 0 10)

P = < 0 005—i e, a highly significant increase in serum magnesium levels in the Bantu as compared with the Europeans

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Serum magnesium levels were then correlated with serum cholesterol levels in a group of Europeans, with the following results:

Serum-cholesterol level (mg. per 100 ml.)	Serum magnesium level (mg. per 100 ml.)	"P" factor (as compared with the mean serum magnesium level in normal European subjects)
121–197 (15 cases) Mean level 170	Range 1·76–2·40 Mean 2·06 (S.D. 0·15)	< 0·005 Highly significant increase
202–250 (22 cases) Mean level 226	Range 1·65–2·40 Mean 1·95 (S.D. 0·20)	0·3 Not significant
255–294 (12 cases) Mean level 273	Range 1·78–2·10 Mean 1·95 (S.D. 0·09)	0·3 Not significant
310–389 (21 cases) Mean level 348	Range 1·27–2·15 Mean 1·76 (S.D. 0·18)	< 0·005 Highly significant decrease
402–586 (10 cases) Mean level 470	Range 1·25–2·10 Mean 1·71 (S.D. 0·25)	< 0·005 Highly significant decrease

These results show (1) that the serum-magnesium level is significantly higher in the non-European than in the European, and (2) that a definite correlation exists between serum-magnesium and serum-cholesterol levels. Normal serum-magnesium levels are found in the normocholesterolæmic group (cholesterol 200–300 mg. per 100 ml.). Where the serum-cholesterol content is low (120–197 mg.) the magnesium content is significantly increased, and is almost identical with the figure found in the non-European. The hypercholesterolæmic group (cholesterol 310–586 mg.) shows a significantly lowered magnesium level when compared with the normal European and a very highly significantly lowered level when compared with the normal non-European.

These findings suggest that the part played by magnesium in diet and nutrition requires further study. The possible rôle of this element in cholesterol metabolism, and indirectly perhaps in atherogenesis, has not been fully appreciated, studied, or recognised.

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New Inventions

A COMBINED BED-CRADLE AND FOOT-SUPPORT FOR USE WITH LEG TRACTION

WHEN weight-extension is used on a leg, there is a tendency for the patient to be pulled down the bed. To correct his position he pulls on the handle suspended from the Balkan beam and obtains counter-pressure by pushing the back of his heel against the bed. The skin in the part thus subjected to pressure is thin, and often a sore develops on it despite all nursing care. The combined foot-board and bed-cradle here described was evolved as a means of taking the counter-pressure on the thick skin of the sole and heel, which is well adapted to weight-bearing (fig. 1).

The bed-cradle (fig. 2) (24 × 28 × 18 in., 61 × 71 × 46 cm.) is made up of $^5/_8$ in. (1·5 cm.) conduit tubing, to which are welded four metal strips 18 × $1^1/_4$ × $^3/_{16}$ in. (46 × 3 × 0·5 cm.). In each strip there are fourteen holes, $1^1/_4$ in. (3 cm.) apart. The strips are so fitted that the holes in the upper ones are immediately above those in the lower ones.

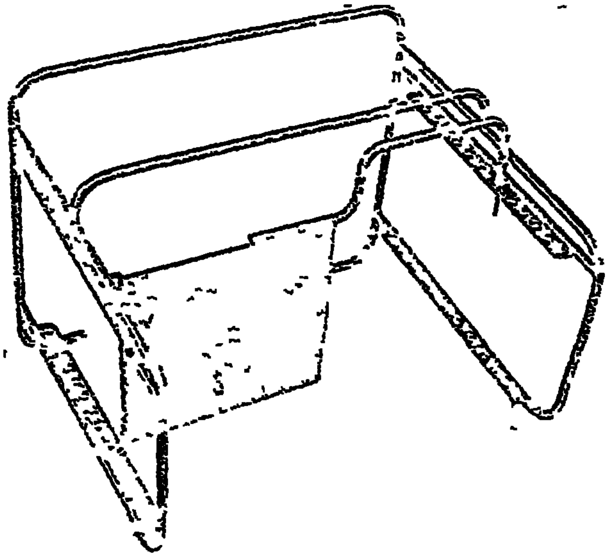

Fig. 2

The foot-support consists of a board $13^1/_2$ × 12 × $^1/_2$ in. (34 × 30·5 × 1 cm.), to three corners of which are attached brackets which can be dropped into the holes in the steel strips. The series of holes makes the appliance adjustable for patients of varying heights. To allow for extension, the board is only half the width of the cradle. It can be used for either leg by lifting it out of place and reversing it.

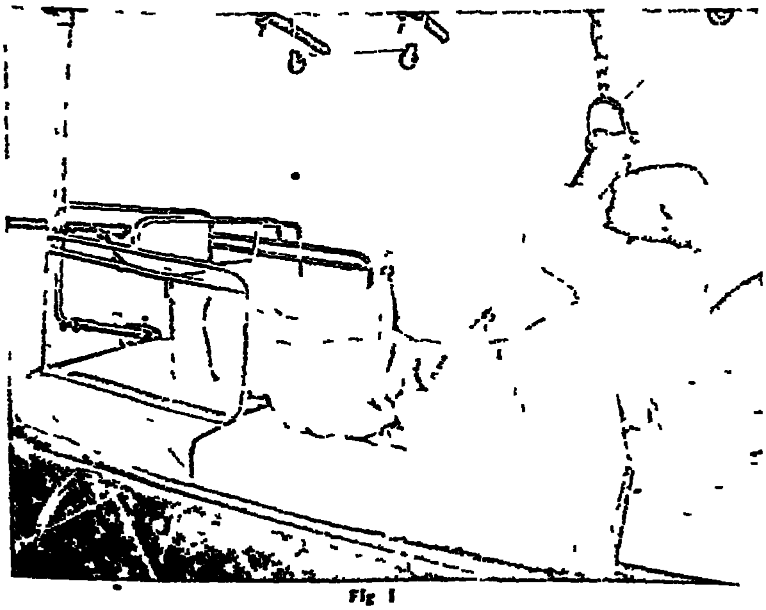

Fig. 1

The cost of the materials was about *17s. 6d.* The device can be made in one and a half days, so with labour the total cost is *£3 7s. 6d.*

I am very grateful to the engineer (Mr. E. G. Ingram) and the fitter (Mr. E. T. Powell) of the Royal Buckinghamshire Hospital, Aylesbury, who not only made the apparatus but provided several useful suggestions. I am indebted to the department of clinical photography, Stoke Mandeville Hospital, Aylesbury, for the photographs.

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Medical Societies

ROYAL SOCIETY OF MEDICINE

Chronic Relapsing Pancreatitis

A MEETING of the section of surgery was held on May 1, with Mr ERIC CROOK in the chair

Dr H DOUBILET (New York) emphasised the physiological unity of the biliary and pancreatic system In his experience of some 500 cases of relapsing pancreatitis treated by sphincterotomy, the two duct systems always terminated in a single common opening into the duodenum Recurrent pancreatitis was caused by reflux of bile up the pancreatic ducts as a result of spasm of the muscle surrounding this common channel, and could be cured by division of this muscle Such spasm could be caused by the local application of hydrochloric acid, and had been shown to cause reflux the reflux of bile concentrated by the gall-bladder was particularly deleterious, and accordingly cholecystectomy could be effective even if the gall-bladder was normal Clinically spasm of this sphincteric muscle resulted from pain, emotional stimuli, and distension of the common bile-duct Morphine caused similar spasm, and should not be used to relieve pain in pancreatitis

Dr Doubilet described his technique of catheterisation of the pancreatic duct at the time of operation, which enabled contrast medium to be injected into the duct system as long as the tube remained in situ When the disease was in a quiescent phase such X-ray examination showed a dilated tortuous duct and main branches, but when active inflammation was present there was an alteration in the permeability of the duct epithelium allowing the dye to suffuse out and opacify the affected part of the gland There was no evidence that pancreatitis was caused by obstruction of the pancreatic duct itself Pain in pancreatitis was due partly to increased pressure in the pancreatic duct system, and partly to chemical irritation and inflammation of the tissues

As the pancreas was a retroperitoneal organ, rupture of the duct system would allow a highly irritant exudate to spread throughout the retroperitoneal space as well as within the peritoneal cavity Fibrosis consequent upon this exudate could obstruct the transverse and descending colon Alternatively the exudate may collect locally to form a pseudocyst, and Dr Doubilet showed radiographs demonstrating that these cysts communicated with the pancreatic duct system, and could be cured by adequate drainage by sphincterotomy

Relapsing pancreatitis could almost always be cured by sphincterotomy with division of the muscle surrounding the common opening of the biliary and pancreatic systems If there were calculi in the main duct they should be removed if this was not possible, caudal pancreaticojejunostomy might infrequently be indicated After a properly performed sphincterotomy, with division of the papilla for 8–10 mm proximally from its opening, reflux from the duodenum did not occur, being prevented by the duodenal muscle coat, but reflux from the common bile duct was no longer possible, as could be shown by testing with hydrochloric acid The regenerative capacity of the pancreas was great, and after sphincterotomy a severely damaged pancreas could return almost to normal, as shown by secretin tests and histological studies But until regeneration was complete the pancreas was peculiarly and specifically sensitive to alcohol and fats, which could provoke further attacks Accordingly the patient must be warned to avoid these substances for 6–18 months after operation

Dr Doubilet showed a film taken with an image-intensifier illustrating the function of the sphincteric mechanism around the opening of the pancreatic and biliary ducts The films were taken in a patient with a cholecystostomy tube, which was used to inject radio-opaque fluid Reflux up the pancreatic duct was clearly seen following painful stimuli and distension of the common bile duct after sphincterotomy this reflux could no longer be produced The film also illustrated dramatically the churning mixing action of the duodenum after the introduction of fat, in contrast to its relative inactivity when carbohydrate and protein were injected

Mr RODNEY SMITH pointed out that relapsing pancreatitis appeared to be less common in Great Britain than in America, and the difference in incidence was not entirely explained by a failure to recognise the disease in this country He agreed that, in his experience, relapsing pancreatitis was nearly always associated with biliary reflux, but that did not mean that every isolated instance of acute pancreatitis was due to this cause Further, it was a common observation from routine postoperative cholangiography that minor degrees of reflux often occurred without precipitating pancreatitis He suggested that acute pancreatitis probably caused changes in the duct epithelium, and that thereafter if recurrent biliary reflux occurred the patient would suffer recurrent attacks of pancreatitis

Mr Rodney Smith showed cine cholangiograms illustrating pancreatic reflux There was no doubt that this reflux occurred in relapsing pancreatitis, and that its prevention was important This was most simply done by the operation of sphincterotomy, which carried a low risk and was usually the operation of choice Nevertheless on occasion other operations might be required Sometimes there was very severe œdema and fibrosis, with a rigid, thickened duodenum and an obstructed bile duct in such cases biliary diversion by cholecystoduodenostomy or cholecystojejunostomy might be the operation of choice If there was heavy calcification of the pancreas with a mass of calculi blocking the main duct, the distal pancreas should be excised, the duct cleared of stones and then anastomosed to a Roux loop of jejunum (caudal pancreaticojejunostomy) Division of the splanchnic nerves had been recommended for the relief of the pain, and there seem no doubt that this operation did relieve the pain, but cholangiographic studies showed that it did not prevent reflux and it should accordingly be regarded as an illogical form of treatment Excision of the head of the pancreas, pancreatoduodenectomy, also had some place in treatment and good results had been obtained, but owing to the extensive fibrosis binding the pancreas to the portal vein and adjacent structures, this was both a difficult and dangerous operation, which should not be undertaken unless there were categorical indications

Dr W I CARD (Edinburgh) said that, as seen by the physician, the condition usually presented either as a problem of undiagnosed abdominal pain or of steatorrhœa with nutritional deficiency, pain being more prominent early in the disease and nutritional changes late Pain was due to a rise of pressure in the pancreatic duct system, and could sometimes be provoked by giving secretin and morphine, after which it could be relieved by amyl nitrite After the operation of sphincterotomy secretin and morphine no longer precipitated pain

The pain of pancreatic disease might often be difficult to differentiate from that of biliary origin, but it tended to last longer At times ulcers in the second part of the duodenum gave rise to pain closely simulating pancreatitis, as might peri-Vaterine duodenal diverticula An acute exacerbation could usually be managed by gastric suction and the administration of pethidine or morphine, atropine, and glyceryl trinitrate

In all cases of pancreatic disease pancreatic function tests, if properly performed, were undoubtedly useful Secretin by itself did not stimulate pancreatic enzyme production, and as the output of amylase seemed the most sensitive indication of pancreatic function, better results were obtained by a combined secretin and pancreozymin test, this latter hormone stimulating the pancreas to secrete amylase Dr Card illustrated the results obtained by this test in several cases of chronic pancreatitis, as compared with the normal The glucose-tolerance test was invaluable in differentiating pancreatic from intestinal steatorrhœa In the treatment of pancreatic insufficiency, pancreatin by mouth was often successful

AMERICAN PROCTOLOGIC SOCIETY

THE society met in New Orleans under the presidency of Dr **RUFUS C ALLEY** (Lexington, Kentucky) on April 24-27

Tropical Diseases

Dr **JOHN McGIVNEY** (Galveston, Texas) described the perianal subcutaneous lesions associated with the penetration of the hookworm larva, *Ankylostoma braziliense* from moist sand after previous deposition in ova from from the excreta of cats and dogs, these were treatable with carbon-dioxide snow or ethyl chloride, chloroquinone diphosphate being given systemically

Dr **PORFIRIO M RECIO** (Manila, Philippines) described the lesions which result from infestation with *Schistosoma japonicum*, prevalent in the Philippines, large [illegible] liver, and rarely brain are affected The colonic lesions pass through hyperæmic, suppurative, ulcerative and adenomatous and granulomatous stages until, as with *hæmatobium* in the bladder, carcinoma supervenes There is no effective treatment after penetration of the parasite excision or resection of the colon is necessary for the granulomatous or carcinomatous degenerations, and the opportunity should be taken to remove the appendix since embolism of its blood-supply by ova frequently produces gangrene

Colonic Volvulus

Dr **IRVING A. LEVIN** (New Orleans Louisiana) gave an account of 74 cases of colonic volvulus admitted to hospital between 1945 and 1955 There were 11 deaths (14 8%), the sigmoid was involved in 63 cases (10 deaths), and the cæcum in 11 cases (1 death) The correct diagnosis was made before laparotomy in the cæcal form only once, there was a tendency to recurrence after simple detorsion and fixation, so right hemicolectomy was advised For the sigmoid volvulus proctoscopic reduction by the passage of a deflating rubber tube was frequently effective, and this was followed by sigmoid resection to obviate recurrence There was little danger of perforation of the bowel by the tube there being only 2 instances of this in 182 reported proctologic reductions, but care must be taken to ensure that gangrene of the bowel was not present after successful non-operative reduction

Diverticulitis

Dr **RICHARD L BUCK** (New Orleans, Louisiana) reported 256 cases of diverticulosis and diverticulitis out of a total of 327,871 admissions to the Charity Hospital Louisiana, in a six-year period 131 were uncomplicated and required no surgery In cases complicated by perforation or obstruction there was a mortality of 50% in only 1 case was the bladder involved 75% of the patients were over 60 years old, pain was the commonest symptom, with bleeding second in order of frequency

Rectal Procidentia

Dr **NORMAN D NIGRO** (Detroit Michigan) described an operation for cure of rectal procidentia by means of a fascial sling reinforcing the atrophic puborectalis muscle fixed to the pubes in front and passing behind the rectum at its junction with the anus, operative approach was achieved by removing the coccyx and passing the sling forwards to be attached to the pubes through a retropubic approach Dr **A F CASTRO** (Washington D C) preferred to treat rectal procidentia by anterior resection of the redundant bowel, and had had no recurrences after this procedure

Anorectal Surgery

After excision of piles or fissure, Dr **V R MANNING** Philadelphia Pa) favours covering the raw area with a sliding graft of perianal skin and Dr **CHARLES E POPE** Evanston Illinois) direct suture after lateral relieving incisions

Dr **JAMES A FERGUSON** (Grand Rapids Michigan) described a method of hæmorrhoidectomy with complete closure of all wounds with simple catgut suture, undertaken in 8080 patients with few complications and little morbidity

Dr **M J ANDERSON** (Rochester Minnesota) had studied perianal hidradenitis suppurativa—an intractable condition often associated with acne and sometimes mistaken for pilonidal sinus and simple fistula-in-ano—and demonstrated that apocrine glands were only secondarily involved and could not certainly be regarded as the source of the condition, eccrine glands also became affected as did hair-follicles and sebaceous glands Malignant change complicated long-standing cases

Polyps and Cancer of Colon and Rectum

Dr **W A FAUSTER** (Minneapolis, Minnesota) did not consider the "second look" procedure reasonable as a routine, though possibly useful as an experiment, nor did he think that it will prove to have been worth while

Dr **RUPERT TURNBULL** (Cleveland, Ohio) reported that in a series of 86 cases of colorectal polyps locally removed through the colon, only 3 patients had died of cancer he felt that, since pathologists reported malignant change in only 10% of apparently benign polyps, radical surgery was not necessary and that this was borne out by the facts presented

Dr **S J FIGIEL** (Detroit, Michigan) advocated radiodiagnosis of colonic polyps by means of a barium enema, using 120 kV with compression over the area of bowel under study

Dr **MERRILL O HINES** (New Orleans, Louisiana) emphasised the fluid and electrolyte loss from villous tumours, so great might this be that patients with villous tumours were sometimes admitted in severe electrolyte depletion, 30% of these lesions showed malignant change

Ulcerative Colitis

Mr **STANLEY AYLETT** (London) advocated preservation of the rectum in the surgical treatment of ulcerative colitis he reported on 54 patients submitted to ileorectal anastomosis

Mr **B N BROOKE** (Birmingham, England) discussed the need for electrolyte therapy to replace loss from an ileostomy approximately 300 m eq per litre was excreted from the ileostomy and was the additional sodium requirement in the immediate postoperative period this fell to 150 m eq per litre in the established case Potassium loss was a preoperative problem which ileostomy tended to correct Cortisone appeared to conserve sodium, as expected, while potassium concentration in the ileostomy fluid increased, but the total excretion from ileostomy and urine was not increased since the volume of excretion from both sources was reduced by cortisone

Dr **GEORGE LUMB** (Memphis, Tennessee) described biopsy studies of the rectum from which he concluded that though quiescence of the disease might be manifest histologically it was impossible to predict from biopsy specimens how long a remission would persist

Britain's National Health Service

Mr **A LAWRENCE ABEL**, who at the beginning of the meeting had received the honour of free citizenship of the town of New Orleans delivered the Mathews oration Dr Mathews had been the first surgeon to undertake proctological practice, thus founding the specialty of proctology, he had advised young men to travel widely and then set up practice in a town of their choice Mr Abel felt that this would still be good advice to young men anywhere except in Great Britain today He then developed the thesis of his oration by enumerating the dissatisfactions of certain elements of the medical profession in this country and indicted the Government for what he regarded as failures in "socialised medicine"

Reviews of Books

A Manual of Human Anatomy

J T AITKEN, M D reader in anatomy, University College, London, G CAUSEY, M B, F R C S, professor of anatomy, Royal College of Surgeons London, J JOSEPH, M D, M R C O G, reader in anatomy, Guy's Hospital Medical School, London, D A SHOLL, B SC, reader in anatomy, University College, London, J Z YOUNG, M A, F R S, professor of anatomy, University College, London Edinburgh and London E & S Livingstone 1956 and 1957 Vol 1, *Thorax and Upper Limb*, pp 162, 14*s*, Vol 2, *Head and Neck*, pp 180, 16*s*, Vol 3, *Abdomen and Pelvis*, pp 127, 12*s* 6*d*, Vol 4, *Lower Limb*, pp 117, 12*s* 6*d*, Vol 5, *Central Nervous System*, pp 128, 12*s* 6*d*

ACCORDING to a preface, this work aims "to give the student of human anatomy a method of dissecting the body and to guide him as to the extent of the knowledge expected of him in the second medical examination" Development is occasionally considered The volumes are well produced, with plastic covers and a ring-binding which has advantages in the dissecting-room, where they stay open comfortably at any desired page The illustrations are diagrammatic, and colour is freely used At the end of each manual is a suggested scheme for practical classes in osteology and surface anatomy The text is clearly written, and much anatomical detail has been suppressed in favour of brief discussions on the functional aspects These functional sections are a welcome feature which should do much to preserve the student's initial enthusiasm Simplified anatomy books are now in the ascendant, and apparently the examiners are satisfied, is it too much to hope for a similar simplification of the textbooks in other preclinical subjects?

New Bases of Electrocardiography

DEMETRIO SODI-PALLARES, M D, chief of the department of electrocardiography at the National Institute of Cardiology of Mexico English translation by ROYALL M CALDER, M D, clinical professor of medicine, Graduate School, Baylor University London Henry Kimpton 1957 Pp 727 £6 15*s*

THE empirical accumulation of knowledge about the electrocardiogram, and its remarkable diagnostic accuracy in expert hands, tended to retard interest in the principles underlying its interpretation The introduction of unipolar leads and the extended use of chest leads have, however, encouraged clinicians to take the more rational view of electrocardiography, which the fundamental work, particularly of F N Wilson and his colleagues, has made possible Modern methods of calculating the electrical axis of the heart and of vector analysis have now brought electrocardiographic interpretation near to scientific exactitude, and much useful information has come from a study of the intracavitary potentials of the heart The time was clearly ripe for a postscript to Lewis's classic *Mechanism and Graphic Registration of the Heart Beat* Dr Sodi-Pallares's valuable book has now been effectively translated into English

The bases of electrocardiography are lucidly surveyed in introductory chapters on the principles of electricity and electrophysiology, and then applied to the major abnormalities of heart disease The initial chapters, though solid reading, are clear and reasonably easy to follow, and many clinician will be glad that the mathematical aspects have been relegate to an appendix The theoretical implications of the maj- abnormalities are minutely discussed, and the more important original work on each is critically and judicially reviewed The chapter on myocardial injury is particularly valuable and illuminates a number of clinical problems

The contributions from Sodi Pallares's laboratory includ important studies of the activation process of the heart b direct endocardial leads in dogs and intracavitary leads i man These are of the greatest interest particularly in relatio to the activation of the interventricular septum and th nature of bundle branch block Too many details of experimental procedure would clearly be inappropriate in a textbook, but one could wish to know more of the technica methods employed without necessarily having to consult th original papers The diagrams, though generally excellent are sometimes overcrowded and not clearly lettered

The book must be nearly indispensable to anyon seriously interested in electrocardiography

Allergic Dermatoses due to Physical Agents

Edited by RUDOLF L BAER, M D, assistant professor o clinical dermatology and syphilology, New York University Postgraduate Medical School Philadelphi and Montreal J B Lippincott London Pitma Medical Publishing 1957 Pp 110 24*s*

THIS book contains essays by the editor and six othe contributors (including Stephan Epstein and Stephe Rothman) which were previously published in th *American Practitioner* They are concerned with th theoretical and clinical aspects of skin changes produce by "allergic" responses to light, heat, cold, and traum in the sense of external pressure The book brings togethe helpful information on subjects which are badly discussed in most dermatological textbooks, and it wil interest others besides skin physicians and teachers Its value is enhanced by detailed bibliographies and a good index

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Dorland's Illustrated Medical Dictionary (Philadelphi and London W B Saunders 1957 Pp 1598 87*s* 6*d*)—Dr W A Newman Dorland having died last year at the ripe age of 92 after editing 22 editions of *The American Illustrated Medical Dictionary*, this 23rd edition has been rechristened in his honour Apart from the addition of many new words there appear to be few changes The page size has been slightly enlarged to accommodate the newcomers, some names of plants and non medical words—e g, *abattoir*—have been dropped, and the article on medical etymology has been moved from the front to the back of the book As a sign of modern spoon feeding, after having had 22 editions withou such a section, we now have one of 4 pages entitled Notes on Use of This Dictionary Some errors in the 22nd edition—e g, *etiocholanolone* and the obvious one under *porphobilinogen*—have been corrected This excellent new edition will be heartily welcomed by those acquainted with its predecessors and can be thoroughly recommended to those to whom it is being introduced for the first time

Public Health and Social Services (4th ed London Edward Arnold 1957 Pp 160 9*s*)—From being an elementary textbook to teach pupil midwives how they could expect to fit into the pattern of the personal health services, this little book has changed during its four editions into a more comprehensive outline of our wider social services The authors are Dr Dennis Geffen, Mr Leslie Farrer Brown and Dr M D Warren It is a handy size for a nurse's pocket, but it cannot do much more than point the way towards more specialised guides

The Therapy of Bronchial Asthma (*Proceedings of the International Round Table Friendship Meeting of Allergologists* Leiden H E Stenfert Kroese N V 1956 Pp 354 50*s*)—The treatments discussed in this report of a symposium held in 1955 range from surgery to thermal spas The speakers came from Europe Israel and the United States, this country is represented by Dr A W Frankland, Dr Denis Leigh, Dr Kate Maunsell Dr R S B Pearson, and Dr D A Williams The proceedings are published in English, save for one paper in French, and they are edited by Mr Dr W J Quarles Van Ufford

THE LANCET

LONDON SATURDAY MAY 18, 1957

Surgical Treatment of Ischæmic Heart-disease

In historical order the surgical treatment of ischæmic heart-disease takes precedence over operations for congenital and valvular disorders, but whereas these have rapidly established themselves as standard procedures, **Wood**[1] feels—more than twenty years after the pioneer work of **Beck**[2] in America and **O'Shaughnessy**[3] in this country—that "operations [for ischæmic heart-disease] have not yet graduated from the experimental class." Recent reports from **Beck** and his fellow-workers[4,5] suggest however, that the mass of ingenious experiments in the intervening years is now beginning to bear fruit. Ischæmic heart-disease includes many clinical states—ranging from mild infrequent anginal attacks to massive infarction—which differ in their pathology, symptoms, signs and prognosis but which have an inadequate coronary circulation as a common feature and of this atheroma of the coronary arteries is by far the commonest cause. Symptomatically both medicine and surgery can offer a fair measure of relief to most patients but the surgical method, consisting in sympathetic denervation is not usually the symptomatic treatment of choice owing to the operative mortality and the occasionally unpleasant side effects. (The theoretical objection that it deprives patients of a useful warning signal has not been proved valid in practice even when pain is abolished a curious though not unpleasant, sensation of impending ischæmia remains.[6,7]) At the other extreme both medicine and surgery are still powerless to prevent or deal with coronary atheroma the primary cause of the disease. Between the highest and the lowest aim—curative and symptomatic treatment—**Beck's** operation has been designed to enable the heart to work adequately with an inadequate blood supply.

As has happened time and again with the elaboration of new operations **Beck's** work has thrown fresh light on old-established theoretical concepts. **Beck** clearly distinguishes two types of death from coronary-artery disease—one , due to electric currents in the heart which destroy the coördinated mechanism [of the cardiac cycle] the other due to muscle failure and destruction.[4] Currents which kill by initiating ventricular fibrillation—with or without actual muscle-destruction—arise in the electrically unstable heart , and electrical instability of the myocardium results not from an absolute shortage but from an uneven distribution of oxygen. Even the deeply cyanosed heart may remain electrically stable so long as it is uniformly cyanosed but electrical stability is destroyed by the 'oxygen differential' at the point of contact between cyanosed and oxygenated myocardium. Whether electrical instability leads to ventricular fibrillation depends on the strength of the current which the oxygen differential generates and on the threshold of fibrillation —a term by which **Beck** refers to the heart's disposition to fibrillate under prevailing working conditions. **Beck** believes that this dual concept of death from coronary-artery disease strikes at the very foundation of the coronary problem'. There is in his view no obligate relationship between abnormal currents and destruction of heart-muscle and he supports this view by the absence of infarcts old or recent, in a third of all victims of coronary-artery disease, and by the fact that extensive destruction of heart muscle resulting in failure occurs without producing currents strong enough to fibrillate the heart'.[4] The practical implication of this distinction is that one potentially lethal effect of coronary insufficiency is far more amenable to prophylactic surgery than the other. "There are two ways in which the crippled coronary circulation can be helped. One is by an even distribution of the blood that enters these arteries the other is by the addition of blood to that which enters the diseased arteries." Very little can be done at present to increase the amount of blood entering the coronary circulation coring out atheromatous plaques and other forms of direct arterial surgery are still beset with unsolved technical difficulties. Experimental attempts to anastomose systemic arteries, such as the internal mammary, with coronary arteries have not yet met with success and operations to convert the coronary sinus into an outlet for arterial blood even when dramatically successful at first do not maintain a reversed flow for more than a few months. To ensure a more even distribution of arterial blood is far simpler and this alone may suffice to abolish potentially lethal oxygen differentials.

Beck's operation consists essentially of four steps. First the coronary sinus is constricted to a diameter of about 3 mm by a ligature passed around it 2–3 cm from its opening into the right auricle. **Beck** claims that this allows a somewhat greater extraction of oxygen from the venous blood that—by causing mild venous stasis—it diminishes oxygen differentials in the presence of arterial occlusion and that it also produces inter-coronary channels. On the other hand this manœuvre is bound to increase capillary pressure and theoretically at least this may reduce the total inflow of blood into the coronary arteries. (If approach to the sinus proves technically difficult **Beck** advises that it should be omitted.) The second step is abrasion of the lining of the parietal pericardium and of the epicardial surface of the heart in order to bring about an inflammatory reaction which will induce the formation of new inter-coronary channels. Thirdly coarsely ground asbestos is applied to the denuded surface, and, finally, mediastinal fat is brought into contact with this area so that it can act as a graft None of these measures is new, but each step in the carefully planned sequence is said to contribute to the final result

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[1] Wood, P. *Brit. med. Bull.* 19[illegible] 11, 2[illegible]
[2] Beck, C. S. *Ann. Surg.* 193[illegible] 102, [illegible]01; *J. thorac. Surg.* 1936, 5, [illegible]
[3] O'Shaughnessy, L. *Lancet*, 1937, i, 1[illegible]
[4] Beck, C. S., Brofman, B. L. *Ann. intern. Med.* 19[illegible] 45, [illegible]
[5] Brofman, B. L. *J. Amer. med. Ass.* 1956, 162, 16[illegible]
[6] White, J. C., Bland, E. F. *Medicine*, 194[illegible] 27, 1.
[7] Lindgren, I. *Acta med. scand.* 1950, 138, suppl. 243.

Whatever criticisms may be levelled against this operation—several modifications have already been proposed[8–10]—it has the merit on first principles of seeking to imitate and supplement rather than to distort a natural process Post-mortem findings in men confirm experimental findings in dogs that an intercoronary circulation is established across the anatomical watersheds with progressive occlusion of any of the major coronary arteries[11 12], and this seems to be the heart's natural defence against threatening anoxia Furthermore, it seems that about 9% of people have congenital inter-coronary communications[12], and patients who make spectacular recoveries from major coronary occlusions may well belong to this fortunate minority The justification of **Beck**'s operation rests on experimental and post mortem evidence that occlusive coronary disease cannot promote an effective intercoronary circulation until it is severe, and on clinical evidence of dangerous oxygen differentials even with mild or moderate stenosis "The purpose of the operation is to place more people into the favourable [9%] group" who have an abundant inter-coronary network of arteries Negative merits of the procedure are its remarkably low immediate mortality (no death in the last 100 consecutive cases in the series of **Beck** and **Brofman**[4]) and technical simplicity, which eliminates from the operation the dangerous element of haste In the absence of congestive heart-failure, gross cardiac enlargement, and progressive symptoms (and not less than six months after an infarct) **Beck** advocates it for all cases of angina pectoris and of coronary insufficiency, and even for selected symptomless patients with a strong family history of early death from coronary disease It must be admitted, on the other hand, that—though **Brofman**[5] contrasts the "expected" mortality of 30%[7] with the postoperative mortality of 18% in 137 consecutive patients[5]—a follow-up period of from six months to five years cannot be regarded as adequate for so unpredictable a disease There is no accurate way of measuring either the degree of coronary insufficiency or the number of natural inter-coronary channels in any individual patient, and a carefully controlled trial, over at least ten years, of large, comparative groups will be necessary before the value of the operation in prolonging life can be assessed In their evaluation of symptomatic relief **Beck** and **Brofman** have been gratified by the results, but there are notorious pitfalls when patients "act as their own controls,"[5] especially when they have a disease where a strong psychologial element is increasingly difficult to exclude Nevertheless there is a good case for giving the operation an extensive trial, and results so far offer grounds for sober optimism

Young People Starting Work

The Certifying Factory Surgeon, as he was then called, was one of the earliest instruments created by the State in its attempt to safeguard the health of young people Originally, his primary function was to act as a check on their employment in contravention of age limits imposed by statute, and his critics said that he was sometimes too willing to believe that stunted youngsters were of the prescribed age The Factory Act of 1874 made it necessary for a child to have a surgeon's certificate that he was 13 before he entered on full-time work free from schooling, but the Act was often evaded **Housden**[1] tells how a Birmingham brass-founder, seeing a lad who looked very young, asked his age The boy replied that he was 13, he knew he was 13 because his mother told him so But when asked how old he was before his mother told him he was 13, he replied "9", and further investigation showed that, though duly certified, he was only 9 years old Another side of the certifying surgeon's job—one that assumed added importance with the years—was to satisfy himself that the children passing before him were physically fit for the work they were required to perform, but disability was prevalent and standards low, and it may have been that here again the surgeon felt that he could not afford to be too critical "Passing before" is perhaps the correct expression remuneration was small and facilities for any examination were sometimes absent Under the prevailing conditions it was hard to do good work Now circumstances have greatly changed, though there are still some difficulties The newer outlook is intended to be much more positive It is the declared intention of the State that the work of supervising young entrants to industry should dovetail with that of the School Medical Service, the records of which are available to the Appointed Factory Doctor on request In practice, these records are not very often sought, and when sought they cannot always be produced by return of post, and there are inevitably cases in which the recorded findings of the school health service do not altogether coincide with those of the factory doctor

Herford,[2] as an appointed factory doctor, presents a study of adolescents at work in the Slough area (predominantly light industry) His experience leads him to conclude that the work of the appointed factory doctor, suitably reoriented to make full use of his unique opportunities, could contribute far more to constructive medicine than it has done hitherto He points out that the Ince Committee, which considered in detail most of the agencies concerned with the welfare of youth in industry, made no mention of the work of the appointed factory doctor, and that the Youth Employment Service, set up in 1948 as a result of the Ince report, has had little contact with him From this, **Herford** goes on to make recommendations for the improvement of the appointed factory doctor's work and the increase of his contribution to the welfare of young people He comes to the conclusion that the appointment of such doctors should be essentially whole

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[8] King E S J Surgery of the Heart Baltimore, 1941

[9] Mason G A *Lancet* 1951 i, 759

[10] Thompson, S A Plachta A *J Amer med Ass* 1953 152 678

[11] Zoll P M Wessler S Schlesinger M J *Circulation* 1951 4, 797

[12] Beck C S Leighninger D S *J Amer med Ass* 1955 159, 1264

[1] Housden L The Prevention of Cruelty to Children London 1955

[2] Herford M E M Youth at Work London Max Parrish & Co 1957 Pp 154 18s 6*d*

time, that they should belong primarily to the staff of H M Medical Inspectorate of Factories, though they should also hold an appointment with the local authority as an assistant school medical officer, that all young persons should be examined regardless of occupation, that the appointed factory doctor should be medical adviser to the Youth Employment Service and should be provided with a secretary seconded from the staff of that service, that school medical records should be submitted automatically to the appointed factory doctor when the children leave school, and that it would be an advantage to have the appointed factory doctor associated with a university department

There will be general agreement about the need for skilled vocational guidance for young people entering industry (especially for those at either end of the scale of physical and mental fitness), for even in these days the choice of a career is left to blind chance—very much a matter of trial and error The best use is by no means always made of our really able young people, and many of the handicapped could be helped to better things [3] As to how improvement can be made, the issues are neither entirely industrial nor entirely medical, decisions turn largely on the background and inclination of the youth and often on the attitude of the parents It would, we believe, be right for the family doctor to take a more active part in vocational guidance, especially of the handicapped child if he would familiarise himself with the nature and demands of the industry of his area none could do it better, and it is fascinating and rewarding work This would not remove the need for a person specially appointed to do the kind of work done by the appointed factory doctor (who has, of course, other statutory duties), but in general we are not persuaded that the multiplication of official doctors would be a good thing, or even economically sound In practice, HERFORD's proposals would probably imply organisation on a geographical basis corresponding to that of the major health authorities, and whether that offers the best prospect of an improvement is open to doubt The questions he has raised call for careful study How best to further the well-being of young people starting work is not just a problem of industrial health, is not this important task one that should fall within the ambit of the general health service itself?

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[3] Ferguson T MacPhail A N, McVean M I Employment Problems of Disabled Youth in Glasgow Medical Research Council memorandum no 28 1952

Annotations

THE PREGNANCY AND THE CHILD

MEDICINE is frequently enriched by contributions from other disciplines, and Dr Stott's article from an institute of education, which we publish this week, could prove to be the starting-point of a new approach to some of the processes concerned in mental retardation In a carefully controlled study of 102 mentally retarded children he has found an association between retardation, congenital malformation, and frequent ill health in early life, and he has connected this syndrome with physical and emotional disorders in the mother during pregnancy He therefore suggests that stress in pregnancy may determine biological inferiority in the child, either directly or by facilitating a latent genetic influence But in considering the evidence for this hypothesis it should be noted that the survey was retrospective and that the analysed data are based on the mothers' recollection supported by medical records and health visitors' cards No genetic histories were obtained, and, apart from the knowledge that the retarded children were of normal appearance, we have no details of their clinical classification

Little is yet known about the genesis either of undifferentiated mental retardation or of congenital malformations in man Certainly, normal development can be altered by prenatal environmental influences, but in the case of congenital malformations there is general agreement that the noxious influences must be in operation at the time of organ differentiation, which in the human fœtus is completed by the 12th week of intra-uterine life Anomalies arising after this must be traumatic or regressive changes due to mechanical or chemical agents, and for an illustration of the fact that grave damage to the mother does not necessarily affect the infant in utero one need look no further than the remarkable case recorded by Mr Rowbotham and his associates on p 1016

Experiments on animals have confirmed this time specificity of environmental influences and have also indicated the wide variety of physical and chemical disturbances which may produce congenital malformations The present position has been summarised by Gluecksohn Waelsch [1]

> ' . . . thus we have reached . . . the central problem facing all 'teratologists,' namely that of the mechanisms by which causal agents produce malformations It is of utmost importance to realize that the nature of these mechanisms is independent of the nature of the causal agent In this respect genetically caused abnormalities do not differ in any way from those produced by deleterious agents, e g, X rays hormones, anti metabolites, nutritional deficiencies or others The pathways by which they achieve their end effects may be the same or different but they are independent of whether the original deviation from normal was caused by a gene or some other factor '

Though it is evident that in animals many different maternal conditions may produce a common final syndrome in the embryo, experience with man is by no means so clear The syndromes associated with maternal rubella and irradiation appear not only time-specific but also to some extent type specific Rubella is associated with deafness, cataract, and congenital heart disease, while irradiation is associated with microcephaly Apart from these two conditions, no other environmental factors have been proved consistently to cause congenital defects in the human fœtus Among several surveys, those of Carter [2] and Creamer [3] are specially valuable here Carter investigated many maternal illnesses during pregnancy with negative results, and Creamer in a controlled follow up study of the children of mothers with pregnancy toxæmia found no preponderance of either congenital malformations or early ill health The known associations of congenital malformations with multiple pregnancy, prematurity, multiparity, pregnancy in very young or elderly mothers, and male infants [4] [5] are probably not environmentally determined

Even less clear are the facts in regard to mental retardation A high proportion of mental defectives may have congenital malformations of the brain,[6] but these are not necessarily due to noxious environment Moreover mental defect is sometimes undoubtedly caused by perinatal damage to the brain.[7] Without genetic data and birth histories in Dr Stott's cases it is hard to say whether an alternative explanation to that advanced by him might be more reasonable in terms of current knowledge.

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[1] Gluecksohn Waelsch S *Pediatrics* 1957 19 777

[2] Carter C O *J Obstet Gynæc Brit Emp* 1950 57 897

[3] Creamer B *Ibid*, 1955 62, 914

[4] Hendricks C H *Obstet Gynec* 1955 6 592

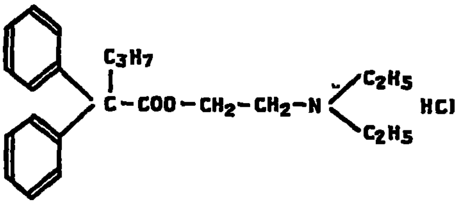
[5] Davis M E Potter F L *Pediatrics* 1957 19 719

[6] Malamud N *Amer J ment Defic* 1954 58 438

Since existing explanations account for only a small proportion of mentally retarded children, it is impossible to ignore Dr Stott's hypothesis of what might be termed intra-uterine protophrenia, and to test this hypothesis in a prospective manner an investigation on a large scale should be undertaken as a multi-disciplinary project. Meanwhile, however, there is no need to add to the anxieties of the pregnant woman by making premature suggestions that she can worry herself into bearing an abnormal child.

BIOTRANSFORMATION BLOCKADE

A FEW years ago much interest was aroused by reports of the remarkable properties of a compound related to a spasmolytic 'Trasentin'. Given the code name of SKF 525 A, this compound is β-diethylaminoethyldiphenylpropylacetate hydrochloride.



Trasentin differs in having no propyl radical.

The striking feature of the action of SKF 525 A is that, in doses at which it has no obvious effects itself, it greatly prolongs the action of various drugs on the central nervous system. Thus pre-treatment with SKF 525 A increases the duration of hypnosis after administration of hexobarbitone in mice by 15 times and in rats by 37 times. In rats, doses of hexobarbitone which alone were ineffective produced sleep for an average of 35.2 minutes when SKF 525-A 25 mg per kg had previously been given by mouth.[8] Amounts as small as 1 mg per kg significantly prolonged hexobarbitone hypnosis in mice, but even at 50 mg per kg, SKF 525 A did not notably alter the toxicity of hexobarbitone in rats. The effect is not evident with all barbiturates, thus the action of pentobarbitone is prolonged but not that of its thio analogue, thiopentone. The action of diethyl ether or nitrous oxide is not prolonged, whereas that of some other central-nervous-system depressants (including chloral hydrate, morphine, codeine, pethidine, amidopyrine, and phenytoin) is prolonged, as are the stimulant actions of amphetamine sulphate and of strychnine. Such effects might be produced by one or more of several possible mechanisms[9], but there is clear evidence that SKF 525 A interferes with the rate of metabolism or biotransformation of the drug concerned.[9 10] It inhibits the enzyme systems which oxidise the side chains of hexobarbitone and pentobarbitone, deaminate amphetamine, convert codeine to morphine by ether cleavage, conjugate morphine, and dealkylate pethidine, amidopyrine, and ephedrine. It was found that these enzyme-systems were located in the microsomal fractions of liver homogenates, but also required reduced triphosphopyridine nucleotide (TPNH) and oxygen. These seemed to be supplied in the supernatant of centrifuged liver homogenate. A requirement for TPNH rather than TPN indicates an unusual oxidative pathway, and the normal cytochrome system does not seem to be involved. That a peroxide-like intermediate takes part is suggested by the work of Brodie et al.[11] The possibility that SKF 525-A acts by blocking the oxidation of TPNH is not borne out by experiment.[10] Furthermore, it does not inhibit certain enzyme-systems which require TPNH and oxygen, or which require TPNH but proceed anaerobically. It does interfere with conjugation of morphine and hydrolysis of procaine by enzyme systems which do not require TPNH. Iproniazid, the isopropyl derivative of isoniazid, has been shown to block the same drug enzyme systems as does SKF 525-A.[12]

There is no clear therapeutic use for SKF 525 A, but it opens up an important field for the further study of drug metabolism.[13] Brodie[11] has put forward the idea that the "microsomal enzyme systems of liver may be there to 'detoxicate' foreign compounds". Substrates normally present perhaps have specific mechanisms for their metabolism, the foreign compounds being dealt with by rather non-specific microsomal systems. It seems that the microsomal drug enzyme systems may be absent in lower animals, and this may explain species differences in tolerance to certain drugs—exemplified in frogs, which excrete hexobarbitone unchanged.

THE AFFAIR AT BATH

BATH was used as a healing centre by the Romans. The Bath General Hospital, built with money raised by Beau Nash and opened in 1742, has latterly been an important centre for the treatment of rheumatism, and in 1934 it changed its name to the Royal National Hospital for Rheumatic Diseases. Even then it badly needed rebuilding, and funds were raised for the purpose, but the war prevented their use, and in 1942 part of the hospital was destroyed by a bomb. When the National Health Service began, the money (£130,000, of which £89,000 had been specifically subscribed for the new building) was taken away for the common pool. As it was supposed that plans for a new building would nevertheless be fulfilled, the hospital was neither repaired nor modernised.

Its present condition is deplorable. The research laboratory is partly in the mortuary and the "plaster room" is a corridor. There is no operating theatre at all, the wards are ill arranged, the lifts are inefficient, and the X ray department was condemned ten years ago. Yet, because of the spirit of the staff, and the quality of their work, patients are admitted to the 130 beds from all over the country, and even from abroad. The demand on it proves that, even though many large general hospitals have their own rheumatism units, a valuable purpose is served by having *at least* one such special hospital, of national standing, where rheumatism is intensively studied and standards can be set. Despite all difficulties, Bath has so far managed to maintain a notable team in which the patient gets expert care from physician, orthopædic surgeon, radiologist, physiotherapist, occupational therapist, and social worker—all especially interested in his condition.

That such a hospital should become a casualty of reorganisation shows that the reorganisation is faulty. With so much else to do, the regional board puts regional needs first and finds itself unable to give more than third priority to a rebuilding project which it regards as a national as much as a local responsibility. The Ministry of Health, on the other hand, takes the view that money for capital expenditure on hospitals should be distributed through the regional boards. Both arguments sound reasonable enough in themselves, but neither justifies the progressive administrative destruction of a valuable institution. Under the National Health Service no effort has been made to fulfil the particular object for which the hospital raised what was then a large sum of money To many people that object still seems important, and if they are wrong, they are entitled at least to a full explanation of why the Bath Hospital can properly be allowed to disintegrate Otherwise, if the Ministry seriously wants the public to retain their interest in hospitals, and resume their former habit of benefaction, it will have to reconsider its decisions

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[7] *Lancet* 1957 i 572.

Cook L, Toner J L, Fellows E J *J Pharmacol* 1954 111 131.

Axelrod J, Reichenthal J, Brodie B B *Ibid* 1954 112 49.

Cooper J R, Axelrod J, Brodie B B *Ibid* p 55.

[11] Brodie, B B, Axelrod J, Cooper J R, Gaudette L, La Du B N, Mitoma C, Udenfriend S *Science* 1955 121 603.

[12] Fouts J R, Brodie B B *J Pharmacol* 1956 116 480.

[13] Brodie B B *J Pharm Pharmacol* 1956, 8 1.

THE BOMB TESTS

As Lord Cherwell was at pains to emphasise in the House of Lords (in the speech reported on p 1046), no-one who is not in possession of secret details about the British nuclear weapons can really say what the result of the forthcoming tests will be But these details may not be so important, for what is far from secret and matters much more is the mounting quantity of radioactive substances that are being released in test explosions and which can be measured as they fall out by anyone who cares to take the trouble If the plan for Christmas Island is to fire fusion bombs with no great quantity of fissionable material added, then the amount of radioactive substances released will be small, and on the existing evidence the hazard to health will be negligible Even if some of the so called "dirty" bombs are exploded, the disastrous consequences prophesied by some people are still improbable Nevertheless, we persist in our view that the continuation of test explosions increases the chances of doing serious harm to a sizeable number of people and that negotiations for the abolition of such tests should be undertaken with a far greater sense of urgency than the Government have hitherto shown We are alarmed at what may happen if tests go on much longer and we are unconvinced that harm has not already been done It seems that the Government, in their attitude to the control of nuclear tests, are depending too much on certain reassuring facts and not making enough allowance for the big gaps in knowledge

The extent of what is known about radioactive fallout was examined by Dr Willard F. Libby, commissioner of the United States Atomic Energy Commission, in an able address to the American Physical Society on April 26, and we reported some of his remarks last week [1] By the data at his command, he is convinced that the risk to the health of the world's population from nuclear testing at the present rate is small As Dr Libby pointed out, there is good reason to believe that most of the spontaneous mutations of the human species are not due to radiation but to other causes For this and other reasons, therefore, the genetic effects of irradiation of the gonads by radioactive fallout from tests so far carried out is likely to be very small The Medical Research Council committee [2] put the population dose to the gonads from fallout at less than 1% of the natural background radiation (The alarming figure they gave for the addition made by diagnostic radiology was at least 22%) But, though the gonad dose from fallout is at present small, therefore compared with some other sources, there is no escaping the fact that any additional exposure, from whatever source, must be expected to raise the mutation rate and the effect of radiation to which the whole population is exposed, such as that from fallout, is likely to be a particularly telling addition The genetic risk of past and future nuclear explosions has certainly been exaggerated in some quarters, but it seems far wiser to exaggerate than underestimate, as Lord Cherwell does when he says that "even the most cautious experts agree that the effect of adding an extra 100% or 200% to the natural background dose would be negligible The M R C committee, on whose findings Lord Cherwell puts we think, too optimistic an interpretation said

> "… we feel bound to state our opinion that it is unlikely that any authoritative recommendation will name a figure for permissible radiation dose to the whole population, additional to that received from the natural background, which is more than twice that of the general value for natural background radiation The recommended value may, indeed, be appreciably lower than this"

In coming to the conclusion that strontium 90 in bone had not reached, and was unlikely soon to reach, anything like a dangerous level, Dr Libby based much of his argument on a comparison between cosmic rays and the radiation from strontium 90, which has a radioactive daughter, yttrium 90, emitting energetic β rays The ionisation density along the track of these rays is very similar to that generated by the mu-mesons of cosmic rays and their disintegration electrons But, though it is widely believed that radiations of the same ionisation density have very similar biological effects for the same energy absorbed, it is not yet certain that the effects of an external radiation like cosmic rays are a valid standard for assessing what a radioactive substance fixed in the body can do Moreover a comparison between leukæmia and bone-cancer statistics in people exposed to different doses of cosmic radiation, because of the altitudes at which they live, may not be as reassuring as Dr Libby believes Only vital statistics for large populations living at high altitudes would be fully convincing on this point To argue from the effects of cosmic rays that it is safe to go on releasing strontium 90 may be fallacious it would perhaps be wiser to rely on a study of the action of strontium 90 in animals, and here the findings so far reported are much less comforting in their implications for man

Disquiet about strontium 90 in bone springs largely from the uncertainty about the existence of a threshold concentration below which there is no risk of leukæmia or tumour formation In an appendix to the M R C report, Mayneord and Mitchell referred to the lack of information about the action of very small doses and to the animal experiments that had led some investigators to postulate a threshold level They added

> "It appears however that each unit quantity of radiostrontium absorbed by the bone confers a certain probability of bone tumour formation, the tumour development time perhaps decreasing and the tumour incidence increasing with the dose On the whole, the experiments seem in favour of a proportionality between the frequency of tumours produced in a given length of time and the amount of radioactive material in the body even at low dose levels"

If there is no threshold, the body burden of 1 microcurie laid down by the International Commission on Radiological Protection as "permissible" for those exposed to strontium 90 in their work may be too high, and the burden of 0 1 microcurie now held to be acceptable for the general population, with its proportion of young children, may be similarly misleading

On the assumption that a proportional relationship between strontium-90 content of bone and tumour formation applies to very small doses, the Atomic Scientists' Association estimated that a hydrogen bomb of Bikini type, exploded high up, may eventually produce bone cancers in 1000 people for every million tons of T N T of equivalent explosive power The cautious statement [3] of the association's committee emphasised that the no threshold hypothesis was the most pessimistic view, but if it is correct the committee's figures may be an underestimate, since they did not allow for the radiation dose in children before or after birth To dismiss as brusquely as Lord Cherwell does the views of Professor Rotblat's committee is to accept a grim responsibility

A linear relationship between exposure to radiation and subsequent damage was suggested by a study of leukæmia in patients with ankylosing spondylitis treated by irradiation Some other relationship may ultimately prove to be the correct one; but in another appendix to the M.R.C. report Court Brown and Doll said that there was no evidence of a threshold below which no increase in leukæmia was produced. On the other hand, as Loutit[4] has observed, there are reasons why leukæmia should not be taken as a model for all radiation-induced malignancies, and what little quantitative evidence there is of the carcinogenic properties of radiostrontium suggests that the relationship is not linear and that there is some form of threshold or effective latent period. Much is still dangerously uncertain, and the correct conclusion, as Loutit puts it, "in the present state of scientific knowledge is that a linear relationship sets the limit and indicates the worst possible conditions, so that it would be prudent to go easy until the real facts are ascertained." It is against the Government's apparent reluctance to do all they can to "go easy" by pressing for an early agreement on the limitation or abolition of nuclear explosions that we protest.

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[1] *Lancet* May 11 1957 p 9[illegible]

[2] Hazards to Man of Nuclear and Allied Radiations Cmd 9780 H M Stationery Office See *Lancet* 1956 i 999

[3] *Lancet* April 27 1957 p 878

LONDON TROPICAL MEDICINE

IN medicine, 1899 was a very long time ago; and in his fascinating account of the first fifty years of the School of Tropical Medicine in London Sir Philip Manson-Bahr[5] shows incidentally how much the world has been changed by that originally modest enterprise.

At the end of the 19th century, Britain had a vast tropical empire, in many parts of which the death-rates were appallingly high. The doctors sent to the Colonies were often ill equipped even to use what knowledge our profession then possessed of tropical diseases; and Patrick Manson, returning to England after twenty-three years in the East, saw that his most important task was to promote a school for teaching and research. Appointed medical officer to the Colonial Office in 1897, he enlisted the support of Joseph Chamberlain (his Secretary of State), as well as of the General Medical Council; and two years later the London School of Tropical Medicine, associated with the Albert Dock Hospital, was opened with 28 students. (The Liverpool school had begun work six months before.)

At first most of the students were sent by the Colonial Office, but many came from missionary societies, the Forces, and other organisations, and in 1912 the school was much enlarged. The Dockland site had advantages in that the students were secluded from the London whirl, but after the first world war a move was made to central London, where a hotel in Endsleigh Gardens became the combined school and hospital under one roof. Then in 1925 the school was merged in the London School of Hygiene and Tropical Medicine, and in 1929 the fine new buildings in Gower Street were opened. Two years later it became part of the University of London, and soon afterwards it incorporated the Ross Institute and took over the malaria laboratory at Horton Hospital, Epsom. The Hospital for Tropical Diseases remained at Endsleigh Gardens until it was closed at the outbreak of the second world war, after which teaching continued in the Dreadnought and other hospitals, and from 1944 in a former nursing home in Devonshire Street. With the passing of the National Health Service Act the decision was taken not to build the new hospital for which many of us hoped; and instead a section of St. Pancras Hospital became in 1949 the clinical centre of the school, under the board of governors of University College Hospital. With the end of the fifty years this book closes.

Sir Philip was for a decade director of the clinical division of the school; and his very large acquaintance will find in his history the qualities they could expect—the knowledge, the zest, the humour, and the humanity that bring such stories to life—not to mention the miscellaneous pictures. The official facts are all there; but so are the people who made the facts and whom they merely reflect. Perhaps nobody but this author could (or would) have attempted to provide biographies of a hundred of these people—doctors, scientists, and technicians—some of them long since part of medical history but others still working at the school. Even the reader who looks at nothing but these biographies will get some idea of the achievement of London tropical medicine through its exciting expeditions and its exciting discoveries, still happily continuing.

Sir Philip likens the school to an insect which has passed through the egg, larval, and pupal stages, to blossom forth as a full fledged imago. But it performed great feats even in the earthbound or submarine stages of this analogy, and who can say where it may soar on wings?

RADIOGRAPHERS IN THE N.H.S.

USEFUL though arbitration can be in settling a disputed issue, the arbitrator does not necessarily take a long view; and in the National Health Service the use of arbitration does not in any way absolve the Ministry of Health of its responsibility for seeing that the service is properly maintained. If the Ministry is inclined to think that further attention to the shortage of radiographers is unnecessary because they had an award last November from the Industrial Court, we hope it will look again at the facts of a disturbing situation.

We need not recapitulate the criticisms of the award which have been made at length in our correspondence columns. Nor need we reproduce all the arguments lately set out in the Society of Radiographers' dignified statement to the press.[1] For the moment we are concerned chiefly with the evidence that despite, or because of, the award the radiographic services of the N.H.S. are deteriorating and will continue to do so. A reduction in the number of radiographers and the amount of work they do might be intelligible as part of a deliberate policy, fully discussed with the Central Health Services Council before it was adopted; but it is wholly unacceptable if it arises merely from the Government's antiquated conviction that in public services people need not be paid the kind of salaries they could earn outside.

The Society of Radiographers says[1] that whereas the Ministry last November estimated the general shortage at about 20% *it is now nearer 25%*. Some local shortages are so acute that departments have already restricted their services—the latest example being a warning that "the X-ray departments in the Lewisham Hospital Group will soon be manned by a 'skeleton staff.'"[2] In some places departments have been kept open only by radiographers working at a pressure which neither can nor should be continued for long periods. That in time of difficulty virtue should be its own reward is in keeping with the medical tradition; but, when one expects people to be ready to make whatever personal sacrifices are required to keep an institution running, one cannot also expect them to accept, permanently, a lower rate of pay than their skill and quality should command. The Society of Radiographers, pointing out that its own problems are closely related to similar ones in other parts of the N.H.S., puts its case fairly and with restraint:

> "The National Health Service is a social experiment of wide scope: those who are involved in it expected stresses and strains during its formative years and were prepared to make sacrifices to overcome them. But the society is sure that the general public, who use the service, would not wish these conditions to be regarded as other than temporary maladjustments and that they would not wish them to persist at the risk of a serious handicap on the service as a whole."

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[4] Loutit, J. F. *Brit. med. J.* April 20, 1957, p. 944.

[5] *History of the School of Tropical Medicine in London 1899–1949.* By Sir PHILIP MANSON-BAHR, F.R.C.P. Memoir no. 11 of the London School of Hygiene and Tropical Medicine. London: H. K. Lewis. 1956. Pp. 329. 50s.

[1] Present Shortage of Radiographers: its Content, Causes and Possible Results. Memorandum from the Society of Radiographers, 32, Welbeck Street, London, W.1.

[2] *Evening Standard*, April 29, 1957.

Special Articles

THE MAGNITUDE AND COST OF MENTAL ILLNESS IN THE COMMUNITY*

Sir Frederick Armer
KBE, CB, MC
CHAIRMAN, BOARD OF CONTROL, MINISTRY OF HEALTH

The public are beginning to take an interest in the mental health problem, but they do not realise what a transformation has taken place in mental hospitals during recent years. People are beginning to lose their fear of the mental hospital, and voluntary patients are flocking to the hospitals. I have been in the Ministry of Health for thirty seven years and I have visited a good many hospitals. A visit to a mental hospital in the 1920s was a depressing experience. Most of the hospitals were drab in the extreme and the patients were sullen and often violent, regarding the nurses as gaolers. They had the atmosphere of the old poor law institutions which, indeed, in many respects they were. But if you go into our *mental hospitals today you will find*, with some exceptions, that the places have been brightened up with light paint and a good deal of imagination, and that good relations exist between patients and staff. Before the war it was common in the wards of mental hospitals for visitors to have things thrown at them; patients are now more amenable, because of a better understanding of their needs, the expansion of the open door principle, and, not least, the use of drugs which research has placed at the disposal of the hospitals. Brighter as the picture is, the hospitals are working under heavy pressure and overcrowding.

VOLUNTARY AND CERTIFIED

In speaking of the growing use of our mental hospitals by voluntary patients we are apt to talk of percentages. We say that about 75% of the patients now entering the hospitals do so voluntarily. This is true, but it does not convey to the ordinary man what is really happening. In fact, it might lead him to think that of every four patients entering mental hospitals three who otherwise would have been certified now go in as volunteers. This is not the picture at all. The number of patients entering our hospitals as certified patients is not decreasing; in fact, it has risen during the past few years and now stands at between 18 000 and 19,000 a year. It is the number of voluntary patients that is going up by leaps and bounds; it has more than doubled in the past ten years, from 27,000 in 1947 to 60 000 last year. I think there are three reasons why this large increase in the number of voluntary patients has not yet been reflected in a reduction in the number of certified patients. One reason is the increase in the number of certified old people—it is not always possible to secure treatment for them without certification. The second is that many of the voluntary patients are receiving treatment at an early stage and would not have become sufficiently ill to be certifiable for a number of years. But the main reason is that large numbers of the voluntary patients although mentally ill and needing treatment would never have become sufficiently ill to be certifiable. This means that our mental hospitals are making an impact on that vast amount of non-certifiable mental illness that [illegible] exists in the community.

With all this quick turnover of voluntary patients there remains the hard core of the more [illegible] patients. Their number has remained [illegible] constant [illegible] the years at about [illegible]. [illegible] in spite of advances [illegible] mental hospitals [illegible] more than a year and nearly 50% more than ten years. In other words 60,000 patients have been in mental hospitals for more than ten years.

Their only hope is in research. For example, schizophrenia is a mystery but it fills a third of the 150,000 occupied mental hospital beds in this country.

THE COST

You may ask why should laymen be interested in what might be regarded as a medical problem? Apart from the humanitarian aspect, there is a serious economic aspect which must be of concern to us all. Mental illness and mental deficiency cases occupy nearly half the hospital beds in this country, and the cost for treatment, ascertainment, care, and aftercare is about £60–70 million per year chargeable to public funds. And we know that in the community at large between a quarter and a third of all absence from work due to sickness is on account of mental and neurotic illness. That does not tell us much until we begin to look at the figures. It means that 80 million days of work are lost every year through mental and neurotic illness involving a loss of some £120 million per year in wages and, of course, a large loss of production. In addition, about £20 million a year is paid out of sickness benefit funds to these sufferers. This is a very serious economic problem and we are bound to ask ourselves: "Is it inevitable that there should be all this mental illness in the community at large? What are the means of preventing it? Is it inevitable that 60,000 patients should have to spend more than ten years in mental hospitals, and is it inevitable that mental illness is a concomitant of old age?" *Research* is the only answer to these questions.

VOLUNTARY EFFORT

You may ask—people do ask—why is it necessary for a voluntary fund to be raised for this research; why does not the Government provide the money and carry it out? The Medical Research Council do in fact spend a considerable amount on research into mental illness and mental deficiency, but it is difficult for the Government to provide out of taxes enough money to meet all the many demands on them, and voluntary funds are an invaluable help.

It is more than a question of money. A voluntary body with funds at its disposal can do things which a Government department cannot do. It can inspire enthusiasm and create a crusading spirit which no Government department is equipped to do. And in this field a crusading spirit is very necessary.

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* From an address [illegible] general meeting of the Mental Health Research Fund on [illegible] 1957.

WORLD HEALTH ORGANISATION

The tenth World Health Assembly was opened in Geneva on May 7 by Prof. J. Parisot, the outgoing president, who declared that more importance [illegible] given to industrial development than to systematic research into measures to ensure the safety of the worker." He emphasised the special possible dangers of trials of atomic weapons. Dr. S. H. Al Wahbi (Iraq) was elected president, and in his address he welcomed the delegates from Ghana and from four countries which have resumed active membership.

Dr. M. G. Candau, the Director-General, claimed that eradication was the only possible solution of the malaria problem, and it was the most economical one. Dr. John E. Fogarty, a member of the United States Congress, said that his government had invited the World Health Assembly to meet next year in the United States. [illegible] Mudaliar (India) proposed that the Assembly should appeal to all governments to stop atomic bomb tests. He was supported by [illegible] [illegible] the People's Republic of [illegible] member of W.H.O. [illegible]

[illegible]

Before Our Time

THE CRISIS OF 1911-13

Lloyd George and the Doctors

SIR JOHN CONYBEARE

K B E, M C, M A, D M Oxfd, F R C P

THE present dispute with the Government makes it interesting and perhaps not unprofitable to recall what was perhaps the biggest and the most critical fight which has ever taken place between a Government and the medical profession This followed the introduction of the National Insurance Bill by Mr Lloyd George on May 4, 1911, and lasted with increasing bitterness until the British Medical Association withdrew its opposition

It must be borne in mind that the B M A 's opposition to the National Insurance Bill was not over remuneration alone It also involved such questions as payment by capitation fee, freedom of choice of doctor, contract practice, and control of the medical service by laymen A brief digression on the conditions of medical practice in the earlier years of the 19th century may help to explain the background of the struggle

Conditions of Medical Practice

In 1912 the total number of practitioners on the Medical Register was 41,053 Of these approximately 9000 were abroad or in the Services Of the other 32,000, probably well over 20,000 were in general practice, working single handed or in partnership The remaining 12,000 doctors included consultants and specialists (far fewer than they are today), those holding junior appointments in hospitals (voluntary or municipal), those engaged in public health or teaching posts, and the retired In addition, however, to the above, there were many who spent long years as assistants to the owners of general practices, particularly those in industrial areas Not infrequently the assistant resided above the surgery, sometimes in rather poor quarters, doing the night work, while his principal had his home in a residential district, often some miles from the practice Salaries of assistants were low Practices were bought and sold, and in normal circumstances, especially in industrial areas, the purchaser could be reasonably sure of retaining most of the patients Payments received from the sale of practices were of course regarded by the Inland Revenue as capital and not income—an important feature after 1914 when income tax had become burdensome

Before the National Insurance Act many practitioners in industrial areas held appointments with friendly societies and undertook the medical care of members on a capitation-fee basis This usually included both medical attention and drugs The annual capitation fee, according to a statement by the medical secretary of the B M A, was sometimes as low as 2*s* 6*d*, though the average was about 4*s* It was estimated that contract practice in all its forms provided for more than half the working population of the country Although currency has depreciated since 1914, there can be little doubt that doctors in working-class areas were grossly underpaid, and that the conditions under which they had to work resulted in what on the whole was inadequate service to the patient Moreover the friendly societies exercised considerably too much control over the doctors whom they paid so poorly It is not surprising, therefore, that when the National Insurance Bill appeared on the horizon it met a hot reception from the medical fraternity, so many of whom had for years had every reason for dissatisfaction at the prospect of a big increase in contract practice

Medical Aspects of the Bill

The National Insurance Bill introduced compulsory insurance under a contributory scheme for all manual workers and all other employed persons with incomes below £160 a year The benefits included, insurance against sickness and unemployment and the Bill also provided free medical attention The value of the Bill as a far-reaching measure of social reform was acknowledged on all sides, but from the beginning the B M A, which represented a majority of practitioners, criticised the terms, both financial and administrative, under which medical care of the insured was to be provided Nor did the B M A waste any time in formulating their demands On May 31, 1911, the main heads of policy were approved unanimously by a Special Representative Meeting These formed the basis of the "six cardinal points," which became the minimum demands of the B M A

In slightly condensed form, these were

1 Income limit of £2 a week for those entitled to medical benefit

2 Free choice of doctor

3 Medical benefits not to be administered by friendly societies

4 Method of remuneration to be according to the preference of the majority of doctors in each district

5 Amount of remuneration to be what the profession considers adequate

6 Demand for adequate medical representation on all committees

Mr Lloyd George attended a B M A Representative Meeting He spoke in a conciliatory vein and replied to many questions put to him by the chairman The point on which the Chancellor was most emphatic was that of the income limit of £2 a week This demand by the association would in his opinion be vetoed by all parties in the House of Commons As regards method of remuneration he felt that payments for individual attendances, however attractive in theory, would not be practicable In general he was in favour of free choice of doctor and thought that medical benefits should be administered by health committees and not by friendly societies

From a very early stage it was clear that, although the Bill would lead to a great increase in contract practice with capitation fees, the chief objections were financial The *British Medical Journal* of May 13, 1911 (only nine days after the introduction of the Bill) emphasises this

> "In considering the position with which the profession now finds itself confronted, it is, perhaps, unfortunate, but certainly inevitable, that the question of remuneration must bulk large"

Over and over again the limitation of medical benefits to those with incomes of £2 a week or below is stated as a sine qua non if the medical profession is to accept service under the Act Nor is there any concealment of the motives Practitioners felt that capitation fees for patients earning £2–3 a week would not compensate them for the loss of private fees from this group Living in 1957, it is only fair to bear in mind that a weekly wage of £2 in pre 1914 days was by no means rock bottom Indeed many earned far less Thus in the early years of the century agricultural labourers and many others were judged fortunate if they were paid even £1 a week

Meeting followed meeting, nor were they attended by general practitioners alone On June 1, 1911, a mass meeting of members of the profession was held at the Connaught Rooms in London On the platform were the presidents of the Royal Colleges (Sir Thomas Barlow and Mr H T Butlin) and other famous consultants including Sir Victor Horsley and Sir William Church Sir Thomas Barlow was out of touch with the spirit of the meeting but Mr Butlin was cheered to the echo when he recounted an experience of his own when he had operated on a Jewish woman in the East End of London

He told the meeting that, although the patient's husband and family belonged to a club paying one penny a week each for their doctoring, there had been no difficulty in paying his fee of 100 guineas for the operation, besides the nursing-home expenses Mr Butlin and his audience were well satisfied that no person with an income of over £100 a year should be allowed to participate in the medical benefits of the Bill

Other speakers were even more emphatic Dr Tonkin (Fulham) thought the income limit should be £70 and not £100, while vociferous cheering greeted a peroration by a Dr Townsend "if we have to go under, we would go under fighting and would not be starved out"

As enthusiasm waxed at successive B M A meetings, new demands were formulated in addition to the six cardinal points—special fees for night calls and emergencies, payment for illnesses caused by misconduct, anæsthetic fees, and mileage payments Wigan went the whole hog and adopted a resolution "that all clauses of the Bill which relate to medical attendance are bad, and should be deleted from the measure"

By July, 1911, the B M A had made good progress in circularising not only their own members but all doctors, enclosing a form of undertaking which the recipients were asked to sign and return In this somewhat verbose document they undertook not to give any service under the Bill except by permission of the B M A They were also asked to sign a Memorial to the Government and Parliament In the same circular the medical secretary of the B M A, Mr J Smith Whitaker, of whom more anon, appealed for donations to Defence Funds, both central and local Although the response to the Undertaking was good—ultimately 27,000 out of some 40,000 on the register—the Defence Fund was less satisfactory in spite of repeated demands throughout the campaign, only 13,000 subscribed The total subscribed or guaranteed was quite insufficient to be of any value for its purpose of financing doctors who lost money by their refusal to accept service under the Bill

The Insurance Bill and Voluntary Hospitals

By mid-1911 members of the B M A were beginning to turn their attention to voluntary hospitals and their staff The Ashton-under-Lyne division unanimously "Viewed with disfavour the apathy displayed by the medical faculties of many universities and teaching schools" Cardiff went one better and suggested that all the honorary staffs of hospitals insist on payment for treatment of insured persons A little later, a letter from Mr W F Brook, F R C S, in the *British Medical Journal* estimated that if all honorary staff insisted on payment they would receive some £16 million annually Mr Brook was confident that this sum would be forthwith donated to the B M A Defence Fund Mr Chas Wray, F R C S, was in favour of calling out all the honorary staff and students in the Kingdom unless the Government gave in

The voluntary hospitals were disturbed at the prospect of a loss of income from subscriptions by the public if the Bill became law, and there was some discussion regarding charges to insured persons, but no serious attempt seems to have been made to bring treatment in hospital into the medical benefits under the Bill

Trouble in the B M A

On Nov 30, 1911, Mr Asquith as Prime Minister invited the medical secretary of the B M A, Mr J Smith Whitaker, to become deputy chairman of the Insurance Commissioners Mr Smith Whitaker, whatever his private views may have been, had in his capacity as medical secretary been the chief executive organiser of the B M A.'s opposition to the Bill Before replying to the Prime Minister's invitation he placed the decision in the hands of the council of the B M A After a long discussion the council by 38 votes to 3 advised acceptance of the post on the ground that it would be of great advantage to the profession to have in the important position of vice chairman a medical man who understood, and was sympathetic to, the attitude and aims of the B M A

It did not take long for the storm to break Within a few days of the news of the appointment, meetings of B M A branches and divisions were passing resolutions condemning the action of the council Dr F J Smith, physician to the London Hospital, wrote to the *Times* a letter headed "The Great Betrayal," in which it was clear that open warfare was developing between the B M A and many of its members who were anxious for more drastic action The official policy of the B M A was not to refuse to work the Bill on *any* terms, as desired by the extremists, but to demand our *own* terms

At Manchester on Dec 14, 1911, the insurgents held a meeting to establish a National Medical Union, the object of which was organised refusal of service under the Bill The policy of the B M A was denounced as "negotiate and procrastinate" Wild scenes of disorder occurred and speakers, including Sir James Barr, who tried to defend the council's action, were howled down A similar meeting of rebels was held in Birmingham, but the largest and most highly emotional meeting was held at the Queen's Hall in London on Dec 19 The hall and galleries were packed long before the meeting started Stirring music was played on the great organ and as the chairman, Sir Watson Cheyne, came on the platform to the strains of *Rule Britannia* the audience rose and sung lustily The platform party included Sir William Osler, Dr F J Smith, and many other consultants The audience was emotionally labile—roars of applause, shouts of "No, No," "Never," cheers and groans Sir Victor Horsley had a particularly hot reception Amid shouts of "traitor," "Did Lloyd George send you?" he was refused a hearing Sir William Osler took a poor view of the behaviour of the audience and wrote to the *British Medical Journal* to that effect

The organisers of the Queen's Hall meeting followed it up by founding the B M A Reform Committee, the object of which was to 'ginger up" the B M A and to "end or mend" the council

Meetings followed one another at a great speed The South Western branch of the B M A held one at which no less than 38 resolutions, amendments, and riders were proposed and often voted upon The B M A Reform Committee opened an office in London and called for funds, their object now being to get counsel to draft an amending Bill Doctors in Poplar pressed a Poplar Medical Union to look after their local professional interests A meeting of Socialist doctors was in favour of a properly organised State Medical Service, but regarded the National Insurance Bill as the next best thing for the time being

Since Dec 16 when the Bill had become law it seems that some of the less belligerent were beginning to wonder whether the profession was really likely to defeat the Government Thus a well attended meeting of the Hampstead division by a small majority failed to demand the resignation of the council or to refuse to work under the Act The Sunderland division also supported the B M A as against rebellious organisations, as did the South Midland branch On the other hand the rebels were still active, and the B M A Reform Committee outbid the six cardinal points of the B M A with a programme of eight points

Mr Lloyd George was not slow to respond to the attacks launched by the profession On Feb 12, 1912, in the London Opera House he addressed a primarily Liberal audience His attitude towards the doctors and the B M A was more conciliatory than that of his audience, to judge by interjections, such as "Hang the doctors" He did, however, point out that in the event of the doctors boycotting the Act, the Government had large "suspensory powers" and would be obliged to hand over the funds for medical benefits to the friendly societies, who would then be free to bargain with the doctors individually—bargaining in which the doctor would be likely to come off worst

On Feb 20, 1912, a Special Representative Meeting of the B M A was held in Guildhall, London The first business was a motion that the chairman, Dr Maclean, be asked to resign the chair After a very long discussion —more in sorrow than in anger, as far as Dr Maclean's critics were concerned—a card vote supported Dr Maclean by 78 to 63 Furthermore a proposal that the council should be instructed at once to cease negotiations with the Government and the Insurance Commissioners was defeated What amounted to a vote of censure on the council was not carried Evidently representatives were beginning to be exhausted by the length of the meeting, for Dr Helme, an advocate of drastic action, alluded to "empty benches"

Meanwhile there was increasing disquiet about the Defence Funds or rather the inadequate response to appeals This is reflected in correspondence in the *British Medical Journal*, where the fund is sometimes—perhaps rather unfortunately—referred to as a "strike fund" The B M A circularised branches and divisions asking for guarantees and subscriptions, but without it seems much success

By mid 1912 the appointed day for the inauguration of the medical benefits section of the Act was only six months off If, as seemed probable, the Government were not going to give way, and the medical men stood by their pledges not to accept service under the Act, it was essential for the profession to have plans for the future In June, 1912, the State Sickness Insurance Committee of the B M A produced two alternative schemes for a Public Medical Service The main difference between the two schemes was that one was based upon a capitation system of payment, while in the other there was to be payment per attendance Both schemes were to work on a regional basis and were to be entirely under the control of the medical practitioners in the area The fees—a few pence weekly—were to be collected by collectors on a salary and not a commission basis Later two further alternative schemes were produced, but it is unnecessary to go into details, for all turned out to be castles in the air

Eclipse of the Moderates

The continued pressure of members holding extremist views, and the formation of what were almost rival bodies, such as the National Medical Union, encouraged the B M A to adopt a more determined attitude The *British Medical Journal* of June 22, 1912, warns members that they must not accept appointments on provisional insurance committees formed under the Act, nor even accept medical appointments in the sanatoria under the Act

Attempts were made to bring pressure on consultants and practitioners The latter were urged to employ only those consultants who had signed the pledge Every doctor was pressed to refuse to employ as a locum-tenens or an assistant anyone who had not signed Honorary staffs of hospitals were told to limit appointments as house officers and registrars to those who had signified their adhesion to the policy of the association Moreover the original undertaking, signed in 1911 by some 27,000 practitioners, was judged to be not wide enough, and a new pledge was circulated for signature This so called "pledge complementary to the undertaking" bound its signatories to place in the hands of provisional medical committees their resignations from every form of contract-practice appointment These resignations would be handed in when the State Sickness Insurance Committee judged the time to be ripe

The much-abused council having learnt from the Smith Whitaker episode the danger of making decisions submitted to the divisions and Representative Body alternative sets of recommendations

1 Breaking off negotiations
2 Continuing negotiations

At the Annual Representative Meeting held on July 19, 1912, there was long discussion of these alternative policies put forward by council, and with some minor qualifications it was decided to break off negotiations

One suggestion made, which indicates the strength of feeling among representatives, was that the General Medical Council should be approached with a view to their dealing with "blacklegs" as guilty of infamous conduct It was also proposed that the names of those members of honorary staffs of hospitals who had not signed the supplementary pledge should be circulated to secretaries of divisions Fears of actions for libel negatived this suggestion

The Last Three Months

The turn of the tide may be said to have come on Oct 23, 1912, when Mr Lloyd George addressed a conference of the Advisory Committee In an able and conciliatory speech he reviewed the types of medical practice among the industrial classes He felt that in many cases contract practice was underpaid and announced that, largely as the result of advice from the eminent medical men on the Advisory Committee, the Government had decided to increase the remuneration The suggested rate of 6*s* including drugs was raised to 9*s* for each insured person Of this 9*s* the sum of 1*s* 6*d* would be for drugs and 6*d* as a reserve to cover cost of drugs, if these exceeded 1*s* 6*d* If, however, this sum was not exceeded, the extra 6*d* went to the doctors

Although the Chancellor's offer did not come up to the demands of the B M A—i e, 8*s* 6*d* per insured person per annum, exclusive of drugs, it was a great advance on the rates paid by friendly societies for contract practice and clearly went a long way towards placating practitioners in the industrial areas

It was soon apparent that a more conciliatory attitude was developing A large private meeting of practitioners held in London on Nov 5, 1912, urged negotiation The correspondence pages of the *British Medical Journal* included many letters counselling negotiation and acceptance of the Government terms

The B M A extremists, and even more the rebels such as the National Medical Union, failed to see the red light At a special Representative Meeting in London on Nov 19, 1912, a motion to refuse to work the Act was carried by an overriding majority, but it was decided to appoint five members to interview the Chancellor These five were to report to the State Sickness Insurance Committee, who were to report to the B M A council who in turn, if necessary, were to refer questions at issue to the divisions of the B M A This lengthy procedure seems to bear out Mr Lloyd George's complaint that negotiation with the doctors was difficult if not impossible because no one body or committee was ever given power to bargain or negotiate

The interview between Mr Lloyd George and the five selected members of the B M A bore no fruit, and the council put the following question to divisions

> "*Are you in favour of the Association* calling upon the profession to refuse to enter into any agreement with local Insurance Committees to give service under *the Act* upon the terms and conditions now finally offered by *the Government* ?"

The council asked that returns from all divisions should be delivered to the central office by Dec 16, 1912 The results of the voting, published in the *British Medical Journal* on Dec 21, 1912, were

For refusal to serve	11,219
Against refusal to serve	2408

The total number of doctors who voted, including both members and non-members of the B M A, was 13,627 The number who had signed the B M A undertaking and pledge was 27,400 This suggests that half of those who had signed pledges abstained from voting

Meanwhile schism was spreading An organisation known as the National Insurance Practitioner's Association met in London on Dec 13, 1912, with Dr Lauriston Shaw in the chair It was attended by some 300 to 400 doctors The object of the association was to protect the interests of doctors who desired to accept service under the Act

A Special Representative Meeting on Dec 21, 1912, offered scope for fighting speeches on both sides, but the meeting voted in favour of refusing service under the Act by 182 to 21 amid loud and prolonged applause

The appointed day was now only three weeks off The Christmas truce was barely over when, on Jan 2, 1913, Mr Lloyd George announced that already nearly 10,000 doctors had joined the panels In districts where there was a shortage, he said, it might be necessary to close the panels temporarily and install a salaried service Fortunately these drastic measures never became necessary, as more and more doctors placed themselves on the panel

The die-hards still had a last fling On Jan 7, 1913, the London Medical Committee organised a protest meeting at the Queen's Hall with a former Lord Mayor, Sir Thomas Crosby, in the chair, supported by many well known consultants After patriotic music on the organ, Dr E B Turner and others denounced the Act and particularly Mr Lloyd George, who was likened to a "malign comet with a daily lengthening tail of inconsistent statements, repudiated utterances and promises unfulfilled"

The end was now in sight In all areas doctors hastened to join the panels, and in a debate in the House of Commons on Jan 7, 1913, Mr Lloyd George announced that 15,000 doctors had accepted service under the Act

The final scene was enacted at the Special Representative Meeting on Jan 18, 1913, when a motion to release all practitioners from their pledges and undertakings and was passed by 115 to 35 divisions In actual fact a majority of those concerned had already released themselves

It is interesting to speculate whether more favourable terms might have been obtained had the B M A taken up a less dictatorial attitude There is little doubt that the Chancellor handled the problem with consummate skill The appointment of the Medical Secretary, Mr Smith Whitaker, as deputy chairman of the commissioners split the B M A into two factions, the unexpected raising of the capitation fee pacified many of the moderates, and a few threats at the end rapidly filled the panels

The aphorism that history repeats itself is far from being always true The circumstances of every problem or dispute must necessarily differ widely, depending on the personality of the actors, the attitude of the spectators and the period in which the stage is set But the circumstances of the present dispute have some points in common with those of the days of the National Insurance Act of 1911 In each the public and the press were and are on the whole critical of the standpoint of the doctors The proportion of the profession engaged in general practice is considerably lower than in 1911, being probably not much over 25% The number of those looking for opportunities to get into general practices is large and many of these have spent long and sometimes depressing periods as assistants and trainee assistants Perhaps, however, the most striking difference between 1911 and today is that Mr Lloyd George was offering members of the medical profession entry into a new service, whereas in 1957 they are being asked by the B M A to consider resigning from an established, paid, and pensionable service

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Conference

HUMANE TECHNIQUE IN THE LABORATORY

If we decide that experiments should be performed on living animals, it is our duty to ensure that their suffering is the least possible At a symposium held in London on May 8 by the Universities Federation for Animal Welfare (UFAW) with Prof P B MEDAWAR, F.R S, in the chair, the theme was that suffering could be reduced, and the value of experiments simultaneously increased, by *replacement* of animals by other systems, by *reduction* in the numbers used, and by *refinements* in technique

Major C W HUME, the secretary-general, opened the proceedings with a comparison of the warm-blooded and cold-blooded aspects of war and of experiment Thus the general might consider his soldiers, and the scientist his animals, as units or as individuals To neglect the warm blooded aspects was not only callous but incompetent, he pointed out that the soldier who is not cared for may fight less well, and he quoted Starling as saying that many experimental results were vitiated because the physiological effects of pain had not been eliminated

Dr W LANE-PETTER said that now about $2^1/_2$ million laboratory animals were used in this country each year, and the number was increasing by nearly 8% annually; we must plan for future needs He thought that bad husbandry was responsible for many losses—an interpretation which was criticised in the discussion Miss PHYLLIS CROFT, PH D, said that a humane technique involved asking such questions as "Is the experiment necessary? Has similar work been done before? Is the technique appropriate? Are the numbers and method such that most knowledge will be gained from the fewest animals? Can animals be replaced?" She drew attention to the importance of properly trained technicians, and to unnecessary suffering caused by, for example, delayed euthanasia and inappropriate housing conditions (e g, cats and mice in cages in the same room) The pulse-rate and electrical resistance of the skin could be used as a measure of pain suffered by animals Answering a question, Dr CROFT said that the definition of a necessary experiment must be left to the integrity of the experimenter The chairman suggested that an experiment prefaced by "I wonder what would happen if ?" is usually not necessary Mr W M S RUSSELL, D PHIL, pointed out that the experimental animal was usually a model for the human It was irrational to suppose that the animal nearest to the human was therefore the most appropriate, for certain other (e g, electronic or bacterial) models might eliminate variables A general theory was needed to decide where and how replacement of animals, especially mammals, was indicated

The next three speakers described ways of replacing animals Mr G SYKES said that, for assay of B vitamins and amino acids, microbes were often more sensitive and convenient than mammals He spoke at length on these techniques Mr F. K SANDERS, *D PHIL*, spoke as a virologist Animal tissues (egg and tissue cultures) could be used for growing viruses, they had not the disadvantages of antibody formation or the presence of latent viruses In tissue cultures, moreover, cytopathogenic effects were sometimes specific Contamination could be satisfactorily suppressed by addition of penicillin, streptomycin, and nystatin, and tissue-cultures could now be bought commercially He described an ingenious method of counting viruses using a tissue culture in a plate and vital staining, so that dead groups of cells (i e, those infected by virus) showed up as pale spots He pointed out that one animal, painlessly killed, could provide 20 plates of cells, and 4000 units of information of greater precision than would be possible using 4000 animals Mr W Grey Walter, Sc D, spoke of the "artificial zoology" thriving in many centres in Europe and America He gave a brief, stimulating, and lively account of his models of segments of nerve, of "*Machina speculatrix*," with its two reflexes, and of Cora, the conditioned-reflex analogue, which can behave neurotically His electronic "animals" and preparations were useful for investigation and especially for teaching When they broke, he said, they did so with a loud clear bang

The conference then turned to means of reducing the number of animals used Major Hume explained the fallacy of assuming that using a large number of animals always gave a truer picture it might introduce error by including a more heterogeneous population Statistical methods would give more reliable results and allow the use of fewer animals He said that wide difference in the responses of patients would swamp small inaccuracies in the assay Dr Lane Petter discussed the genetic foundations for producing animals as nearly uniform as possible, and Mr M R A Chance, Ph D, described the profound effects on the physiology of rats of minor environmental changes, such as altering the number in a cage The conditions making for uniformity were those in which the rats were happiest In the discussion, it was pointed out that the law required high accuracy in bio-assay, even though variations in clinical response often made such accuracy unimportant in practice

The final section of the conference was devoted to humane refinements in technique Dr Chance insisted that the environmental conditions, the response, and the units in which they are mentioned must all be specified, or the work could not be repeated He pointed out that rats normally slept by day and ran a lot, and that their metabolism was adjusted accordingly, this must be allowed for Dr Croft gave an account of methods of anæsthesia, emphasising technical points to reduce fear (such as full preparation to eliminate delay at the start, and the avoidance of regional anæsthesia where possible) She warned against dangers peculiar to modern techniques—e g, species difference in synergism where several drugs were used, and the possibility of an animal waking up while paralysed by a relaxant Activity too early after a relaxant might lead to muscular pain Dr Russell discussed ingenious means of refinement where this might seem impossible—i e, in experiments on stress itself For instance, certain birds would not approach another of the same species except to mate, and then the male approached the female with a pivoting action, of which the turning away component was an avoiding reaction and a sign of stress Such birds could be used to test the effects of a drug designed to combat fear

In the discussion, Mr A L Bacharach said that, in view of species differences, tests of toxicity might appropriately be confined to one species, for the effect in man might still be different even if many species were used Other speakers mentioned the unfortunate impression that would have been gained from tests of histamine confined to rats or, conversely, of penicillin confined to guineapigs, and emphasised the need for good animal technicians An excellent 16 mm sound film (which may be borrowed free from UFAW, 7a, Lamb's Conduit Passage, London, W C 1) was then shown, demonstrating methods of handling the common laboratory animals

In England Now

A Running Commentary by Peripatetic Correspondents

I suppose there has always been in medicine a kind of Priest of the Grove whose name could be invoked when the inexplicable had to be explained or a "cause" adduced for the "idiopathic" Evil spirits, witchcraft, planetary influence (immortalised as influenza), miasmata, and the like have reigned and been displaced In our own time auto-intoxication, -ptosis, the septic focus, hypovitaminosis, endocrine imbalance, and allergy have donned the mantle and either lost it altogether or found moth in it They come and go but we can't do without them, a Word of Power we must have Now that the glint in Allergy's eye is fading a little, "Stress" seems to be shaping nicely for the succession He's a promising candidate, so pleomorphic, almost like Proteus, but I wonder if he isn't overreaching himself a bit He's gone adjectival, sprouted a hyphen, and is claiming as his own a whole bunch of maladies which but yesterday owed allegiance solely to Allergy or else went about as free and independent morbid entities He calls them "Stress diseases" They include, I am almost sure, asthma, migraine, thyrotoxicosis, gastric and perhaps duodenal ulcer, eczema, urticaria and the neurodermatoses, ulcerative colitis, rheumatoid arthritis, and many of their friends and relations

"But what *causes* it, doctor?" "It's a stress disease, Madam" Most satisfying to both parties! So pleasant in its implications! But true and going to last? I wonder Take my teichopsia—surely no less a member of the band than migraine True, it first appeared under the mild stress of writing what I fondly hoped might be a prize essay, but it didn't stop me nor, I am sure, did I blame it for my ill-success In forty-five years since then it has appeared perhaps half a dozen times Stresses there have been, too—traumatic, bacterial, circumstantial, professional, familial, personal How could there not have been? But never have stress and spectrum come together or had any perceptible time-relation The same goes for asthma If sleeping under the stars on a lawn or on the deck of a moored yacht during a blissfully happy summer holiday was "stress," then, of course, the case is clear enough But was it? Forty years back I was asked to accept the view that "happy people don't get Graves's disease" and I was very ready to do so But when I put the proposition the other day to a physician, surgeon, and registrar at a world-famous thyroid clinic they would have none of it

I'm almost sure that if Stress is wise he will drop his hyphen and take his place quietly by the side of Constitution and Fate, much as he may dislike their company

* * *

It took a great deal of my professional and spare time to perfect my two-finger-action distance-controlled modification to the hypodermic syringe It really was a delightful contrivance, a gleaming chrome, sparkling stainless-steel, extended plunger—and strong too My big worry was whether anybody else had invented or, worse, even patented it, because I liked to think of my name being perpetuated by thousands of doctors through the ages each time they said "Sister, please hand me the syringe with Gubbin's modification" In essence, it allowed a doctor, or the patient, himself, to give an injection from a distance The long flexible extension to the plunger of the syringe would enable an anæsthetist, for instance, to continue an injection into a vein in the dorsum of the foot without moving away from the head of the patient The fact that it was a little stiffer when used at its full distance prompted me to seek perfection and ask for the help of our local scientific and optical instrument-makers

I must admit I was a bit narked when it was returned attached to my camera (which they had taken ages to repair) as a remote-control trigger

* * *

The machine which Willie Bill operated was about the size and dimensions of a shop-front, and quite dwarfed Willie Bill, who was a wispy youth with a weary stance and a semi detached mandible His teachers had described him as bone-idle, and his family as one who was "nobbut tenpence to t'shillin'" But Willie paid as little attention to them as to anything else outside the local cinema

He had decided that he resembled Elvis Presley, refused to have his hair cut, and lowed dismally and adenoidally through most of his working day Luckily for his workmates, Willie Bill's machine made much more noise than Willie Bill It was his task to supply it with slabs of heavy cardboard, which he pushed into a large horizontal slot at the level of his waist Once they were inside, a powerful knife descended and sliced them into shape Its designers had provided the machine with every safety device they could think of, but what they hadn't thought of was that Willie Bill would lash up these devices with bits of bootlace to stop them getting in his way Everybody, from the Chairman of Directors (who had attended night-school with Willie Bill's father) to Dan'l Hargreaves the overlooker (who happened to be Willie Bill's uncle), had spoken severely to Willie Bill about such recklessness "Tha'll be workin' this here cutter single-handed yet lad," said Dan'l grimly on several occasions while undoing his nephew's handiwork Willie Bill's mates contented themselves by laying bets on how many fingers, and when, and by asking him at the end of a shift if he could still count up to ten without taking his boots off

About three feet above Willie Bill's head the machine had a shelf-like projection upon which he assembled his collection of pin-up girls By cricking his neck he could gaze rapturously at these delights It was to move Miss Diana Dors to a more delectable angle that Willie Bill climbed on to the lip of the slot where the cardboard was inserted, and unwisely poked his toes inside

I hurriedly left my lunch and arrived at Willie Bill's house to find him reclining on the sofa in the front room with both his feet swathed in bandages He held a pint pot of tea in one hand and half a teacake in the other and was telling the tale to an enthralled "fan-club" of neighbours Having cleared the front room, I removed the factory first-aid man's excellently applied bandages from Willie Bill's feet the only damage was the loss of the terminal half-inch of both great-toes "Ah wouldn't mind so much," said his mother, relieved and angry, "if he hadn't gone to work in his new socks"

But Willie Bill really had the last word "It 'ull make them at t'Works look a bit silly, will this 'ere," he said, waving his teacake complacently, "me gettin' me toes chopped off when they've allus been sooa cocksure it 'ud be me fingers"

* * *

Queer thing about the babies I see nowadays—they are ravenous Their appetite is phenomenal, really, but as it is so common we don't wonder at it In the old days a baby was expected to double his birth-weight at six months Now they often double their birth-weight at three months—some even at two You just can't shovel the food into them fast enough "Self-demand feeding" we primly term this stoking-up process Of course nowadays many expectant mothers go on to diets —some as low as 1000 and 1200 calories, I'm told Are the babies being born too hungry? In the old days the antenatal mothers were on self-demand (unless toxæmic or what-have-you) and the babies went on a rigid schedule Now the expectant mothers go on a rigid schedule and the babies are on self-demand

* * *

THE JUNIOR HOSPITAL MEDICAL OFFICER

Broke, broke, broke
  Once more in the red I see
And I would that my tongue could utter
  The thoughts that arise in me

O well for consultants, part time,
  O well for the rich G P
Whose car expenses, and carpets, and maids
  Are covered by Schedule D

O well for the hospital cooks,
  The porters, the stokers, the chars
Who draw double pay for their work at weekends,
  And roll away home in big cars

But woe for the J H M O
  With no political powers—
For eight hundred quid he must travail a year,
  Be on call all the twenty four hours

Letters to the Editor

RADIOLOGICAL HAZARDS TO PATIENTS

SIR,—A committee was set up last year by the Secretary of State for Scotland and the Minister of Health "to review the present practice in diagnostic radiology and the radiotherapy of non-malignant conditions, with the object of considering the hazards involved"

This review was recommended by the Medical Research Council in their report on *The Hazard to Man of Nuclear and Allied Radiations*, for they found that medical radiology is in fact the chief source of the extra radiation to which we are now exposed They emphasised the genetic damage which might be caused by irradiation of the gonads, and it is this damage with which our committee is chiefly concerned Its importance is difficult to assess, but it means that we must not neglect even very small sources of radiation

Since I fear that our inquiries are bound to add to the work of busy people I hope you will allow me to describe the investigations which we have in mind. Our first requirement is a more accurate estimate of the amount of gonadal radiation over the whole population, for the genetic hazard depends ultimately on the total rather than on the individual dose and we must know the present figure if we are to keep in touch with future developments To obtain such a base line we need a survey of the total number and type of X-ray examinations carried out within a given period, followed by estimations of the gonadal dose in a representative sample

We have already sent out detailed questionnaires to make a census of all medical and dental procedures involving X rays and radioactive substances, and a similar more limited inquiry will be made six months hence to take care of any seasonal fluctuations which might affect the result To measure the probable dose to the gonads in different radiological procedures we are asking a number of hospital physicists to make a detailed investigation in a sample group of about 100 hospitals This will enlarge the excellent surveys which have been carried out already in particular departments, and when it is finished we shall have a figure for the total gonadal radiation in this country which should be at least more accurate than any former estimates, here or elsewhere

We are told that any exposure of the gonads may induce some mutations and that all mutations are more likely to be harmful than beneficial But medical radiology must not be unduly hampered the possible harm to the race must be set against the certain benefit to the individual We must aim, however, at reducing all unnecessary exposure of the gonads and with this in view the committee has formed small specialist groups which are to consider individual procedures in different clinical fields and to suggest measures for improving their safety

In seeking through your columns to put this information before the profession as a whole, my committee hopes to enlist the interest of all those whose work touches on the use of X rays and radioactive substances We are fully aware of the inconvenience and extra work we are causing and we have learnt with regret of occasional failures in our arrangements for giving notice of the survey But we believe that the final result will justify what we are doing We live in a period when a rise in the level of man made radiation cannot be ruled out and ought not to go undetected It is disturbing to think that medical radiology may be causing unnecessary exposure of the gonads and that it may cause more if we take no steps to measure the present level We hope that all doctors and dentists will cooperate with us in our work

Trinity College,
Cambridge

ADRIAN

VACCINATION AGAINST POLIOMYELITIS

SIR,—There is at the present time serious anxiety in both the medical profession and the general public about the failure of the programme to protect our population against poliomyelitis by vaccination; this anxiety has now found voice in the national press. Why, it is asked, in view of the shortage of vaccine produced in this country, is our inadequate supply not supplemented from the U.S.A. and Canada, where it is plentiful? It may be useful to review the relevant facts.

The principle of vaccination against poliomyelitis was accepted over a year ago, when we were told that children in the age group 2–9 years would be the first recipients, and that it was expected that 2 million children would receive the vaccine in the first year. In the event, not 2 million but rather less than 200,000, or approximately 1 in 30 of the 6 million children in this age-group, received their first two doses last year, and this year doses for only 500,000 children have so far been released—after considerable doubt whether they were, in fact, safe. In spite of official optimistic pronouncements future supplies are still uncertain, since the next batches have not yet passed the safety and efficiency tests and like previous batches may have to be thrown away.

The poliomyelitis programme introduced with such rejoicing has, in fact, failed dismally. There can, indeed, hardly be said to be a programme at all; not only has the age group selected for protection last year not received the promised vaccine, but the equally, or perhaps more, urgent claims of other groups have not even been considered. Particularly noticeable has been the failure to meet the pressing needs of persons in particular danger of contracting the disease because of either increased susceptibility or increased exposure. In this connection one must mention the urgent need to protect expectant mothers (because of their particular susceptibility), doctors and hospital, nursing, and ambulance personnel (because of their particular exposure), and, of course, persons travelling to areas of high incidence, notably Service personnel and their families, all of whom contribute disproportionately to the quota of fatal and severely paralysed cases claimed annually by poliomyelitis.

The failure of the vaccination programme is attributed to difficulties, not unexpected, in the production of British vaccine.

> Only two firms are making vaccine in this country. They are struggling gallantly with the difficulties of a process with which they are unfamiliar—difficulties increased by the generally admitted lack of virological facilities in this country at the present time. One firm has so far not produced any vaccine at all, though it hopes to be in production by the summer; the other has produced the small amount of vaccine so far issued by the Ministry of Health. Both firms are working under stress of urgency, which cannot be conducive to the best long-term results, and it is no secret that the manufacturers, through no fault of their own, are having to throw away whole batches of vaccine as unsafe or unsatisfactory, with the result that the amount of vaccine available falls short of forecasts.

But why must our programme be confined within the tiny limits of British production, when there is already a vast production capacity of vaccine, well-proven for safety and efficiency, in the U.S.A. and Canada?

Since the initial Cutter incident in 1955 led to tightening of the control on production and testing, over 60 million persons have received Salk vaccine prepared in the U.S.A. and Canada, and the safety of the production and testing of vaccine in those countries must by now be accepted as unimpeachable. In addition, both epidemiological and laboratory findings confirm the effectiveness of Salk vaccine in preventing paralytic poliomyelitis. An obvious solution to our problem is to supplement our own inadequate supplies of vaccine with imported vaccine from the U.S.A. and Canada. We have, in fact, been assured that, should we apply for it now, we could receive immediately sufficient vaccine to protect at least 4 million people, and that further supplies could follow after a short interval. Why then can doctors in this country not obtain this well-tried vaccine, either under the N.H.S. or by private purchase?

We are assured that commercial considerations, dollar currency restrictions, and internal economy could, none of them, be allowed to influence the decision against the import of vaccine. Yet what else can explain that it is impossible for firms to get an import licence for vaccine of the highest repute, which must be regarded as an essential substance for the prevention of paralysis by poliomyelitis? Its import is, in fact, prohibited not only by dollar restrictions, but also in the Therapeutic Substances Regulations.

Semi-official statements have suggested as an excuse that American and Canadian vaccines are not safe, because the type-I strain used in their preparation is the Mahoney strain and it was the Mahoney strain which, because it had not been killed, was responsible for the Cutter incident in 1955. The Cutter incident occurred because batches of vaccine were inadequately tested before they were used and live virus was present in the vaccine. The whole purpose of the improved production methods and safety regulations introduced after the incident was to ensure that (*a*) the testing machinery should not be by-passed and (*b*) the testing procedures should be as safe as human ingenuity could devise. The successful vaccination without incident of over 60 million people bears witness to the fact that both objectives have been achieved and that Salk vaccine is a safe weapon against poliomyelitis. It is, of course, not so much the virulence of the strains used that matters, as the guarantee that all three strains—of types I, II, and III respectively—are killed before the vaccine can be issued for use.

The large-scale, smoothly running production and testing procedures so carefully developed and well tried in the U.S.A. and Canada must be regarded as second to none in the world. Certainly they are not second to those at present in use in this country, where manufacturers, however able, must be regarded as working under very difficult conditions.

The alarming rise in notifications for poliomyelitis in the first quarter of this year stresses the urgency of our need for vaccine *this year*. Last year the notifications were comparatively low and the high figures this year must be regarded, not as the overspill of last year's epidemic, but as the beginning of a severe 1957 epidemic. No one can be sure that we are going to have a severe epidemic this year, but the signs are bad and, certainly, no one can say that we are *not* going to have one. Already we are admitting to this hospital, at what should be our slack period for poliomyelitis, an unusual number of fresh cases with severe *permanent* respiratory and locomotor paralysis. Some of them are in the 2–9 age group, who should have been protected last year; others are from outside this age group, illustrating in their tragedy the hopeless inadequacy of a programme confined to an age group which provides rather *less* than half of the fatal and severely disabled cases occurring annually in this country.

Medical officers of health and general practitioners assure me that, could they receive vaccine now, there would be no delays in its injection. General practitioners, the school health service, infant welfare clinics, antenatal clinics, hospital personnel, and Service doctors could combine in an "operation vaccine," which would ensure protection of all the priority groups and a high proportion of the rest of the population within three months and would undoubtedly cause a dramatic fall in notifications, and save many at present destined for death or paralysis.

In taking his decision on the import of vaccine, the Minister of Health must weigh the risks carefully: on the one hand, the theoretical danger of using American vaccine, already well-tried, and trusted not only by the distinguished American and Canadian virologists and epidemiologists concerned in the vaccination programmes in their countries, but also by their counterparts in other countries in Europe, South Africa, and South America, now importing Salk vaccine for the protection of their populations; on the other hand, both the *certainty* that, unless this vaccine is used, the homes of thousands of adults and children will suffer the disaster of poliomyelitis this year, as they do every year, and the *possibility* that we are, in fact, at the beginning of a severe epidemic, such as this country has not yet experienced, but which we cannot, without vaccine, hope to escape much longer. These risks are the only considerations which can weigh in the Minister's decision. Not dollar restrictions; not internal economy (the cost of the prevention of poliomyelitis will in one or two years be redeemed by the saving of the, at present appalling, cost of the care and support of the permanently paralysed); not the hurt pride of technical advisers; not a misplaced loyalty to British products; above all not the desire in some "research" quarters to carry out "controlled studies" of the incidence of the disease in the vaccinated and the unvaccinated, must be allowed to weigh with a Minister whose primary concern is the care of the nation's health.

The announcement that vaccine is to be imported freely, to supplement our present inadequate supplies, would give tremendous relief to an anxiety which is rapidly becoming intolerable.

No one, of course, need accept vaccine, British or American, if he does not wish to; but at least the protection will be available. The important step is for the Minister to apply immediately for allocations of the exportable surpluses of vaccine of the U.S.A. and Canada, and to remove the currency and the import restrictions that are at present depriving our population of access to an essential medical preparation. Whether the Ministry of Health can be persuaded to sponsor a nation-wide campaign for the unlimited free vaccination of our population against poliomyelitis, or whether it is left to the initiative of general practitioners, medical officers of health, and those concerned with the care of specially exposed groups to purchase the protection out of other funds is a question secondary to the main issue of the availability of supplies of vaccine, sufficient to give protection now to all who want it, before the annual toll of tragedy is claimed by this now preventable disease.

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These workers plainly regard the existence of the "cæsarean-section syndrome" with profound scepticism because they have not been seeing it. I suggest that this is due to the excellent prophylaxis they have been practising, just as some workers rarely saw retrolental fibroplasia long before its cause was determined. I believe that the cæsarean-section syndrome can occur, for I have observed it. I also believe that it does not differ from the pulmonary syndrome of the newborn, except that it may occur in full-term babies, whereas it is virtually confined to premature deliveries when these take place per vaginam. This provides an important clue to its ætiology and strongly suggests that it is preventable. Finally, it is my belief that such apparently diverse pathological findings as pulmonary congestion and œdema, pulmonary hyaline membrane, intra-alveolar hæmorrhage, cerebral œdema, and cerebral intraventricular hæmorrhage may be inter-related and result from similar factors.

It seems to me that the important point in the immediate after-delivery care of these babies is the *delayed ligation of the umbilical cord*, as practised by Strang et al. and many other workers. This may allow time for respiration and expansion of the lungs to occur before the baby's hitherto sole supply of oxygen is cut off and harmful effects from acute asphyxia have resulted. It is also possible that the increased volume of blood obtained from the placenta may help to fill the pulmonary capillaries and assist in alveolar expansion.[1]

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SENIOR REGISTRARS AND CONSULTANT APPOINTMENTS

SIR,—I hesitate to cross swords with so able a controversialist as my friend Dr Hubble I venture, however, to dispute his implication last week that "it is the way of English medicine" for a consultant to pass (so far at least as hospital work is concerned) straight from a state of pupillage to one of complete responsibility Surely it was the custom, in most of our teaching hospitals and in many of the large non teaching voluntary institutions, for a newcomer to the then honorary staff to be appointed in some such grade as that of assistant physician or assistant surgeon In the case of Dr Hubble's own parent hospital, I seem to remember reading the tribute paid on retiral by Lord Horder to one who had long been his junior, Dr A E Gow

I am not here concerned to argue whether what has happened in the past should, under new conditions, continue to happen in the future But I do think it important to establish clearly what did happen in the past

University of Sheffield J G McCrie

FÆX

SIR,—Dr Derbes, in his letter last week, overlooks the possible confusion between "fæces" and yeast (*fæx siccata*), sometimes, but not I think now often, used for the more modern *cerevisiæ fermentum* Perhaps the use of the word *fæx* for yeast is not known in the U S A

London, W C 2 George B Kilgour

TREATMENT OF HIRSCHSPRUNG'S DISEASE BY SWENSON'S OPERATION

SIR,—I was interested to read the article by Mr G G Wyllie (April 27) on the management of 152 cases of Hirschsprung's disease by rectosigmoidectomy The argument put forward for this type of operation is now well established, but I was perturbed at the degree of bowel disturbance after a successful operation Mr Wyllie says that treatment for constipation was required in 34 cases The constipation was caused either by failure to appreciate the sensation of a full rectum or by "colonic inertia" due to leaving in situ the considerably dilated non-diseased colon Moreover, of 102 children over 3 years old, 41 had lack of full rectal control with some incontinence, and the number with enuresis was higher than would normally be expected One gets the impression that the results are not as good as one would hope for on theoretical grounds

Therefore I feel that some mention should be made of State[1] in Minneapolis, who treated a series of 16 patients, with very satisfactory results, by left hemicolectomy, removing dilated bowel and the "physiological stricture" in the rectosigmoid He doubted whether the ganglion theory was the complete answer, and felt that the dilated colon might be the abnormal lesion, perhaps of parasympathetic origin

State left the rectum in situ and thus did not disturb nervi erigentes Mr Wyllie makes no mention of the risk that pelvic dissection may cause impotence, but the follow-up period may not be long enough yet to assess adequately this factor This is not a theoretical risk, since mobilisation of the rectum in adults to remove cancer or long standing abnormalities carries a definite risk of producing impotence

The only criticism on theoretical grounds of left hemicolectomy is that recurrence, with further constipation, may follow incomplete removal of the aganglionic segment of bowel As constipation is common after the Swenson operation it would seem logical to allow the child to grow up to manhood, constipated or not, with the maximum chance of developing to normal "Kinsey standard" Nevertheless, as State's good results have been confirmed at this hospital, surely left hemicolectomy is worthy of a trial in the first instance, even if Swenson's operation is done later—perhaps after many years

The Gordon Hospital,
London S W 1 C I Cooling

RELEASE OF HISTAMINE IN URTICARIA PIGMENTOSA

SIR,—Dr Hamrin (April 27) reported a case of urticaria pigmentosa in a patient who was sensitive to acetyl salicylic acid (aspirin) He raises the question whether intolerance to aspirin may be caused by histamine release and not a true allergic (antigen antibody) reaction Mast cells, which are found in large numbers in the skin in urticaria pigmentosa,[1] are very rich in histamine Any cellular injury, including mild trauma or an antigen antibody reaction, will release cellular histamine Aspirin sensitivity causing angioneurotic (Quincke) œdema is the commonest drug sensitivity seen in a general allergy clinic In a patient who is sensitive to aspirin and who has urticaria pigmentosa, the reaction is likely to be severe because of the large amounts of histamine that can be released I have seen 4 patients with urticaria pigmentosa who have later become sensitive to bee or wasp stings They reacted very severely when stung only after they had become sensitive The reaction in each case was a generalised urticaria, with difficulty in breathing and unconsciousness, in under five minutes In any proved case of urticaria pigmentosa it is advisable to ask whether there has ever been a severe untoward reaction (due to an induced sensitivity) following an injection (e g, penicillin), drug taking (e g, aspirin) or a sting (e g, by a bee) This association was described at the European Congress in Allergy last year[2]

A W Frankland

ANTIGEN-ANTIBODY RESPONSES IN MULTIPLE SCLEROSIS

SIR,—Your annotation of April 13 refers to work done at Oxford by Dr Honor Smith and her colleagues on this subject The mode of investigation was lumbar intrathecal injections of tuberculin The patients with this disease were all volunteers and, you state, "a control group of psychotic patients was used for comparison" Surely I cannot be alone in finding this state of affairs disturbing ? Even the experimental work with the diseased group may not be as permissible as appears on the surface Any patient with a progressive incurable disease will snatch at any procedure, however hazardous, offered with whatever explanations and reservations The pressure to volunteer is enormous as I know, with regret, from past errors of my own in this respect But allowing that the work was justifiable in this group, what are we to say about the psychotics who were submitted to an undertaking with considerable risks ? Were they volunteers ?

To experiment on patients who are fully aware of the situation and accept it is one thing—though I have indicated that even here there are reasons for caution To experiment on those who cannot understand what is happening, cannot give permission, cannot possibly benefit, and may suffer serious *consequences*, is quite another and calls for the severest *condemnation*

London, W 1 David Le Vay

*** We have shown this letter to Dr Honor Smith and Dr Ritchie Russell, whose reply follows —*Ed L*

SIR,—We sympathise with Mr Le Vay's sentiments, but he is inaccurate in suggesting that a dangerous experiment was carried out on mental patients—"who cannot possibly benefit, and may suffer serious consequences"—simply in order to provide controls for our observations on disseminated sclerosis. As the earlier papers quoted in our communication show, the observations on mental patients were made several years ago in the course of a study into the widely canvassed question of the possible parts played by tuberculosis and by alterations in the blood-C.S.F. barrier in the ætiology of mental disease. At the same time it was considered that the transient pyrexia and cerebral hyperæmia that accompany the reactions might well be beneficial in mental disease. In point of fact, the reactions were invariably well tolerated, no adverse results were ever seen, and the hazard was undoubtedly less than that incurred by, say, electroconvulsion therapy.

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[1] State, D *Surg Gynec Obstet* 1952, 95, 201

[1] Riley J F West, G B *J Physiol* 1953 120 528
[2] Frankland A W Proceedings of the European Congress of Allergology 1956 vol I, p 501

However, the lack of adequate volunteers is a constant hindrance to the research-worker, and doctors themselves often act as such. It might be well worth while to establish a Corps of Volunteers of those who are prepared to face a certain risk for the benefit of others.

Radcliffe Infirmary,
Oxford.

HONOR SMITH
W. RITCHIE RUSSELL.

SUBUNGUAL HÆMATOMA

SIR,—Surely much the most simple—and painless—method of dealing with this condition is, after the application of iodine, to break through the thin membrane at one corner at the base of the nail where it is stretched and taut through the nail being pushed up by the accumulation of blood underneath. This can easily be done with a sterile needle and the blood evacuated.

If blood re-accumulates, as is often the case, it is easy to repeat the process.

Leiston, Suffolk. D. G. GARNETT.

REDUCED EFFECT OF HETEROLOGOUS INTRINSIC FACTOR

SIR,—Since I have noted the same phenomenon as that reported by Dr. Schwartz and his colleagues (April 13), I should like to give a short account of my results.

In December, 1953, I started an investigation of an oral preparation containing hog intrinsic factor with vitamin B_{12} ('Bifacton,' N.V. Organon). 22 patients were followed for more than two years by serial blood counts and serum-vitamin B_{12} estimations, using *Euglena gracilis* as test organism. In most patients the serum vitamin B_{12} soon began to decrease. After varying lengths of time the levels became subnormal (less than 100 µµg. vitamin B_{12} per ml. serum). After that, hæmatological relapses became increasingly common.

After two years, 10 patients had relapsed, 5 had normal blood counts but subnormal serum-vitamin B_{12} (pre-relapse), and 7 were normal. Increasing the dose neither increased the serum vitamin B_{12} levels nor improved the anæmia. For example, one patient, who initially had a complete remission on 2 tablets daily, after eighteen months relapsed while being treated with 4 tablets a day. Each tablet contains 7.5 µg. of vitamin B_{12} and 0.5 oral *U.S.P.* units of factor. In the 10 patients who relapsed, the length of time between the first subnormal serum vitamin B_{12} value and the relapse varied from four to twenty-two months, with a mean of thirteen months.

A Schilling test, using 0.5 µC (0.5 µg.) of vitamin B_{12} containing ^{58}Co, was performed on 5 of the 10 patients in relapse. When the test dose was given with water the patients excreted 0–0.4% of the given dose. With bifacton intrinsic factor the corresponding urinary excretion ranged from 0.2 to 0.7%, but the excretion was increased to 7–23% when the patients were given a test dose in 100 ml. of normal human gastric juice.

At that time, I thought it might be interesting to know whether another preparation of intrinsic factor from the same animal would show the same phenomenon. Two of the patients mentioned above were tested with 'Bendogen' (Kabi). Both showed a normal excretion (14% and 23%). There was thus evidence that the refractoriness had been induced by the treatment.

A third patient already refractory to bifacton after treatment for twenty-two months was transferred to therapy with bendogen for two months. A Schilling test was then performed with water, bifacton, bendogen, and human gastric juice. The urinary excretion values were found to be 0, 0.6%, 2.4%, and 17% respectively.

I have treated 6 patients with bendogen who had a subnormal serum-vitamin-B_{12} following protracted bifacton treatment (pre-relapse cases). In all cases the serum-vitamin-B_{12} concentration initially increased to within normal limits. Then the levels began to fall as at the beginning of the bifacton treatment. 3 patients have now reached subnormal serum levels of vitamin B_{12}. I hope to be able to show a double refractoriness, both to bifacton and bendogen, in these cases.

In view of these experiences I do not consider oral treatment to be rational in pernicious anæmia.

These results were reported at the meeting of the Swedish Medical Society in December, 1956. A detailed account of the experiments will be published later.

Institute of Medical Chemistry,
University of Uppsala, Sweden.

ANDREAS KILLANDER.

MEDICAL STAFFS OF MENTAL HOSPITALS

SIR,—The letter from Dr. Strauss and others (May 4) is timely. Judging by the situation in this region, the comprehensive review of psychiatric services which they propose is urgently needed. In the Leeds Hospital Region, whereas the number of psychiatric inpatients has risen comparatively little (i.e., from 10,783 in 1948 to 11,347 in 1956) the admission-rate has *almost doubled*, from 2850 admissions in 1948 to 5400 (of which 74% were voluntary) in 1956.

There has also been a big rise in the number of new outpatients seen annually, from 1650 in 1948 to 3100 in 1955. In addition, the number of outpatient attendances per new outpatient seen has risen from 2.9 in 1948 to 5.5 in 1955. No data are available from which to estimate the increase of outpatient work since 1955, but the lengthy waiting-lists that have accumulated make it evident that the demand has far outstripped the provision.

In this region there has been some increase in the senior staff in the psychiatric hospitals in that, whereas there were 16 consultants and 10 senior hospital medical officers (S.H.M.O.s) in 1948, in 1956 there were 25 consultants and 19 S.H.M.O.s. The senior staff has therefore risen from a total of 26 to 44. Nevertheless, even with this rise, the current senior-staff/inpatient ratio is still only 1/258. When it is borne in mind that these psychiatrists, in addition to the treatment of inpatients in psychiatric hospitals (whose admission rates have doubled since 1948) have to provide the outpatient services, which have expanded equally greatly, it will be evident that their numbers are inadequate to enable them to devote as much time as they would wish either to the treatment of individual patients, whether acute or chronic, inpatient or outpatient, or to the training and supervision of their junior colleagues.

Department of Psychiatry,
University of Leeds.

G. R. HARGREAVES.

SIR,—Dr. Strauss and others rightly emphasised the need for an increase in the medical staffs of mental hospitals. There is also need for increased facilities for outpatient electroconvulsion therapy, which would reduce the overcrowding in most admission units, benefit the patients, and result in a substantial economy to the National Health Service.

The increasing number of patients attending psychiatric outpatient clinics is not altogether a reflection of the success with which they are being treated. It arises as much from the changing conditions of general practice, too well known to need repeating. A large proportion of these patients would, however, be better dealt with by their general practitioner, familiar as he is with them over long periods of time. The lack of special training in psychotherapy should not deter him. Few psychiatrists have had any either, and at the level at which it can be given in outpatient departments this is unlikely to be of any significance

Glengall Mental Hospital
Ayr
HARRY B MILLER

SIR,—Having read the important letter by my revered teacher Dr Strauss and his co signatories I should like to make a few observations

Where are the mental hospitals to obtain "the substantial increase" of staff required by the letter? To secure adequate staff is very difficult, especially in the junior ranks in the provinces Further, in the Metropolitan area some four years ago a situation arose where four hospitals had applied for a registrar yet only two candidates turned up for interview Psychiatry as a specialty lacks the glamour attaching, for instance, to surgery and obstetrics

There is another consideration The D P M is held to be requisite for advancement in the mental health service, and in advertisements for junior posts one reads the famous statement "Every facility will be given for studying for the D P M" On arriving at a mental hospital the junior doctor will find that, if the staff is small, he is required to be on duty two or three days a week and at weekends, which prevents his attending clinical demonstrations at teaching hospitals and a course of systematic lectures It is in fact virtually impossible to hold a full time hospital appointment and at the same time do regular work for the diploma, especially part II

One wonders, however, whether this diploma is as valuable as is claimed In recent years a number of S H M O appointments have been made by regional boards to candidates without it or with part I only Recently I was informed that in a highly psychiatric type of service—the Prison Service—only 4 of the 40–50 doctors possess the diploma

There would, I think, be considerable inducement to enter the mental-hospital service if promotion were to be made automatic What I mean is this After, say, ten years' faithful work in one or more mental hospitals, a junior doctor (registrar or J H M O) could reasonably anticipate being made S H M O This would speed up promotion and would give encouragement to those seeking higher appointments

Dr Strauss's letter raises many very important issues, which deserve urgent consideration

Royal Earlswood Institution,
Redhill, Surrey
J B GURNEY SMITH

CHRONIC BRONCHITIS AND SMOKING

SIR,—Dr Lennox Johnston (April 27) gives a pungent summary of the extreme arguments against smoking I am personally a life long non-smoker, and privately should enjoy a talk with him Between us, we should agree upon the antisocial outlook of many addicts, but we should differ as to the best method of discouraging the habit Dr Johnston and I are in a minority, and in convincing smokers we shall get further by a more subtle approach His ingenious exercise in psychopathology will not make much impression An Arabian proverb says "It is good to know the truth—but it is better to speak of palm trees"

We have to begin somewhere, and the whole difficulty lies in the fact that, to smokers, smoking is a pleasure This it is absurd to deny, although, like coffee, alcohol, overeating, and other sociabilities, it may also be reprehensible We can hope to be more successful in influencing the young who have never begun to smoke, but anyone who remembers the old fashioned 'temperance" propaganda—based on bottles of hobnail liver—will not care for Dr Lennox Johnston's dogmatism He is a valiant fighter for the truth, but hardly a wise teacher

London, W C 1
HARLEY WILLIAMS

SIR,—In reply to Dr Charles Corfield (May 4), I smoked for 12 years and tried adequately the various methods of smoking and the various kinds of smokes I have no need therefore to ask Sir Winston Churchill or anyone else about smoking and enjoyment Surprisingly, however, Sir Winston's assessment of the enjoyment of smoking was, like my own, negative "If I were to live my life again," he wrote, "I would eschew the habit of smoking"[1] Why he did not do so there and then, I do not know Perhaps its showmanship value, in his exceptional case, counted with him

Wallasey, Cheshire
LENNOX JOHNSTON

SIR,—I read with delight Dr Corfield's letter Thank heavens someone has had the courage to point out in your august columns that smoking is enjoyable And thousands of aged smokers down the centuries can't all be wrong

If I suggest, however, that there is a little more to the gentle art than chain smoking, some may think I have an axe to grind I have And the way it cleaves through some of the less scientific prejudice expressed in your correspondence columns gives me almost as much pleasure as smoking

Alfred Dunhill Ltd,
30 Duke Street,
London S W 1
ALFRED H DUNHILL

THE STUDENT AND SEX EDUCATION

SIR,—I am grateful to Professor McLaren and Mr Rossiter (May 4) for their kind remarks on my article in your issue of April 20 While we appear to agree on the need for dealing with this problem, there is a difference in emphasis on the method of approach At Birmingham and several other universities, students are fortunate in having not only enlightened teachers with a broad vision of the larger spiritual aspects, but also the facilities for individual teaching, but the replies to my questionary indicate that these conditions do not exist at certain other universities

Professor McLaren's suggestion of the educational value of a resident 3 months in an obstetric unit is only valid provided that during that time the student is in contact with a teacher who is himself aware of these problems (and especially of their spiritual aspects) and is himself free from inhibition in his teaching and discussion of these problems Some of the replies to my questionary indicate that some teachers are actually antagonistic to any discussion of them whatsoever

I did not mean to suggest that instruction on sex matters should be given only by systematic lectures Rather my suggestion was put forward merely to make the student (and perhaps some of his teachers!) aware of the existence of these problems and so enable them to find, either from books or individuals, the help that they may require In the last analysis it is true, as Mr Rossiter rightly says, that it is personal experience of marriage which is the best teacher Although the number of married students is increasing, their personal experience cannot be a substitute for instruction I should hate, as much as Professor McLaren does, to see this subject becoming a required study for an examination with a special paper But no examinations are required to make students take an interest, for indeed they will cut other lectures to listen to something which penetrates so deeply into the problems of their own lives I can confirm the experience of Dr Sylvia Dawkins at University College Hospital, whose lecture on contraception[2] packed the lecture theatre to the doors When I was invited to give a similar lecture at Manchester University over a year ago, the theatre was crowded with students At many universities the sole lecture given on sex is one by Dr Marie Stopes on contraception, which, in my view, is hardly adequate, contraception is perhaps the least important part of the sex education of the student

The real difficulty facing teaching staffs is to decide who is to give this teaching, and, in some cases, who is to teach the teachers For sex is not the specific province of either gynæcologist, psychiatrist, or minister of religion May not the answer be that an experienced general practitioner should lecture with the support of a panel of gynæcologist, psychiatrist, and minister of religion? The apprenticeship of students to family doctors (as recommended by the College of General Practitioners) would provide excellent opportunities for such teaching, though I am aware of the difficulties in choosing doctors for this purpose Nevertheless, I feel that a few systematic lectures to senior students could provide them with information not otherwise easily obtained and would enable them at least to ask questions of their teachers about problems which, previously, they had not known to exist

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[1] *Strand Magazine* March 1931
[2] See *Lancet*, 1956, ii, 1057

Manchester　**Bernard Sandler**

COMMON-ROOMS FOR PATIENTS

Sir,—In children's hospitals, it is usual to have play-rooms near the wards, for the use of children not confined to bed Could not the same principle be applied with advantage to adults in general hospitals?

I visualise two types of common-room for this purpose a "quiet" one for elderly people and those recovering from serious illnesses and operations, and an "active" room containing ping-pong table, occupational therapy apparatus, &c, for the less incapacitated

Instead of aimlessly wandering round the hospital in their dressing-gowns, ambulant patients would be able to enjoy the benefits of convalescence while still under hospital supervision

I am sure many readers would be interested to know what is being done about this problem in Great Britain

Cape Town.　**I Mirvish**

HOSPITAL INFECTION

Sir,—As one working in an isolation hospital, I have followed the recent correspondence in your columns with great interest

I must agree with much of what Dr Marsh says in his letter of May 4 As he so aptly states, hospital infection is no new thing After all, it was one of the major causes of death in hospital in the 19th century

Surely its control simply represents the application of common epidemiological principles to special circumstances In this regard the experience gained in the administration of fever hospitals seems to have been forgotten or ignored This is not surprising, resulting as it does from the now commonly held views on hospital administration in general and on the future of fever hospitals in particular

For years before the National Health Service was formed, medical administration in fever hospitals was constantly grappling with the problem of cross infection The principles of barrier nursing and then cubicle nursing were intensively practised in them It was by their rigid application that so many different infections could be treated

I have deliberately used the past tense, because the present day accent on the purely clinical aspects of hospital work has led and will lead to a new generation of doctors and nurses lacking any basic epidemiological training or background Although the contribution of the bacteriologists in hospital and laboratory cannot be ignored, nevertheless much of our existing epidemiological knowledge was built up not by them but by medical officers of health in the field and medical administrators in fever hospitals That both should now be ignored is certainly a sign of the times

If, as seems likely, ultimate official policy is to dispense with fever hospitals as such, then, I submit, the main training ground in hospital epidemiology will be lost Nowadays many of these hospitals face grave nursing shortages It would certainly be to their mutual advantage if all nurses in general training were obliged to do six months training in a fever hospital before their S R N examination, for surely one of the main factors in preventing hospital infection is the nurse with sound epidemiological knowledge

Ilford Isolation Hospital
Chadwell Heath, Essex　**I M Librach**

CLINICAL THERMOMETERS

Sir,—In his letter last week Dr Widlake asks why the so-called half-minute clinical thermometer requires at least two minutes to record a correct reading I have asked this question for fifty years and do not know the answer yet I have not found it in any book which I have consulted A few years ago I was told that the mark "half-minute" was the manufacturers' guarantee that, if the thermometer is placed in warm water about blood heat, it would record the temperature correctly in that time I have asked various of my associates but not one of them has heard this explanation or indeed any other In a letter published two years ago[1] I gave this explanation and asked if it was correct I had hoped that some manufacturer would reply, but none did so Surely it is time that this mystery, which has puzzled the medical and nursing professions for many decades, was cleared up by those who must know the explanation

London W 8　**Henry Tidy**

ATTEMPTS TO PROPAGATE RUBELLA VIRUS IN TISSUE-CULTURE

Sir,—A previous publication[2] reported the appearance of lesions in monkey-kidney tissue-cultures inoculated with rubella throat washings Similar lesions were absent or scarce in control cultures The lesions did not appear in the presence of convalescent human serum

Further passages of both inoculated and control cultures became contaminated with one or more agents derived from kidney tissue or medium[3–5] The passages were discontinued Attempts were made to reproduce the viral lesions in kidney cultures derived from monkeys whose serum contained no neutralising antibody to the contaminating agents To the culture medium was added 2% heated (56°C for 30 minutes) monkey serum containing such antibody No specific lesions appeared and nonspecific lesions were not completely eliminated[6]

Inoculated and control cultures of the latter series were treated with convalescent rubella gamma globulin coupled to fluorescein isocyanate, by a method similar to that of Coons[7] Specific staining of inoculated, but not control, cultures was demonstrated in some experiments, but could not be regularly reproduced[6]

Supernatant from fifth-passage inoculated cultures showing presumed viral lesions was sprayed into the noses of eight human volunteers aged 9 to 27 years, with no history of rubella[3] This material represented a 10^{-10} dilution of original throat washing, the technique of spraying has been described elsewhere[8] After incubation periods of 19, 19, and 20 days respectively three volunteers developed a mild and transient exanthema, low fever (99°–100°F) and slight but definite enlargement of postauricular lymph glands The clinical picture was consistent with a diagnosis of very mild rubella, but was not sufficiently definite to allow a firm diagnosis to be made

Throughout this work there were occasional suggestions that rubella virus was multiplying in monkey-kidney cultures In review, however, we feel the evidence for this propagation was too slender to warrant the conclusion that rubella virus was regularly growing in tissue cultures of monkey-kidney cells The investigation has been discontinued

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[1] *Brit med J* 1955 i 1426
[2] Anderson S G *Lancet* 1954 ii 1107
[3] The Director's Annual Report of the Walter and Eliza Hall Institute 1954–55, p 23
[4] Rustigian R Johnston P, Reihart H *Proc Soc exp Biol N Y* 1955 88 8
[5] Hull R N Minner J R Smith J W *Amer J Hyg* 1956 63 204
[6] The Director's Annual Report of the Walter and Eliza Hall Institute 1955–56 p 21
[7] Coons A H, Kaplan M H *J exp Med* 1950, 91 1
[8] Anderson S G *J Immunol* 1949 62 29

I am very happy to acknowledge the cooperation, in various aspects of this investigation, of Mr G L Ada, Miss J Beveridge, Dr J O'Dea, Dr A A Ferris, Dr E L French, and Dr H McLorinan The constant advice of Sir Macfarlane Burnet, F R S, has been invaluable

The Walter and Eliza Hall Institute
of Medical Research, Melbourne,
Australia

S G ANDERSON

TARGET CELLS AND SWEAT

SIR,—For the past year or two I have noticed that as the summer approaches, the number of blood-films containing target cells, presented for my inspection, increases On inquiry most were found to be taken from sanatorium patients, as opposed to outpatients and those in the general medical and surgical wards Those particularly affected were the convalescent, who were enjoying the sun If a venepuncture is done at the same time as a finger-prick, the target cells are not present in the films made from venous blood As target cells are readily produced by the addition of a trace of hypertonic solution to the blood, I suspect that the finger-prick pierces an actively secreting sweat gland This seems to be at least one explanation of this well recognised artefact

Braintree, Essex

A I D PRENTICE

TREATMENT OF A DIABETIC DOG

SIR,—I wonder whether some of your readers would be interested to know of the successful management of diabetes mellitus in a dog

The dog, Teddy, aged 9 years and weighing 29½ lb, developed severe thirst and polyuria three and a half months ago He was overweight, and had been so since he was neutered some years previously He was sleeping a great deal, he had an anxious expression, and his gait was rather hesitant Urine examinations revealed heavy glycosuria

A veterinary colleague was consulted and, as a short course of dieting made no impression on the symptoms or glycosuria, insulin treatment was begun

The disease must have been in its early stages For the first month it was easily controlled with a morning injection of protamine zinc insulin of 10 or 12 units For the next two months the diabetes relentlessly progressed in intensity Although the dose of insulin was increased almost daily, and eventually soluble insulin was added to the protamine zinc, it seemed impossible to control the disease

Just over two weeks ago, however, the diabetes became stabilised on 100 units of insulin (52 units soluble plus 48 units protamine zinc) given as a single morning injection The urine is clear, but ¼–½% "sugar" appears in the urine if the dose of insulin is lowered to 96 units

Fortunately a young member of my family is an expert at collecting specimens He, Teddy, and a bowl adjourn down the garden, once or twice a day, to a convenient tree and soon return equipped to carry out a 'Clinitest'

The dog has two meals a day of meat and biscuits He has maintained his weight and is now very alert and lively At no time has there been any tendency to hypoglycæmia Night vision may be slightly impaired

Teddy fortunately does not resent the injections, which are given through the loose skin on the neck or along the back He has developed a conditioned reflex, realising that the injection is followed by his breakfast, and on some days I find him waiting for me outside the surgery door

Our veterinary friend has been unable to find any clinical evidence of pituitary or adrenal disease, and pancreatic function seems to be otherwise normal

As the original experimental work on insulin was carried out on dogs, I felt it would be pleasant to record a severe case of diabetes in a dog which has benefited from that work

Thames Ditton Surrey

C HOWICK SMITH

ÆTIOLOGY OF PRE-ECLAMPSIA

SIR,—Mr Theobald (March 30) challenges the connection between bilateral cortical necrosis and toxæmia and questions my view that uterine tension is concerned in pre eclampsia Regarding the former, although the supervention of cortical necrosis on toxæmia is rare, the connection does exist as I will show

Experimentally, moderate cortical ischæmia can be produced by the resistance to stretch of the rabbit's uterus[1] Similar moderate ischæmic changes follow moderate stimulation of the renal nerves while the most severe stimulation of these leads to the severest degrees of renal shutdown In the milder ischæmia, as a result of such stimulation there is an exudate into Bowman's capsule similar to that revealed by renal biopsy in pre eclampsia while in the most severe ischæmia thus provoked all the changes of cortical necrosis are reproduced Nephron dissections separate the renal damage into the purely ischæmic and the ischæmic plus toxic They have shown that in the rare cases of eclampsia ending in fatal anuria, and in anuric concealed accidental hæmorrhage, the histological findings are indistinguishable In *both*, nephron dissection reveals only an ischæmic lesion—a fact also significant in excluding a toxin from the ætiology It seems therefore that in cortical necrosis the changes are the severest seen in states of cortical ischæmia, and that pre eclampsia per se is a much milder stage Clinically the dramatic manifestation of severe cortical ischæmia is anuria—a condition always due to marked renal shutdown

The connection between anuria thus appreciated and eclampsia is further revealed by the effects of administration of hypertonic saline to the anuric who as a result develops œdema, hypertension, and fits—the typical pre eclamptic/eclamptic state[2], while further, if the sequence is reversed and the experimental animal is rendered anuric by renin after salt and water retention had been potentiated by previous deoxycortone[3] and salt administration, œdema, hypertension, and fits result also Both the foregoing reveal the close though occult relationship of an acutely shutdown kidney with the eclamptic process when salt and water retention is an accompaniment

That the uterorenal reflex is essentially responsible for the anuria of concealed accidental hæmorrhage is evident from the extreme stretch resistance of the myometrium, and the clinical improvement after rupture of the membranes and splanchnic block The presence of a lesser degree of shutdown in pre eclampsia is indicated by the histological findings of renal biopsy, by the clinical signs (all of which *can* be entirely due to cortical ischæmia), by the reduced glomerular filtration rate,[4] and by the benefit conferred by measures which reduce renal resistance (e g, spinal anæsthesia, hydrallazine)

Obstetric anuria is thus an acute and severe shutdown, without previous accumulation of salt and water, unless pre eclampsia precedes it Pre eclampsia, on the other hand, is a less severe, gradual, and continuing ischæmia not attaining a complete shutdown usually, leading to salt and water accumulation and to consequent toxæmic manifestations

Mr Morris (April 13) has doubts about the relationship of myometrial *tension to pre eclampsia* In pregnancies complicated by hydramnios and twins, there is a greater likelihood of toxæmia, and in concealed accidental hæmorrhage the retention of blood can also provoke toxæmia In all these conditions intra uterine pressure is increased, but, apart from this obvious change, there is a more important association emphasised by the ætiological significance of primiparity in toxæmia—and that is the change in tension evoked. The explanation lies in the formula

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[1] McGaughey H S Weller H Parker Anslow W *Amer J Obstet Gynec* 1956 72 589

[2] Dieckmann, W J Toxemia of Pregnancy St Louis 1952 p 447

[3] Renzi A A Gaunt R *Ciba Symp* 1954, 6 1 30

[4] Page, E W *Gestation* Transactions of the 3rd Conference Josiah Macy Jun Foundation New York 1956 p 83

$$\text{Tension} = \frac{\text{pressure} \times \text{radius}}{2}$$

Increase in tension is the basic cause of toxæmia. As Reynolds[5] has pointed out, the radius of curvature of the primigravid uterus—invariably cylindrical after mid-term—is much greater than that of the usually globular multigravid uterus. Moreover, the contractions of labour can aggravate toxæmia, again reflecting the harm done by increased tension; while sustained contractions, with their tensioning effect, can initiate toxæmia as Nixon has shown.

Experimentally, increased tension is manifest in reduction of the myometrial circulation, as demonstrated in toxæmia by Mr Morris and his colleagues and others. Mr Morris found in one case that toxæmia lessened after fœtal death and the myometrial circulation improved though the fœtus had been retained. Here, tension may have become less because of the reduced tone of the dead fœtus and the withdrawal of hormonal stimuli to the myometrium. Corner and Csapo have shown that œstrogen increases the isometric tension of the uterus, which depends on the actomyosin content of the muscle. Adenosine, an actomyosin derivative, is much increased in toxæmia, for Green has found this increase of circulating adenosine in toxæmia ascribable to ischæmia of the uterine muscle and reflecting its increased tensions as well.

Clinically, Parviainen and his colleagues have shown that uterine tone is increased in nearly every case of severe toxæmia. Others have found an increase in blood pressure accompanying heightened uterine tonus.

Pre-eclampsia and acute glomerulonephritis are clinically very similar—œdema, hypertension, albuminuria, and maybe fits. Renal biopsy confirms the reversibility of the changes in both conditions and shows the similarity of the exudate in Bowman's capsule and the bloodlessness of the glomerulus. Both in pre-eclampsia and acute glomerulonephritis, the glomerular filtration rate is reduced. A significant recent finding is that salt induces hypertension at certain stages of acute glomerulonephritis[6]; this corresponds closely to the effect noted in toxæmia by Dieckmann—an effect that could be based on an accompanying renal ischæmia.

Apart from the confusion between tension and pressure, to which Dr Smyth (May 4) has referred, another explanation for the apparent exceptions to the tension-ischæmic link is the variable response of the kidney (e.g., the different incidence of recovery from nephritis after scarlet fever, the higher incidence of hypertension in older pregnant women, and the variable effect of posture and rest). Mr Morris's contention that serotonin can be held responsible for the cortical necrosis of concealed accidental hæmorrhage can be completely refuted by the fact that this hormone is responsible for characteristic symptomatology (especially severe dyspnœa) in argentaffinoma—symptoms never encountered in obstetric anuria; while his difficulty in accepting the Hæmex reaction as an explanation of the renal reflex postulated would be entirely removed by a realisation that the effector materials in question act as stimuli only while they are in the fresh state.

I agree with Dr Schuurmans (April 20) that the adrenals are concerned in hypertension in pregnancy, but as I argued at the meeting of the Royal Society of Medicine on Feb. 22, the corticoids (or any other hormones)[7] are not the primary cause. I cannot now deploy these arguments again, but one further fact may be added: cortisone-induced hypertension is maintained in spite of sodium deprivation and therefore cortisone cannot be responsible for the hypertension of toxæmia, which can often be reduced by restricting salt intake.

A sound knowledge of the problems involved emphasises the futility of a demand for direct measurements of these ætiological factors, while awareness of the fixity of the fœtal head and the difficulty of version in the primipara equally emphasise heightened tension.

London, W 1 JOHN SOPHIAN

SERUM-CYANOCOBALAMIN LEVEL IN CHRONIC INTESTINAL DISORDERS

SIR,—I have read with interest the article by Dr Meynell and his co-workers (May 4) on this subject, but am not as surprised as they are at the incidence of cyanocobalamin deficiency that they have found in idiopathic steatorrhœa. I am quoted in their excellent article as having found only 1 patient with a low serum-cyanocobalamin level among 29 with intestinal malabsorption of the sprue type. This statement is, however, misleading, as reference to table I of my paper,[1] will show. This table was concerned in particular with an investigation into folic-acid absorption; in fact, the serum-cyanocobalamin levels were given for only 17 patients, 6 of whom did not have megaloblastic anæmia. With 1 exception, no attempt was made to measure the serum-cyanocobalamin levels of patients who had been treated with cyanocobalamin or liver injections, and no doubt several of these had had low serum-cyanocobalamin levels before such therapy was given. At present we are investigating some of these patients by measurement of the absorption of labelled cyanocobalamin, and there is, as expected, evidence, in some, of malabsorption not only of folic acid but also of cyanocobalamin.

Department of Medicine,
University of Edinburgh. R H GIRDWOOD

EFFECTS OF ASCORBIC ACID ON THE HEART

SIR,—The oxidation/reduction processes play a very important, and possibly a decisive, rôle in the origin of electric potentials in living tissues. According to many authors, at least one phase of the action current depends on these processes. We are investigating the effects of ascorbic acid on the course of the action currents in the frog's heart, isolated and in situ.

In the first series of experiments we exposed the heart to a concentration of 1 in 10 ascorbic acid. Almost immediately there was a big increase in electric potential in the fading-out phase of the action current, which showed itself as an increase in the height of the T wave of the electrocardiogram (E C G).

In the second series of experiments we produced a low S T segment and inversion of the T wave by the use of strophanthin K. If the heart was then exposed to a 1 in 10 solution of the sodium salt of ascorbic acid, these effects were reversed: the S T segment became isoelectric, and the T wave positive.

With the heart in situ the same effects were seen, but they proceeded more slowly. No similar effects were seen in control experiments using other acids.

Ascorbic acid was used because it is readily available and not toxic. We explain the lack of effect on the E C G of ascorbic acid in the usual doses by the fact that it is altered in the pulmonary circulation and reaches the coronary arteries in an inactive form.

It might be possible to use ascorbic acid clinically in massive doses (e g , 10 g daily intravenously) to prevent the electrocardiographic changes typical of digitalis. Ascorbic acid might be protective in cases where digitalis is indicated in the presence of coronary insufficiency. In emergencies a massive intra-arterial dose could be given.

Wroclaw, Poland. S M EIMERL-WITKOWSKI.

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[5] Reynolds S R M Contr Embryol 1949 no 213 Amer J Obstet Gynec 1950 59 529 Reynolds S R M Baker, J T Contr Embryol 1951 34 592

[6] Chassin H Rev cubana Pediat 1955 27 1

[7] Sophian J Amer J Obstet Gynec 1956 72 643

[1] Girdwood, R H Quart J Med 1956, 25 87

Parliament

The Bomb Tests

In the debate on defence policy in the House of Lords on May 8, Lord **Cherwell** (formerly Prof F A Lindemann) stoutly defended the Government's intention to test nuclear weapons in the Pacific, and he discounted the risks to health of such tests as "negligible, not to say non-existent"

The British tests, he said, could not in any circumstances cause any significant increase in the number of stillbirths or defective children or of cases of leukæmia or bone cancer The question had been investigated by the highest authorities, who had agreed that the risks were negligible But people tended to believe the views of much less knowledgeable men, whose assertions were widely circulated as though they were the last word It was quite a joke now in scientific circles that if anyone wished to be advertised in the newspapers as a great nuclear expert, he had only to say that the British tests should be stopped Lord Cherwell was shocked to see that The Lancet had seen fit to countenance this campaign and had supported the views of "some unofficial group" which contradicted flatly the conclusions of the Medical Research Council committee It was amazing that such a journal should have so little regard for the leaders of the profession Among other cardinal errors, Lord Cherwell continued, the conclusions countenanced by The Lancet were based on the assertion that 0 1 microcurie of radium would cause 1 man in 200 to get bone cancer According to the International Commission on Radiological Protection, this quantity was permissible, and "permissible" was defined as "not expected to cause appreciable bodily injury to a person at any time during his lifetime"

It was very undesirable, Lord Cherwell declared, that such tendentious views, clearly based on wishful thinking, directly at variance with the conclusions of the most distinguished men who formed the International Commission, should be promulgated as though they were authoritative This sort of thing became particularly obnoxious when universally respected figures like the Pope and Dr Schweitzer were persuaded to intervene

The gamma radiation to which we were exposed from the fission products of all tests up to date was 150 times weaker than natural background radiation To frighten people by making out that this slight increase, two-thirds of 1%, was going to increase the mutation-rate by an appreciable fraction was deliberately dishonest Even the most cautious experts agreed that the effect of adding an extra 100% or 200% to the natural background dose would be negligible Yet 0 6%, according to our vociferous cranks, meant danger to the human race

Strontium 90 seemed to frighten people just because it had been linked with the hated word "cancer" According to the Medical Research Council's investigation, the amount of strontium 90 which we had absorbed up to date was 1000 times less than the amount considered safe for people working in factories where radioactive materials were used "Even if we allow a factor 10," Lord Cherwell remarked, "in case infants absorb more strontium than adults, we still have in hand a safety factor of 100"

No-one could be sure what would happen with radiation of such low intensity, but, Lord Cherwell added, "if anyone were to tell you that because half the people who took one grain of some poison died it followed that taking one six-hundredth of a grain would kill 1 person in 1200, I think you would be rather surprised I am not saying it is quite impossible in radioactive things, but it seems unusual"

Only those who had detailed knowledge of the design of the British bombs and knew how much strontium was produced in the detonator or blanket could form any idea of the amount the Christmas Island test would add to the atmosphere It was montrous that, lacking this essential datum, anyone should allow the assertion to appear in the press that the débris of every megaton equivalent would kill a thousand people

Referring again to those who opposed the continuation of nuclear tests, Lord Cherwell said "these well-meaning dupes forget that even if the tests did add to some tiny extent to the number of people who suffer from bone cancer or to the number of stillbirths, this would be a small price to pay for developing a really effective deterrent which would prevent war" It was moonshine to insist that radiation from débris of nuclear tests would cause adverse genetic effects, and, as for strontium 90 in bone, even the most pessimistic assumptions had only been able to make out that this amounted to a hundredth or even less of the quantity which the International Commission had declared safe for industrial workers These questions were plain scientific matters of fact There was no party issue involved at any rate there ought not to be

*** This debate is discussed in an editorial on p 1029

The National Health Service Contribution

On May 8 Mr **Dennis Vosper**, the Minister of Health, introduced the second reading of the Bill which increases the direct contribution from all insured people towards the National Health Service It also gives the health service contribution a separate existence and ends its administrative symbiosis with the National Insurance contribution Though, for reasons of convenience and economy, the health service contribution will continue to be collected under the shelter of the National Insurance stamp, its independence will be recognised by overprinting on the stamp the words "includes (rate) health service" Mr Vosper promised that when a new stamp is introduced the words would be incorporated in the design

Most of the points raised in the debate had been mentioned in what was described as the "preliminary canter" on the ways-and-means resolution[1] The Opposition regarded the increased charge as a regressive poll-tax and feared that the Government intended that contributions should play an ever larger part in financing the service The Government denied that it was their intention to shift the whole burden of the cost to either contributions or charges, but they wished to restore the balance between contributions and taxes which held when the service was started

Behind the financial cross-talk it was clear that speakers on both sides of the House felt that the National Health Service, though admittedly expensive, was a valuable national asset Several speakers made it plain that if people were asked to pay this extra contribution they should be sure of getting value for their money The preventive and industrial services, and hospital buildings, were given as examples of parts of the service on which more money could profitably be spent It was also clear that there was some uneasiness about the prescription charges Many people would be reconciled *to even larger contributions by the discontinuance of this charge on the sick*

Extension of Domiciliary Services for *Old People*

On May 10 Mr **Ronald Williams** moved the second reading of a private member's Bill which seeks to amend the National Assistance Act, 1948, so as to empower local authorities to make their own arrangements for domiciliary services for old people At present local authorities may only contribute to the funds of voluntary organisations which offer these services to old people Mr Williams *emphasised that it was not intended that the* Bill should in any way prejudice voluntary work, but there were many areas where old people were living in distressing circumstances and no voluntary organisations existed

Mr **Vosper**, the Minister of Health, said that this work seemed particularly suitable for voluntary organisations, and if the Bill received the assent of the House he hoped that wherever possible a local authority would use a local voluntary organisation as its agent He reminded Members that several local authorities had already, by private Bills, obtained powers of this kind The present Bill, he pointed *out*, empowered local authorities other than county and county-borough councils to provide these services and seemed to envisage the employment by the smaller authorities of visitors to render them About this he admitted that he was uneasy, for he feared that it might lead to fragmentation At present domiciliary workers were employed only by county and county-borough councils and he felt that the domiciliary health and welfare services should be kept together as a team He also thought it would be wiser to await the completion of the review of local government and its finance Apart from these reservations the Government was in favour of the Bill in principle and would not oppose it, but would seek to improve it in committee

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[1] See *Lancet*, May 11, 1957, p 989

The Bill was given a second reading

Visits to Mental-hospital Patients

On May 10 on the adjournment Mr **NORMAN DODDS** suggested that the attitude of the Ministry of Health to his requests to visit a patient in a mental hospital "revealed a disturbing state of affairs suggesting a deterioration in the safeguards affecting the liberty of the individual under our mental laws" His request, he related, had been referred to the medical superintendent of the hospital with whom, he was told, the final decision rested This he submitted was in fact not so, and he quoted regulations to show that the final authority was the Board of Control Why, he asked, had he not been informed that the board had an interest in the matter? He suggested that the board had ceased to be the instrument that it was set up to be—the safeguard of the liberty of the individual Not only had the board moved into the Ministry of Health building but its members held appointments on the staff of the Ministry

Mr **J K VAUGHAN-MORGAN**, parliamentary secretary to the Ministry, replied that the Board of Control still retained the duties originally held by the Board of Control and by the Commissioners in Lunacy in respect of the liberty of the subject The board was an independent body constituted by the Mental Deficiency Act, 1913 It was reorganised in 1930, and in 1948 certain functions were taken from it, but it retained the residual duties that it previously had Apart from the power to make statutory regulations and the power to direct the chairman as to the arrangements for the administrative business of the board, there was no statutory provision whatever which gave the Minister power in any way to control the board in the performance of its duties

Turning to the relationship of the Minister to the medical superintendent, he said that the superintendent was employed by the regional hospital board Under the terms of the National Health Service Act the Minister could indirectly, via the board, issue a direction to him on any subject, but whatever the legal position might be, no Minister would for a moment consider directing a medical superintendent on any matter such as this when that medical superintendent was primarily responsible for the health and welfare of a patient A visit to a patient detained in a mental-deficiency hospital might be paid at such times as the superintendent might direct If the superintendent did not direct, no visit could be paid The Board of Control could override the medical superintendent about visits to a patient, but the Minister could not direct or overrule the Board of Control

QUESTION TIME

Nuclear Tests

Dr **BARNETT STROSS** asked the Prime Minister whether he was aware that no threshold dose for radiostrontium might exist and that tests of nuclear weapons might already be responsible for some 50,000 cases of bone tumour in the future, and if he would therefore postpone the proposed British tests in the Pacific —Mr **R A BUTLER**, the Home Secretary and Lord Privy Seal, replied I assume that the hon Member has in mind statements in a report published by the Atomic Scientists' Association. I would draw his attention to the careful reservations made by the authors, they state

> In giving these estimates it must be emphasised again that apart from the considerable margin of error due to lack of adequate data they are based on the as yet unproved hypothesis of a proportional relationship applying to very small doses From this point of view they represent the most pessimistic approach

I am informed that the estimates made in this report are interpretations of factual evidence which was available last year to the Medical Research Council's special committee, but that the latter did not consider it an adequate basis to justify their making such calculations In these circumstances, the Government are not prepared to postpone the proposed tests

Dr **STROSS** Whilst accepting the quotations, may I ask whether the Minister does not agree that, although no one dare be dogmatic about this rather, terrifying risk that we are discussing and there is some doubt, any benefit of the doubt must be given to posterity, and that we have no right to be euphemistic or optimistic about this matter and the only possible way of approach is by pessimism and not by optimism?—Mr **BUTLER** I have in mind that the data available was before the M R C's special committee a year ago and we had it in mind at that time Therefore, I am not prepared on behalf of the Government to make an answer, on behalf of the Prime Minister, saying that we would abandon the tests on the basis of the atomic scientists' report which comes a year later I am prepared to take the matter most seriously, but I am not prepared to give any further conclusion

Mr **HUGH GAITSKELL** In view of the length of time which has elapsed since the M R C's report, the number of statements made by scientists in various countries, and the amount of additional evidence made available, could the Minister ask the M R C for a further report to bring the matter up to date?—Mr **BUTLER** I am certainly ready to do this, but I must honestly say that, since the M R C's report was published, no relevant new fact has become available as far as we are aware. Some fresh estimates have been made of the rate of accumulation of radiostrontium in human bone, but according to the information in my possession it would not be worth while doing what the right hon Gentleman suggests I will, however, certainly consider the suggestion and discuss it with my right hon Friend

Mr **N W HAMILTON** Will the Minister, in view of the conflicting views of world scientists on the harmful effects of nuclear bomb explosions, initiate the calling of an international conference of scientists in order to ascertain at least the minimum area of agreement?—Mr **BUTLER** The United Nations set up, in 1955, a Scientific Committee on the Effects of Atomic Radiation The committee, consisting of most respectable representatives of the most respectable nations, last met in Geneva from April 8 to 19 The whole question of radiation hazards and the effects of strontium 90 was considered by the committee, which is still collecting information, on which it will take some time to reach conclusions As this is an international body of scientists I should prefer to give it an opportunity to reach conclusions before we do anything else

Mr **GEORGE THOMAS** In view of the disturbing statement made yesterday by the Joint Parliamentary Secretary to the Ministry of Agriculture, Fisheries, and Food about the rate of strontium radiation found in the Welsh mountains and in that district[1] is not the Minister prepared to recognise that this is a new factor? How long have the Government had information about this, and will they continue to increase the amount of radiostrontium on these hills thereby risking the well being of future generations?—Mr **BUTLER** Those of us who have responsibility in these matters realise that strontium on herbage, especially on elevations such as the Welsh mountains, is the most easy to calculate But there is nothing I can *add at present to the reply* given by my right hon Friend the Prime Minister that so far the present averages measured in the United Kingdom are 67 of a unit for children under five years of age and much less for the rest of the population The International Commission on Radiological Protection accepted 1000 units as a maximum allowable for workers in special occupations Therefore, so far, although it is a matter of concern that on herbage on elevations especially in the Welsh mountains, there should be this deposit, we do not think the matter has reached a stage about which we need be unduly alarmed

Mr **ANEURIN BEVAN** Is it not extraordinary, when there is not doubt about the fact that these poisons are being spread throughout the atmosphere and that they are irreversible, that we should proceed to these tests before we get the report from the international body of scientists? If the extent of the poisoning is unknown but the fact that it is occurring is known, would it not be more civilised to stop all tests until we have the report?—Mr **BUTLER** The right hon Gentleman is ignoring the march of science It may be that through the process of tests we may find that the radiation effect is less marked than it is thought to be at present It is certainly not the intention of the Government, for reasons of scientific appraisal and for reasons of the defence of the country, to abandon the tests at the present time Mr **BEVAN** As far as we understand, there is no doubt about the fact that poisoning is taking place There is no doubt either that the poisoning is irreversible What there is doubt about at the moment is its extent Would it not, therefore, seem to be reasonable to everybody in all parties that until the facts are established by the international body of scientists, no more poisoning should be permitted ?—Mr BUTLER No, Sir I have said that for two reasons, namely, the scientific and the question of national defence, we think the tests should proceed in the interests of all

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[1] See *Lancet*, May 11, 1957 p 990

Mr GAITSKELL Can the Minister seriously argue that a postponement of these tests until the report is available would seriously endanger our national defence, or, indeed, interfere with the march of science ?—Mr BUTLER I am following, with I think absolute justice, the line which the Prime Minister has followed, and I think rightly followed, for the two reasons I have given—namely, in the forward march of science tests are necessary, they are also necessary in the interests of national defence

Day Hospitals

Day hospitals for the treatment of mental and nervous illness exist under the following regional hospital boards and boards of governors

Leeds
  St James' Hospital, Leeds
  Scalebor Park Hospital Burley in Wharfedale
  De la Pole Hospital, Hull
Sheffield
  Drury House, Leicester Road Narborough, Leicestershire
North West Metropolitan
  38, Marlborough Place, St John's Wood, London N W 8
North East Metropolitan
  Goodmayes Hospital, Goodmayes, Essex
South East Metropolitan
  38, Mason's Hill, Bromley Kent
South Western
  12, Grove Road, Redland Bristol, 6
Wales
  Whitchurch Hospital, Cardiff
Birmingham
  Uffculme Clinic Queensbridge Road, Birmingham 13
  All Saints' Hospital, Winson Green Birmingham 18
  Highcroft Hospital, Erdington, Birmingham 23
Manchester
  Oldham and District General Hospital Oldham
  Westhulme Hospital Oldham
  Cowley Road Hospital, Oxford
Bethlem Royal and Maudsley
  Bethlem Royal Hospital Beckenham
  Maudsley Hospital, London S E 5

Arsenic in Foods

Statutory limits for arsenic in foods are to be laid down and regulations will be introduced as soon as practicable based on the Food Standards Committee's recommendations of Jan 31, 1955 Full details of the proposed regulations will be circulated for consideration by the interests concerned

Public Health

POLIOMYELITIS VACCINATION

THE Ministry of Health has informed local health authorities that poliomyelitis vaccine will be distributed throughout the summer, although it will be left to medical officers of health, in the light of local conditions, to decide whether to continue or suspend vaccinations in their area It will be remembered that last year vaccination was suspended at the end of June That decision was taken because of the possible danger that vaccination during an outbreak might provoke poliomyelitis Since then the Minister of Health has sought the advice of the Joint Committee on Poliomyelitis Vaccination, which in turn asked for information from public-health services in countries which have had considerable experience with poliomyelitis vaccine, including the U S A and Australia No evidence has been obtained from these sources that poliomyelitis vaccination can provoke paralytic disease Paralytic poliomyelitis following inoculation has been associated particularly with alum-precipitated diphtheria toxoid and combined diphtheria-pertussis inoculation, whereas pertussis vaccine alone has not been associated with inoculation poliomyelitis in this country [1] Poliomyelitis vaccine seems to be similar to pertussis vaccine in this respect, and the committee felt that in general vaccination against poliomyelitis need not be suspended when the disease is prevalent

It has also been announced that the next groups to be offered poliomyelitis vaccine will be children born in 1955 and 1956 Afterwards children born in the years 1947–54 who were not previously registered will be offered another opportunity Parents will be asked to express in writing their wish to have their children vaccinated, and they are advised to watch for announcements from their local medical officer of health As before, two doses of vaccine will be given Until the end of April, sufficient vaccine for three quarters of a million children had been released The vaccine has been produced by one firm, but it is hoped that a second firm will soon come into production Suggestions have appeared in the press that extra vaccine should be imported from the U S A, but one difficulty about this is that British vaccine has been made with a less virulent strain of type 1 virus than that which is used in American vaccine, and it is argued that this change of strain has been an important factor in the safety of British poliomyelitis vaccine

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[1] See *Lancet*, 1956 ii, 1249

MEAT HYGIENE

A W H O monograph [1] brings together the latest information about the safe processing of meat from producer to consumer, emphasising that there is no room for complacency over meat hygiene either in under developed or in advanced countries No country can afford the disruption of activities in the home, or in the population generally, due to meat-borne diseases Meat hygiene also has an important economic rôle in averting losses in meat or its by-products and in preventing diseases which are transmissible to other domestic animals

In part I, C E Dolman considers the zoonoses, including the less well known ones such as pasteurellosis, leptospirosis, and listerellosis Not everyone may agree with his suggestion that in some parts of the world meat-inspection regulations and procedures respecting tuberculous cattle are probably too lenient This matter is reviewed exhaustively by H Drieux in the monograph

The section on slaughter includes many useful data In Britain all animals intended for human food must be stunned by means of a mechanically operated instrument, except animals slaughtered ritually for consumption by Mohammedans or Jews The admissibility on humane grounds of these ritual methods of slaughter has concerned health authorities and welfare societies for many years, and it is perhaps regrettable that the experts concerned with this monograph did not pronounce on this important subject A brief reference is made to a new method of pig stunning by inhalation of carbon dioxide gas—a method now being used in large abattoirs in the U S A and Scandinavia

Part IV deals with post mortem inspection H Thornton describes the general principles for this inspection and the judgment of diseased carcases and discusses the code of judgment in Britain, known as Memo 3/Meat Elsewhere the question is discussed whether codes of judgment should be discretionary or statutory, prescribing the form the post mortem examination should take and the judgments to be applied when the carcase or organs are abnormal or diseased Attention is drawn to the inspection problems presented by animals which are *slaughtered in emergency*, and to the value of bacteriology in judging fitness of such carcases for food

The techniques of bacteriological examinations and biochemical tests are dealt with by A Jepsen, who provides indisputable evidence that the extensive use of these tests brings greater accuracy to judgment, and is the means of saving much meat which would otherwise be condemned The monograph recommends that any slaughterhouse of importance should have its own laboratory where bacteriological and biochemical tests can be applied in any suspected case

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[1] Meat Hygiene World Health Organisation monograph series no 33 H M Stationery Office P O Box no 569 London S E 1 Pp 527 30s

In a section on the judgment of carcases affected with tuberculosis attention is drawn to the importance of recognising the nature of the lesions, for this indicates whether the disease is quiescent or whether it is active and likely to be disseminating bacilli throughout the systemic circulation Although meat as well as milk can cause tuberculosis in man, it is now clear that the possibility of infection through the digestive tract from meat carefully freed of tuberculous lesions is extremely small

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Obituary

WILLIAM HOWARD TYTLER

B A , M B Toronto

Dr W H Tytler, formerly professor of tuberculosis in the Welsh National School of Medicine at Cardiff, died on May 6 at Banchory, Kincardineshire, at the age of 71

He was born at Guelph, Ontario, and the first part of his life was spent in Canada and the United States After graduating M B from the University of Toronto in 1909 he held hospital posts in Montreal and Hamilton and later became assistant pathologist to the New York Hospital In the 1914–18 war he served in the Canadian Army Medical Corps in France and Belgium When he was demobilised he came to this country to work with the Medical Research Council at Hampstead During the three years he spent on the staff of the council he visited West Africa with the first Yellow Fever Commission

In 1922 Dr Tytler began his work in Wales when he was appointed bacteriologist to the central tuberculosis laboratory of the Welsh National Memorial Association at Cardiff, and he held this post until 1938 when he became professor of tuberculosis in the Welsh National School of Medicine He resigned from the chair in 1949 to become consultant adviser on tuberculosis laboratories to the World Health Organisation, and in this post he travelled extensively in Europe, India, and the Far East He retired in 1952 to take up poultry-farming in Scotland A keen gardener, he applied scientific knowledge to producing vegetables easily

S H G writes

Bill Tytler was shy and retiring, but once one was accepted as a friend he became a most charming and entertaining colleague His modesty overcome, he would tell of his experiences with Noguchi and others, and it was easy to realise the width of his knowledge and that his interests were both national and international He was of a restless inquiring nature and he had an able brain, trained to be precise and logical Undergraduate teaching was irksome to him and students sometimes had difficulty in following his trend of thought, but he was always in his element when discussing with postgraduates some abstruse problem in tuberculosis He was essentially a bacteriologist and never professed to be a clinician His publications were few but of outstanding quality, and his memorandum on B C G vaccination prepared in 1944 did much to influence those in authority to introduce its use to this country in 1949

All those who knew him well have derived much good from his companionship

In 1945 he married Miss Eileen Sellar, who survives him

BERNARD EHRENFRIED MYERS

C M G , M D Edin , F R C P

Dr Bernard Myers, consulting physician to the Royal Waterloo Hospital for Children and Women died at his home in London on May 9 at the age of 85

He was born at Auckland, and he was educated in New Zealand at Wellington College He came to this country to study medicine and he graduated M B in 1898 from the University of Edinburgh After holding a demonstratorship of anatomy there he took his M D with commendation in 1900 Afterwards he turned more and more to work among women and children He held clinical clerkships at the Coombe Hospital in Dublin and at the Hospital for Sick Children, Great Ormond Street, and the Royal Waterloo Hospital in London He began to write papers and booklets on child care, home nursing, and infant feeding and in 1910 he set out his plan for a model crêche About this time he joined the staffs of the Western General Dispensary and the Royal Waterloo Hospital

Dr Myers always maintained close ties with New Zealand, during the 1914–18 war he served as acting director of medical services to the New Zealand Expeditionary Force, and in 1917 he was appointed C M G in recognition of this work After the war he returned to his consulting practice in London His book on *Diseases of Children* appeared in 1922 and that on *Modern Infant Feeding* in 1930 In 1933 he was elected F R C P , and in 1937 he gave the unexpended balance of the funds of the St Marylebone Children's Clinic to the college to institute the Charles West lecture on the diseases of children Dr Myers was a past-president of the West London Medico-Chirurgical Society For many years he was consulting physician to the New Zealand government in London and commissioner in the United Kingdom for the New Zealand Red Cross

G S writes

A room in a dispensary off the Edgware Road in the 'twenties—an atmosphere of smells and cries inseparable from a children's department, white coated voluntary nurses weighing and measuring infants, and supervising it all, with courtesy, geniality, and obvious love, a gentle, rather stage type doctor This is my first memory of Bernard Myers As the years passed, these memories were strengthened At the Royal Waterloo Hospital, where I was his colleague for many years, he was for long the pædiatrician and will be remembered for his kindness and his skill with his small patients Highly regarded by all of us, he was a man of intense loyalty and could be relied on in any controversy—for there were controversies even in those days

His interests were varied He was proud to have been elected president of the West London Medical Society, and, working with him there too, I know how much time and thought he gave to the society His genial chairmanship of the annual dinner will long be remembered He was equally popular at the Savage Club and at the Waterloo Hospital dining club

In his passing at a ripe age I think that courtesy and kindness and a love for all humanity, especially children, are my outstanding recollections There have been more famous pædiatricians but never a greater gentleman

Dr Myers's wife died in 1953 He is survived by their three daughters

WALTER LIDWELL HARNETT

C I E , M A M D Camb , F R C S

When in 1934 Colonel Harnett retired from the Indian Medical Service after almost 30 years of distinguished service as a surgeon and teacher, he lost no time in embarking on a fresh career, and his thirteen years' work as medical secretary of the clinical cancer research committee of the British Empire Cancer Campaign were spent in compiling the monumental *Survey of Cancer in London* which appeared in 1952

He was born in 1879, the son of Dr W J Harnett F R C P E , of Barnet From the City of London School he went with an exhibition to St John's College, Cambridge, and after taking a first in the natural sciences tripos in 1899 he continued his medical studies at St Thomas's Hospital, where he held a university scholarship He qualified in 1903 and took the F R C S the following year He was a house-surgeon and assistant pathologist at St Thomas's before passing into the Indian Medical Service in 1907 The same year he won the Montefiore prize at the Royal Army Medical College After four years' military duty he was sent in 1911 as civil surgeon to Gauhati in Assam In 1914 he was posted to Bengal as resident surgeon at Calcutta Medical College During the 1914–18 war he was recalled to military duties and he served on the North-West Frontier, at Salonika, and, after the armistice, in Constantinople In 1925 he was appointed superintendent of the Campbell Medical School in Calcutta and he was also surgeon to the governor of Bengal For the four years before he retired in 1934 he was professor of surgery at the Medical College of Calcutta, and his quality as a teacher and his pioneer work in orthopædics were recognised when he was appointed C I E in 1933

Soon after his return to this country he began his work with the British Empire Cancer Campaign, and of his new career S C writes

It seems but yesterday since Harnett retired from his main job in life, "being a surgeon in India," and yet it is about 20 years Since his so called retirement he carved for himself a second career and in this period acquired many friends I only knew him in this second phase, and learned to appreciate his mixture of gentleness and determination, his politeness, his accuracy of thought, his desire to serve the British Empire Cancer Campaign, and his frustrations with his material Imagine this man, so punctilious in his pursuit of accuracy, faced with follow-up cards filled in by busy, harassed, temporary registrars at "a bob a card" Imagine this in war time, when cards relating to the civilian cancer patient were remote from the main interest of most doctors Yet with these slender twigs of death records, he built a monument, *The Survey of Cancer in London* Whatever the value of this statistical review—and all such studies are of transient interest only—it gave him a background for his intellectual life He got acquainted with the younger generation of hospital doctors in Greater London, he visited them, even pursued them at times, he discussed his work with them and then quietly saw the older generation and tried to balance the views

I cannot speak of him as a colonel or an operating surgeon, only as a retired colonel, a paper surgeon, yet in the 20 years I knew him, I got to like him more and more, and to respect his character If in the Valhalla he just joined there are record cards, I feel sure he could not resist taking them for scrutiny to Lockhart-Mummery, and saying what he so often said to me "you think this is true?" If the pursuit of truth is an achievement in itself, Harnett has achieved his ideal His memory will long linger with all who knew him

Colonel Harnett leaves a widow, formerly Miss Nellie Bartingale There were no children of the marriage He died on April 24, while attending the funeral of a friend with whom he had served in India

DAVID JONES THOMAS
M R C S, D P H

Dr Thomas, who died at Salisbury on May 4, at the age of 84, was for more than thirty years medical officer of health for Acton He was born in Newcastle Emlyn, Carmarthenshire, and qualified at the London Hospital in 1899 After serving as Sir Frederick Treves's house-surgeon, he took the D P H in 1900 and was appointed M O H at Merthyr Tydfil the same year In those days outbreaks of smallpox and typhoid fever were commonplace, and Dr Thomas even encountered an epidemic of typhus In 1907 he was appointed M O H for Acton He held this post at a time when many advances in preventive medicine were being made and he was one of the pioneers of diphtheria immunisation

A colleague writes

Dr Thomas will be remembered as an intensely patriotic Welshman, a man of deep religious convictions, and a distinguished freemason His hobby was the study of early parochial registers He married Gwladys Roberts, the Welsh singer, and cared for her during her long illness until her death last year They had four children, two of whom are doctors Dr Thomas's life was one of hard work and unselfishness Many Welsh folk will hear of his passing with "hiraeth"

Dr GEORGE AUDEN

P R K writes

It is now nearly 30 years since Dr Auden first welcomed me to Birmingham as a very junior colleague of his, and from then till his death I had the benefit of his inspiring friendship His learning, his clarity of thought, his energy, and the simplicity—even austerity—of his life were known far and wide To have had his friendship was a privilege Such men are rare indeed, and I for one will never forget *Ave atque vale*

Births, Marriages, and Deaths

BIRTHS

HERBERTSON —On April 27 at Cambridge, to Margaret and Basil Herbertson—a son Michael Jonathan

Diary of the Week

MAY 19 TO 25

Monday, 20th

UNIVERSITY OF LONDON
5 P M (St Mary's Hospital Medical School Paddington, W 2) Prof G W Thorn (Harvard University) Studies on Aldosterone Secretion in Man (First of two lectures)

POSTGRADUATE MEDICAL SCHOOL OF LONDON Ducane Road, W 12
4 P M Dr W S C Copeman Steroid Treatment in Rheumatoid Arthritis

Tuesday, 21st

UNIVERSITY COLLEGE LONDON Gower Street W C 1
5 30 P M Sir Cyril Burt, D SC, Inheritance of Mental Ability (Walter Van Dyke Bingham lecture)

UNIVERSITY OF LONDON
5 P M (St Mary's Hospital Medical School Paddington W 2) Prof Thorn Some Effects of Adrenal Cortical Steroids on Intermediary Metabolism (Second of two lectures)

MEDICAL RESEARCH COUNCIL
5 P M (National Institute for Medical Research Mill Hill N W 7) Dr P C Zamecnik (Boston) Recent Studies on Protein Synthesis

INSTITUTE OF DERMATOLOGY, Lisle Street, W C 2
5 30 P M Dr D O'Neill Emotional Aspects of Skin Diseases (First of two lectures)

WEST END HOSPITAL FOR NEUROLOGY AND NEUROSURGERY, 91 Dean Street, W 1
5 30 P M Mr L C Oliver Surgical Aspects of Head Injuries

UNIVERSITY OF LIVERPOOL
5 15 P M Prof J B S Haldane, F R S Idiosyncrasy or Genetics and Medicine

UNIVERSITY OF DUBLIN
4 30 P M (School of Physic, Trinity College) Prof Adolph H Schultz (Zürich) Past and Present Views of Man's Specialisations (John Mallet Purser lecture)

Wednesday, 22nd

ROYAL SOCIETY OF MEDICINE, 1 Wimpole Street, W 1
5 P M *Endocrinology* Dr R W Luxton Dr Deborah Doniach Mr Vaughan Hudson, Dr A D Thomson Hashimoto's Disease

POSTGRADUATE MEDICAL SCHOOL OF LONDON
2 P M Dr B A D Stocker Heritable Transformations of Bacteria

INSTITUTE OF DERMATOLOGY
5 30 P M Dr I A Magnus Epidermal Energy Relationships in Health and Disease

INSTITUTE OF DISEASES OF THE CHEST Brompton, S W 3
5 P M Dr Joseph Smart Pleural Neoplasms

BRITISH ASSOCIATION OF SPORT AND MEDICINE
5 30 P M (London Hospital Medical School, E 1) Sir Adolphe Abrahams Stitch and Cramp

BIRMINGHAM MEDICAL INSTITUTE, 36 Harborne Road Edgbaston
8 P M *Psychiatry* Dr C A H Watts Dr G A Wray, Dr A M Spencer Who Should be Sent to a Mental Hospital?

Thursday, 23rd

ROYAL SOCIETY OF MEDICINE
4 P M *Urology* Dr James Robertson Diabetes in Urology Mr G F Murnaghan Dynamics of the Renal Pelvis

ST MARY'S HOSPITAL MEDICAL SCHOOL
5 P M Dr S Udenfriend (Bethesda, U S A) Biogenesis and Metabolism of 5 hydroxytryptophan

INSTITUTE OF DERMATOLOGY
5 30 P M Dr O'Neill Emotional Aspects of Skin Diseases (Second of two lectures)

NUFFIELD ORTHOPÆDIC CENTRE, Wingfield Morris Orthopædic Hospital, Oxford
8 30 P M Mr William Waugh Pathology of the Tarsal Navicular

HONYMAN GILLESPIE LECTURE
5 P M (University New Buildings, Teviot Place Edinburgh) Prof J C Goligher Surgery of Ulcerative Colitis

UNIVERSITY OF ST ANDREWS, Queen's College, Small's Wynd Dundee
5 P M Prof Robert Cruickshank Acute Respiratory Infections in Childhood

Friday, 24th

ROYAL COLLEGE OF OBSTETRICIANS AND GYNÆCOLOGISTS, 58, Queen Anne Street W 1
5 P M Dr Claud Taylor Mesodermal Mixed Tumours of the Female Genital Tract (William Blair Bell lecture)

ROYAL SOCIETY OF MEDICINE
5 P M *Pædiatrics* Dr Dermod MacCarthy Mr G H Macnab Mr D F Ellison Nash Dr L Guttmann Problems of Spina Bifida Cystica
8 15 P M *Obstetrics & Gynæcology* Dr Cicely Williams Mr H B Parry Prof G Gordon Lennon, Mr C K Vartan Prevention of Eclampsia

POSTGRADUATE MEDICAL SCHOOL OF LONDON
10 A M Mr E G Muir Pathology, Treatment and Results in Malignant Disease of the Large Bowel

ST MARY'S HOSPITAL MEDICAL SCHOOL
5 P M Mr S Bender Obstetric Problems in General Practice

INSTITUTE OF LARYNGOLOGY AND OTOLOGY 330 Gray's Inn Road W C 1
3 30 P M Mr G H Howells Sinusitis

UNIVERSITY OF OXFORD
9 15 A M (Radcliffe Infirmary, Oxford) Dr Sheila Sherlock Jaundice

Notes and News

A NEW CUMBRIAN HOSPITAL

In 1945, the hospital survey of the North West recommended to the Ministry of Health that West Cumberland was the one area where permission should be given for building a new hospital It is an isolated industrial area with a population of 140,000, nearly 40 miles from the nearest alternative hospital centre The present hospitals are small and uneconomical, and provide a total of 400 beds where (according to Ministry standards) 900 are needed Moreover, industrial developments (including the atomic centre at Sellafield) are causing an influx of population, and an existing hospital block for geriatric patients has had to be abandoned because of subsidence damage

Two possible sites in the area were vested in the Minister, of which one was in use as a park The other (acquired by the trustees of Whitehaven Hospital before 1939) was chosen it lies on the Millom Road, 2 miles from the centre of Whitehaven. The hospital is to contain 438 beds and will cost some £3 million It will provide for special illnesses not otherwise catered for in the area, and it is expected that patients needing special investigation will gravitate there The Workington Infirmary is being enlarged to become a hospital of 170 beds, to deal with most of the routine medical and surgical work in the borough and an increasing proportion of elderly sick patients

The work is planned in stages, of which the first (conversion of the mansion house on the site to a 41-bed unit for tuberculosis and chest disease) is complete The second will include the erection of all the one storey buildings (geriatric, mental-illness, and infectious disease units, and ancillary services), this will be complete in the autumn of 1959 The third provides for the main hospital block with wards accommodating the major specialties, and operating-theatres and laboratories The fourth will see the erection of a 40 bed maternity unit, the present maternity accommodation at the old Whitehaven Hospital should suffice until this stage is reached

Difficulties in staffing are expected The phasing of the construction should help to solve these by allowing gradual recruitment The nurse-training school in West Cumberland has been reorganised and a recruiting drive is to be launched A new school for assistant nurses has been set up at Workington and a new school of radiography at Carlisle, and the number of laboratory technicians in training has been increased

The tuberculosis block was opened formally on Jan 17 The last phase should be complete and the hospital fully occupied in the summer of 1963

WORKING PATIENTS

Since 1954 the men patients at Fulbourn Hospital, Cambridge, have been gradually drawn into a more active way of life As the report of the hospital for 1956 shows, the benefits of occupation are already becoming apparent and the shape of the new life of the hospital has begun to emerge Although the number of men treated has risen by 26% over the past two years, the number of resident men patients has fallen by 8% and in 1956 stood at 341 13 patients (11 of them long stay) were going out to work every day, during the year 37 patients had gone out to work of whom 17 were discharged (including 4 long stay patients) The work included such jobs as aircraft fitter, meat-pie packer, and cement-worker They have ' all lived a fuller life mixed with the outside world and earned useful money " Indeed during 1956 they contributed £1600 to the hospital for their keep Other patients have worked inside the hospital on piece work such as packing car radio fittings, soldering electrical joints for television aerials, and surfacing wireless fronts

The effort to find more occupations for the women patients began later and is not yet so far advanced, but the wards are already quieter, and there is less sedation and incontinence It is doubtful whether it will be possible greatly to reduce the number of long stay women patients, for nearly half of all the women patients are old age pensioners, and over a quarter of them have been in the hospital for more than twenty years The longevity of women and modern drugs are gradually filling the hospital with aged long term women patients few of whom really need psychiatric nursing, and, as the report wistfully points out until alternative care is offered to these patients Fulbourn will be unable to get on with what is really its proper work—the treatment of the young housewives and middle aged mothers with families who need temporary psychiatric help

TUBERCULOSIS CONTACTS AT WORK

Dr F A Nash, medical director of the South-West London Mass X-ray Service, has lately reported [1] a series of surveys of firms one of whose employees has contracted tuberculosis This was done in two ways (1) when a chest physician notified a case of tuberculosis, he told the director of the mass X-ray service where the patient was last working, and the firm was then offered mass radiography in the usual way, without mention of the reason (2) all firms covered by the service in the area were asked to approach the service when a case of tuberculosis was diagnosed

In the first group, by the end of 1955 thirty-two firms had been visited and 63% of the 12,326 employees radiographed 85 people (1 1%) were found to have lesions, probably tuberculous, needing clinic supervision In the second group nineteen firms were visited 62% of their 11,107 employees were radiographed, and 49 (0 7%) had lesions needing supervision

The age and sex composition of these firms were similar to those of firms examined in routine surveys, where the incidence of cases found is typically 0 44% in the same area On the other hand, the proportion of employees who had not been radiographed before was much higher (44% as against 26 5%) *No other obvious factor (such as poverty or bad working-conditions)* differentiated the firms where these contacts were found from others Probably they are firms which have not been visited by mass X-ray units Findings in the surveys also suggest that radiography of his workmates protects the individual from contact with infection

University of Oxford

On May 2 the following degrees were conferred

D M—E J L Lowbury J D L Reinhold, W H Taylor, W R T Turner

B M—D S Ellis I A Riley (in absentia)

On June 26 the honorary degree of D.LITT will be conferred on Dr J F Fulton, Sterling professor of the history of medicine in the University of Yale

University of Cambridge

On May 4 the degree of M B was conferred on D H H Metcalfe

University of Birmingham

Prof A P Thomson's term of office as dean of the faculty of medicine has been extended to Sept 30, 1959 He will then be succeeded by Mr A. L d'Abreu, part-time reader in thoracic surgery and consultant surgeon to the United Birmingham Hospitals

The following have been given the title of university clinical lecturer

Obstetrics and Gynæcology—Dr H Roberts

Anæsthetics—Dr Ann A Guest, Dr J M. Inglis, Dr R E Lee, and Dr W L Price

Radiology—Dr P Jacobs and Dr C P Moxon

Royal College of Surgeons of England

At a meeting of the council on May 9, with Sir Harry Platt, the president, in the chair, the Cecil Joll prize was presented to Prof P R Allison (Oxford)

Dr G G Lyttle, Dr G F Burnell, Dr R F Guymer, Surgeon Vice Admiral R C May, and Prof P K. Chanmugam were admitted to the fellowship, having been elected as medical practitioners of twenty years standing

A Jacksonian prize was presented to Mr Alan H. Hunt and a certificate of honourable mention to Mr R E Horton. The Gilbert Blane medal for 1957 was awarded to Surgeon Commander S Miles, and the Begley prize to Miss Sybil Birtwistle

Postgraduate diplomas and diplomas of membership were conferred on the candidates named in the report of the comitia of the Royal College of Physicians (*Lancet*, May 4, 1957, p 942) A diploma of membership was also conferred on J J. Key

British National Conference on Social Work

The theme of this conference's meeting in Edinburgh from Aug 11 to 14 is to be children and young people The chairman will be Prof Alan Moncrieff Other medical speakers will include Prof Richard Ellis, Dr G W Ireland, and Sir Sydney Smith Further particulars may be had from the secretary of the National Council of Social Service, 26, Bedford Square, London, W C 1

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[1] Nash F A *Brit J Tuberc* 1957, 51, 151

Royal College of Physicians of Edinburgh

At a meeting of the college on May 7, with Sir Stanley Davidson, the president, in the chair, the following were elected to the membership

Alexander Slessor D M Douglas, Sheila P V Sherlock W G Macfie J G Opie D M Prinsley D E Anderson, Mirko Michael Kubik, K B Yuill J P Anderson J C Davidson A D Stuart, Beatrice S Chinniah, T P Telfer Kartar Singh Rai J M Walker, J P Lavender A J Cameron G D Forwell, E V Pieris, Muhammad Ibrahim Memon, Philine Theophila Pieris J I Forbes Leela Nil Shourie Shyama Pada Khatua P W A Botha, Francis Lothe, G P McNicol J N Park, E G Warburton, Gobindram Arjundas, C P Dancaster, Debabrata Sarma Sheila R Esrachowitz Hans de Villiers Heese W J Fessel, W D Smith

A motion was passed unanimously that the college agree to coöperate with the Royal Commission on the remuneration of doctors and dentists and to submit evidence

Royal College of Surgeons of Edinburgh

At a meeting of the college held on May 10, with Sir Walter Mercer, the president, in the chair, the following were admitted to the fellowship

B M Andrea A C Arulpragasam J R Badger D D Beard, K S Brearley J J Breitenbach Madhav Ramchandra Chaudhary, J E *Choo* Kenneth *Clark*, I A Coombes, K B Cornwell, R G Denniss J A Doig, G R Gordon Syed Abdullah Hussaini, Kevin *Johns Rasmus de Ramner Jooste*, Koratti Ardhanariswar Kalyanam I J Kaplan L P Bandara Kiriella, Bernard Lotzof, H L J Lusby, D O MacPhail, E Matthews, F A Meintjes P R Myerscough J G B Myles, C V Petersen, W H Raynham, A A Roux J N Segelov, Marakada Venugopal Shetty, Tribhuan Pati Singh M D M Staunton, I B Taft Ram Narayan Tiwary, Cyril Toker W K M C Watkins, H G Watts, D W Whiteway G B Wylie

Royal Faculty of Physicians and Surgeons of Glasgow

At a meeting of the faculty on May 6, with Prof Stanley Alstead, the president, in the chair, the following were admitted fellows of faculty

Varghese Benjamin J W Howie (*qua* physician) B T Hammond J D L Kirstein, C J Longland, Maung Shwe Tin (*qua* surgeon)

Birmingham Medical Institute

This institute will close its library and office at 154, Great Charles Street on May 17 and will reopen on Monday, May 27, at 36, Harborne Road, Edgbaston The local offices of the following organisations also will move to 36, Harborne Road Birmingham Local Medical Committee, British Medical Association, Medical Insurance Agency, and Medical Benevolent Society

World Health Organisation

Dr W Aeg Timmerman has been appointed assistant director general in charge of central technical services, in succession to Dr H S Gear

Born in The Hague in 1893 Dr Timmerman studied at the University of Leiden and worked for several years at the Institut Pasteur in Bandung, Java before he was appointed in 1934 director of the national institute for public health in the Netherlands He held that position until 1950 when he joined the staff of W H O as director of the division of therapeutic substances

Dr Gear is remaining in Geneva to complete some technical studies on behalf of W H O

Clean Air Council

This council has now been set up, under section 23 of the Clean Air Act, 1956, to help the Minister of Housing and Local Government to keep under review the progress made in abating the pollution of the air in England and Wales, and to obtain the advice of people with special knowledge, experience, or responsibility of prevention of pollution The Minister himself will be chairman, and his parliamentary secretary and the parliamentary secretary of the Ministry of Power vice-chairmen The 29 members appointed include Dr C A Bence, a Cardiff alderman, Dr Llewelyn Roberts, M O H for Sheffield, and Prof A B Semple, M O H for Liverpool

General Practice Reform Association

Among resolutions passed at the third annual general meeting held in London on May 4 were

That this meeting welcomes the fact that the Royal Commission is prepared to consider evidence on the remuneration of assistants in general practice

That the 5% interim increase in general practitioner remuneration should be distributed so that as in the case of the hospital doctors those with the lower incomes will receive a higher percentage increase

That the minimum permitted share for a junior partner in any general practice partnership in the National Health Service should be not less than one half of the largest share in the partnership and that an incoming partner's share should be required to reach parity or near parity with that of the other partner(s) in not more than five years from the date of his admission to the partnership

Medical Research Society

Dr Stanley F Bradley, of Columbia University, will deliver a lecture to this society on Friday, May 31, at 5 30 P M at the London School of Hygiene, Keppel Street, W C 1 He is to speak on circulatory adjustments to postural changes

National Society for Mentally Handicapped Children

The annual convention of this society is to be held at County Hall, Westminster Bridge, London, S E 1, on Saturday, May 25, at 10 45 A M The speakers will include Prof R S Illingworth Further particulars may be had from the society, Kingsway Chambers, 162A, Strand, W C 2

British Association for Physical Medicine

At the annual general meeting held at the Middlesex Hospital, London, on April 6, with Dr P Bauwens, the president, in the chair, the following officers and new members of council were elected

Vice president Dr H A Burt, hon treasurer Dr Donald Wilson, hon secretary, Dr G O Storey hon editor, Dr A C Boyle council Dr H J Glanville, Dr S Mattingly, and Dr N R W Simpson

Registers of Medical Auxiliaries

The Board of Registration of Medical Auxiliaries has published new editions of its registers of dispensing opticians, orthoptists, and operating theatre technicians The board also maintains registers of chiropodists and radiographers, and a register of audiology technicians is in course of preparation Copies will be supplied free to doctors on application to the registrar of the board, B M A House, Tavistock Square, London, W C 1

National Birthday Trust Fund

In 1955 the trust set up a steering committee with observers from the Ministry of Health, Department of Health for Scotland, and Welsh Board of Health, and representatives of the Royal College of Obstetricians and Gynæcologists, the British Medical Association, the Society of Medical Officers of Health the College of General Practitioners, and the Royal College of Midwives to consider how best to carry out a survey into stillbirths and infant deaths in the first week of life The *committee have approved the proposals for this* perinatal survey and it is hoped, with the permission of medical officers of health and obstetricians, to invite midwives to collect the information about all births under their care during one week in November and to obtain additional details from the health visitor about the state and health of the baby when it is a few weeks old A pilot scheme has already been carried out in Nottingham

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The late Sir Percival Hartley, F R S has left £1500 to Leeds University *to form the* Hartley Memorial Fund for the promotion and furtherance of advanced study and research work in biochemistry *or in bacteriology*

Appointments

FAIRLAMB, A H, M B Durh, D P H senior M O Hull
MAIR, CATHERINE H, L R C P E assistant M O and school M O, Cumberland
MEDHURST, G A M R C S D M R D consultant radiologist, Kettering/Northampton hospital area
SELLORS, T H, M CH Oxfd F R C S consultant surgeon National Heart Hospital London

Charing Cross Hospital, London
- *COLEMAN, D J*, M B Lond, F F A R C S D A part time consultant *anæsthetist* Wembley Hospital
- PHILIP P F M S Lond F R C S part time consultant surgeon Charing Cross Hospital
- RABINOWITCH, J M B Lond D M R E part time consultant diagnostic radiologist, Harrow Hospital

Navy, Army, and Air Force Institutes
- ARMSTRONG J B, M B Aberd assistant M O, London headquarters
- GEERF ANGELA M M B Lond assistant M O, London headquarters
- GOODHARDT L S, M B Lond assistant M O London headquarters
- KINSMAN F M M R C S assistant M O London headquarters
- McDONALD ALISON D, M D Lond D C H D P H assistant M O London headquarters

Colonial Appointments
- BROWNE R A, M B Aberd D A assistant anæsthetist Barbados
- COOGAN R J L R C P I D I H M O H Jamaica
- GORDON S G M B Lond D T M & H, D I H D D M S Eastern Nigeria
- HALLETT ANTOINETTE I M B Lond D OBST M O Somaliland
- HULSE BERNICE M L M S S A chest physician British Honduras
- ONWU S E, O B E M B Edin, D T M & H D M S, Eastern Nigeria
- PROCOPE C A M M R C S M O Trinidad

LEUKÆMIA *

RONALD BODLEY SCOTT
MA, DM Oxfd, FRCP
PHYSICIAN TO H M THE QUEEN, PHYSICIAN TO ST BARTHOLOMEW'S HOSPITAL

THE topic I have chosen is a latter day affliction, and a glance at the titles of previous Lettsomian lectures shows that leukæmia has never before been their subject. I am, moreover, denied the conventional gestures of filial piety, because it was not until twenty-six years after the death of John Coakley Lettsom that Barth and Donné, at the Hôtel Dieu in Paris, noted "the remarkable predominance of mucous globules" in the blood of a patient with splenic enlargement Their observation was not published for many years (Donné 1844), and the first recorded examples of leukæmia are to be found in the *Edinburgh Medical and Surgical Journal* of Oct 1, 1845, where David Craigie and John Hughes Bennett separately reported cases of hypertrophy of the Spleen and Liver in which Death Took Place from Suppuration of the Blood A few months later Rudolf Virchow (1845) described a case of "Weisses Blut," and there followed an acrimonious wrangle over priority, the faint echoes of which were audible as late as 1885, when William Osler cast the deciding vote for Virchow Undoubtedly Virchow had more insight than his rivals into the nature of the leukæmic process, and in 1847 he introduced the word "leukæmia" and distinguished splenic and lymphatic varieties He had, in Osler's words, "vindicated a place in pathology for the white blood corpuscle"

Although acute leukæmia was described by Friedrick a hundred years ago (1857), further advance awaited Paul Ehrlich's (1891) introduction of specific methods of staining the leucocytes These permitted the recognition of the myeloblast by Otto Naegeli in 1900 and the separation of the cytological varieties of leukæmia Monocytic leukæmia, the last of these to be identified, was not described until 1913 (Reschad and Schilling 1913)

Although leukæmia is something of a parvenu with barely a hundred and twenty years of respectable ancestry, it has recently become the focal point of hæmatology Its inevitably fatal outcome and the youth of many of its victims have aroused the interest and sympathy of the physician and have stirred the emotions of the public, it provides the research-worker with a fertile field for his ventures in the chemotherapy of cancer, and the problems of its ætiology have become the concern of the epidemiologist, the statistician, and the radiologist

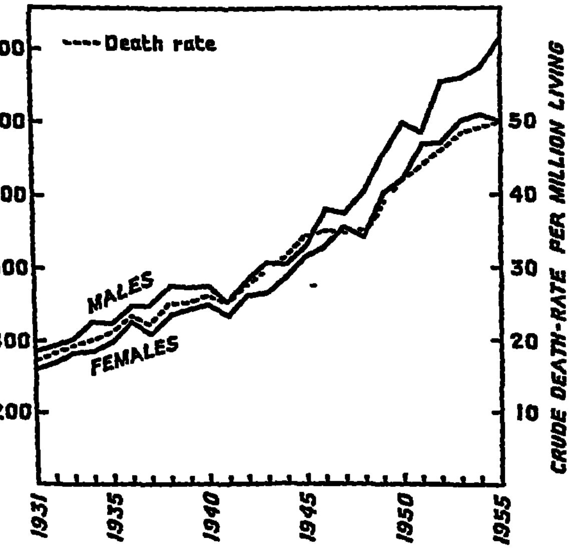

Fig 1—Mortality due to leukæmia in England and Wales 1931–55

These lectures can do little more than touch on some aspects of a subject which has become immense, in the main they will be a record of personal experience of leukæmia, viewed from a clinical and therapeutic standpoint The present series of some 570 patients has not been collected consecutively, it is undoubtedly weighted by selection, and it must not be regarded as a representative sample of the general leukæmic population Nevertheless the patients with acute leukæmia form a consecutive series, and those with the chronic varieties, being unselected, may be claimed as fair examples of the totality of sufferers from these diseases

Incidence of Leukæmia

The disease is still uncommon but its incidence, in all countries from which statistics are available, has shown a steady increase during the past twenty years In England and Wales the crude death-rate per million living was 17 in 1931 and 50 in 1955, or, in absolute numbers, 685 persons were certified as dying from leukæmia in 1931 and 2224 in 1955 (Registrar-General 1956) (fig 1)

At all ages below 65 the number of males dying from this cause exceeds the number of females From 1931 to 1955 the major increase has been in older patients, the age-distribution in 1940 and 1954 are contrasted in fig 2 Similar changes have been reported from other countries (Cooke 1954, Lancaster 1955, Phillips and Owchar 1955, Gunz and Hough 1956) The only two causes of death which have shown a greater rate of increase during this period are carcinoma of the lung and coronary thrombosis

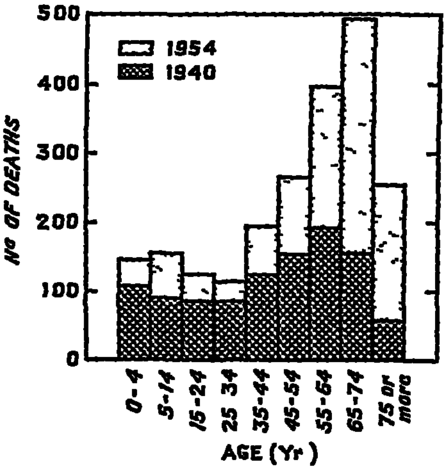

Fig 2—Age-distribution of deaths due to leukæmia in 1940 and 1954

Other vagaries in the incidence of leukæmia are a preponderance of urban over rural dwellers, of well-to do over less well to do, and, in the United States, of white over coloured—although this difference is considerably less when the ages are standardised (Hewitt 1955, Meadors 1956)

It seems likely that more precise diagnosis explains some of this increase but certainly not all It must be accepted that the incidence of the disease is steadily rising

There is still difficulty in estimating the incidence of the various types of leukæmia The variations shown in table I are probably to be attributed to selection, although local differences may play a part

Ætiology of Leukæmia

The nature of the leukæmic process is now generally held to be neoplastic, and, when "cancer" is defined in

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* The first Lettsomian lecture for 1957, delivered before the Medical Society of London on Feb 11 The second and third will appear in forthcoming issues

TABLE I—INCIDENCE OF MAIN VARIETIES OF LEUKÆMIA

Reference	No of cases	Acute (%)	Chronic myeloid (%)	Chronic lymphatic (%)	Undetermined (%)
Wintrobe (1956)	2424	40 1	29 0	30 9	
Gunz and Hough (1956)	553	62 3	17 5	14 5	5 7
MacMahon and Clark (1956)	1636	44 5	19 [illegible]	21 3	11 5
Gauld et al (1953)	647	41 9	26 [illegible]	32 0	

terms of dynamic cell behaviour, there can be little quarrel with this view It is undeniably a purposeless progressive uncoordinated cellular proliferation, superfluous to the needs of the host, and continuing after the evocative stimulus (if one can be identified) has ceased to operate As in other forms of cancer, the abnormality seems to reside within the cells themselves, which exhibit an unrestrained and undisciplined capacity for reproduction The fundamental cause of leukæmia is thus to be sought in the larger mystery of the cause of cancer, and at present we can only fruitfully inquire into the influences which may play some part in initiating this disorder of cellular behaviour

External Agents

In man the only external agent whose importance has been established is ionising radiation Some of the evidence for this contention, which seems irrefutable, is as follows

The incidence of leukæmia in survivors of the atomic bomb in Hiroshima has been four and a half times that of the general population of Japan Its frequency in those severely irradiated at less than 2500 metres from the hypocentre of the explosion was 1 in 172, whereas in those outside this radius it was only 1 in 12,912 (Moloney 1955, Moloney and Kastenbaum 1955)

In patients with ankylosing spondylitis treated by irradiation the deaths from leukæmia amount to between ten and twenty times the expected number (Court Brown and Abbatt 1955, Abbatt and Lea 1956, Court Brown and Doll 1956)

There are reports of leukæmia in patients previously irradiated for thymic tumours or treated with radioactive iodine for thyrotoxicosis (Blom et al 1955, Abbatt et al 1956, Pochin et al 1956)

The mortality from leukæmia in radiologists between the ages of 35 and 74 is three and a half times that of other members of the medical profession, and eight and a half times that of all white males of the same age (Peller 1952)

Diagnostic radiology of the pelvis in pregnancy may increase the chances of leukæmia appearing in the child (Stewart et al 1956)

The evidence that other agents may be leukæmogenic is less convincing

The best attested is perhaps chronic benzene poisoning, the causal efficacy of which is accepted in France as beyond question (Bernard and Braier 1951) I have experience of an instance in which two men were exposed to the fumes of benzene one developed an aplastic anæmia from which he recovered, and the other died from acute myeloblastic leukæmia

Acute leukæmia following marrow aplasia due to chloramphenicol has been recorded (Lebon and Messerschmitt 1955) It has also been reported after agranulocytosis due to sulphonamide (Wilkinson 1955) It seems probable that regeneration of the bone marrow after severe injury may transcend the physiological and assume neoplastic characters

The termination of idiopathic aplastic anæmia in acute leukæmia is well recognised (Wintrobe and Mitchell 1940, Black and Meynell 1951), and I have observed it on 3 occasions

Heredity

A genetic basis for leukæmia has been suggested by the occasional report of several cases in one family

Videbæk (1947) obtained a family history of the disease in 8% of 209 patients, it was particularly frequent in the chronic lymphatic form

Analyses of larger series have not confirmed his claims, Guasch (1954) noted consanguineous leukæmia only 39 times in 8586 collected cases, an incidence of 0 5%

Of my patients, there was a family history of leukæmia in 3 of 228 with chronic lymphatic leukæmia but in none with the other varieties In 1 patient the disease appeared within six months of the death, from the same cause, of her mother, whom she had nursed

There are several records of twins, uniovular and binovular, both developing leukæmia (Cooke 1953, Anderson and Hermann 1955) As a random event it has been estimated that this would happen once in a hundred and fifty years in the United States

It seems likely, therefore, that genetic factors are sometimes operative, but their importance cannot be great

Zoological Distribution

Leukæmia has been reported in almost every species of the animal kingdom, from the vulture to the sea lion (Engelbreth Holm 1942) The relation between the human and animal forms of the disease remains uncertain, but much investigative effort has been expended on the second in the hope of shedding light on the first Most of the research has been directed towards discovery of the cause As long ago as 1908 it was proved that fowl leukæmia was due to a virus which invaded the blood cells and apparently endowed them with malignant qualities (Ellerman and Bang 1908) Beard (Bonar et al 1956) has recently been able to show that there are two distinct, but closely related, viruses which are responsible for avian myeloblastosis and erythroblastosis *No other leukæmia is yet established as due to a virus*

Mouse leukæmia has been the most commonly used for research The mouse is particularly liable to a lymphatic form of the disease, and the importance of genetic factors is shown by the breeding of strains in which 60–70% of individuals eventually die of spontaneous leukæmia It is generally held that transmission is possible only when live cells are inoculated, although recently Gross (1953) and others have claimed successful passage with cell free filtrates A number of different agents apparently influence the incidence of the disease and the susceptibility of animals to inoculation

The application of these observations to the problem of the cause of leukæmia in mice is sufficiently obscure and their relevance to human disease quite unproven Some believe that the agents mentioned disturb cellular equilibrium in a way which initiates the leukæmic process, and that, once established, this perpetuates itself Others cling tenaciously to the viral hypothesis, among these are Schwartz et al (1956), who claim to have recovered from the brains of some patients dying from leukæmia an agent which will accelerate the development of the disease in a susceptible strain of mice

ACUTE LEUKÆMIA

Incidence of Cytological Types

Acute leukæmia is distinguished from the chronic form by the immaturity of the proliferating cells and the rapidity of its course Myeloblastic, lymphoblastic, and monocytic varieties are recognised, but the distinction between the several primitive elements may be difficult, and refuge is often sought in the evasive qualification of

TABLE II—DISTRIBUTION OF 169 CASES OF ACUTE LEUKÆMIA BY CYTOLOGICAL TYPES

Cytological type	Male	Female
Myeloblastic		
"Classical" type	35	44
Erythromyelosis	2	[illegible]
Lymphoblastic		
"Classical" type	23	9
Pure medullary type	10	5
Sternberg type	7	1
Monocytic	12	11
Erythræmia (Di Guglielmo 1926)	4	1
Total	93	76

TABLE III—INCIDENCE OF CYTOLOGICAL TYPES OF ACUTE LEUKÆMIA

Reference	No of cases	Myeloblastic (%)	Lymphoblastic (%)	Monocytic (%)	Undetermined (%)
Rosenthal and Harris (1935)	173	77 4	18 5	4 1	
Gauld et al (1953)	271	25 2	53 4	21 4	
Gunz and Hough (1956)	346	38 2	37 6	2 0	22 2
Present series	169	49 7	33 7	13 6	

"stem cell" There is, therefore, considerable variation in the reported incidence of the different types The present series is not to be regarded as unselected, because leukæmia in childhood is the province of the pædiatrician, and it consequently contains a disproportionate number of adults (table II) This has the effect of reducing the numbers of the lymphoblastic variety, which is particularly common during the first decade The variability of reported series is shown in table III

More males than females fall victim to acute leukæmia, an inequality due to the frequency of the lymphoblastic type in male children The age-incidence of the three varieties shows striking differences (fig 3) Myeloblastic leukæmia is spread evenly throughout the whole span of life, lymphoblastic is predominantly a disease of children, and monocytic affects mainly the middle aged

Clinical Picture

A detailed clinical description of acute leukæmia would be inapposite, and the following account is but a summary review The different cytological varieties seldom present clear-cut clinical differences The ingredients which go to make up the picture are anæmia, a hæmorrhagic state, enlarged lymph-nodes, spleen, and liver, sometimes with infiltrations in other tissues, and secondary infective phenomena The accent may fall sometimes on one and sometimes on another of these features

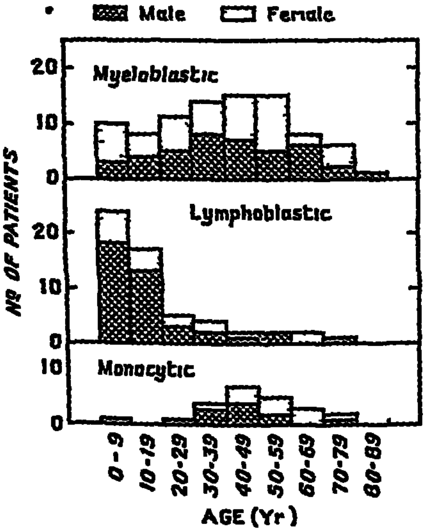

Fig 3—Age-incidence of acute leukæmia.

Myeloblastic Leukæmia

In myeloblastic leukæmia the presenting symptom is usually anæmia, often of insidious onset and often combined with a hæmorrhagic state The spleen may be felt, but lymph-node enlargement is unusual Skin infiltrations, usually papular, are not rare In children subperiosteal chloromatous tumours are occasionally noted Fever is common, and this is more often the result of infection than was previously believed Spongy gums, with ulcerated margins oozing blood, are a familiar feature

Lymphoblastic Leukæmia

Lymphoblastic leukæmia presents in one of three clinical guises anæmia combined with lymph-node enlargement, splenomegaly, enlargement of the liver, and infiltrations in various tissues, may be called the "classical" form of the disease The second, or pure medullary, type is common in young children Here anæmia and perhaps a hæmorrhagic state are the only initial signs There is no enlargement of the liver, spleen, or superficial lymph-nodes In this variety pain in bones and joints is often a prominent symptom, and many patients are admitted to hospital with a diagnosis of rheumatic fever or osteomyelitis The third variant, or the Sternberg type, has been described as acute lymphosarcoma-cell leukæmia, although there seems to be no justification for excluding it from the present category The patient presents with a nodal tumour, usually in the mediastinum, but in 1 of my patients it was in the nasopharynx At this stage the blood-count may be normal, but within a few days to a few weeks lymphoblasts have invaded the blood, the total leucocyte count has risen, perhaps to 200,000 per c mm, and anæmia and thrombocytopenia have made their appearance Some authors believe that the predominant cell in this variety can be distinguished from the lymphoblast of other types of acute lymphoblastic leukæmia

Monocytic Leukæmia

Monocytic leukæmia differs little from myeloblastic in its clinical features, except in its particularly frequent association with gingivitis and stomatitis The cervical lymph-nodes may be enlarged, but rarely are those of other groups affected, the spleen is usually not palpable

Other Forms

Sometimes the anaplastic process affects the precursors of the red blood cells exclusively, and the resulting disorder is termed acute erythræmia or Di Guglielmo's disease (Di Guglielmo 1926) Intermediate forms marked by myeloblastic and erythroblastic proliferation are spoken of as acute erythromyelosis In many instances these cytological changes are transient and later give place to a pure myeloblastic proliferation Their clinical features do not separate them from acute leukæmia *sensu stricto*, fever, profound anæmia, splenohepatomegaly, and a hæmorrhagic state accompany their rapidly progressive decline

Occasionally acute leukæmia declares itself after a long period of ill health whose features have been those of aplastic anæmia, chronic neutropenia, or thrombocytopenia This initial illness has been termed "pre-leukæmia," but the relationship to the conventional form of the disease is uncertain (Block et al 1953) 3 cases of this variety have been excluded from the present series as well as 1 case each of polycythæmia and myelosclerosis terminating in acute leukæmia

Blood Picture

The diagnosis of acute leukæmia is established only by examining the blood and bone marrow Some anæmia is constant The peripheral leucocyte count varies, indeed, leucopenia is rather more common than the high counts previously regarded as characteristic Whatever the total, a proportion of primitive cells is almost always found Thrombocytopenia may be absent in the early stages but with progress of the disease it is invariable

When the changes in the peripheral blood are inconclusive, the diagnosis is established by bone marrow puncture, which will reveal in almost every instance a replacement of the normal cells by myeloblasts, lymphoblasts, or primitive monocytes The interpretation of the erythroblastic, or mixed erythroblastic and myeloblastic, proliferations of Di Guglielmo's disease and erythromyelosis may be difficult to those unfamiliar with these less common variants

Treatment

The management of patients with acute leukæmia presents the physician interested in hæmatology with his greatest challenge The disease remains obstinately fatal, and it has been suggested that humanitarian considerations should forbid attempts to procure remission which can never be more than transient. There can, however, be no doubt in the minds of those who see many of these patients that such an attitude is indefensible. This nihilistic approach demoralises the patient, his relatives, and his medical attendant; moreover it erects an impenetrable barrier against therapeutic advance. Even a few more months of life may be immeasurably precious, and it is the physician's duty to do all that is possible to procure this temporary reprieve.

The fundamental aim of treatment is to control the neoplastic process and restore normal cellular behaviour in the hæmopoietic system; but, before the measures aimed at this goal are described, symptomatic treatment must be considered.

SYMPTOMATIC TREATMENT

The patient with acute leukæmia is a ready victim of infections, general and local. Septicæmia should always be suspected when there is high fever, and, if blood-culture establishes its presence, the appropriate antibiotic should be prescribed. 2 recent patients, in whom complete remissions were later procured, presented with general infections by *Streptococcus hæmolyticus* and *Staphylococcus pyogenes*. Local infections of the mouth, respiratory tract, and skin demand bacteriological identification and the correct antibacterial agent. Monilial invasion of the mouth, throat, and œsophagus is particularly frequent, especially when steroid hormones are used; in such cases 'Nystatin' has proved invaluable. Mouth-washes of 1.5% hydrogen peroxide or of a saturated solution of sodium perborate do much to relieve the discomfort of leukæmic stomatitis.

Routine or prophylactic use of antibiotics is inadvisable. These drugs should be prescribed only when the generally accepted indications exist, and the discomfort of intramuscular injection in the patient with a hæmorrhagic state must be borne in mind.

The importance of the tendency to bleed is shown by the fact that, in 23 of 55 patients examined post mortem, hæmorrhage had apparently been the immediate cause of death, and in 14 of them the bleeding had been intracranial. There is a close parallel between the platelet count and the tendency to bleed; but it is common to see thrombocytopenia without significant bleeding for weeks, or even months, terminating in an explosive and rapidly fatal hæmorrhagic state. It is possible that this sudden change is sometimes brought about by the appearance of a fibrinolysin or a circulating anticoagulant, either of which may owe its origin to bacterial invasion (Freeman 1952). The control of infection is therefore important in control of the hæmorrhagic state. Other measures are of little avail: simple blood-transfusion is seldom effective, but platelet transfusions have some transient benefit, although they rapidly lose their virtue (Stefanini and Bernfeld 1953). The steroid hormones may temporarily decrease the tendency to bleed. Intravenous injections of a chloroform extract of acetone-washed brain may prove valuable (Hayhoe and Whitby 1955).

Electrolyte disturbances are common in the acutely ill leukæmic patient and require correction. A low serum potassium level has been noted in several cases (Videbæk 1951), and in 1 case many of the symptoms were due to hypercalcæmia (Mawdsley and Holman 1957).

Blood-transfusion is the only method of relieving anæmia, but there is some evidence that it may have a more profound effect. Remission has often been noted to follow it (Dreyfus 1948) and this observation was the rationale for exsanguination transfusion, which enjoyed a certain therapeutic vogue a few years ago (Bessis and Dausset 1950). Its action has more recently been attributed to liberation of adrenal steroids as the result of transfusion shock (Bessis 1954). This point has again been underlined by a report of remissions thus induced in 34% of 41 patients (Hayhoe and Whitby 1955). In the present series significant remissions were noted in 9 (19.5%) of 46 patients treated by transfusion alone. Exsanguination-transfusion was undertaken in only 3, but in none of these was the course of the disease obviously altered.

Blood-transfusion has no place as a definitive means of treatment, but it should be prescribed in quantities sufficient to maintain a hæmoglobin level of 9 g. per 100 ml. while attempts are made to control the leukæmic process. It should always be a purposive measure and not a resort *faute de mieux*.

SPECIFIC MEASURES

The agents which may exert partial or complete, although never more than temporary, control over the leukæmic process are the steroid drugs and certain antimetabolites.

Steroid Hormones

Cortisone was shown to inhibit the growth of transplanted lymphosarcoma in mice as long as thirteen years ago (Heilman and Kendall 1944), but it was not used in human leukæmia until 1950 (Farber et al. 1950, Pearson et al. 1950). Analysis of published series shows that of 425 patients treated with cortisone or corticotrophin there was complete remission in 29% and partial in 24% (Fessas et al. 1954). The expression "complete remission" is defined as a disappearance of all symptoms and physical signs of disease, the restoration of a normal blood picture, and the presence in the bone marrow of the sum of "blast" cells and lymphocytes in a proportion of less than 20% of the total. Subsequent experience has shown that complete remission may be expected in children with lymphoblastic leukæmia and not rarely in adults with this form of the disease. In myeloblastic leukæmia it is less commonly obtained in children and in adults rarely. Monocytic leukæmia never responds.

There is, indeed, some evidence that steroid hormones may accelerate the leukæmic process in the last named forms (Fessas et al. 1954). In the present series the results obtained with cortisone or corticotrophin are set out in table IV.

TABLE IV—RESULTS OF TREATMENT OF ACUTE LEUKÆMIA WITH STEROIDS

Cytological type	No. of cases	Remissions	
		Complete	Partial
Myeloblastic			
Adults	13	1	1
Children	5	2	2
Lymphoblastic			
Adults	10	4	2
Children	10	6	2
Monocytic			
Adults	4	0	0
Total	42	11	7

The daily dose of cortisone required is 200–300 mg. in adults and up to 200 mg. in children. Corticotrophin is given by intramuscular injection every six hours in daily doses of 200 mg. for adults and 100 mg. for children, or by intravenous infusion in quantities of 25–50 mg. in eight to twelve hours. Some workers have claimed more satisfactory results in adults by using prednisolone in a dosage as high as 5 g. daily (Hill et al. 1956).

Remission with steroid drugs is usually established in the third or fourth week of treatment. It seldom lasts more than six weeks, and relapse is not prevented by maintenance dosage. If treatment is intermittent second remissions may sometimes be obtained in children, but rarely in adults.

Antimetabolites

An antimetabolite is an agent which obstructs the working of an enzyme system By virtue of its chemical similarity to the metabolite or raw material of the system in question, it becomes united with the enzyme It differs, however, sufficiently from the enzyme to prevent the reaction from proceeding to completion A chemotherapeutic spanner has been thrown into the metabolic works, the pathway is blocked and deficiency of the essential final product results The antimetabolites which have proved of value in acute leukæmia are those which *interfere with the synthesis of nucleic acid*

Folic-acid antagonists—The first to be used were the folic acid antagonists The step was taken empirically after the observation that the leukæmic process was accelerated by giving a folic acid conjugate (Farber et al 1948) Those in common use are the 4-amino antagonists of pteroylglutamic acid (folic acid) aminopterin (4-amino pteroylglutamic acid) and amethopterin or methotrexate (4 amino-N^{10}-methylpteroylglutamic acid) These drugs prevent the conversion of pteroylglutamic acid to citrovorum factor and, by interfering with the action of the second, impede the synthesis of nucleic-acid purines

The folic acid antagonists have little or no place in the treatment of adults, but in children remission is procured in 60–70% of cases of lymphoblastic leukæmia (Burchenal 1952, Fountain 1954) They are given by mouth aminopterin in doses of 0 5–1 0 mg daily in children and up to 3 mg a day in adults, and methotrexate in doses of 2 5–5 0 mg and up to 10 mg a day respectively Remission may not appear for eight weeks, it may endure for as long as two years, but the mean lies between two and three months Second remissions may occur, but resistance finally develops Severe toxic symptoms are not uncommon and may supervene in a few days or be delayed for months the earliest is stomatitis, followed by diarrhœa, vomiting, loss of hair, and sometimes gastro intestinal hæmorrhage

The folic acid antagonists have not been used extensively in this series Partial remission was obtained in 3 of 5 children with myeloblastic, and in 2 of 6 with lymphoblastic, leukæmia 1 of 2 adults with monocytic leukæmia had a short incomplete remission

Mercaptopurine—Many other antimetabolites have been subjected to clinical trial, but the only ones of proved value are the purine antagonists, which interfere with nucleic acid synthesis at a different stage of metabolism The first shown to have an antileukæmic effect was 2 6 diaminopurine (Burchenal et al 1951), but this was rapidly superseded by the more effective 6 mercaptopurine (Burchenal et al 1953) The customary daily dose of this drug is 2 5 mg per kg body weight Three to eight weeks is needed for remission to occur, and toxic effects, other than leucopenia, are rare Treatment is continued until the bone marrow is hypocellular and the sum of lymphocytes plus "blast" cells is below 20% of the total If this has not been achieved at the end of eight weeks the dosage may be doubled, and sometimes a delayed response is noted When remission has been obtained, a maintenance dosage of 2 5–1 25 mg per kg body-weight is continued In this series the smaller dosage has been preferred

Many reports are available of the value of this drug (Conference on 6-Mercaptopurine 1954) In general about a third of the children and about a seventh of the adults treated have shown remission, which lasted from one week for as long as a year, with a mean of three or four months In all cases the disease eventually becomes resistant The chance of remission appears to bear less relation to the cytological variety of leukæmia than when folic acid antagonists are used In the present series 6 mercaptopurine was given to 51 patients with the results set out in table v

TABLE V—RESULTS OF TREATMENT OF ACUTE LEUKÆMIA WITH 6 MERCAPTOPURINE

Cytological type	No of cases	Remissions	
		Complete	Partial
Myeloblastic			
Adults	18	6	3
Children	8	2	3
Lymphoblastic			
Adults	10	5	2
Children	10	5	2
Monocytic			
Adults	5	1	0
Total	51	19	10

Analogues of 6-mercaptopurine, thioguanine, and 6-chloropurine are on trial (Murphy et al 1955) There is some evidence that the second increases the frequency of complete remission in adults (Ellison 1956) In some adults in whom acute leukæmia has become refractory to 6-mercaptopurine a second remission has been obtained with folic-acid antagonists (Ellison 1956)

Azaserine—There is, too, some evidence that a glutamine antagonist, azaserine, will increase the length of remission in children when given with 6 mercaptopurine (Ellison et al 1954, Burchenal et al 1955)

Prognosis

Acute leukæmia remains stubbornly fatal Its course is so variable that figures of average duration have little meaning Analysis of published series has shown that there is no statistical proof of significant increase in the total survival when "specific" drugs are used (Haut et al 1955)

In the present series, in 81 patients treated with blood-transfusion and antibiotics alone the mean length of survival from the first symptom was 20 2 weeks, and in 63 who received in addition "specific" treatment 21 7 weeks These figures provide no cause for optimism, but we have at present 6 patients in complete remission With all humility it may be claimed that there are, at least, grounds for hope and encouragement in this recently acquired ability occasionally to halt for a while the formerly unrelenting malignant process known as acute leukæmia

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THE NATURE AND ORIGIN OF THE MAMMOTROPHIC AGENT PRESENT IN HUMAN FEMALE URINE

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THE urine of normal premenopausal women, when injected into the intact weanling males of certain strains of albino mice, induces an easily recognisable growth response in their primitive mammary glands Histological studies have shown that the essential feature of this response is a highly significant increase in the rate of proliferation of mammary epithelium (Hadfield and Young 1956a) The urine of 57% of normal postmenopausal women also contains this mammotrophic agent (Hadfield and Young 1956b)

It has been found impossible to induce this growth response to urine in the mammæ of intact weanling males of the large majority of available strains of laboratory mice Of 37 strains examined, in 2 only—S A S 3 and Strong A_2G—were the mammæ found to be sensitive to urinary mammotrophin, although all strains reacted promptly and vigorously to ovarian œstrone The 35 strains in which the intact weanling males were insensitive to urinary mammotrophin proved to be equally insensitive to pituitary prolactin alone On the other hand, the 2 strains in which vigorous mammary growth responses were induced by prolactin also showed an identical response to human female urine (Young 1957) These results suggest, but afford no proof, that the mammotrophic agent present in female urine is pituitary prolactin

Acting on this suggestion a trial series of preoperative tests were carried out on seven patients suffering from metastatic breast cancer in whom hypophysectomy was under consideration The urine of three cases was found *to be mammotrophic, and hypophysectomy* in these was *followed* by unmistakable regression of growth in the tumour and its metastases No regression followed the operation in the remaining four patients whose urine failed to produce a mammary response in intact male weanling mice of a strain known to be sensitive both to urinary mammotrophin and to prolactin

These results are admittedly inconclusive, for the reactions were obtained in intact animals Nevertheless they suggest that an estimation of the mammotrophic potency of the urine, by providing information regarding the mammotrophic function of the hypophysis, might be of assistance in the selection of cases of breast cancer likely to benefit from hypophysectomy Such a test, however, carries serious clinical implications, and it would be unjustifiable to advocate its use *until more* is known about the *organ of origin* of the *mammotrophin in* human urine The investigations reported here were designed to solve this problem

It has been established by Lyons, Li, and their associates (1955), using hypophysectomised rats, that an advanced degree of mammary growth and differentiation can be induced in gonadectomised immature males and ovariectomised virgin females by the injection of ovarian œstrogen and progesterone together with pituitary prolactin in a carefully predetermined dose ratio None of *these hormones alone was capable of inducing* proliferation of mammary epithelium, and combinations of them in pairs proved equally ineffective It is difficult, therefore, to escape the conclusion that the "mammogenic triad" of hormones—œstrone, progesterone, and prolactin—is, in the rat at least, directly and specifically responsible not only for lactogenesis but also for the normal proliferation and differentiation of the mammary epithelium which determines the formation of a functionally competent organ

The general plan of the rat experiments of *Lyons* has been followed in the investigations reported in this paper It has been shown that the epithelial proliferation which leads to mammogenesis in hypophysectomised immature male mice *of the Strong* A_2G strain is totally dependent *on the* synergistic action of the same "mammogenic triad" of hormones as controls this process in the rat As the main purpose of the investigations was to determine the nature and origin of the mammotrophic agent present in human female urine, a second series of experiments was carried out in which the prolactin component of the "mammogenic triad" was omitted and unaltered premenopausal female urines, or extracts prepared from such urines, were injected *in* its place

Methods

Age and Weight of Animals

Males of the Strong A_2G strain weaned *at the age of* 21 days were hypophysectomised *between the* 23rd *and* 28th day the body weight at hypophysectomy varying between 9 and 14 grammes The operative technique used was that of Thomas (1938), in which the base of the skull is reached by a lateral pharyngeal approach and the pituitary exposed by dividing the occipito *sphenoidal synchondrosis,* incising the basi occipital bone transversely 2 25 mm behind the synchondrosis, and removing the rhomboidal panel of bone which lies between the incisions This operation becomes more *difficult as* the weanling grows *and* the skull *base* becomes increasingly ossified *and* therefore *more* vascular

Criteria for Total Ablation

The body weight falls for a few days after total hypophysectomy and then rather slowly rises At the 10th

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postoperative day, if total ablation has been achieved, the body-weight has hardly reached the preoperative level but occasionally exceeds it by about 5%. Over the same period, and within the same age range, normal intact untreated A_2G male weanlings were found to show an average gain of 77% of the body-weight. Excluding the animals given prolactin, weight loss, weight stasis, or a gain at the 10th postoperative day not exceeding 5% of the body-weight at operation, was accepted as provisional evidence of total ablation.

Prolactin is contaminated to a varying degree by growth hormone, and hypophysectomised animals given prolactin showed a significantly higher postoperative weight gain than the others, the increase being proportional to the dose of prolactin. A gain not exceeding 7·5% of the body-weight has therefore been accepted as provisional evidence of total ablation in animals given prolactin. On the basis of postoperative weight gain outside these limits, the results obtained in 17% of the hypophysectomised animals have been discarded.

Duration of Injection Period

Two injections of hormones or urine per mouse per day for 5 days were given in all experiments. This does not allow sufficient time for full glandular differentiation and lobule formation in reacting glands, but early acinisation could be clearly discerned in a considerable proportion of them.

Estimation of Mammotrophic Potency

The primitive mammæ of normal intact weanling males grow slowly up to sexual maturity, and in the minority the duct ends show an inconspicuous swelling. Glands in which recent growth acceleration has been induced by hormones or urine show prominent, richly cellular, deeply stained, or partly acinised end-bulbs or "clubs," composed of closely packed undifferentiated epithelium in which mitoses are numerous. Histological studies of weanling male mammæ have demonstrated that the presence of clubs whose diameter is double or more that of their parent duct affords irrefutable evidence of recent and abnormally rapid cellular multiplication induced by a specific exogenous hormonal stimulus. Clubs of this size, including those showing early acinisation, were counted in all the mammæ dissected from animals in each experimental group, and the average number of large, deeply stained "clubs" per gland in the group was estimated. As the mammæ of normal intact weanling males of the Strong A_2G strain bear less than one club per gland (fig. 2, row 1), this figure is taken as being a measure of recently induced growth acceleration and of the "mammotrophic potency" of the stimulus producing it.

Urine and Urinary Extracts

A volume of 0·2 ml. per day per mouse of an untreated early-morning specimen was administered subcutaneously.

Urinary extracts were prepared by a modification of the Lyons method (1934). The dried powder, which keeps indefinitely, was dissolved in a measured volume of normal saline to give a concentration five times greater than urine.

Results

Experiment 1

Neither hormones nor urine was administered to eight hypophysectomised weanlings. Four were killed on the 5th postoperative day and four on the 10th. Of the forty-five mammary glands examined all showed obvious atrophic changes, which were already present by the 5th day (fig. 2, row 2.)

Conclusion.—The mammary glands of the weanling male mouse are totally hormone dependent.

Experiment 2

Œstrone and progesterone were administered to eight hypophysectomised weanlings. In four of these a dose giving an optimal response in the intact animal was injected—i.e., œstrone 0·25 γ and progesterone 1·5 mg. per day per mouse for 5 days. In the remaining four animals this dose was doubled. Forty-four mammary glands were examined, and no sign of a growth response was seen in any.

Conclusion.—The ovarian hormones œstrone and progesterone, at dose levels which produce a vigorous mammary response in intact Strong A_2G weanlings are powerless to induce any proliferation of mammary epithelium in the hypophysectomised weanling males of this strain.

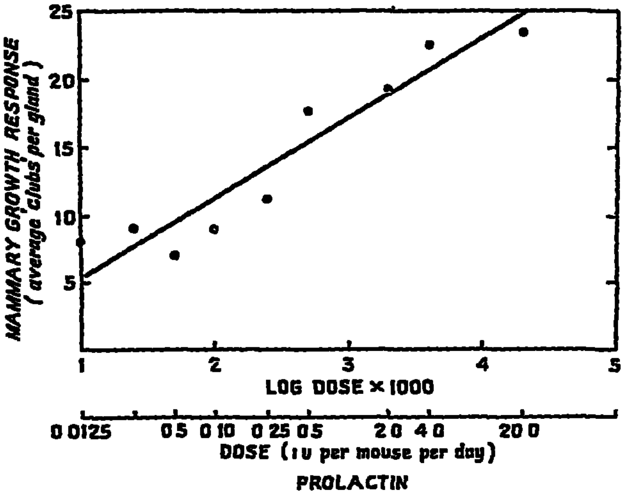


Fig. 1—Dose response curve of mammary growth induced by prolactin (0·0125 to 20 i.u. per day per mouse for five days) in synergism with œstrone and progesterone at constant dose levels.

Experiment 3

Prolactin alone at a dose level which vigorously stimulates mammary growth in the intact weanling (20 international units per day per mouse for 5 days) was administered to five hypophysectomised weanlings. Twenty-three glands were examined. No mammary growth response was seen and in most of the glands there were obvious signs of glandular atrophy.

Conclusion.—Pituitary prolactin alone is not only powerless to stimulate mammary growth in the hypophysectomised weanling male mouse but is incapable of preventing mammary atrophy.

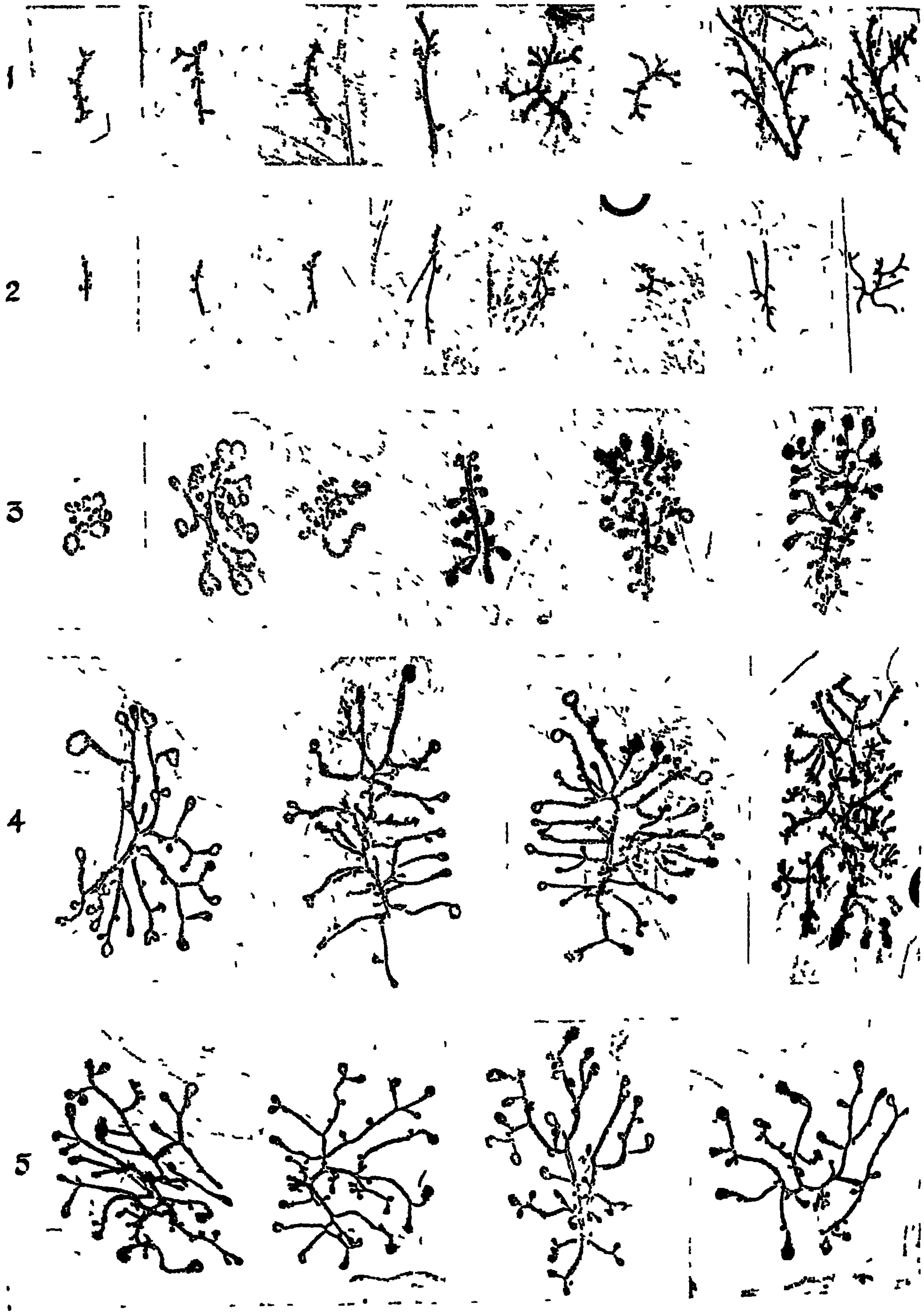
Experiment 4

Œstrone and progesterone together with pituitary prolactin was administered to forty hypophysectomised A_2G weanlings. The dose of prolactin varied from 0·0125 i.u. to 20 i.u. per mouse per day for five days. The dose of ovarian hormones was kept constant at 0·25 γ œstrone and 0·5 mg. progesterone per mouse per day. Two hundred and twenty-eight mammæ were examined. This combination of hormones had induced a vigorous response at all dose levels in all mammary glands in the large majority of animals (fig. 2, rows 3 and 4), and at least 20% of all reacting glands showed early glandular differentiation. The dose response curve is shown in fig. 1.

Conclusion.—The triad of hormones—œstrone, progesterone, and prolactin—is essential for epithelial proliferation and differentiation in the rudimentary mammary glands of the male weanlings of the Strong A_2G strain. As the prolactin used was in all probability contaminated by growth hormone, it is possible that this hormone played a part in the induction of the response, but this seems improbable, for a substantial response was obtained in the mammæ of five animals at the lowest dose level of prolactin (0·0125 i.u. per day per mouse) when the amount of contaminating growth hormone was probably below its threshold value. Furthermore, in none of these animals was there any increase in weight at the 10th postoperative day.

Experiment 5

Pituitary prolactin was omitted from the combination used in experiment 4, and untreated female urines or urinary extract was substituted for it. Œstrone and progesterone were given at the same dose level as in the


1
2
3
4
5

preceding experiment Twenty-three hypophysectomised weanlings were used

Group 1—Five animals given 0 2 ml per day per mouse for 5 days of an unextracted early-morning specimen of urine from a normal premenopausal woman collected on the 20th day of the menstrual cycle

Group 2—Four animals given the same dose of a pooled specimen from three women at the 21st, 22nd, and 25th days of the menstrual cycle

Group 3—Four animals given the same dose of a pooled specimen of postpartum urines collected on the 3rd, 4th, and 5th postpartum days

Group 4—Five animals given a urine extract prepared by a modification of the Lyons method (1934) from 1455 ml of pooled specimens of early morning urine from a normal premenopausal woman collected on the 15th, 16th, 21st, and 27th days of the menstrual cycle The solution of this extract in normal saline represented a concentration five times greater than in urine

Group 5—Five animals given a urine extract prepared by a modification of the Lyons method (1934) from pooled early-morning specimens of urine collected from eight premenopausal women on the 16th, 19th 20th, 21st, 22nd, 23rd, and 24th (2) days of the menstrual cycle The solution of the dried extract in normal saline represented a concentration five times greater than in urine

A hundred and twenty-three mammary glands were examined An unequivocal mammary growth response, indistinguishable from that produced in experiment 4 by the mammogenic triad, was induced by all specimens of urine acting in synergism with œstrone and progesterone (fig 2, row 5) In the following table the mammotrophic potency of the urine in each group is shown with the approximate amount of prolactin in international units which was found requisite in experiment 4 to induce a mammary response of approximately equal intensity (see fig 1)

Group	Mammotrophic potency of urine or extract (average no of clubs per gland)	Approximate equivalent of prolactin in unextracted urine (I U per mouse per day)
1	6	0 016
2	3 5	< 0 01
3	5	0 01
4 (extract)	17 7	1 225
5 (extract)	8	0 04

Conclusion—The urine of premenopausal women can effectively substitute for the prolactin component of the mammogenic triad and induce significant mammary growth responses in the hypophysectomised male weanling mouse It is highly improbable that growth hormone plays more than an insignificant part in this reaction

Discussion

In many ways the weanling male mouse has proved to be an ideal biological test object for the investigation of mammogenesis induced by exogenous stimulation The experiments reported in this paper, using the hypophysectomised male weanling, implicate pituitary prolactin with a considerable degree of certainty as the mammotrophin present in human female urine Further investigation is clearly needed to decide if human urine contains any significant quantity of growth hormone Some of the results obtained by Lyons and his colleagues (1955) suggest that growth hormone plays a part in developing the duct system of the rudimentary mamma of the hypophysectomised immature rat It is abundantly clear, however, that no combination of hormones which does not include prolactin can bring this rudimentary gland to anything approaching the status of a functionally competent organ There is no doubt that many specimens of easily available growth hormone are contaminated by prolactin, and, unless very elaborate precautions are taken in their preparation, many commercial preparations of prolactin contain growth hormone in small and possibly insignificant amounts It seems safe to assume, therefore, that in some of the mammary reactions described in this paper growth hormone may have played a subsidiary part

Certainly the hypophysectomised mouse is far more sensitive to exogenous prolactin and human urine than the intact animal, and yields more uniform mammary reactions

It will be necessary to define the nature of the genetic peculiarity in Strong A_2G mice which endows the male weanlings of this strain with their exceptional mammary reactivity to prolactin and human urine Experiments now nearing completion have shown that the ratio

$$\frac{\text{Testis weight}}{\text{Body weight}}$$

is significantly higher in these animals than in the male weanlings of prolactin insensitive strains

If, as a measure of pituitary mammotrophic function, the mouse test proves to be of clinical value in rationalising the treatment of breast cancer by hypophysectomy the difficulties associated with strain variation could be met by establishing colonies of Strong A_2G mice in centres where hypophysectomy for breast cancer is under investigation

General Conclusions

1 Experimental evidence is produced supporting the conclusion that human female urine contains pituitary prolactin at concentrations varying from 0 01 to 0 25 international units per millilitre

2 It is suggested that an estimation of urinary prolactin may materially assist in the selection of those patients with metastatic breast cancer who are likely to benefit from hypophysectomy

3 It is also suggested that, for the bio-assay of prolactin in human urine, potent urinary extracts (which can be preserved indefinitely) should be injected into hypophysectomised male weanling mice of the Strong A_2G strain

My warmest thanks are due to Dr O Muhlbock director of the Netherlands Cancer Institute, Amsterdam, for kindly providing facilities for me to learn the technique of hypophysectomy in the mouse and it gives me much pleasure to express my gratitude to Dr Kwa Hong Giok, of the same institute for his invaluable advice, encouragement and assistance during the investigations

The urinary extracts were prepared by my colleague Dr F C Greenwood, his assistance has been invaluable I am grateful to Dr W F J Cuthbertson for arranging supplies of mice from the Glaxo Laboratories, and to Messrs Armour who kindly gave me the prolactin

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CAPTION TO ILLUSTRATIONS (FACING)

Fig 2—Photographs of whole-gland mounts (× 10) Mammæ dissected out of "de-fatted" carmine-stained pelt and mounted without sectioning

Row 1—*Slowly growing* unclubbed mammæ of intact untreated male weanling

Row 2—*Atrophic* mammæ produced by total hypophysectomy Neither ovarian hormones nor prolactin when given alone can retard this process

Rows 3 AND 4—*Rapidly growing* heavily clubbed mammæ of totally hypophysectomised male weanling mice reacting to the "mammogenic triad" Row 3 shows the evolution of the reaction Row 4 the maximal response after 5 days' treatment The gland on the extreme right is heavily acinised

Row 5—*Rapidly growing* mammæ of totally hypophysectomised animals reacting to the administration of a combination of an extract of human female urine and the ovarian hormones œstrone and progesterone

MUMPS VIRUS AND SUBACUTE THYROIDITIS

EVIDENCE OF A CAUSAL ASSOCIATION

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Subacute thyroiditis has distinctive clinical and pathological features, it can be clearly differentiated on the one hand from acute pyogenic infections of the thyroid, and on the other, from the forms of chronic thyroiditis described by Riedel and by Hashimoto Its cause is unknown, but the clinical and pathological features are generally admitted to be compatible with infection by an as yet unidentified virus

Subacute thyroiditis is regarded as rare, but a comparatively large number of cases has been seen in Israel in recent years This has provided an opportunity for a renewed search for evidence of a causal virus 14 female patients and 1 male with subacute thyroiditis have been studied from this point of view

Clinical Features

The illness usually started with mild pyrexia, accompanied by pain radiating from the neck to the ears, particularly noticeable on swallowing Swelling and tenderness of the thyroid gland, either bilateral or unilateral, appeared a few days later Tachycardia, sweating, and tendency for the eyes to stare were often seen A few patients complained of abdominal discomfort, but no abnormal physical signs were found

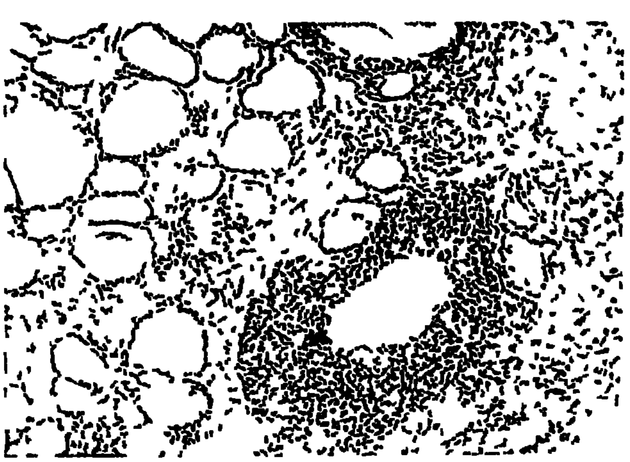

Fig 1—Subacute thyroiditis showing polymorph infiltration round colloid follicle (Hæmatoxylin and eosin × 75)

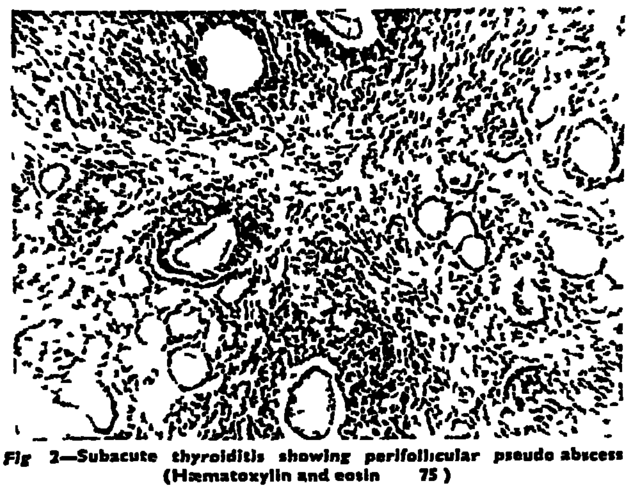

Fig 2—Subacute thyroiditis showing perifollicular pseudo abscess (Hæmatoxylin and eosin × 75)

In our material the progress of the disease was not left to its natural course, in 11 out of 15 cases corticotrophin or cortisone was administered The swelling of the thyroid gland disappeared within seventy two hours after the start of such treatment The pyrexia usually disappeared within twenty four hours In 7 of these cases the pyrexia and painful swelling of the gland recurred after the end of steroid medication In none of our cases was a lasting swelling or myxœdema recorded

10 patients were studied by two of our staff (Dr Harell Steinberg and Dr P Cerniak) for a long time with repeated ^{131}I and protein bound iodine (P B I) studies, and, after six months at most, all reverted to euthyroidism, none later developed either permanent hypothyroidism as reported by Keating et al (1950) or hyperthyroidism as reported by others

Investigations

A mild polymorph leucocytosis (up to 17,000 per c mm) was observed in three quarters of the cases The erythrocyte sedimentation rate was usually raised—above 50 mm in 1 hour (Westergren) in 11 of 15 cases The serum P B I level was above 8 µg per 100 ml in 8 of 11 cases in which it was estimated In contrast the uptake of radio iodine was greatly reduced in 12 of 15 cases The combination of a high P B I and low radio iodine uptake is regarded by most observers as characteristic of subacute thyroiditis

Histology

Biopsy was performed in 4 cases Invasion by inflammatory cells was present in all In 2 cases investigated early in the disease polymorphonuclear cells predominated but lymphocytes predominated in the 2 later cases There was gross disruption of the normal acinar pattern in all 4 cases Giant cells were often seen, probably representing the remains of acini which had been destroyed (figs 1–3)

Complement fixation Tests against Mumps Virus

Complement-fixation tests were performed by the method of Kolmer and Boerner (1941) using Lederle viral antigen

The results are shown in table I Positive results were obtained in 10 of the 11 cases In the 1 negative case (case 4) the histology of the thyroid was atypical

Table II shows the results of the complement fixation tests done long after clinical recovery The tests probably become negative some eight to ten months after the onset

Since a very large proportion of the population has had mumps at one time or another, it was necessary

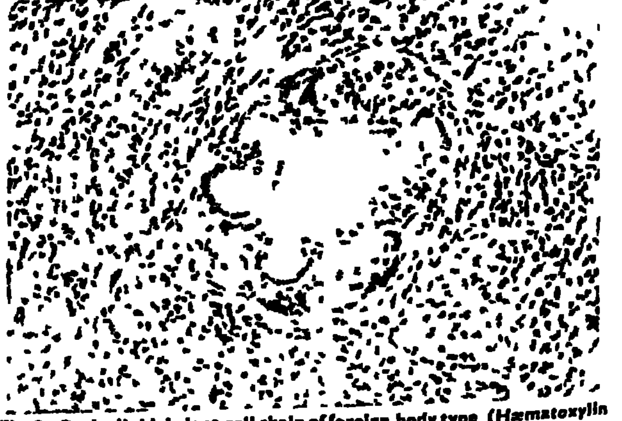

Fig 3—Pericolloidal giant cell chain of foreign body type (Hæmatoxylin and eosin × 150)

to examine numerous controls Of 52 healthy women, aged 30–64, the complement-fixation tests were negative to mumps in 42, and positive in 6 to a titre of 1 10 and in 4 to a titre of 1 20

A further possibility was that the positive complement fixation tests in subacute thyroiditis represented an anamnestic response in persons previously in contact with mumps virus Patients with various diseases, including acute fevers, were therefore studied, with the results shown in table III

From these control studies we concluded that positive complement-fixation tests to a titre of 1 80 or more could be taken as evidence of recent contact with mumps virus

Isolation of a Virus

Attempts to recover a virus from blood and fæces were unsuccessful

In 2 cases in which biopsy was done a virus was recovered from the excised thyroid gland (cases 1 and 3) The specimens were inoculated intracerebrally into mice and hamsters (newborn and adult) and into the yolk-sacs of 8 day fertilised eggs

The results of animal inoculation were negative except in the case of the baby hamsters In a proportion of these animals signs of encephalitis appeared six to nine days after inoculation of the specimens from both patients It proved possible to passage the infective agent by intracerebral injection into further baby hamsters, both with and without Seitz filtration

TABLE I—COMPLEMENT-FIXATION TESTS AGAINST MUMPS VIRUS IN SUBACUTE THYROIDITIS

Case no	Age (yr)	Day of illness	Titre
1	42	6 24 45 128	1 40 1 160 1 160 1 160
2	62	7 22 62	1 40 1 160 1 160
3	30	33 53	1 160 1 40
4	54	6 13 96	Negative Negative Negative
5	24	9 22 223	1 40 1 160 1 80
6	24	9 22	1 80 1 80
7	,3	6 20 53	1 80 1 80 1 40
8	42	4	1 80
9	41	14	1 160
10	38	8 18	1 40 1 160
11	13	30 45	1 80 1 80

Yolk sacs were emulsified five days after inoculation and injected into the amniotic sac of 8 day fertilised eggs After a further five days amniotic fluid was removed and found to agglutinate human group O red cells Hæmagglutination was suppressed by the addition of serum from patients convalescent from classical mumps, and by serum from patients with subacute thyroiditis Serum from healthy female controls did not suppress hæmagglutination or only to an insignificant degree

Discussion

The positive complement fixation tests obtained in 10 of 11 patients with subacute thyroiditis provide evidence of recent contact with mumps virus Isolation of a virus from two affected thyroid glands strongly suggests that it was the cause of the observed pathological changes Specific inhibition of hæmagglutination by convalescent mumps serum establishes the identity of the virus

TABLE II—COMPLEMENT FIXATION TESTS IN PATIENTS AFTER RECOVERY

Case no	Age (yr)	Titre during illness	Interval (months)	Titre after recovery
12	40	Not tested	17	Negative
13	50	Not tested	13	Negative
14	36	Not tested	11	Negative
15	24	1 160	7½	1 80
1	42	1 160	4	1 160

TABLE III—COMPLEMENT FIXATION TESTS IN VARIOUS DISEASES

Diagnosis	No of cases	Titre
Poliomyelitis	2	1 negative, 1 positive 1 20
Encephalitis	9	7 negative, 2 positive 1 20
Brain abscess	1	1 negative
West Nile fever	3	2 negative, 1 positive 1 20
Atypical pneumonia	6	6 negative
Mitral stenosis	2	2 negative
Urticaria	4	4 negative
Thyrotoxicosis	4	4 negative
Thyroid adenoma	1	1 negative
Thyroid cancer	1	1 negative
Hæmorrhagic pancreatitis	2	2 negative
Total	35	31 negative 4 positive 1 20

The hypothesis that the cases of subacute thyroiditis observed during the present outbreak in Israel were caused by infection with mumps virus is quite compatible with the known clinical and epidemiological facts This virus has a predilection for glandular tissue (salivary, pancreatic, lacrimal, testicular, mammary, and ovarian) Although concomitant enlargement of salivary and thyroid glands was not observed in our cases, abdominal pains were not uncommon, and in 3 of 6 cases in which it was looked for a rise in blood-diastase above 200 Somogyi units was observed

During the period when our cases of subacute thyroiditis were discovered the incidence of mumps was particularly high in Israel, the rate per 10,000 having risen from 12 in 1953 to 32 and 44 in 1955 and 1956 In the earlier cases studied a history of contact with mumps was not inquired for, because the possibility of this association had not then occurred to us Of the later cases, 4 had been in close recent contact with cases of classical mumps

In putting forward the suggestion that mumps virus may be the cause of subacute thyroiditis it is important to emphasise that our findings apply only to the local outbreak of this disease in Israel It is quite possible that different ætiological agents are concerned in different places and at different times

Summary

An unusually large number of cases of subacute thyroiditis has been seen in Israel in the past two years The clinical and pathological features of these cases are described

10 of 11 cases had positive complement-fixation tests against mumps virus to a significant titre

A virus thought to be identical with mumps virus was isolated from the thyroid glands of 2 patients with subacute thyroiditis

It is suggested that mumps virus was the cause of the thyroiditis in these patients

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BENIGN GASTRIC ULCER

RISK OF COMPLICATION IN RELATION TO SITE

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THE complication-rate of benign gastric ulcers including those which are under treatment, is high, and the complications of gastric ulcer are less predictable than those of duodenal ulcer Although few surgeons now believe that all gastric ulcers should be cut out because they might be cancerous, gastrectomy remains good treatment for certain benign ulcers Whether it is advisable depends largely on a history of complications in the past and a guess as to their likelihood in the future

To determine the risk of complications of ulcers in various parts of the stomach, I have reviewed the records of 250 personally observed patients with gastric ulcer The ages of the patients at the time of diagnosis ranged from 16 to 88, 62% being between 20 and 50 The diagnosis was established rontgenologically in 245, gastroscopically in 238, and by operation or necropsy in 84 12 patients had two ulcers, 5 had three, and 4 had five, making a total of 288 ulcers The average length of ulcer illness covered by this report was 45 1 months, and the average length of controlled therapy 16 4 months 38 of the patients first came to medical attention because of a complication, therefore, there was a misleading concentration of complications during the observation period

Among 109 patients there were 115 complications (see table), 6 patients having both hæmorrhage and perforation (In view of the high rate of complications observed, it is interesting that double complications were no commoner) There were totals of 77 instances of hæmorrhage, 18 of perforation, 10 of penetration and 10 of obstruction 4 of the penetrations involved the pancreas, 4 the lesser omentum, and 2 the liver

The proportion of ulcers giving rise to complications was highest in the distal part of the stomach and lowest in the proximal, decreasing progressively (53% in the pylorus, 42% in the antrum, 37% in the pars media, and 28% in the cardia and fundus) Also it was found that ulcers of the anterior wall—omitting pyloric ulcers—were far more prone to complication (63%) than those of the lesser curvature (37%), posterior wall (35%), or greater curvature (33%)

Analysis according to the type of complication shows that, with one or two exceptions, apparently governed by the small numbers of cases represented, the risk of hæmorrhage was approximately the same for ulcers in all parts of the stomach Perforation, on the other hand, was far commoner among anterior-wall ulcers, and (surprisingly enough) only 20% of the cases of penetration involved posterior wall ulcers Obstruction, as one might expect, was always caused by distal ulcers, except in one case where constriction across the pars media produced enough hour glass constriction to obstruct

288 BENIGN GASTRIC ULCERS (250 PATIENTS) COMPLICATIONS IN RELATION TO SITE WITHIN THE STOMACH

Site	No of ulcers	Complications (%)			
		Hæmorrhage	Perforation	Penetration	Obstruction
Pylorus	17	29	0	0	24
Antrum					
Lesser curvature	79	28	6	1	3
Greater curvature	18	22	6	6	6
Anterior wall	19	21	32	11	11
Posterior wall	30	30	0	3	0
Pars media					
Lesser curvature	81	26	2	5	1
Greater curvature	5	20	0	0	0
Anterior wall	9	33	22	0	0
Posterior wall	12	25	17	8	0
Cardia and fundus					
Lesser curvature	9	14	0	0	0
Greater curvature	1	0	0	0	0
Anterior wall	2	0	0	0	0
Posterior wall	6	17	0	0	0

ASTHMATIC WHEEZING

COMPRESSION OF THE TRACHEA AND MAJOR BRONCHI AS A CAUSE

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IT is commonly assumed that the typical wheezing during the expiratory phase of the asthmatic attack is produced by a stenosis of the smaller bronchi and bronchioli Opinions differ about the cause of this stenosis Some attribute it to spasm of the bronchial and bronchiolar musculature, others to a partial obstruction by mucus, or œdema and congestion of the bronchial mucosa, or both In this paper we present evidence for another explanation of asthmatic wheezing —namely, that it may be produced, at least partly, by a narrowing of the trachea and larger bronchi

We have already described how typical asthmatic attacks were produced and reproduced under controlled laboratory conditions by exposing patients to allergic or emotional stimuli (Dekker and Groen 1956) These experimentally provoked attacks could begin so suddenly that doubt was cast on the common assumption that spasm in smooth muscle or secretion of mucus were responsible A similarly sudden onset and disappearance of the wheeze is commonly seen in clinical practice—e g , when a patient relates his history This made us doubt the validity of the hypothesis that the wheezing is produced by a mechanism involving the autonomic nervous system, and led us to seek another explanation

Talma (1898a and b) and Strübing (1906) emphasised two points that seem to have been overlooked by most modern authors

(1) The sound heard is exactly identical when the stethoscope is applied to different places on both sides of the thorax and over the trachea This must mean that the typical wheezing is not produced by multiple local stenoses of the smaller air-passages but by a centrally situated narrowing of the trachea or of the major bronchi, whence it is conducted over the entire thorax This narrowing was indeed observed by Van Hoek (cited by Talma 1898a and b), an assistant of Zwaardemaker, and later by Talma (1898a and b) himself through the laryngoscope

(2) Many asthmatics, when asked to demonstrate " how it wheezes " during an attack can produce audible wheezing at will Normal people can also learn to do this This suggests that the wheezing (i e , the stenosis of the upper respiratory passages) can be produced by a *voluntary* effort

Following this line of thought, we have asked ourselves whether this voluntary effort could be mediated through the positive pressure created in the thorax by the powerful contraction of the abdominal, thoracic, and cervical musculature during the typical " asthmatic " expiration During such an expiration the contents of the thorax are compressed by a pressure which is many times higher than normal and high enough to narrow the trachea and the larger bronchi to a considerable degree In the trachea and main bronchi this compression is chiefly caused by the membranaceous part of the wall being pressed into the lumen This has already been suggested, though in somewhat different terms

(Biermer 1870, Einthoven 1892, Sahli 1920) It has been clearly observed by many investigators through the bronchoscope (Von Schrotter 1906, Brünings 1910, Keiper 1914, Lukens 1925, Moore 1925, Daily and Daily 1929, Clerf 1935, Van Loon and Diamond 1942, Leli 1946, Lemoine 1949, Waldbott 1949, Turiaf et al 1952, Lemoine and Garaix 1953, Herzog 1954, Howell 1955, Wyss 1955) and by other authors by bronchography (Di Rienzo 1949a and b, 1953, Stutz 1952, Van Exter 1953), but the possibility that the compression could be the origin of the wheeze, and contribute to the dyspnœa, has not received the attention it deserves

Investigations in Vivo

Healthy people and asthmatic patients were taught to "wheeze" We followed the method indicated by Strübing (1906) to teach wheezing After a short inspiration, a short cough is followed by a prolonged forceful "pressing" expiration Gradually the closure of the glottis, preceding the cough, is omitted and the pressing expirations continued The best results are obtained when the investigator first learns to wheeze himself, and then demonstrates the technique to the subjects Of 17 healthy subjects in whom we tried this manœuvre, 15 were able to imitate the wheeze after a few trials In some of them the resemblance between this artificially induced wheezing and the spontaneous wheeze during the asthmatic attack was most striking Asthma patients similarly learned to wheeze at will and in them the resemblance to the spontaneous wheeze was even more obvious

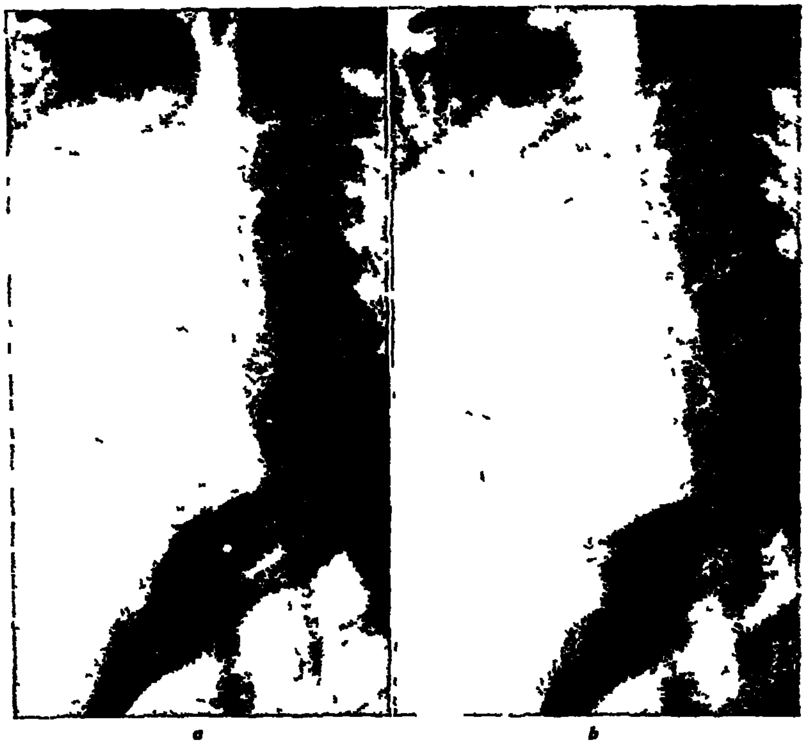
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Fig 2—Radiographs of larynx and trachea (asthmatic patient) (a) during inspiration, (b) during voluntary wheezing expiration

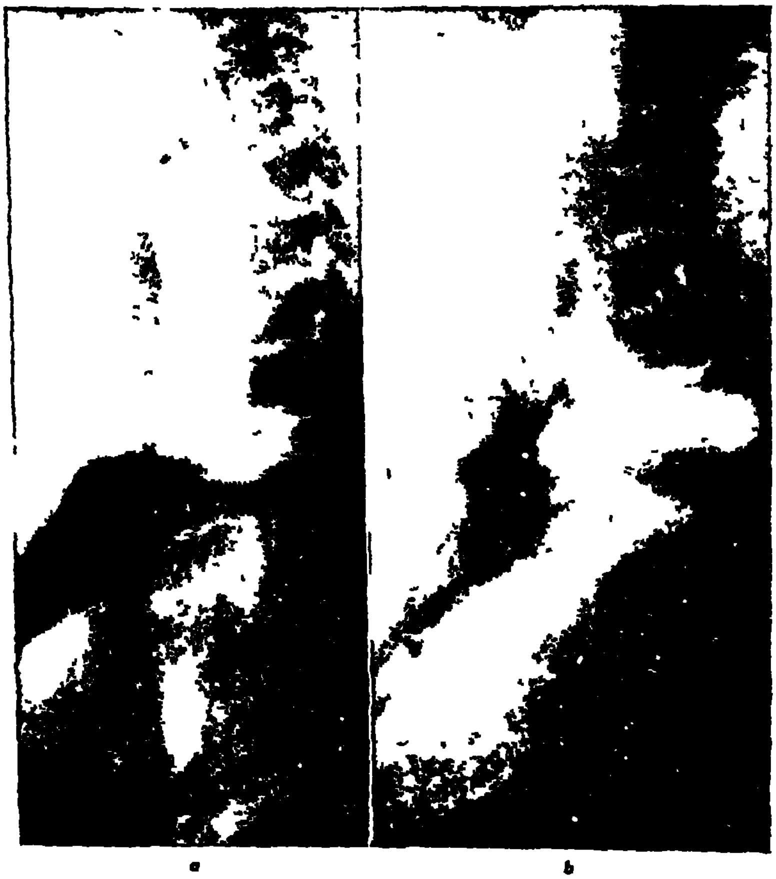
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Fig 1—Radiographs of larynx and trachea (normal subject) (a) during inspiration (b) during voluntary wheezing expiration

The second part of the investigations was radiological Frontal, transverse, and oblique short time exposures were made of the dynamic changes in diameter of the trachea and the main bronchi during inspiration and during a voluntary wheezing expiration, in healthy subjects and in asthmatic patients Similar studies were done on asthmatic patients during spontaneous attacks *

Results

During voluntarily induced "asthmatic" expiration in a normal subject, narrowing of the lumen of the trachea was seen to extend into the lower part of the cervical trachea (fig 1) In our opinion this is due to the propagation of positive pressure inside the cone of cervical musculature (on the anteroposterior exposures it could be seen that the glottis was open during voluntary wheezing expiration)

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* These investigations were carried out in coöperation with Dr R C Ledeboer in the university department of röntgenology under the direction of Prof Dr B G Ziedses des Plantes, they will be published more extensively elsewhere

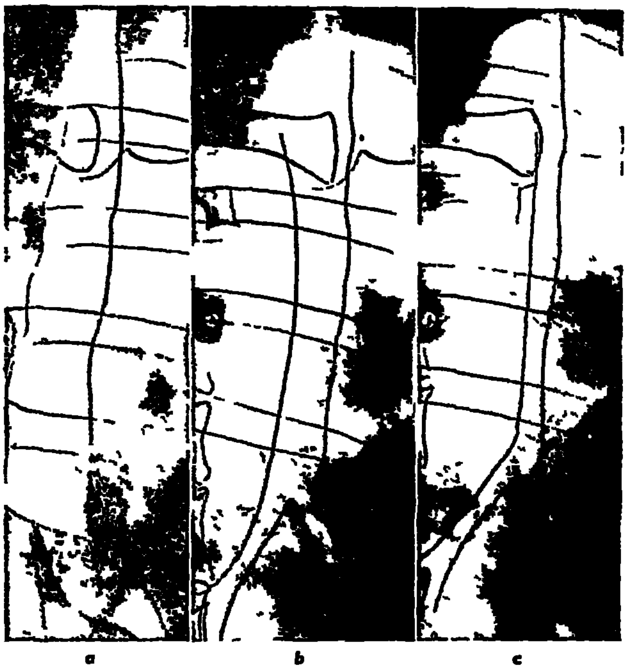

Fig 3—Right oblique radiographs of trachea and main bronchi (emphysematous asthmatic patient) during an attack of dyspnœa (outlines drawn). (*a*) during inspiration; (*b*) during expiration; (*c*) during voluntary wheezing expiration.

An equally considerable narrowing of the main airways was seen during voluntary wheezing expirations in patients with asthma and emphysema (figs 2*b*, 3*c*, 4*c*). The extent and situation of the tracheo bronchial constriction were strikingly similar to those seen in the normal subjects.

Exactly the same type of narrowing of the cervical and thoracic trachea and the major bronchi was found during normal expiration in a patient with emphysema (fig 3*b*) and a patient with asthma (fig 4*b*) during severe spontaneous attacks of dyspnœa.

Experiments in Vitro

The above experiments, together with the demonstration *ad oculos* of the narrowing of the trachea and main bronchi by bronchoscopy and bronchography, do not yet answer the question whether this narrowing is caused by active constriction (e.g., by spasm of the tracheal and bronchial musculature), or is a result of a purely passive compression by the increased thoracic pressure during forceful prolonged expiration. To investigate this we used a human lung obtained at necropsy.† The preparation was put in a glass jar that could be closed by a brass lid. The trachea was tied over a glass cannula that pierced the lid and thus connected the trachea and bronchi with the outside air. By another opening in the lid, air could be pumped in and out of the jar, about 20 times a minute (fig 5). The inspiratory and expiratory pressures of this "respiration" could be varied and measured by a manometer. When the lung "breathed" under a pressure comparable to the physiological pressures in the thorax (i.e., a negative pressure of about 1 cm Hg during inspiration and atmospheric pressure during expiration) a slight widening of the trachea during inspiration was observed but there was no compression during expiration. But when the expiratory pressure inside the jar was increased to 1 cm Hg or more, prolapse of the membranaceous part of the trachea and the main bronchus into the lumen was clearly visible, causing considerable narrowing. This prolapse started early in the expiration (fig 5).

For the study of the "breath sounds" of this preparation, agonal œdema fluid or bronchial exudate were evacuated by suction. When the main air passages were dry, a piece of rubber tubing, attached to a stethoscope was introduced into the tracheal cannula. No wheeze was heard when the lung expired under atmospheric pressure, but when the expiratory pressure in the jar was increased to 2 cm a high pitched wheeze became clearly audible through the stethoscope.

Positive pressures of 1–2 cm Hg (14–27 cm of water) are easily produced in vivo during forced expiration; much higher intrathoracic pressures have been measured directly or through œsophageal catheters during expiration in asthmatic attacks (Dayman 1951, Fry et al 1954, Mead et al 1955, Wyss 1955). Thus a passive compression, comparable to that in these experiments in vitro, may reasonably be supposed to take place in vivo.

In the living subject the posterior wall of the trachea is attached to the anterior wall of the œsophagus, but this does not prevent its being pushed forward during the expiration, as shown by the aforementioned observations. In fact, physiological experiments (Buytendijk 1949) have shown that the walls of the œsophagus behave so passively that the pressure in its lumen can reliably be used for the determination of intrathoracic pressure.

Discussion

These investigations seem to support the hypothesis that high intrathoracic pressure (produced by asthmatic patients during the peculiar *forceful expiration* which is part of the characteristic breathing pattern in this disease) causes a passive compression in the larger air passages which will lead to increased air flow resistance and should seriously be considered as a cause of asthmatic wheezing.

Our observations as yet do not indicate how far down into the intrapulmonary airways this compression

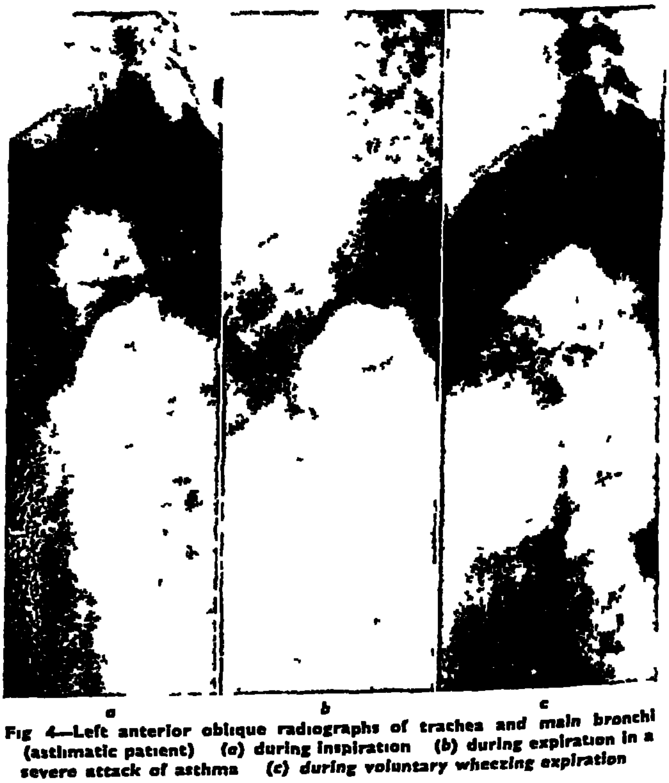

Fig 4—Left anterior oblique radiographs of trachea and main bronchi (asthmatic patient). (*a*) during inspiration; (*b*) during expiration in a severe attack of asthma; (*c*) during voluntary wheezing expiration.

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† We are indebted to Prof Dr H T Deelman and his staff for providing us with this material.

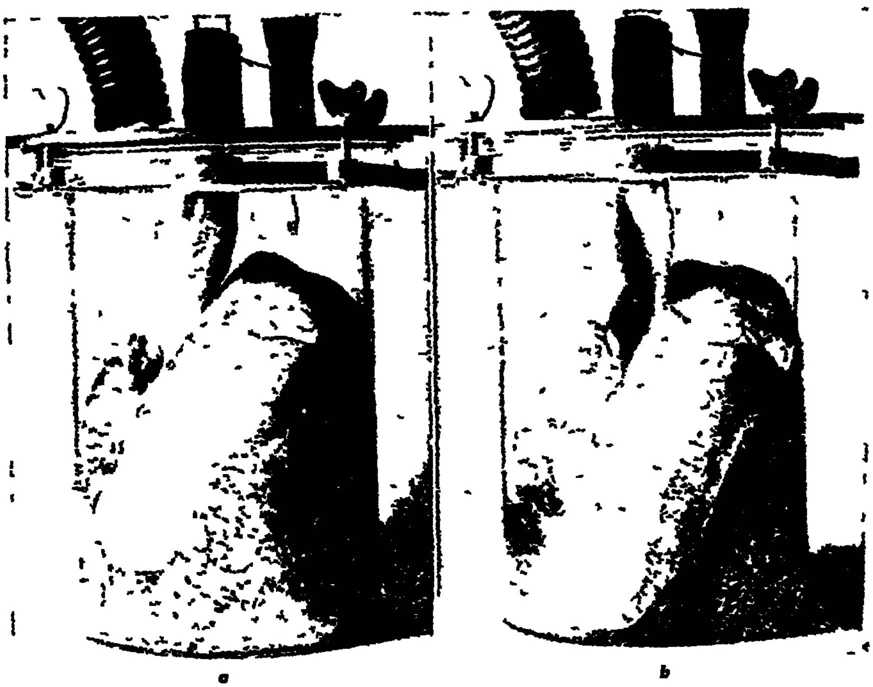

Fig 5—Isolated human lung, "breathing" in a closed jar. (a) mid inspiration, trachea wide open; (b) mid expiration under positive pressure (2 cm Hg), trachea narrowed by impression of posterior wall into lumen.

extends. It is obvious that the high intrathoracic pressure during expiration compresses not only the trachea and major bronchi but also the intrapulmonary air passages, because the intrathoracic pressure is transmitted through the pulmonary tissue. At least three forces, however, oppose this compression:

(1) The rigidity of the walls of the bronchi and bronchioli.

(2) The centrifugal dilating forces of the pulmonary tissue, depending on the state of inflation of the lung (Sonne 1923, Von Neergaard and Wirz 1927, Huizinga 1938, Stutz 1949, Van Exter 1953).

(3) The intraluminal air pressure in the bronchi.

The rigidity of the tracheo-bronchial tree is commonly overestimated. This has led some to assume that the so-called check-valve mechanism is localised only or predominantly in the unsupported bronchioles (Dayman 1951, Fry et al 1954). Others have been so impressed by the tracheo-bronchial collapse observed either through the bronchoscope (Lemoine 1949, Lemoine and Garaix 1953, Herzog 1954) or by radiology (Pohl 1951, Herzog 1954), that abnormal flexibility of the walls was held to be the primary cause of the phenomenon. Even a plastic operation has been developed for this condition (Nissen 1954). But in those cases where abnormal laxity of the walls really existed the sequence of events might well be reversed. Abnormal flexibility might result from the continuous overstressing of the elastic elements in the walls during the continuous compression with each expiration.

Emphysema will lead to loss of the centrifugally dilating forces (Dayman 1951, Fry et al 1954), thus facilitating the compression.

The intrabronchial pressure in the cartilage supported airways would be decreased by any stenosis in the small peripheral bronchi. This might be caused by mucus, congestion of the mucous membrane, or increased muscle tone. Decreased intraluminal pressure in the bronchi leaves the compressing forces unbalanced. Thus bronchiolar stenosis contributes to the expiratory compression of the larger airways. A primary increase of peripheral resistance, however, is not indispensable for the wheezing by passive compression, as is shown by our experiments with normal individuals.

On the other hand, any increased resistance downstream will increase the intraluminal air pressure, thus supporting the walls. Barach and Swenson (1939) emphasised the importance of this mechanism in positive pressure breathing and pursed-lip breathing in the treatment of patients with asthma and emphysema. We can confirm their observation that pursed-lip breathing may momentarily stop the wheeze in these patients.

There is as yet insufficient evidence for a statement on the relative importance of the contribution of the cartilage supported air-ways and the bronchioles in the production of asthmatic wheezing. Some of the finer wheezing heard over the thorax through the stethoscope may originate in the bronchioles, but we feel that the majority of wheezing sounds which can be heard from the patient's mouth at a distance are produced in the larger, cartilage supported, airways. Tubes with a bore of less than 1 mm are poor conductors of sound, especially in the higher frequency ranges (Martini and Müller 1924, Rappaport and Sprague 1951). On the other hand, it is common experience to bronchoscopists that a foreign body in the larger airways produces wheezing indistinguishable from asthmatic wheezing (Jackson 1921, Clerf 1935, Lell 1946).

The influence of the "voluntary" respiration muscles on the diameter, flow resistance, and wheezing of the cartilage supported airways opens interesting possibilities for the explanation of increased outflow resistance (Von Neergaard and Wirz 1927, Dayman 1951, Fry et al 1954, Wyss 1955), the pathways of emotional influences (Groen and Bastiaans 1953, Bastiaans and Groen 1955, Dekker and Groen 1956), and the results of breathing and posture exercises (Saenger 1904, Heckscher 1936, Howell 1955) in asthma.

Summary

We have confirmed old observations that asthmatic patients and normal people can learn to wheeze at will by imitating the typical asthmatic expiration. This voluntarily produced wheezing is indistinguishable from the spontaneous wheezing during asthmatic attacks. X-ray studies during this voluntary wheezing reveal, both in normal subjects and in asthmatic patients, a considerable narrowing of the cervical and thoracic trachea and of the main bronchi. The same narrowing was found in X-ray pictures taken during the expiration in patients with spontaneous asthmatic attacks. In human lungs, obtained at necropsy, which were made to breathe under different pressures in a closed jar, an expiratory pressure of 1 cm Hg or more produced a considerable stenosis by a prolapse of the membranaceous part of the trachea and main bronchi into the lumen. It is postulated that a similar passive compression of the larger air passages, caused by the high intrathoracic expiratory pressure which asthmatic patients produce as a result of their peculiar type of breathing, is an important factor in the production of the asthmatic bronchostenosis and of the expiratory wheezing which is so characteristic of this disease. The importance is

noted of these observations for understanding the mechanisms by which asthmatic attacks are brought about and by which they can disappear with breathing exercises

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A METHOD OF MEASURING THE pH OF BODY-FLUIDS

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THE method described here is especially suitable for measuring the pH of small amounts (about 0 5 ml) of blood The apparatus is simple to use and to maintain and is designed for continuous operation , so there is a delay of only about 5 minutes between blood reaching the laboratory and the measurement of its pH The standard deviation for the reproducibility of pH measurement of blood is 0 005 pH units, which is well within the limits necessary for clinical work

Apparatus

Constant temperature pH Cell (fig 1)

A is the glass electrode with a bulb type membrane and ground glass cone (size B7) fitting into the socket in the neck of the anaerobic chamber (B) The chamber is of 0 4 ml capacity and leads by a capillary about 0 5 mm in diameter to a hollow-key one-way stopcock (C) The barrel of the stopcock has a glass back to prevent fluid and electrical leakage The hollow key is pierced at either end to allow air to escape when the key is inserted into the barrel A little petroleum jelly is applied to the wide end of the key and to the narrow end of the barrel Thus, when the key is inserted into the barrel and rotated, a layer of grease is formed at each end of the stopcock, leaving a clear ring between, around which the KCl forms a conducting path Silicone grease should not be used, because it may interrupt the conducting path The lower opening of the stopcock leads to the reservoir (D) containing 3 5 *M* KCl and the calomel half cell (E), which is of the conventional 3 5 *M* KCl type Glass collars are fused to the top of the vessels containing the glass and calomel electrodes to provide a moat between them and the water bath This moat is kept clean and dry to prevent electrical leakage

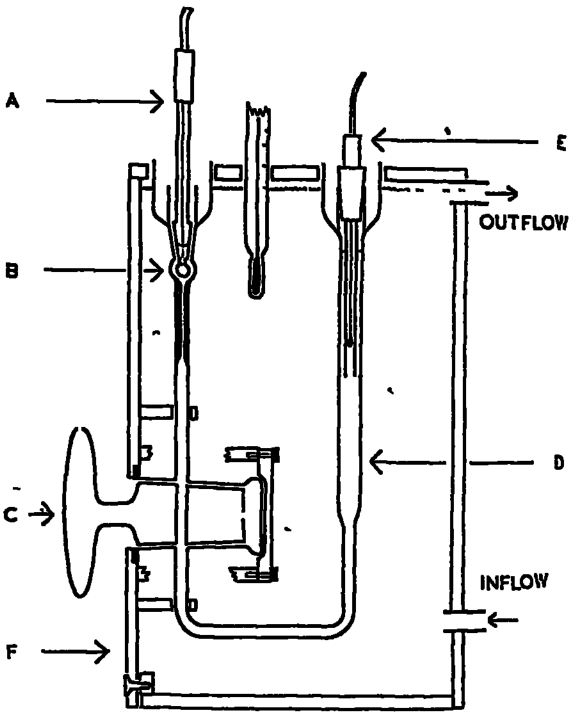

Fig 1—Constant-temperature pH cell A, glass electrode , B, anaerobic chamber , C, stopcock , D, reservoir for 3 5 M KCl , E, calomel electrode , F, perspex box with removable front Inflow and outflow ducts are connected to recirculating pump and thermostatically controlled water-bath

The whole of this glassware is fitted to the detachable front of a ' Perspex ' box (F) The box is surrounded by electrostatic shielding and contains water maintained at 38 0 ± 0 1°C by a thermostatically controlled reservoir water bath and a recirculating pump capable of exchanging the volume of the box every 2 minutes

A thermometer, whose bulb is near the glass electrode chamber, is graduated in tenths of a degree C There is a duplicate chamber to B connected to a distilled water reservoir, in which the glass electrode is stored at 38°C ready for use

Glass Electrode

This consists of a thin bulb of MacInnes Dole glass fused to the stem just below the ground glass cone It is of the standard Ag/AgCl/0 1*M* HCl type with shielded input lead It is mechanically robust and, in our experience, gives constant response for at least nine months

Measuring Apparatus

This is a direct reading millivoltmeter based upon the dynamic capacitor with full scale deflections of 10, 30,

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* N Z University Travelling Scholar

100, 300, and 1000 mV The effect of variations in mains voltage is negligible, and the apparatus may be left running continuously In series with the low-resistance input from the calomel electrode is a potentiometer (fig 2) By means of this a steady back E M F is applied which is adjusted to enable the full length of the appropriate scale to be used for the pH determination

Buffer Solutions

The buffers used and the pH values assigned to them are those described by Hitchcock and Taylor (1938) and recommended by the British Standards Institute (specification 1647 1950) These give virtually the same pH scale as that recommended by the U S National Bureau of Standards (L C 993 - 1950) They are 0 05 M potassium hydrogen phthalate (pH 4 025 at 38°C), a mixture containing 0 025 M disodium hydrogen phosphate and 0 025 M potassium dihydrogen phosphate (pH 6 835 at 38°C), and 0 05 M disodium tetraborate decahydrate (pH 9 070 at 38°C) They are easy to make up and, if a crystal of thymol is added, the former two remain stable for at least two months, the latter for a shorter period

The buffers are prepared by dissolving the proper weight of 'Analar' reagent grade salt in reboiled distilled water of pH 6 7–7 3 and making up to one litre in a volumetric flask Before being weighed, the potassium hydrogen phthalate and the phosphate salts are dried in an oven at 110°C for two hours and cooled in a desiccator Disodium tetraborate decahydrate is dried without heating in a desiccator for forty eight hours These buffers have a high buffering capacity and a low dilution effect Buffers of intermediate value to those described here have not these properties, and we have found that commercially made intermediate buffers designed to have a pH nearer to that of blood soon change from their nominal pH values

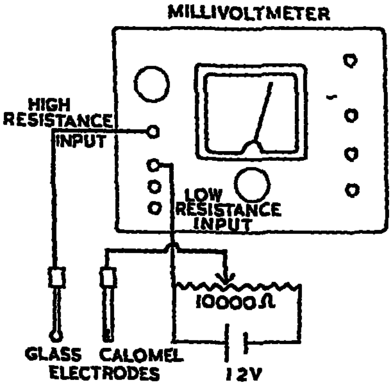

Fig 2—Simple potentiometer to be used in conjunction with millivoltmeter

Technique of Measuring Blood pH

The chamber (fig 1,B) is filled and sucked out several times with distilled water and finally with A R acetone to dry the chamber The stopcock is opened to allow the KCl just to reach the top of the capillary, then closed It is important not to allow KCl to enter the chamber, otherwise significant depression of the pH of the buffer will result owing to a salt effect, and reproducibility will be affected pH 6 835 buffer (a sample of which is kept in the reservoir water-bath) is introduced The glass electrode is lightly dried with filter-paper and inserted The millivoltmeter is switched on to the 100 mV scale After three minutes the potentiometer is adjusted until the millivoltmeter reads between 0 and 10 mV, and an accurate reading is taken On this scale the meter may be read to ±0 1 mV (±0 002 pH units) The buffer is then sucked out and the chamber washed with distilled water and dried with acetone The glass electrode is washed and stored in distilled water in the duplicate chamber The KCl liquid junction is now renewed The glass electrode is withdrawn and dried with filter paper Blood is introduced into the chamber from a syringe with a long needle, which reaches to the bottom of the chamber The glass electrode is immediately inserted and an accurate reading is taken at 1½ minutes The difference in mV multiplied by 0 0162 gives the pH difference between buffer and blood The figure 0 0162 is the theoretical factor relating pH to mV, it is derived from the expression F/0 0023026 R T, where R is the gas constant, F the faraday, and T the absolute temperature In our experience the electrodes may not give exactly this response, so, for more accurate work we allow for this error and any others inherent in the method by calibrating the glass electrode with the pH 4 025, pH 6 835, and pH 9 070 buffers We have found the response linear over this pH range, and in terms of the conversion factor from mV to pH units this response has remained constant within 0 00005 for any one electrode for at least three months

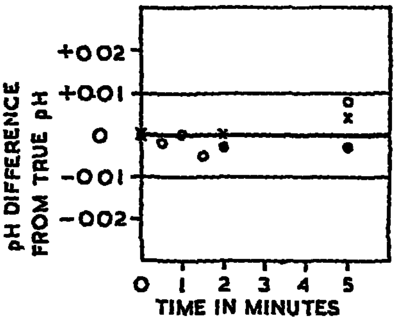

Fig 3—The pH of a sample of blood was measured in the usual way as described in the text. The measurements were repeated after various times of exposure in chamber before electrode was inserted Experiment was repeated thrice Horizontal lines are true pH ± 2S D

The factor has varied from one glass electrode to another within the range 0 0163 to 0 0165 A glass electrode should be checked periodically by this method

Other biological fluids—The pH of other biological fluids may be measured by an exactly similar method using the scale of the millivoltmeter appropriate to the pH range

Some Factors Affecting Measurement of Blood pH

Collection and Storage of Blood

Blood is collected without bubbles into a paraffined or silicone greased syringe containing 0 04 ml (0 2 mg) of heparin per 10 ml of blood The needle is inserted into a cork until pH is measured Since electrolyte estimations are generally to be made on the same sample, fluoride is not added Moreover it is unnecessary because, under these conditions there is no change in the blood pH at room-temperature for at least 30 minutes If the syringe is placed immediately into iced water, there is no change

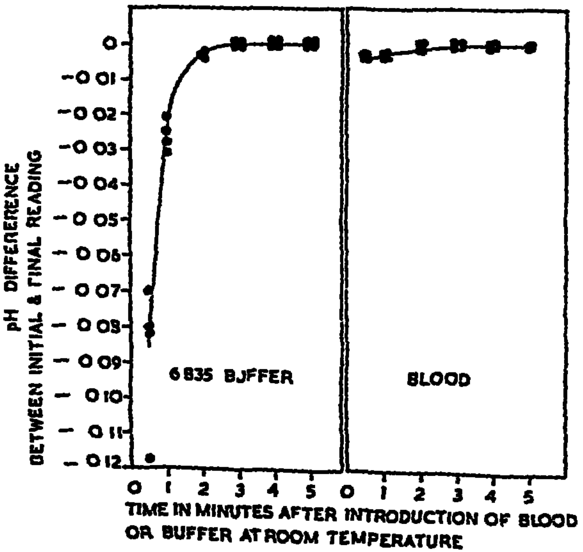

Fig 4—Effect of time after introduction of the sample and glass electrode into chamber, on pH of sample Experiment was performed four times and measurements were made at 38°C.

for four hours (Astrup 1956, Severinghaus et al. 1956, and personal observations).

Anaerobic Conditions

The best way to ensure anaerobic conditions is to send the blood to the laboratory in the syringe. Blood comes into contact with the atmosphere only in the brief period (a few seconds) between its introduction into the chamber and the insertion of the glass electrode. In any case, the blood finally in contact with the electrode has been protected from the air by the blood initially introduced, which is displaced upwards from the bottom of the chamber. By filling the chamber with blood and allowing it to remain exposed to the air for varying periods before the electrode is introduced, it can be shown that no significant pH change attributable to loss of carbon dioxide can be detected with up to 5 minutes' exposure (fig. 3).

Equilibration Time

When buffer is introduced at room-temperature, a steady reading is reached after 3 minutes, this being the time taken to reach thermal equilibrium. When blood is introduced, however, the time taken to reach a steady reading is less—about $1^1/_2$ minutes (fig. 4). This is because the negative temperature coefficient of the pH of blood almost cancels out the positive coefficient of the E.M.F.–pH relationship of this particular cell system.

Since the mV reading with blood remains constant for at least a further 3 minutes after equilibrium is reached, one may assume that the blood pH read after $1^1/_2$ minutes has not been measurably affected by glycolysis.

Reproducibility

The reproducibility of the measurement of the pH difference between two buffers with a pH difference similar to that between 6.835 buffer and blood was tested in the following way.

A buffer of mean measured pH 7.273 was made up, and the mV difference between this buffer and one sample of 6.835 buffer was measured nine times. The standard deviation of the mV differences, expressed in pH units, was 0.0025 (S_1).

A similar experiment was made with a sample of blood transferred anaerobically from a 20 ml. syringe to nine 2 ml. syringes, which were stored in iced water till the pH determination was made. The mean value for pH of the blood was 7.332. The mV difference between one sample of 6.835 buffer and each aliquot of blood was measured. The standard deviation of the mV difference expressed in pH units was 0.005.

The first experiment gives a measure of the reproducibility of measurement of pH with this apparatus. The second is a measure of the reproducibility of measurement of blood pH.

As a measure of the reproducibility with which pH 6.835 buffer may be made up, the mV difference between nine separate preparations of this buffer and one sample of 7.273 buffer was measured. The standard deviation of the mV difference, expressed as pH units, was 0.005 (S_2). By using the results of the first experiment to correct for errors in measurement, a standard deviation of pH .004 ($\sqrt{S_2-S_1}$) is obtained for the pH differences in the nine preparations of buffer.

Stability

We have found that over two to three hours successive introductions of 6.835 buffer give readings which agree to within 0.3 mV (0.005 pH) without adjustment to the potentiometer. These measurements were obtained during pH estimations on numerous samples of blood (about 12 per hour). This shows that repeated standardisations with buffer are unnecessary, at least over this time interval.

Discussion

It has become clear in the past few years that the estimation of the pH of the blood may be of great value in the diagnosis and treatment of numerous clinical conditions, especially those associated with disordered respiration. Respiratory failure is an emergency in which the blood pH and PCO_2 may need to be estimated quickly if correct treatment is to be given. In our efforts to develop a method of measuring the blood pH which would include simplicity, speed, accuracy, and above all reliability we have met with several difficulties.

Accurate control of the temperature of the glass electrode and measurement at the temperature of the patient is essential for blood-pH work. Temperature corrections may apply to normal blood but are unsuitable for pathological blood in which hæmoglobin, serum-protein, and electrolytes may differ greatly from normal.

The most vulnerable part of any system for measuring blood pH is the glass electrode. Until the past year we have used a slightly different electrode and have had a great deal of trouble from sudden unpredictable failure. Various gums were used to seal the pH sensitive bulb to the glass stem bearing the ground glass cone. We believe that the deterioration of the seal led to breakdown of the insulation and to erratic results. We have had no trouble from this source with the present electrodes, which are entirely glass sealed. The electrodes require no special cleaning and are stored in distilled water before use.

The liquid junction between the fluid being measured and the KCl salt bridge poses several problems for which many solutions have been suggested. We have found that a capillary works very well in practice. It has an advantage over porous fibres, sintered glass, and ceramic plugs in that, since protein is not precipitated in it, there is no special problem of cleaning.

The two types of instrument used for measuring the E.M.F. of a pH cell are the potentiometric (null point) and the direct reading. These both incorporate amplifiers for use with the high impedance glass electrode system, based either on electronic valves or dynamic capacitors. The pH cell described here works equally well with both types of instrument. The use of batteries or of accumulators as a source of power is a disadvantage in measuring blood pH, where it is often important to be able to take a reading at short notice. When the battery operated instrument is first switched on, 20 minutes are needed for warming up. If the instrument is left on, the power supply is rapidly exhausted. A mains operated instrument may be left running continuously and then needs no warming-up period.

Accuracy is of more importance here than in much pH work, so that the meter used must have a correspondingly better performance. For greatest accuracy a high zero stability is required if the zero setting is not to be checked constantly for drift. Here the dynamic capacitor has a considerable advantage over the valve operated amplifier because its stability is greater by a factor of at least 10. At the same time, a direct reading meter is simpler and quicker to use than a null point instrument. The chief requirements of a direct reading meter are linearity of response, meter accuracy, and stability of amplifier gain. These have been satisfactorily met in modern instruments.

The final problem to which we wish to draw attention concerns the standard buffer solutions used in blood pH work. The buffers we have described and the pH values ascribed to them have probably the widest acceptance in Great Britain and in the U.S.A. For the results of pH measurements of the accuracy required in biological work to be comparable from laboratory to laboratory it is essential to adopt a common pH scale, such as the Hitchcock Taylor scale described here. We have already mentioned that some intermediate buffers available commercially are far from their nominal value when tested. Others with whom we have discussed this point have had similar experience.

Summary

A method is described of measuring the pH of body-fluids anaerobically and at controlled temperature It is designed for small samples (0 5 ml) and is of suitable accuracy and reliability The method incorporates a specially designed pH cell which is used with a commercially made direct-reading millivoltmeter modified by the incorporation of a simple potentiometer to be suitable for pH measurements

Electronic Instruments Ltd , Richmond, Surrey, England, supplied the 'Vibron Electrometer model 33B, the glass electrode 18395, and the calomel electrode 18357 A pH cell and perspex box based upon our design and a suitable potentiometer may also be obtained from them Townson & Mercer Ltd , Croydon, England, supplied the thermostat bath and recirculating pump model 'BX 148/U' We wish to thank Dr G Mattock and Dr J Jackson for their helpful comments on the manuscript

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Hitchcock D I Taylor A C (1938) *J Amer chem Soc* 60 2710
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Medical Societies

AMERICAN SURGICAL ASSOCIATION

THIS association's annual meeting was held in Chicago from May 8 to 10, under the chairmanship of Dr LOYAL DAVIS (Chicago, Ill.)

Injury Due to Atomic Explosion

Dr JOHN MORTON (Rochester, N Y) had seen Americans, Japanese, and Marshall Islanders burned by the fallout of radioactive dust following the explosion of the H bomb at Bikini Injury was mainly due to β irradiation causing epilation, vesication, and purpura superficially, with fever, vomiting, diarrhœa and failure of blood coagulation , mortality was approximately 50% in those exposed to 200r, 100% after 600r Ulceration starting at a late stage had been seen in some who had recovered from the acute effects

Dr J GARROTT ALLEN (Chicago, Ill) had studied the effects of γ-irradiation on dogs Though all had died after receiving 300r it was difficult to predict which would survive following lesser doses , 300–400r in a single exposure was fatal to man In dogs surviving non-lethal doses the white blood-cells returned to normal only after 30 days, thrombocytes after 50 days, and red blood cells after 75 days Supportive treatment with blood and platelet infusions and antibiotics during this period had no effect on the eventual outcome There was therefore no effective treatment, though shielding of the head at the time of exposure reduced mortality , additional shielding of the spleen and long bones improved the chances of survival Surgery for debridement of wounds and the reduction of fractures must be undertaken during the first 48 hours or after the 30th day since operative interference within this period caused death the real cause of which was not understood In the event of atomic war the policy of delayed primary or secondary suture would therefore have to be revised

Dr J BARRETT BROWN (St Louis Miss) referred to the dangers of exposure to electron streams for those working with cathode-ray tubes Accidents of this nature caused burns which became manifest 2–4 weeks later

Wound Infection

Dr CHESTER W HOWE (Boston, Mass) said that at the Massachusetts Memorial Hospitals the infection-rate after clean operations had been 1% in 1949 but had risen to 4% in 1953 and persisted at that rate till 1956 , the investigation concerned approximately 1200 operations each year Over the same period the incidence of infections with *Staphylococcus aureus* had increased from 57 to 80% and antibiotic-resistant strains had developed There appeared to be no relation to the staphylococcal carrier-rate, which was 99% in 1953 but had fallen to 73% in 1956 The increased incidence of infection had occurred wholly in patients operated on by the junior staff for in the private wards the incidence had remained at 1% throughout the period of study

Dr DERYL HART (Durham N C) said that ultraviolet radiation had solved this problem, and that operating-theatres so equipped were quickly sterilised

Dr HENRY T BAHNSON (Baltimore, Md) described 5 cases of staphylococcal bacteræmia and septicæmia following the use of silk sutures within the heart or great vessels , infection persisted until the sutures were removed and replaced by catgut or wire

Dr OSCAR CREECH, jun (New Orleans Louisiana), analysed 558 cases of tetanus seen between 1942 and 1956 , the mortality-rate had fallen from 43% in 1943 to 33% in 1956, and antibiotic therapy appeared to have been relatively ineffective Antitoxin was still the main line of defence , 75% of the deaths occurred during the first 4 days of the disease, and the outcome appeared to be related more to the amount of toxin produced than to the effects of treatment Only 1 case had been seen in a patient previously receiving *tetanus toxoid*

Complication of Œsophagogastric Resection

Benign gastric ulcer in 4 patients after œsophagogastric resection for carcinoma was discussed by Dr CURTIS A SMITH (Chicago, Ill), who suggested that it might result from delay in gastric emptying due to the inevitable vagotomy, since experimentally increased secretion in Heidenhain pouches had been found under these circumstances Gastro-enterostomy in 1 case had effected a cure for 6 years He felt that œsophagogastric resection should always be accompanied by gastro-enterostomy

Hypoparathyroidism

Peptic ulcer was one of the indications of hypoparathyroidism cited by Dr LEON GOLDMAN (San Francisco, California), the others being nephrolithiasis, bone lesions, and acute hypercalcæmia, in that order of frequency, though there were sometimes no leading symptoms The serum-calcium might not always be significantly elevated and he described a further diagnostic test involving the assessment of renal tubular reabsorption of phosphorus, which was low in 20 of 21 cases in which there was no uræmia

Calcium Metabolism

Dr GEORGE H CLOWES (Cleveland, Ohio) had seen hypotension unrelated to low blood volume during and after prolonged operations, particularly intrathoracic procedures incurring hyperkapnia and hypoxia causing respiratory and metabolic acidosis He found that the blood calcium fell before the end of the operation with an associated rise in circulating phosphate and lactate The protein bound fraction of calcium was not affected and the hypocalcæmia was due to a fall in ionised calcium , incomplete oxygenation might be a cause, as might citrate in blood replacement.

Nitrogen Balance

Dr WILLIAM D HOLDEN (Cleveland, Ohio) presented metabolic studies demonstrating that nitrogen deficit after surgical operations was due to a failure of adequate nitrogen intake in the postoperative period With appropriate intravenous nitrogenous intake using hydrolysates positive balance could be maintained, patients would not ingest sufficient nitrogen when left to eat what they wished, and the negative *nitrogen balance* under these circumstances exactly correlated with the degree of nitrogen starvation But, owing to tissue breakdown, equilibrium could not be obtained in *inflammatory states*

Cardiovascular Surgery

Dr CONRAD R LAM (Detroit, Michigan) showed the value of cardiac arrest induced by an intracardiac injection of acetylcholine while extracorporeal circulation was being maintained Intraventricular septal defects could then be sutured in a quiet dry heart, this had been achieved in 35 out of 50 patients operated on thus, the others having other cardiac defects There had been no increased incidence of atrioventricular block

Extracorporeal circulation had enabled Dr DENTON A COOLEY (Houston, Texas) to excise aortic aneurysms, the circulation being maintained from the left atrium to the left femoral artery for thoracic aneurysms, and from the thoracic aorta to the left femoral artery for upper abdominal aneurysms even when impinging upon the thorax

Dr C WALTON LILLEHEI (Minneapolis, Minnesota) had repaired a ruptured aneurysm of the sinus of Valsalva in 3 cases with the aid of extracorporeal circulation The patients were aged 10, 19, and 37, and the clinical histories revealed that the aneurysms had ruptured suddenly causing a fistulæ with a shunt of blood-flow from left to right heart, operative cures were complete

Dr W G BIGELOW (Toronto, Ontario) reported 20 cases in which open heart surgery was undertaken with only 2 deaths, using an improved method of hypothermia designed to avoid rewarming shock due to metabolic acidosis by avoidance of shivering and peripheral vasoconstriction with the use of chlorpromazine, and by inducing respiratory alkalosis during cooling and operation The use of heparinised rather than citrated blood had permitted ventricular fibrillation to be corrected when it developed

Dr CHAMP LYONS (Birmingham, Alabama) had used by-pass grafts to overcome the effects of thrombosis of the internal carotid artery Dr RICHARD WARREN (Boston, Mass) advocated arteriography in all hemiplegics since some cases were due to carotid thrombosis and were therefore treatable

Dr HOWARD MAHORNER (New Orleans, Louisiana) suggested that in massive thrombosis of femoral or subclavian veins the clot should be sucked out and a course of heparin be given, he had done 16 such operations with good results in 12

Dr WILLIAM G ANLYAN (Durham, N C) had studied 453 cases of venous thrombo embolism and in 19 had seen severe arterial spasm which was relieved by heparin, perhaps because of its antagonism to 5 hydroxytryptamine In half of 66 patients with pulmonary embolism there had been no clinical evidence of venous thrombosis elsewhere He could find no evidence of association between venous thrombosis and occult cancer, 792 cases of bronchial, gastric, and pancreatic carcinoma had yielded only 5 cases of thrombosis, in none of 26 cases of "idiopathic" thrombosis had full investigation revealed cancer

Cancer

Dr GEORGE E MOORE (Buffalo, N Y) had studied cancer cells circulating in the blood stream, in 52% of 179 cases of carcinoma at different sites and in 75% of cases of carcinoma of the stomach, malignant cells were seen in smears prepared from the peripheral blood Samples of blood were prepared by adding a fibrinogen heparin mixture and permitting gentle erythrocyte sedimentation, smears were made from the buffy upper layer, which contained white cells and malignant cells Scanning was tedious and required an average of 3 hours per case It was emphasised in discussion that many circulating malignant cells must be destroyed since there was no definite correlation on follow up between metastasisation and survival on the one hand and the earlier observation of circulating cells on the other Nevertheless Dr JULIAN JOHNSON (Philadelphia, Pa), who had followed 218 patients to 5 years after resection of the lung, had found only 3% survivors among those with vascular invasion as opposed to 71% among others, 88% survived 5 years when neither vessels nor lymph-nodes were involved Survival was related more to the absence of vascular than of lymphatic invasion

Dr MILLAR BELL (Chicago, Ill) presented experimental work showing that nitrogen mustard had a retarding effect on malignant cells injected into the portal vein of rats and was most effective when administered within an hour of the malignant inoculation

Dr WARREN H COLE (Chicago, Ill) was treating patients on these lines with appropriate control series, 65 patients with abdominal malignancy had been given nitrogen mustard 0 1 mg per kg body weight with a maximum total dose of 30 mg in three administrations, the first intraperitoneal and the others intravenous He said that this treatment should be avoided in patients over the age of 70, that leucopenia could be disregarded unless the white cell count fell by more than 3000, and that blood transfusions should be given from the 8th day to counter hæmopoietic depression

Dr R K GILCHRIST (Chicago, Ill) had been exploring the possibility of destroying the lymph gland field draining a malignant area by means of induced heat Fine particles of Fe_2O_3, 0 02–0 1 μ in size, would after injection pass to lymph glands but would not pass through them, high frequency currents of 12,000 watts applied externally rapidly raised the temperature in glands in laboratory animals

Dr JONATHAN E RHOADS (Philadelphia, Pa) made a plea for Whipple's type of operation in cases of pancreatico duodenal carcinoma, of 17 cases submitted to resection, there were 6 survivors for 5 years among those with growths of the ampulla of Vater, the common bile duct, and the duodenum, but none among those with cancer of the head of the pancreas Dr JAMES T PRIESTLEY (Rochester, Minn), however, had had 15% 5-year survival following excision of lesions of the pancreatic head

Choledocho-jejunostomy

Dr ALFRED M LARGE (Detroit, Michigan) had undertaken experimental work which indicated that biliary infection following choledocho jejunostomy occurred because of reflux through the stoma into the gall bladder, cholecystitis ensued with gall stone formation If the gall bladder was removed at the time of the anastomosis, infection did not occur in the biliary tree He presented clinical evidence to support his experimental findings and advocated cholecystectomy in association with biliary anastomosis to intestine Dr JOHN H MULHOLLAND (New York), on the other hand, did not regard reflux as the cause

Experimental Pancreatitis

Dr DANIEL W ELLIOTT (Columbus, Ohio) had shown experimentally that pancreatitis did not follow the reflux of bile into the pancreatic duct, but that pancreatic enzymes, which were secreted at a higher pressure than bile, passed into the biliary system where trypsinogen became activated on mixing with the bile, and the mixture, if then passed into the pancreatic duct, caused hæmorrhagic pancreatitis

Hepatic Cirrhosis

Dr **FREDERIC W TAYLOR** (Indianapolis, Indiana) had induced cirrhosis in animals by the repeated injection of silicon dioxide into the portal system over a period of 3 years; portal hypertension was not then associated with cirrhosis

It was observed by Dr **NATHAN A WOMACK** (Chapel Hill, N C) that venous dilatation in patients with cirrhosis was not always accompanied by a rise of pressure in the portal systems, the vascular dilatation might be hormonal

Dr **WILLIAM P LONGMIRE** (Los Angeles, California) had found that Evans-blue injected into the hepatic artery was immediately found in the portal system of cirrhotic patients, whereas in health there was a delay due to the usual circulation-time; this indicated an arterio portal shunt This view was supported by the work of Dr. **RICHARD M PETERS** (Chapel Hill, N C) in determinations of oxygen saturation in portal venous blood under experimental conditions

Dr **WOMACK** thought that the shunt might be in the gastric mucosa as demonstrated by Bentley and his colleagues at Newcastle upon Tyne.

Treatment of Ascites

Dr **CHARLES G NEUMANN** (New York, N Y) presented the results of ileo-entectrophy in 4 survivors of 10 patients treated thus for ascites A segment of ileum was resected, and with its mesentery intact its mucosal surface was exposed by opening the segment longitudinally close to the mesentery, cæcum and ascending colon were removed so that the ileal segment could be attached by its serosa to the right posterior abdominal wall, the omentum was removed, gastrostomy obviated postoperative intubation, which might have induced hæmorrhage from œsophageal varices Ascitic fluid had been absorbed in all 4 survivors The colon was not suitable for ascitic absorption, because of its greater tendency to secrete mucus

Hirschsprung's Disease

Dr **OVAR SWENSON** (Boston, Mass) presented the results of resection of aganglionic segments in 200 patients with Hirschsprung's disease There were 6 deaths and 5 lost to follow-up 73 patients had been followed for 5–10 years; 72 were well, 1 had recurrent diarrhœa To 5 years the figures were 64 followed, 63 well, 1 with chronic constipation, to 2 years 52 followed, 49 well, 3 with recurrent diarrhœa

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Reviews of Books

Functions of Autonomic Transmitters

The Abraham Flexner Lectures, series no 13 J HAROLD BURN, M.D, professor of pharmacology, Oxford University London Bailliere, Tindall & Cox U S.A Waverly Press Inc 1956 Pp 228 40*s*

Professor Burn delivered the thirteenth series of Abraham Flexner lectures at Vanderbilt University last year They are now reproduced in this book

Two chapters are devoted to the actions of acetylcholine with special reference to its function in controlling contraction of heart muscle and ciliary movement A further chapter describes the actions of noradrenaline, and the problems associated with change in the sensitivity of denervated structures are fully discussed The common properties of local anæsthetics, drugs with a quinidine like action, spasmolytics and antihistamines are related to their ability to depress the action of acetylcholine in the tissues concerned Much of this fundamental research has been carried out in Professor Burn s laboratory, and he writes with the authority of many years spent in the study of the problems of autonomic transmission. The first and last chapters are of more general interest, dealing with some aspects of medical education and research the antidiuretic effects of smoking, and the influence of alcohol on motor-car driving

Physiologists and pharmacologists working in this special field will wish to have Dr Burn's book at hand In most of the chapters they will find interesting suggestions for further research

1957 Supplement to the British Pharmaceutical Codex 1954

London Pharmaceutical Press £1 7*s* 6*d*

THIS supplement contains 44 new monographs, including 10 which relate to drugs added to the *British Pharmacopœia* by the Addendum of 1955 The changing face of therapeutics is reflected in the inclusion of a substantial number of potent drugs such as acetazolamide, meclozine hydrochloride pentolinium tartrate, phenoxymethylpenicillin, and tetracycline hydrochloride There is a long list of older preparations which have been modified and the corresponding monographs have been appropriately amended

The importance of the *B P C* has been greatly increased in recent years by the inclusion of well-written sections on the actions and uses of the drugs listed Hence this publication is not only invaluable for pharmacists who need a book of reference which has a wider scope than the *B.P*, but is a first-class investment for the medical practitioner and specialist

Progress in Nuclear Energy Medical Sciences

Series VII vol I Edited by J C BUGHER, The Rockefeller Foundation, New York; J COURSAGET, C.E.A Society, J F LOUTIT Medical Research Council, A.E.R.E, Harwell. London and New York Pergamon Press 1956 Pp 165 42*s*

THE first volume of a series, this book is based on papers presented at the Geneva conference on the peaceful uses of atomic energy

Each of the seven chapters summarises in a slightly different way the work and papers of many authors, yet each remains a coherent account and not simply a list of statements and references The first four chapters deal with the main clinical medical uses of radioactive isotopes and the last three with radiation protection and legislation, and radiation dosimetry Industrial and general public-health aspects of radiation exposure and protection might perhaps have received fuller treatment Nevertheless, this is a good book and a useful work of reference

The Head and Neck in Roentgen Diagnosis

2nd ed Vols I and II EUGENE P PENDERGRASS, M.D, professor of radiology and chairman of the department of radiology, University of Pennsylvania, J PARSONS SCHAEFFER, M D, PH D emeritus professor of anatomy and director of the Daniel Baugh Institute of Anatomy, Jefferson Medical College, PHILIP J HODES, M D, professor of radiology, University of Pennsylvania Springfield Ill Charles C Thomas Oxford Blackwell Scientific Publications 1956 Pp 1759 £14

AFTER a lapse of fifteen years, another edition of this book has been produced, dedicated to the memory of Prof H K Pancoast, the original author The text has been completely rewritten and now covers every aspect of the radiology of the head and neck There are excellent chapters on the examination of the brain by angiography and ventriculography Throughout the book, the common and often misleading variations of normal are distinguished from the frankly pathological Diseases which may affect the head and neck, though they originate in other parts of the body, have been included The clinical and pathological as well as the radiological findings are incorporated in a straightforward narrative, backed up with enough detail of anatomy, differential diagnosis, and radiographic technique to make it one of the better textbooks available in the English language

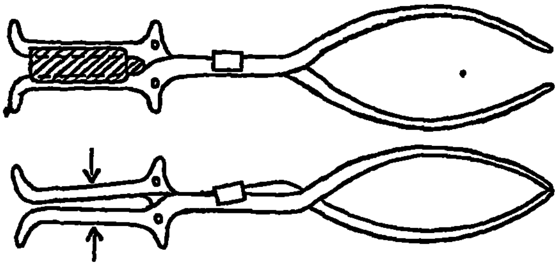
Lumbar Puncture and Spinal Analgesia (2nd ed Edinburgh and London E & S Livingstone 1957 Pp 142 25s) —The second edition of this very helpful little monograph by Sir Robert Macintosh will be as acceptable as the first in providing a refreshing approach to an old subject, by one who speaks from long experience and with mature opinion In the interval between the two editions the courts have decided some important cases in which neurological complications of spinal analgesia figured conspicuously This book emphasises clearly the importance of proper sterilisation in avoiding these complications

Regulation and Mode of Action of Thyroid Hormones (*Ciba Foundation Colloquia on Endocrinology* Vol 10 London J & A Churchill 1957 Pp 304 48s) —This is the report of a conference held last June under the chairmanship of Dr Rosalind Pitt Rivers and attended by speakers from Europe and North and South America The papers are edited by Dr G E W Wolstenholme and Miss Elaine C P Millar, A R I C

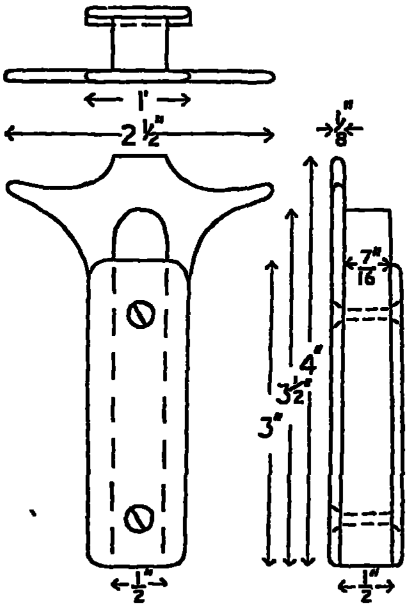
New Inventions

KIELLAND'S FORCEPS HANDLE-LOCK

THE sliding-lock mechanism of Kielland's obstetric forceps, which is necessary for the easy articulation of the blades and for the correction of asynclitism, results in a gap between the handles and a lack of stability Any grip applied to the handles with the forceps correctly applied will cause a crushing force to the fœtal head



The handle-lock illustrated is made of stainless steel and is applied after asynclitism has been corrected It ensures a firm grip of the handle without any tendency to crush the head It produces perfect alignment of the blades, and, because the Kielland's handles are wedge shaped it will not slip off



Holborn Surgical and Veterinary Instruments Ltd , Margate Road, Broadstairs, are proposing to make the handle lock in solid stainless steel

J M HOLMES

Guy's Hospital, London M D Lond, M R C O G

A MODIFICATION OF THE TONGUE-PLATE OF THE BOYLE-DAVIS GAG

IN oropharyngeal surgery, tracheal intubation is well recognised as a valuable means of maintaining control of the airway at a light level of anæsthesia The disadvantages of intubation by the nasal route are such that there may be a place for a means whereby it can be avoided in the commonest of all oropharyngeal operations—namely, tonsillectomy

A simple modification of the tongue-plate of the Boyle Davis gag allows tonsillectomy in children and adults to be performed after orotracheal intubation without the tube encroaching on the field of operation (fig 1)

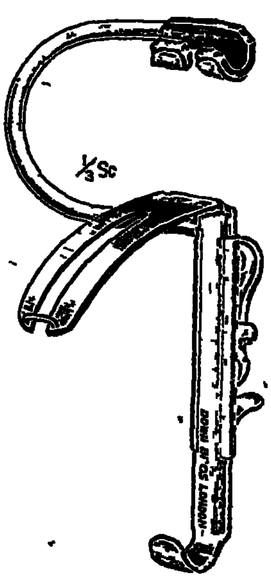


Fig 1

A slot is cut in three quarters of the length of the tongue plate and the lingual aspect of the slot bevelled to accommodate the tube A metal bridge is fitted at the distal end of the slot to prevent the tube wedging in it The lingual surface of the tongue plate proximal to the slot is grooved slightly to hold the tube centrally

Anæsthesia is induced and an endotracheal tube is passed through the mouth This is fixed so that it lies centrally over the tongue, lips, and incisor teeth The surgeon then inserts the gag by sliding the bridge at the distal end of the tongue plate over the tube within the mouth Care must be taken at this stage to ensure that the central fixation of the tube is not disturbed

The tongue plates are made in three sizes, the largest being suitable for adults (fig 2) It is recommended that Magill's tubes sizes 1–3 be used with the 3 in tongue plate, sizes 3–6 with the 3½ in tongue plate, and sizes 7–10 with the 4 in tongue plate

Tongue-plates incorporating a similar idea have been described previously[1,2] This modification, which was introduced at the section of anæsthetics of the Royal Society of Medicine on March 1, is recommended on the grounds of simplicity and the fact that standard tongue plates may, if desired, be modified by the manufacturers

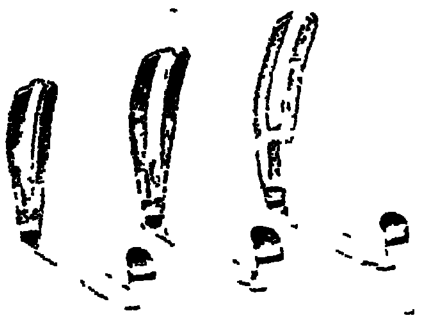


Fig 2

The modified tongue plates may be obtained from Messrs Down Bros and Mayer & Phelps Ltd , 32, New Cavendish Street, London, W 1

ANDREW DOUGHTY

Kingston Hospital Group M B Lond , F F A R C S , D A

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1 Humby G Hawksley M *Brit med J* 1943, i, 317
2 Monro J S C *Ibid*, 1948 i, 267

THE LANCET

LONDON   SATURDAY, MAY 25, 1957

The Immunology of Thyroid Disease

A year ago it might have seemed preposterous to suggest that immunology had anything important to contribute to the study of diseases of the thyroid gland. Yet on May 8 the section of experimental medicine of the Royal Society of Medicine was able to hold on this topic a full-length discussion whose liveliness showed clearly that a new and stimulating idea has been injected into medical thought.

The guest of honour was Prof. E. Witebsky, whose main interest for the past twenty-eight years has been organ-specificity as demonstrated by immunological reactions particularly in relation to the thyroid gland. In the past few years he and his colleagues at Buffalo have been observing the response of animals to the injection of extracts of thyroid glands derived from the same species. These observations have driven Professor Witebsky, with considerable reluctance, to admit that true auto-antibodies can be formed—a conclusion which appears to defy the principle of *horror autotoxicus* enunciated many years ago by his old master Ehrlich. Witebsky and his colleagues have actually demonstrated that a rabbit can make antibodies against an extract of its own excised thyroid. These antibodies are by no means merely an academic curiosity, for they have been shown to be associated with constant and often severe damage to the animal's thyroid when this has been left in situ.[1]

Professor Witebsky relates that it was his colleague at Buffalo, Dr. Douglas Riggs, who first looked down the microscope at sections of the damaged thyroids of his rabbits and made the significant remark: "That looks like Hashimoto's thyroiditis." Witebsky was quick to follow up the implications of this comment, and soon showed that in clinical cases of Hashimoto's thyroiditis (lymphadenoid goitre) there were circulating antibodies against extracts of human thyroid gland. He was slow to publish his results, and he has been anticipated by the entirely independent observations made at the Middlesex Hospital by Dr. Roitt, Dr. Doniach and their colleagues.[2] These workers started from the observation (already recorded by Fromm et al.[3] and by Luxton and Cooke[4]) that patients with Hashimoto's thyroiditis tend to have an unusually large amount of circulating γ globulin, commonly associated with abnormal flocculation tests. Doniach and Roitt had the happy thought that the excess γ globulin might actually represent circulating antibody. They made an extract of normal thyroid gland, added it to serum from patients with Hashimoto's thyroiditis, and obtained easily demonstrable precipitates. The amount of these precipitates is quite startling to immunologists, who normally regard the human animal as a poor producer of precipitating antibodies.

The next development was that both Witebsky, and Roitt and Doniach, showed quite clearly that purified human thyroglobulin could replace thyroid extract for the demonstration of these reactions. Similarly the rabbit antibodies and thyroid reactions can be evoked equally well by the use of rabbit thyroglobulin. Professor Witebsky added the warning that no-one so far has obtained a thyroglobulin which can be regarded as pure; the preparation made in his own laboratory, which he thinks is probably the best yet made, still contains 5% or more of impurities. Provisionally, however, it seems to be agreed that thyroglobulin itself is probably the antigen which provokes the auto immune response, and this idea is supported by studies with fluorescent antibodies. By this technique Professor Witebsky found that when labelled antibody is brought into contact with sections of rabbit thyroid it becomes concentrated mainly in the region of the colloid within the acini. Dr. R. G. White, of the London Hospital, has done the same thing with human thyroids, using serum from cases of Hashimoto's thyroiditis, and here too the antibody was concentrated in the colloid. To remove any doubts about the possibility of irrelevant iso-antibodies he has demonstrated the same phenomenon in the thyroid of a patient with Hashimoto's thyroiditis, applying the patient's own serum. Again the antibodies collected in the colloid of the few remaining active acini, providing convincing evidence of auto-immunity caught in the act. Small amounts of antigen (detected by the labelled antibody) also appeared to be present in some of the cells which invade the thyroid in large numbers in this disease.

Dr. White had also made use of the fluorescing technique to detect the corresponding antibody. The adjacent lymph-nodes are often enlarged in Hashimoto's thyroiditis, and White very reasonably argued that this might be because they were called on to produce at least a large part of the antibody to thyroglobulin. He took one of these lymph-nodes and applied to it first thyroglobulin, and then labelled antibody to detect the thyroglobulin. The marker collected in discrete spots which could be interpreted as the sites of antibody formation. On the basis of these results he put forward the suggestion that antibody is formed in three stages. An initial leak of thyroglobulin attracts a collection of lymphocytes and plasma cells within the thyroid, which themselves make antibody locally. Cellular destruction resulting from the antigen antibody reaction may cause the release of more thyroglobulin, thus initiating a sort of chain-reaction. Some of this thyroglobulin escapes into the surrounding lymph-nodes, where the second stage of antibody formation is stimulated. Finally some thyroglobulin gets into the general circulation, so that antibodies are produced by other tissues and become demonstrable in the serum.

There is still some uncertainty as to the best way of demonstrating the circulating antibodies. The first method to be employed was that of simple precipitation. In suitable cases this method can be most spectacular, but it is not very sensitive. By this method in Britain precipitating antibodies have been found in only about half the cases of Hashimoto's thyroiditis, and Professor Witebsky's experience in Buffalo has been even more disappointing. He prefers a method in which tanned red cells are coated with antigen and then agglutinated by the antibody. In his hands this technique has been specific and astonishingly sensitive, both in rabbits and man, with serum titres up to the fantastic figure of 1 : 2,000,000. Yet even with this sensitive instrument he could still detect antibodies in only a minority of cases of Hashimoto's thyroiditis. The discrepancy between his results and those of the British workers may lie in the realm of diagnosis; at least this seems a more likely explanation than that some radical difference exists between Hashimoto's thyroiditis in Buffalo and in London Pathologists are by no means agreed as to which cases should be called Hashimoto's thyroiditis, and which are better described as chronic non-specific thyroiditis Possibly before long the responsibility for diagnosis will be taken over from them by the immunologists The third—and most controversial—method of detecting antibodies is by complement-fixation Professor WITEBSKY has had no success with this method in man, though it is sensitive and reliable in detecting antibodies in immunised rabbits Dr ROITT likewise has had little success in detecting antibodies in this way Dr WHITE, on the other hand, using thyroglobulin prepared from thyrotoxic thyroids as his antigen, has been able to detect complement-fixing antibodies in nearly all cases of Hashimoto's thyroiditis which he has examined So, too, has Dr J R ANDERSON, of Glasgow, his antigen is an extract of thyrotoxic thyroid Dr W R TROTTER, Dr G BELYAVIN, and Miss A WADDAMS, of University College Hospital, have had a mixed experience At first, using an extract of normal thyroid as their antigen, they were quite unable to detect complement-fixing antibody, but later, using an extract of thyrotoxic thyroid, they found antibodies in almost all their cases of Hashimoto's thyroiditis Their preliminary separation experiments with an extract of a thyrotoxic gland indeed suggest that the precipitating and complement-fixing antigens may be distinct substances This suggestion is interesting in that it implies that the complement-fixing antigen may be specific to thyrotoxicosis, which would at once broaden the scope of the investigation to include this mysterious disease But both Dr WHITE and Dr ANDERSON have obtained complement-fixation with extracts of normal thyroid, though the titres were much lower than with thyrotoxic thyroids At least all workers seem to agree that for complement-fixing tests thyroid extracts from patients with thyrotoxicosis provide the best antigen Complement-fixing antibodies have been found in nearly all cases of Hashimoto's thyroiditis, in at least half of all cases of spontaneous myxœdema, in a substantial proportion of cases of thyrotoxicosis, and occasionally in normal subjects This distribution is reminiscent of the distribution of what is often termed lymphadenoid change—that is, destruction of thyroid tissue and its replacement by an infiltration of lymphocytic cells There may well be a correlation here, but it has not yet been proved

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[1] Rose N R Witebsky E J Immunol 1956 76 417

[2] Roitt I M Doniach D Campbell P N Hudson R V Lancet 1956 ii 820

[3] Fromm G A Lascano E F Bur G E Escalante D Prensa med argent 1953 67 162

[4] Luxton R W Cooke R T Lancet, 1956 ii 105

It now seems that the initial event in Hashimoto's thyroiditis is the leakage of thyroglobulin out of the thyroid acini Within the acinus thyroglobulin may be supposed to lead a secluded life, cut off from all contact with antibody-forming cells Hence it dodges the principle of immunological tolerance so ably expounded by Prof P B MEDAWAR, F R S, and his colleagues The body's antibody-forming cells are not introduced to thyroglobulin in fœtal life, so it remains a stranger to them for ever after To these cells a stranger is a foe A small leakage of thyroglobulin therefore immediately attracts the attention of wandering antibody-producers, they collect in the thyroid, cellular destruction follows and more thyroglobulin is liberated, whereupon more antibody is produced It is easy to see that such a process, once set going, may be self-perpetuating This picture is an attractive one, and remarkably complete In fact leaves only one thing unexplained what sets t process going ? No-one so far seems able to provid satisfying answer to this question We should, ho ever, be well content with the progress made in a ve short time The invasion of the thyroid field by t immunologists has begun well The troops have be got ashore, and have secured a beachhead T subsequent development of the operation should well worth watching

Towards Safer Clothing

THE past hundred years have seen great chang in the clothing materials used by women and childre Woollen garments, including flannel, and natur silk have been largely replaced by cotton fabri and artificial silks (rayons), and, in general, the newer fabrics have been of lighter weight—in oth words, less closely woven These changes hav considerably increased the risk of serious burning accidents The woollens and natural silks did not ignite easily, and, if they did catch fire, the flame did not spread rapidly so much is known to every man who has scorched his trousers standing by a fire But with the cottons and rayons—especially those of light weight—the sequence of events is very different Momentary contact (2–4 seconds) with a flame or the element of an electric fire is enough to ignite the material, and within half a minute most of a child's nightdress may be burning fiercely—especially if, as often happens, she runs about in terror and so fans the flames By the early days of this century it was apparent that the increasingly popular *flannelette*—i e, cotton material with a slightly fluffed-up surface—was associated with many fatal accidents to children In 1905 *The Lancet* declared "The days of flannelette should be speedily numbered" In 1908 the Home Office appointed a committee to consider the matter, but before any effective action could be taken the 1914–18 war diverted attention In the past fifty years there have been something like 25,000 deaths from clothing burns in England and Wales, and about four times that number of people have received very serious injuries After the 1939–45 war COLEBROOK and his colleagues [1–5] repeatedly called attention to the matter, stressing the danger of unguarded heating appliances and also of highly flammable clothing materials In 1952 Parliament passed the Heating Appliances (Fireguards) Act, and in 1956 specifications for a standard guard for coal fires were issued by the British Standards Institution [6] These measures will certainly help to reduce the risk of clothing accidents in homes But the menace of highly flammable clothing remains

To deal with this a committee was set up in 1956 by the British Standards Institution, and its report has now been published [7] The committee was fortunate in that a preliminary investigation had just been made by D L LAWSON and his colleagues

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[1] Colebrook L *Mon Bull Minist Hlth Lab Serv* 1946, 5 214

[2] Colebrook L Colebrook V *Lancet* 1949 ii 181

[3] Colebrook L Colebrook V *Ibid* 1951 ii 579

[4] Colebrook L *Text Merc Argus* 1953 77, 335

[5] Colebrook L Colebrook V Bull J P Jackson D M *Brit med J* 1956 i 1379

[6] Fireguards for Solid Fuel Fires B S 1956 no 2788

[7] *The Flammability of Apparel Fabrics in Relation to Domestic Burning Accidents* B S I 1957 PD 2777

in the laboratories of the Fire Research Organisation and the Department of Scientific and Industrial Research into the different methods of assessing the flammability risks associated with various clothing fabrics[8] By an ingenious device which measures accurately the time taken for flame to travel vertically upwards over 100 inches of the material under test, LAWSON et al had established the "flame-resistance rating" for a large number of fabrics Broadly speaking there were three categories the very light-weight materials, such as organdie, over which flame travelled 100 in in 8–25 seconds (that is their ratings were expressed as 8–25), the medium-weight cottons and viscose rayons, including flannelette and winceyette and mixtures of these with wool which had a rating of 25–70, and the medium and heavy weight woollens, natural silks nylons and 'Terylene' (if untreated with flammable "finishes"), and some flame-proofed fabrics, all of which had a rating of 100–300 A subsequent study of 82 garments which had been involved in clothing burns showed that the great majority were of materials in the middle group, rated at 25–70, the most common having a rating of 40–50 Few burns had been caused by the most highly flammable materials (rated at 8–35), not because these are not dangerous, but because they are seldom worn by comparison with the materials rated at 25–70, many of which are in daily use—for instance, for children's nightdresses and women's dresses None of the 82 burns had been caused by materials rated above 140

In the light of these findings the committee considered whether all clothing fabrics offered for sale should in future be graded according to their flammability rating, but it finally decided that this would not at present be in the public interest Instead it concluded that a "level of safety" should be designated and that fabrics rated at or above that level "should be warranted as such and identified accordingly"—presumably by the familiar B S I kite mark Fabrics so marked will not, of course, be guaranteed as completely non-combustible (all fabrics will burn if exposed long enough to sufficient heat) but garments made from them will burn so slowly if they should catch fire, that the wearer will have a good chance of putting out the flame before it has spread enough to cause a serious burn This designation of a level of safety should prove a notable advance But there is one difficulty Under the Fabrics (Misdescription) Act, passed in 1952 and now largely forgotten, it became an offence to describe a material as possessing "in any degree" the quality of 'non inflammability' unless it passes a very stringent test (failure to ignite on exposure to flame for 12 seconds) A few fabrics which reach the level of safety now proposed by the committee might just fail to pass the severe test of the 1952 Act, and so could not legally carry the B S I safety mark To get over this difficulty the Act may have to be repealed

The committee also stresses the importance of pressing on with the development of "flame proofing" processes, which would bring many cottons and rayons within the safety zone It calls attention once again to the importance of avoiding loose-flowing garments—e g, nightdresses for children—and to the overriding need for guarding all heating appliances Finally it emphasises that more effective propaganda is required to make the public aware of the risks of clothing burns and more eager to demand safe materials Doctors can help to eliminate clothing burns by advocating safer clothing materials and passing on the committee's other recommendations—especially with regard to the guarding of electric and gas fires bought before the Fireguards Act came into force

Cutaneous Pain

APPARENTLY various cutaneous sensations can be painful, but it is not now believed that intense stimulation of nerve-endings of any type can cause pain On the contrary, it is thought that the specialised nerve-ends can respond only to appropriate stimuli and that all forms of pain arise from the unencapsulated free nerve-ends which lie among the epidermal cells The nerve-fibrils from these run into a nerve-net, or delta, which in turn unifies through branches, to become a pain-carrying nerve-fibre There is overlapping, but not continuity, of peripheral-nerve nets Anatomically somatic sensory-nerve fibres are divided into C fibres, which are small in diameter and along which impulses travel more slowly than in the other, or A fibres Thus the shape and timing of the electrical potential changes during the passage of an impulse are typical and recognisable It is possible, then, to apply to skin various stimuli known to be painful and at the same time record the potential changes in the sensory nerve, the pattern of these being a clear pointer to the type of nerve-fibre carrying the impulse From evidence such as this it has been shown that the thinnest and most slowly conducting fibres of the A group are responsible for carrying the sensation of immediate or first pain, and that C fibres, conducting even more slowly, give rise to delayed or second pain With this limited number of fibre-types, how is it that pain can vary not only in degree but in quality and can be elicited by a wide variety of stimuli—all of which, incidentally, are calculated to damage tissues[2] That the nerve-ends are undifferentiated probably accounts for the range of physical and mechanical stimuli to which they respond Many of the apparent differences in sensation depend on the duration as well as the intensity of the painful stimulus, for pain differs from most other types of sensation in that it does not adapt, or decline with time Some of the differences depend on central ramifications The pain nerve-ends also react to chemical stimuli and some workers find it difficult to account for all the features of pain especially abnormal types, without postulating the release of a chemical from damaged tissues This substance might act by sensitising the nerves—i e, reducing their threshold—or by causing them to discharge even after the painful stimulus has long ceased In this connection LEWIS[1] tested skin extracts and found that they had pain-producing properties, and he went far towards defining the conditions in which they were most effective He did not identify the substance responsible, but believed that it was not histamine

One of the difficulties of this subject is to develop a means of measuring and recording the intensity and duration of pain. One method is that used by **Keele** and his co-workers,[2] which depends on the subject's estimate of pain but gives reproducible results. According to the intensity of pain the subject gives more or less of a turn to a handle which raises or lowers a pointer writing on smoked paper. In this way a permanent record is obtained of the intensity, duration, and fluctuations in the pain felt. **Keele** et al.[3] placed solutions of substances to be tested on the exposed base of a blister made by a standard method—usually by application of a small cantharides plaster. The subject was, of course, unaware of the nature of the solutions applied. It was found that high dilutions of acetylcholine (ACh) were immediately painful; 5-hydroxytryptamine (5-H.T.) gave rise to delayed pain; and histamine diluted 10^{-3} or 10^{-4} times was painful, but when diluted 10^{-5} or 10^{-6} times caused only itching. The action of these three compounds, which are widely distributed in body tissues and fluids, was compared with that of some of the body-fluids themselves. Blister fluid, for instance, immediately after collection had no pain-producing substance (P.P.S.); if the fluid was kept in a silicone-lined container P.P.S. developed only slowly, but if the fluid was in contact with glass P.P.S. appeared in a few minutes. The same behaviour was seen in other exudates, such as that from the knee-joint of patients with rheumatoid arthritis, from pleural effusions, and from protein-rich ascitic and hydrocele fluid. Human whole blood also reacted similarly. Pain-producing activity was greatest after five to eight minutes and then began to decline until after about an hour 90% of activity had gone. Were these fluids pain-producing because of their content of the fairly simple substances previously tested? With the help of another test the answer was found to be No. Originally the search was for a method more convenient than the frequent blistering of friends and other volunteers, as well as for some means of accurately comparing known chemicals with the unknown P.P.S. in mixed fluids. The isolated rat uterus suspended in a bath of saline solution proved useful. First, it was found that P.P.S. caused the uterine muscle to contract, and that, whereas the action of ACh was antagonised by atropine, that of P.P.S. was not. Histamine though causing pain had not caused the uterus to contract, and diluted P.P.S. did not cause itching. H.T. was at first the most probable candidate for the position of P.P.S., but, again, substances which blocked the action of H.T. on the uterus did not block that of P.P.S.

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[8] Lawson, D. L., Webster, C. T., Gregsten, M. J. J. Text. Inst. 1955, 46, T [illegible]

[1] Lewis, T. The Blood Vessels of the Human Skin and their Responses London, 1927

The activation of body-fluids by contact with glass suggested some similarity to blood-clotting, and it was further found that protein-poor fluids did not produce P.P.S., but there were dissimilarities that ruled out any direct relationship. Possibly P.P.S. is linked with some early stage of thromboplastin formation; but the evidence suggested that it might be a breakdown product of protein, possibly a polypeptide. By comparative tests the chemical and physiological behaviour of P.P.S. and bradykinin were found to be closely alike. Now, proteolytic enzymes abound in tissues, and it is known that in normal conditions stimulation of the chorda tympani nerve releases from the submandibular gland an enzyme which acts on plasma to form a bradykinin-like substance.[4] Also, tissue damage releases an active proteolytic enzyme from skin.[5] There is, then, nothing unreasonable in the idea that injured tissue may release an enzyme which acts on some component of plasma-proteins to form bradykinin, or something very like it, and that this substance causes pain, as it can be shown to do. During the time it is present in the tissues it may well affect the nerve threshold to other forms of stimulus. The decline in P.P.S. activity of body-fluids is probably due to the presence of other enzymes which hydrolyse it to an inactive state. If indeed bradykinin and P.P.S. prove to be identical, or even if bradykinin is only one of a group of similar substances, that is an important and useful step towards further understanding of the great problem of pain.

Annotations

TELEVISION AND MEDICINE

Television was first publicly demonstrated in Great Britain in 1928, and in the same year John Baird demonstrated colour television. A surgical operation was first televised in black and white (at the Johns Hopkins University) in 1947, and in colour (at the American Medical Association's convention in Atlantic City) two years later. Since then television for medical meetings and teaching has been developed extensively in the United States, and closed-circuit units have been installed in hospitals in London, Paris, and elsewhere. The first colour-television demonstrations of surgery in Great Britain will take place this summer.

Television is particularly suitable for demonstrating new or modified operative techniques to surgical colleagues. Because of its immediacy it is valuable for illustrating a talk, and the surgeon can discuss with his audience the rationale of each stage as he performs it. But there is a risk that the selected patient may prove unsuitable for the intended operation or that routine steps, such as procuring hæmostasis, may take unduly long. Both of these disadvantages may be avoided by using film; and rare or unique operations, such as the separation of conjoined twins, demand a permanent record, so here film has an undisputed advantage.

In medical schools television has little to commend it. A reel of film is shown much more easily—*and cheaply*—than a television demonstration requiring on each occasion, in addition to the clinical material, cameras, lighting equipment, crew, production staff, and lecturer. But conceivably a programme originating in one school might be broadcast to several others so that students might benefit from teaching sessions at several centres in addition to their own. Such a scheme has been attempted in the United States, where a handbook has been prepared for producers of medical television programmes.[6] It is becoming increasingly recognised that a medical student gains little from watching operations on a screen; in the short time he spends in the operating theatre as an undergraduate he should learn primarily the conventions of sterile techniques and how to assist a surgeon usefully. This is now appreciated by most British film makers, and only some 6% of the 1700 medical films available here show surgical procedures. Television might be applied more usefully to demonstrating cytological and bacteriological slides; and it may also prove useful as an image intensifier in conjunction with radiographic screening.

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[2] Armstrong, D., Dry, R. M. L., Keele, C. A., Markham, J. W. *J. Physiol.* 1953, 120, 326.

[3] Armstrong, D., Jepson, J. B., Keele, C. A., Stewart, J. W. *Ibid*, 1957, 135, 350.

[4] Hilton, S. M., Lewis, G. P. *Ibid*, 1955, 129, 253.

[5] Beloff, A., Peters, R. A. *Ibid*, 1945, 103, 461.

[6] Warren, E. TV in Medical Education. Chicago, 1955.

For the non specialist, television has an important future in public-health education and programmes of general medical interest. In America medical cases are presented in at least one regular weekly programme and in France endoscopies have been demonstrated on the national television service.

WHEEZING

WHEEZING is the most obvious sign of an acute asthmatic attack. Like many other familiar phenomena, it has had comparatively little serious thought, and until quite recently hardly anyone has suggested that it may not arise (as generally supposed) from the passage of air through constricted bronchioles. The paper we publish this week by Dr Dekker and Dr Groen should serve at least as a basis for a review of the prevalent ideas. Briefly, they maintain that the wheezing sound is generated in the larger bronchi and trachea by the rapid and turbulent flow of respiratory gases through them when they are constricted by pressure from without: the pressure is applied within the thorax by the force of expiratory muscular contraction against the high resistance to gas flow offered by the constricted bronchioles. In their scheme of events bronchiolar constriction does not itself cause wheezing at all.

This explanation is not so unlikely as it may seem at first. One point in its favour is that the actual volume of gas flowing through a bronchiole during expiration must be very small indeed and probably flow is streamline in character; these are not the conditions in which one would expect audible sounds, which require that flow should be turbulent and be of enough volume to generate sound waves of suitable power and frequency. A clinical observation which adds support is the well-known "pursed lip" breathing often seen in emphysematous patients. By adopting this mode of expiration, pressure is built up within the bronchial tree which helps to prevent collapse of the larger branches.

The investigations on normal people are of interest in relation to so called psychogenic asthma. It is easy to see how patients with anxiety states might acquire the same trick of wheezing expiration—and also why their asthma might be completely cured by psychotherapy.

VITAMIN D AND THE PARATHYROIDS

WHEN Albright and Reifenstein[1] drew attention to the similarities between the metabolic effects of vitamin D and of parathyroid hormone, they were not convinced that either exerted a direct "calcæmic" action on bone; but since then both substances have been found to possess this property. Thus experimentally it has been shown beyond doubt that parathyroid extract raises the serum-calcium even after nephrectomy[2] and that vitamin D raises the serum calcium of rachitic rats in conditions which make it impossible to ascribe this effect to increased absorption of calcium from the intestine.[3] The close similarity between the effects of vitamin D and of parathyroid hormone on bone is underlined by Barnicot's observation[4 5] that local implants of calciferol and parathyroid-gland tissue evoke the same osteoclastic reaction.

The inference that vitamin D and parathyroid hormone are both concerned in regulating the equilibrium which is believed to exist between the calcium and phosphate ions in the extracellular fluid and the crystals of a calcium-phosphate compound in the skeleton[6 7] may shed some light on related problems. It explains the hypercalcæmia which may be induced by very large doses of vitamin D (never adequately explained by the action of vitamin D on absorption of calcium), and it may account for the secondary hyperparathyroidism often seen in rickets and osteomalacia. If vitamin D normally contributes to the maintenance of the serum-calcium level, its deficiency would tend to lower the calcium content and stimulate the parathyroid glands, leading to the parathyroid hyperplasia seen in rickets,[8] and to the radiographic[9] and histological[10] manifestations of parathyroid overactivity reported in osteomalacia. In fact, such parathyroid overactivity is very probably responsible for the high phosphate-clearance observed in osteomalacia,[11] and so for the low serum-phosphate in this condition which cannot be attributed to malabsorption of phosphorus. But lack of vitamin D does not always set in train this course of events. Hypocalcæmic tetany is another familiar manifestation of this deficiency; but its precise relationship to rickets has never been fully understood. If rickets is regarded as a manifestation of secondary hyperparathyroidism, hypocalcæmia may legitimately be regarded as an indication of parathyroid insufficiency, particularly when—as is often the case—the content of inorganic phosphate in the serum is high. The reason for this parathyroid insufficiency is unknown.

Nutritional deficiency of vitamin D has become a rare cause of rickets and tetany, but both these conditions may arise in steatorrhœa. They are then indistinguishable from the corresponding conditions produced by nutritional deficiency (except in the dosage of oral calciferol which they need), and are commonly attributed to malabsorption of fat-soluble vitamin D,[12] though Dent[13] has suggested that there may be some additional metabolic disorder present. In a letter on p. 1086, Dr Jackson suggests that steatorrhœa and hypoparathyroidism are significantly associated, and he draws attention to reported cases presenting both disorders. He cites the attractive suggestions of Salvesen and Boe[14] that patients with steatorrhœa may develop either osteomalacia or tetany according to the response of their parathyroids to hypocalcæmia; and he suggests that some particular significance should be attached to the apparently high prevalence of parathyroid insufficiency in steatorrhœa.[15] There may, of course, be evidence of endocrine insufficiency in steatorrhœa,[16] and possibly parathyroid insufficiency should be regarded as a particular manifestation of this general disorder; in fact, amenorrhœa and 'absent' body hair were prominent features in Dr Jackson's own case.[17] If, on the other hand, these patients are in fact suffering from a deficiency of vitamin D, it seems more reasonable to seek a single explanation for the tetany of steatorrhœa and that of nutritional avitaminosis D.

The hypothesis that the parathyroids either respond to hypocalcæmia and cause osteomalacia, or fail to respond and cause tetany, seems to be an oversimplification. Thus it fails to take into account or to explain the vital fact that tetany and rickets may be found in the same patient. This is true not only of nutritional vitamin-D deficiency, in which tetany is almost invariably associated with rickets, though rickets is only occasionally accompanied by tetany,[18] but also of the malabsorption syndrome.[19] In both types of vitamin-D deficiency, however, it seems that whereas rickets may precede tetany, tetany rarely if ever develops into rickets.[18]

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[1] Albright F Reifenstein, E C The Parathyroid Glands and Metabolic Bone Disease Baltimore 1948

[2] Ingalls T H, Donaldson G A Albright F *J clin Invest* 1943 22 603

[3] Carlsson A Lindquist B *Acta phys scand* 1955 35 53

[4] Barnicot, N A *J Anat Lond* 1948 82 233

[5] Barnicot N A *Ibid* 1951 85 120

[6] See *Lancet* 1955 ii 183

[7] Copp D H *Amer J Med* 1957 22 275

[8] Pappenheimer A M Minor, J *J med Res* 1921 42 391

[9] Davies D R, Dent C E Willcox A *Brit med J* 1956, ii 1133

[10] Lang F J *Beitr path Anat* 1931 87 142

[11] Nordin B E C Fraser R *In* Proceedings of Ciba Foundation Symposium on Bone Structure and Metabolism London 1956

[12] Bodansky M Bodansky, O The Biochemistry of Disease New York 1952

[13] Dent C E *Brit med J* 1956 ii 1546

[14] Salvesen H A Böe J *Acta med scand* 1953 146 290

[15] Salvesen, H A Böe J *Acta endocr Copenhagen* 1953 14 214

[16] Wintrobe M M Clinical Hæmatology London 1956

[17] Jackson W P U Hoffenburg R Linder, G C, Irwin L *J clin Endocrin* 1956 16 1043

[18] Hess A F Rickets Osteomalacia and Tetany London 1930

[19] Bloom A *Proc R Soc Med* 1955 48 321

These observations can be reconciled if it is accepted that the parathyroid glands may become "exhausted." On this hypothesis, an indeterminate period of parathyroid overactivity may lead to rickets or osteomalacia, but may culminate in parathyroid failure and tetany. The two possible parathyroid responses postulated by Salvesen and Boe can be regarded as the two extreme examples, but between them there can exist every degree of parathyroid activity represented by different combinations of serum contents of calcium and phosphate. A normal serum-calcium with a low serum-phosphate suggests complete parathyroid compensation; a low serum calcium with a high serum-phosphate, complete parathyroid failure. Between these two extremes, the development of rickets will depend on the product of Ca × P in the extracellular fluid, and the development of tetany on the absolute content of calcium ions.

The possibility remains that the hypoparathyroid state is more common in steatorrhœa than in nutritional vitamin-D deficiency, or that it differs in some other way in the two conditions. If Dr Jackson can show this to be the case, his suggestion will be greatly strengthened.

THE ENZYME DEFECT IN GALACTOSÆMIA

Two years ago[1] we discussed the genetically determined inborn error of metabolism known as galactosæmia. Some of the questions raised then remain unanswered —for example, whether children with this metabolic error would be entirely protected from harm if they were kept on a lactose-free diet from birth. But another problem —the exact nature of the enzyme deficiency—has been solved. In 1955 Schwarz et al.[2] had taken the first step by showing that the red cells of galactosæmic children who had just had a milk feed contained an accumulation of galactose-1-phosphate, but not of glucose-1-phosphate. Therefore galactose was being metabolised to galactose-1-phosphate, but a stage in the conversion of galactose-1-phosphate to glucose-1-phosphate was imperfect.

This transformation involves three stages. First, galactose-1-phosphate combines with uridine diphosphoglucose to give glucose-1-phosphate and uridine diphosphogalactose. Second, uridine diphosphogalactose is transformed to uridine diphosphoglucose. Third, uridine diphosphoglucose reacts with inorganic pyrophosphate to give uridine triphosphate and glucose-1-phosphate. Kalckar et al. have shown in hæmolysates[3] and in liver homogenates[4] from patients with the disease that it is the enzyme for the first stage, galactose-1-phosphate uridyl transferase, that is missing.

It is useful to know that the enzyme defect may be shown in cord-blood cells immediately after birth, so that in families at risk affected infants may be identified and put on a lactose-free diet from birth. Holzel and Komrower,[5] in 1955, produced evidence that some of the parents, who are themselves heterozygous for the gene responsible for galactosæmia, had an abnormal galactose-tolerance curve. Unfortunately Kalckar and his associates[3] have not been able to detect any abnormality in the amount of galactose-1-phosphate uridyl transferase in parents.

It is a striking example of the uniformity of many biological processes in the animal kingdom that four mutant forms of the bacillus *Escherichia coli* are known with the same enzyme defect.[6] Three other galactose-negative mutants of the bacillus lack instead the enzyme galactokinase concerned in the first step of all—the conversion of galactose to galactose-1-phosphate—but these have as yet no human counterparts.

ATYPICAL ACID-FAST BACILLI

MANY investigators have isolated from patients strains of mycobacteria which, for want of a better name, are called "atypical acid-fast bacilli." These bacilli are not new,[1 2] but in recent years they seem to have been recognised much more commonly. In man they are associated with pulmonary lesions, often serious and progressive, which in every way resemble typical pulmonary tuberculosis[3]; but unhappily their response to most antituberculous drugs is poor.

It is not yet certain whether these organisms comprise a homogeneous group or several different types. They differ from typical tubercle bacilli not only in their drug sensitivity pattern but also in being chromogenic, and in showing greater catalase activity, poor cord formation, a negative neutral-red reaction, and avirulence for guineapigs. Usually they can be distinguished from typical acid-fast saprophytes by a rather slower growth rate, especially at room temperature (though they grow faster than typical tubercle bacilli) and by the type of lesions in certain laboratory animals. Wolinsky et al.[3] found that in each of three cases of infection by these organisms in man, the strains produced orange or yellow pigment; but in two they did so only in light. Crow et al.[4] describe 69 such cases, in which the organisms seemed to fall into three main groups judged by growth on Lowenstein-Jensen medium. In 64 cases the strains produced smooth, slow-growing buff colonies which became orange as the cultures aged; in 3 the strains were more chromogenic but otherwise similar; and in 2 the strains gave rough colonies similar to those of *Mycobacterium tuberculosis* except that they grew much more rapidly—though not so rapidly as recognised acid-fast saprophytes.

Pathologically, according to Crow et al., these organisms give rise to lesions differing in no way from those due to typical tubercle bacilli; but the disease is less readily communicated: in none of their 69 cases was more than one member of a household known to be infected. On the other hand, the response to antituberculous treatment is disappointing: of 56 cases reviewed by Crow et al. only a third showed sputum conversion on chemotherapy.

These studies and others[5–7] make it clear that atypical acid-fast bacilli present a fairly serious problem. It can hardly be doubted that infections with these organisms have become more prevalent since chemotherapy has been widely used; and conceivably they represent mutants induced or selected by chemotherapy —a hypothesis that seems to be supported by the partial resistance of most strains to antituberculous drugs. Thus, incomplete treatment of tuberculosis due to drug-sensitive typical bacilli may carry the danger of fostering these drug-resistant atypical forms, though so far this has by no means been proved. Meanwhile infections with these atypical organisms should, it seems, be treated as are infections with typical bacilli, and, despite their seemingly lesser infectivity, public-health measures should be applied no less rigorously than is usual in tuberculosis.

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[1] *Lancet* 1955 ii 77.
[2] Schwarz V, Golberg L, Komrower G M, Holzel, A *Biochem J* 1955 59 xxii.
[3] Kalckar H M, Anderson E P, Isselbacher K J *Biochim biophys acta* 1956 20 262.
[4] Anderson E P, Kalckar H M, Isselbacher K J *Science* 1957 125 113.
[5] Holzel A, Komrower G M *Arch Dis Childh* 1955, 30, 155.
[6] Kurahashi K *Science* 1957, 125 114.

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Special Articles

METALLIC CORROSION IN ORTHOPÆDIC SURGERY

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Whenever metal is inserted in the human body it becomes subjected to the corrosive attack of the body-fluids Venable et al (1937) drew attention to this phenomenon and suggested that a simple means of reducing the risk of corrosion would be to avoid the use of more than one metal in any particular operation Discussions of the dangers accompanying the insertion of "mixed metals," and descriptions of investigations carried out to discover a metal which could confidently be adopted as standard, have been published periodically throughout the last two decades But, although this work is well known to many surgeons, the recent paper by Cater and Hicks (1956) shows that in some hospitals insufficient attention has been paid to this aspect of surgery Until the basic principles put forward in a series of papers by Venable and Stuck some twenty years ago are clearly understood and accepted (and if necessary protected by an official standardisation of the materials used for implants), there is little point in taking precautions to avoid the secondary causes of corrosion and the possible tissue reactions which can result from them The first step in preventing metallic corrosion in surgery must be the use of a single passive metal for all the components of an implant

The physiological behaviour of the body during trauma and the subsequent healing processes create the environment within which the metal implant has to fulfil its purpose The pH value and the redox potential will vary with time, and also from place to place on the surface of the metal These variations cannot readily be controlled but their effect could be minimised by the careful selection of the particular metal best suited to withstand these electrochemical conditions Clearly the use of two different metals in a region with such a complex electrochemical nature is an invitation to disaster Most metal implants are subjected to mechanical stress when fixed in the body, in many cases there may also be fretting between different components of the appliance Both these phenomena can influence the corrosion of metal, and they too should be borne in mind when selecting the most suitable metal for use in orthopædic surgery It would be dangerous, however, to believe that such a standardisation will solve all the problems created by the use of metals in orthopædic surgery The insertion of "mixed metals" is by far the most important cause of corrosion, but it is by no means the only one The factors which can influence the corrosion resistance of metals have been fully discussed by Evans (1946)

There is clear evidence that even when a single passivated metal is used, a tissue reaction is occasionally observed in the region surrounding the implant, and it is important that the need to select the metal must not obscure the complementary need for proper treatment of the implants both before and during insertion Many metals derive their high resistance to corrosion from an impervious layer of oxide which protects them from the surrounding liquid But such an insulating barrier is effective only so long as it remains intact If it is damaged, corrosion will occur at the places where the metal and the liquid come into contact, the attack will continue unless the product of the electrochemical reaction is insoluble and is deposited at the corrosion site, thus making good the protective coating

The special characteristic of stainless steels is that they are clothed in a protective film which in normal circumstances is self sealing In this respect they differ from the noble metals which are intrinsically inert It is clear that the selection and use of a stainless steel will be vitiated if, during the operation, the passivating surface film is so damaged that the sealing process cannot re-form the protective layer before continuing corrosion is established Any treatment which increases the chance of a breakdown in the passivity of the metal ought to be avoided whenever possible, and especially during the operation The manner in which the implants are handled can have an important influence on their subsequent chemical behaviour

The importance of the correct choice of tools should be appreciated Experiments using radio-isotope techniques have shown that during an orthopædic operation small fragments of metal are plucked from the surface of the tools and become welded to the implant These particles from the tool are buried with the appliance in the body

The composition of the metal tools is usually different from that of the implant There is evidence that such foreign fragments can initiate a reaction resulting in the corrosion of the buried metal Analytical evidence supports this view the concentration of metal ions in the tissues surrounding parts of the implant which have been handled by tools are many times higher than normal, even when there is no visible sign of corrosion or tarnishing whereas the concentration in the tissues adjacent to unhandled parts of the same appliance are normal A full account of these experiments has been given by Bowden, Williamson, and Laing (1955)

It has been suggested (Capener 1956) that surgeons and manufacturers should have official guidance in their choice of suitable metal for implants It might be useful if this included recommendations on the methods of handling the implants, and on the nature and composition of the tools used for inserting them, so that their corrosion resistance shall not be needlessly impaired

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PROFESSIONALISM AND BUREAUCRACY

In his Winchester Address, given on May 15 under the auspices of the Winchester division of the British Medical Association, Mr Graham Hutton began by considering what has been happening in all kinds of human societies during "this terrible but exciting 20th century"

THREEFOLD CHANGE

1 *Technical*—The techniques of control over Nature have immeasurably multiplied and accelerated, and it is good that human powers over inhuman powers are being so rapidly increased But it is bad that increased human power is used—or abused—to stress human beings beyond their normal tolerances, or to frustrate their natural modes of expression and development, or to compel them to behave as machines

2 *Political* —Whereas the course of last century all over the world, was liberal, in humanistic terms, the course of the 20th century has been towards more and more collective restraint of individuals Everywhere the State has steadily increased its power over individual lives, and in almost every walk of life Because of the first or technical change, this second or political change has brought benefit to millions in many nations it has permitted the removal of old evils But, both in democracies and in dictatorships, power over the individual and the family has been concentrated in a more and more centralised form of State apparatus

> "We realise that in our own country and society today economic, professional, trade union legal, travel, and other freedoms are not what they were They are narrower, not at the administrative centres of these sectors of life, but on the periphery where the individual members live and operate Even apart from, and under the centralising political power of the State, these other sectors of individual life—in business, trade unions, professions, vocations, sport, commercialised pleasures and leisures, and media of publication and radio communication—are all of them more centralised, more collectively organised in larger administrative units "

As the first or technical change has shrunk the whole world and crammed the human race cheek by jowl, so has the second or political change unfolded everywhere—the concentration of vastly enhanced social or political power in the hands of the few, and the once vaunted "rule of Law" has given way everywhere to the contemporary rule of laws and regulations affecting more and more of individual life

3 *Specialisation* —The third change is an ever-deepening, ever narrowing specialisation which further weakens the powers, potentials, and freedoms of the citizen The individual—learner, researcher, operative, technician, professional man, trade unionist, or manager—sees his own mastery of only a little part of a widening field becoming smaller and smaller, and himself becoming ever more dependent upon the results of other people's work, which he cannot understand or control

So universal is this third change in mankind's social process that precisely the same kind of complaints about it arise in America, in Russia, in India, in Africa—in school and university and other training curricula, in religions, castes, social classes, income brackets of all levels, and so on The burden of complaint is the same—that distinguishing individualities are tending to be ironed out, that differentials and varieties are being flattened, and that frustration of human potentials follows specialisation Then, through such frustration, bad social outbreaks occur the system of law and custom rights and duties, sentiments and beliefs and values begins to lose its binding force Either as individuals or as functional or other groups, men begin to rebel, to become "anti minded," against their own society Today this phase—the era of social revolution—is world-wide for the first time

RUSSIAN LABORATORY

Perhaps the most significant event of the post war era, Mr Hutton thought, will prove to be the working out of these revolutionary social changes in Communist Russia Western and other countries can learn much from what has happened inside the Russian social laboratory during the past decade or two

At its beginning forty years ago, Russian society was dedicated to equality, and it soon took away all powers and privileges of trades unions, professions, vocations, and other self governing voluntary and functional groupings But because of the technical needs of all society everywhere (in our time as in Plato's) a new set of groupings, orders, castes, classes, and functional elites speedily came about—nearly all of them necessarily organised on the lines of the former professional and other functional groups As modern techniques advanced—in economic science, medicine, the arts—it was the *professions*, not merely the State's agents or functionaries, who gathered esteem, powers, and privileges

One feature of the convulsions in Russia and other Communist lands during the past three years needs to be noted for its long term significance It is that the uprush of protest against flattening and standardisation by the omnipotent State, against unqualified egalitarianism, and against the tyrannies of an all pervasive bureaucracy have occurred in the ranks of the experts—the people with long-acquired and long-trained vocations whom a modern society needs more and more It is among this younger generation of Communists—among the experts and artists, the technicians, and the professional persons above all—that the ferment of dissatisfaction with the bureaucracy is greatest

DIFFERENTIALS

"At both the superficially seeming opposite poles of world politics today, in North America and in Soviet Russia, really substantial differential rewards for differential responsibilities and differential expertnesses are the order of the day," said Mr Hutton, "while here in British society, which is lagging behind those in material progress and mixed-up between them in its social and political organisation, our skilled workers moan about the erosion of their 'differentials' in wages, the salaried folk can complain of the same process, and the folk of technical prowess and professional responsibility are the most savagely penalised and discriminated against of all"

The material sacrifices due to the last war have fallen, net and on balance, upon only about one fifth of the British people, which includes three twentieths who are the old and retired at all levels of income (some very poor and on National Assistance) and all the skilled, trained, and responsible paid leaders of the nation Just as an examination and a justification of equality of treatment for everybody is long overdue in our political and social system, so is an examination of the distribution of rewards for responsibilities "Somewhere around the current figure of £1000–£1500 a year gross for a bread winner—no matter what his training or responsibilities, or how big his family, or what his hours of work or conditions of service—British society seems to shut up shop in consideration of him"

Looking at the needs of medicine, of the expanded atomic energy programme, of the highway and railway networks, of slum clearance, of education in all its forms, and of new equipment for all our industries, "we shall better appreciate our overriding need not to penalise, but positively to stimulate and increase differential rewards for, any and every citizen who can command such enhanced rewards in virtue of his abilities, responsibilities, and social contributions"

> "What we have undergone in the past eleven post war years, in a world of technical revolution, has merely been a revolution in the apparatus of the State and in its administration We have had no post war revolution of thought and ideals and imagination"

THE PROFESSIONS

If British professional bodies are to play their part in the reshaping of our people's thought and the reform of our national institutions, they must first be sure that on balance what they propose to do will primarily benefit the community or communities they serve

> "The justification for a profession, which guards its own standards of training, can only be that in so doing it constantly proves its contributive power to the community is kept at top pitch Any profession will lapse in public esteem if either it fails to do that, or fails to make public why the State or some other factor beyond its power prevents it from doing it

The great power of our professions still resides in their vocational mission, their safeguarding of training and education, and their rôle—quite apart from their particular skills—in turning out the well rounded, socially adjusted, contributory and responsible leaders of the nation in all its walks of life It is perhaps this last rôle which is so often overlooked in our land today Without wise leaders, without a widely trained and humanistic élite, any society on earth, both today and in the even more technical complexity of the future, will perish It is as much the function of our professions—and pre eminently of yours—to turn out members of such a national elite, as it is to turn out technically qualified young men who are certified as able to perform certain skills adequately The professions would gain, I think, if they were to emphasise that aspect, in season and out of season, and, above all, if they were to see, in their educational curricula which still remain largely under their own safeguarding, that they did not merely turn out technically adequate young men, but young men who were in addition humane, rounded, and adjustable to a rapidly changing social context "

Contemplating the hectic experimentation in North America at one extreme and in Russia at the other, we need not (concluded Mr Hutton) despair or repine Technically it is well within our scope to succeed, in any sector of social life, as well or better There is no economic reason why we should not But if we bring it off, it will primarily be due to leadership, and that must still come largely from our professions "It is therefore up to them to set their own standards, and then to fight for them until they prevail There is nothing wrong in that for the nation On the contrary, I think this nation has everything to gain from it "

REGIONAL HOSPITAL BOARDS
AND BOARDS OF GOVERNORS OF TEACHING HOSPITALS

THE Minister of Health has appointed, or reappointed, the following as chairmen of boards New appointments are indicated with an asterisk

Leeds Regional Hospital Board —Major J C Hunter, M C

South West Metropolitan Regional Hospital Board —A G Linfield, O B E, J P

Oxford Regional Hospital Board —Sir George Schuster, K C S I, K C M G, C B E, M C

Birmingham Regional Hospital Board —* E W Thompson, M A, J P

United Newcastle upon Tyne Hospitals —* Sir Walter Drummond

United Leeds Hospitals —Sir George Martin, K B E, LL D, J P

United Sheffield Hospitals —Alderman A Ballard, C B E

United Cambridge Hospitals —Roger H Parker, M C, D L, M A

United Oxford Hospitals —Sir David Lindsay Keir, M A, LL D

United Cardiff Hospitals —Alderman Thomas Evans, C B E, J P

United Birmingham Hospitals —Evan A Norton, M A

St Bartholomew's Hospital —Sir George Aylwen

London Hospital —Sir John Mann

University College Hospital —Sir Alexander Maxwell, K C M G

Middlesex Hospital —Lord Astor of Hever, D LITT, J P

Charing Cross Hospital —Lord Inman, P C, J P

St George's Hospital —Viscount Ingleby

Westminster Hospital —Lord Nathan of Churt, P C, T D, F S A, D L

St Mary's Hospital —Edgar E Lawley

Guy's Hospital —Lord Cunliffe

King's College Hospital —Marquess of Normanby, M B E

St Thomas's Hospital —Sir Arthur Howard, K B E, C V O, D L

Hammersmith, West London, and St Mark's Hospital —Sir Desmond Morton, K C B, C M G, M C

Royal National Throat, Nose and Ear Hospital —Ernest Taylor

St John's Hospital for Diseases of the Skin —J A M Ellison Macartney

The Hospitals for Diseases of the Chest —Sir John Gilmour

Royal National Orthopædic Hospital —Sir Henry Floyd, C B, C B E

National Heart Hospital —J M Oakes, M C, D L, J P

St Peter's, St Paul's, and St Philip's Hospitals —Laurence Bevan

Royal Marsden Hospital —J M Wallace

REGIONAL HOSPITAL BOARDS

The following doctors have been appointed or reappointed to the boards They will hold office till March 31, 1960

Newcastle —C N Armstrong, R E Jowett, R S Venters

Leeds —W A Hyslop, G Whyte Watson

Sheffield —G H Gibson J L A Grout, C S O'Flynn

East Anglia —A Leslie Banks, K J Grant

North West Metropolitan —E C Warner, Katharine Lloyd Williams, *F C Wilkinson

North East Metropolitan —T Rowland Hill, J Arthur Moody, R W Reid

South East Metropolitan —Sir William Kelsey Fry, V F Hall, W G Masefield, * H W L Molesworth

South West Metropolitan —A Lawrence Abel, Sir Geoffrey Todd

Oxford —C V Gledhill

South Western —R J Brocklehurst, L C Hill, A V Neale

Wales —J P J Jenkins, A Trevor Jones, Emyr Wyn Jones, E K Roy Thomas

Birmingham —J H Sheldon, A P Thomson

Manchester —V F Lambert, R W Luxton, Miles Parkes, Sir Harry Platt

Liverpool —W M Frazer, H L Sheehan

BOARDS OF GOVERNORS

The following doctors have been appointed or reappointed to boards of governors They will hold office till March 31, 1960

St Bartholomew's Hospital —Charles Harris, J Basil Hume, E G Tuckwell

London Hospital —J Graham, G T Hankey, * William Evans, * Dorothy Russell

Royal Free Hospital —Gladys Hill, Katharine Lloyd Williams, Margaret MacPherson, * Una Ledingham

University College Hospital —Sir George MacRobert, Wilson Smith, * Sir James Kilpatrick

Middlesex Hospital —* A J B Goldsmith, * C A Keele, * B R M Johnson, * D H Patey

Charing Cross Hospital —D H Campbell, E Grundy, H G E Williams, * Norman Tanner

St George's Hospital —C Bowdler Henry, Rodney Smith, * H W Gordon

Westminster Hospital —A Lawrence Abel, H E Harding, Edward Stanley Lee, R J V Pulvertaft

St Mary's Hospital —A G Cross, Robert Cruickshank, G B Mitchell Heggs, Leonard Simpson, * Denis Brinton, * W D W Brooks

Guy's Hospital —Maurice Campbell, Sir William Kelsey Fry, * G F Gibberd

King's College Hospital —H L Glyn Hughes, Sir Cecil Wakeley, * Wilfrid Sheldon

St Thomas's Hospital —T Pomfret Kilner, Sir Max Page, A J Wrigley

Hammersmith, West London, and St Mark's Hospitals —R Cove Smith, Sir Allen Daley, Cuthbert Dukes, Sir Francis Fraser

Hospital for Sick Children —G H Newns, Bernard Schlesinger, D Innes Williams, * R E Bonham Carter, * J A Scott

National Hospital for Nervous Diseases —Sir Russell Brain, J St C Elkington, M Kremer

Royal National Throat, Nose and Ear Hospital —J C Hogg, G H Howells, * T V L Critchlow

Moorfields Hospital —* G G Penman

Bethlem Royal and Maudsley Hospitals —C P Blacker

St John's Hospital for Diseases of the Skin —Janet Aitken, S Cochrane Shanks, * L Forman

Hospitals for Diseases of the Chest —Sir Russell Brock, J L Livingstone K Robson, Vernon Thompson

Royal National Orthopædic Hospital —C H Lack, R Nassim

National Heart Hospital—H A Bulman, * T F Cotton

St Peter's, St Paul's, and St Philip's Hospitals—A R C Higham, * H G Hanley

Royal Marsden Hospital—P E Thompson Hancock

Queen Charlotte's and Chelsea Hospitals—H G E Arthure, J B Blaikley, Charles Newman

Eastman Dental Hospital—R A Broderick, Sir William Kelsey Fry

United Newcastle upon Tyne Hospitals—C N Armstrong

United Leeds Hospitals—Digby Chamberlain, * A S Johnstone

United Sheffield Hospitals—John Wilkie, * J C Anderson

United Cambridge Hospitals—Janet Bottomley, S H Walford

United Oxford Hospitals—L K Ledger, A R H Williamson, * R G Macbeth, * J A Stallworthy

United Bristol Hospitals—R J Brocklehurst, T F Hewer * C D Evans, * A Miller

United Cardiff Hospitals—Leonard Howells, * Hugh Harley

United Birmingham Hospitals—B M Wilmott Dobbie, F A R Stammers

United Manchester Hospitals—W I C Morris, Sir Harry Platt, * J F Wilkinson

United Liverpool Hospitals—W M Frazer, C A Wells, * E Wyn Jones

TERMINOLOGY OF HEREDITARY HÆMOGLOBINOPATHIES INVOLVING HÆMOGLOBIN VARIANTS

THE Colonial Medical Research Committee's Working Party on Sickle-cell Trait and Sickle-cell Anæmia * has issued the following recommendations which, it says, are based on immediate practical requirements rather than on fundamental theoretical considerations, and are put forward at the present time solely with the aim of discouraging the growth of ambiguous systems of terminology until an agreed international system has been devised

General

(*a*) The term " sickle cell disease " should be used to denote any pathological condition which is, in part, attributable to sickling of the red cells The term " sickle cell anæmia " should be reserved to denote the presumably homozygous state Its use is (strictly) conditional upon the demonstration of homozygosity from family studies

(*b*) Fœtal hæmoglobin is excluded from the present discussion of terminology, though its persistence in varying degree is an often observed feature of states involving the hæmoglobin variants Statements regarding its occurrence should be made as part of the biochemical findings

(*c*) The Working Party appreciates the desirability of having a complete statement of the Hb variants actually present, preferably in order of decreasing proportions, leaving the clinician to decide if an actual (or potential) pathological situation needs to be described, and the geneticist to state how the observed combination of Hb variants has arisen The Working Party also appreciates the undesirability of using a terminology with genetic implications in the absence of family studies

(*d*) The term " hæmoglobinopathy " should be used to denote a condition in which the production of normal adult hæmoglobin (Hb–A) is partly or wholy suppressed and it is partly or wholly replaced by one or more hæmoglobin variants, which may include fœtal type hæmoglobin (Hb–F)

Specific

(*a*) The term " sickle cell should be hyphenated when used as an adjective

(*b*) Excluding Hb–F from consideration, the biochemical state involving Hb–A and any other one hæmoglobin variant (Hb–X) should be described as Hb–X trait "

(*c*) The term " disease " and not the term " anæmia ' should be used generally to denote pathological conditions associated with hæmoglobin variants

(*d*) The term thalassæmia " should be retained because the genetic variants of thalassæmia present themselves as such These variants should be described as ' Hb–C/thalassæmia " Hb–E/thalassæmia,' &c The term " thalassæmia ' should be used rather than the terms " Cooley s anæmia " " microcythemia," &c The qualifying terms " major " and " minor ' are in practice used to denote the presumably homozygous and heterozygous states respectively, but their use in this way is (strictly) conditional on supporting evidence for the nature of the genotype from family studies

(*e*) A morbid condition, not presenting itself as sickle-cell disease or as a variant of thalassæmia, but produced by any one or two Hb variants, in the absence of Hb–A, should be described as a " disease "—e g, " Hb–C disease," " Hb–C/Hb–D disease " (hypothetical) It is appreciated that some of the possible combinations are not yet known to produce morbidity in adults

Examples of Known Hæmoglobin Combinations

A	Normal adult
A + F	Infants
A + F	Thalassæmia
S + F	Sickle-cell anæmia
A + S	Sickle cell trait
A + S + F	Sickle cell/thalassæmia
C (+ F)	Hb–C disease
A + C	Hb–C trait
A + C + F	Hb–C/thalassæmia
S + C (+ F)	Sickle cell/Hb–C disease
D	Hb–D disease
A + D	Hb–D trait
S + D (+ F)	Sickle cell/Hb–D disease
E (+ F)	Hb–E disease
A + E	Hb–E trait
E + F (+ A ?)	Hb–E/thalassæmia
G	Hb–G disease
A + G	Hb–G trait
A + I	Hb–I trait
A + H	Hb–H trait
A + J	Hb–J trait

In the above examples, the hæmoglobin variants given in parentheses are not always found

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* The members of the Working Party are Prof A W Woodruff (chairman) Dr A C Allison Prof P C C Garnham Dr H Lehmann Dr F Lawthwaite Prof B G Maegraith Dr A E Mourant Dr A B Raper Dr J C White and Dr G H Beaven (secretary)

Public Health

Health in Scotland

LAST year in Scotland the infant mortality rate fell to the lowest level on record and there was evidence of continuing gain in the health of children (in Glasgow and Edinburgh, boys aged 13 in 1955 were a stone heavier and 4 inches taller than the boys of 1913), but the death rate in men aged 45–64 increased slightly [1] In this group the dangers were from lung cancer, bronchitis, and heart disease—particularly coronary thrombosis, which was responsible for 15 6% of all deaths Physicians and surgeons had a death-rate from coronary thrombosis 73% above the average, and other professional and managerial groups had similarly high rates An interesting table in the report on the year compares the death rates from cancer at various sites in 1931–35 with those in 1953–55 At most sites the rates were about the same in the two periods At some (especially the lymph glands) there was a fall, at others (such as the urogenital tract in men, the cervix in women, and the pancreas in both sexes) a slight rise, but in the lung (including trachea and bronchi) the rate had risen threefold in women and sevenfold in men In the brain the rises were surprisingly high—ninefold in women and twelvefold in men—and this is attributed in the report to better diagnosis

The report emphasises that simple trends of death rates have lost some of their significance as indices of the nation's health, and more account should be taken of sickness and disablement, though information here is insufficient The greatest losses of time from work were caused by respiratory tuberculosis, psychosis and neurosis, bronchitis and pneumonia, and rheumatism A two year mass radiography campaign is now in progress

The numbers of hospital admissions and discharges, of bottles of blood transfused, of outpatient attendances, and of nurses employed all continued to rise Eight major hospital schemes were under construction Voluntary admissions to mental hospitals numbered 6587 (compared with 3975 in 1950) The report express-concern at the rise in the number of prescriptions for phenobarbitone (2 million, or over 10% of all prescriptions) and other sedatives, and in the number of deaths *attributed to such drugs (77, compared with 18 in 1948)* Some of these deaths were suicidal, some accidental Accidents continue to be a major cause of death and disability, in 1955, 192 babies under a year died by accident and only 35 from all infectious diseases (including tuberculosis but not pneumonia) There are many more serious accidents at home than at work or on the roads, in 1950–55, 48% of the fatal accidents in males and 85% of those in females were at home In 1955 there were 1120 deaths in Scotland from home accidents, besides many severe injuries Most of the fatalities were in children under 5 years or people over 65 The biggest hazards for the old were falls and accidental gas-poisoning, for infants, suffocation (in bed or by inhalation of food) Deaths from burns and scalds, and from poisoning by solids and liquids, were next in order of frequency If anything, the accident-rate was increasing, and it is good to learn that research on these matters is being done in Scotland, and that home accidents are "now regarded as a problem within the sphere of local authorities"

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[1] Report of the Department for Health for Scotland 1956 H M Stationery Office Pp 147 5s 6d

Poliomyelitis

In the week ended May 11, uncorrected figures for poliomyelitis notifications were (previous week in parentheses) paralytic 39 (35), non-paralytic 30 (25), total 69 (60) The figures remain well above the seasonal average From 1948 to 1956 the highest previous total for the corresponding week of the year was 36 (in 1953) The total number of cases this year (up to and including the 19th week) is 825, the highest corresponding figure in 1948–56 was 649 in 1950 Last year the total at this stage was 480 The districts particularly affected include Barnet (66 3 cases this year per 100,000 population), Stevenage (49 9), Colchester (43 6), and Tendring (near Colchester) (40 7)

Suspected Smallpox

A soldier stationed at Perham Down, Wiltshire, has been taken to an isolation ward in Reading because he may have smallpox[1] The unit affected is the 39th Heavy Regiment, Royal Artillery 8 men who had been living in the same room are in an isolation ward in the camp and between 400 and 500 men of the unit are confined to camp for revaccination Reports suggest that the soldier has not been abroad recently

More Dental Decay in Children

In his report for 1956, Dr R G Davies, principal school medical officer for Huddersfield, speaks of the "very regrettable" increase in the incidence of dental decay among younger children With a decrease, or the possibility of a decrease, in the number of dental officers, he added, it was easy to see that restorative dentistry would not be able to cope with this trend if it continued The solution would have to be found not in extractions or even in conservative treatment but in some means of preventing dental decay Unless methods such as fluoridation proved a short cut, the only answer lay in the education of parents and children in the prevention of dental disease

B C G Vaccination

The Research Defence Society has produced a pamphlet[2] setting out the answers to the questions that most parents ask about B C G vaccination The pamphlet explains why and how vaccination is performed in this country and says firmly, in assessing the vaccine's effectiveness, "it is no longer possible to doubt the usefulness of B C G vaccination" Questions are also answered about the preparation and safety-testing of the vaccine

In England Now

A Running Commentary by Peripatetic Correspondents

It is odd that, though there are universities, postgraduate schools, lecturers, and textbooks galore devoted to the training of a consultant, there is no theoretical training for the thorniest obstacle of all—the selection committee's interview Fortunately benevolent officialdom has recognised this, and supplies unlimited practical experience

Thus, everyone knows that the post of consultant *omphologist to* Slumtown will *go* either *to* Bloggs, aged 43, with seventeen relevant letters after his name, and who has written two books, or else to Snooks, aged 41, with only fourteen letters and one book to his credit, but who is well favoured locally, and thought to be a promising young man Despite this, McGregor, Smith, Jones, and O'Hara, mere striplings in their late 30s, will be summoned from the four corners of the *kingdom* They will be senior registrars, usually laughingly called "transitional," and though they spend the rest of the year on an income which keeps them a bare fraction from the breadline, officialdom suddenly pretends *to* believe that *they* lead a champagne-and-caviare existence, and would refuse to come unless brought first-class So there they are in their best blue suits, only distinguishable by the slight fraying at the cuffs from all the other people who travel first-class on expense accounts

At the interview the questions are as unchangeable as the signs and symptoms of appendicitis, so that there is plenty of scope for textbook coverage "What interests have you outside medicine?" "As an omphologist, what do you consider should be your relations with the Xiphisternist?" "Is there any particular branch of omphology in which you are interested?" and so on These questions are so standard that publication of an unusual one would be as interesting as the report on a case of nagana on St Kilda The taxpayer would be saved a lot of money if this routine information were available in print, but until some enterprising author appears, we shall have to continue our little trips, even though we are only 37 and have a bare eleven letters *to our name*

* * *

Why don't I keep my big mouth shut? Since birth I have been 100% tone-deaf my nursemaid winced at the discords, the kindergarten mistress asked me not to sing in the carols, the French master tore his hair All in vain, Hi-Fi is lost in the ataxic cilia of my cochleæ Consequently all foreign languages are beyond me I haven't a clue what all those mouthings mean without the explanatory *manual* gesticulations Thank Heaven most of the world speaks English and seems to get a kick out of airing it to provide my material comforts But when in Rome, or Stockholm, or Oslo, I really do try to merge into some of their less *exotic* background habits. On a visit to a large camp of young people I was invited to dine at the top-table on the first evening With punctilious courtesy we stood behind our chairs until the whole company was assembled in the dining hall The Commandant gave three sharp raps on the table with his knife, and spoke a couple of dozen words in Norwegian Everyone bowed their heads and looked most solemn I said "Amen" rather loudly and sat down It seemed the obvious way of joining my hosts in spirit, but the top-table looked distinctly startled For want of anything better as an opening conversational gambit, I leaned across to our interpreter and enquired if the *Commandant's* words were the usual form of Norwegian grace When the howls had died down, I gathered the horrible truth of his translation 'If you want any beer you must buy it yourselves"

* * *

Samples of the latest tranquilliser reached Singapore, appropriately enough, the same day as the news of the success of the Singapore "Merdeka" Mission to London They lay on my desk until Maundy Thursday when I packed my bag for the annual general meeting of the Malaya branch of the B M A, held this year in Kuala Lumpur

The journey north was delightful and we made excellent time until we reached a check point at Gemas, at the beginning of one of the "food denial areas" which have been so successful in starving the bandits out of the jungle Here I reported I had two apples, but was prepared to jettison them if they were prohibited No, a reasonable quantity of fresh fruit was permitted, but could I please produce them for inspection? I opened my bag, but most of my interest was taken up by the very thorough examination of the car in front where a tin of sardines had just been produced in triumph from under the hubcap of a rear wheel My attention was drawn back sharply to my own bag when the examining Gurkha soldier asked "What is this?" holding out the samples I'm not an expert Malay scholar at best, and in any case I doubt if even the director of the new Agency for Malay Language and Literature has got round to inventing a Malay word for "tranquilliser" yet, so I told him it was headache medicine A conference was held with a Malay policeman and a Malay civilian and they became so grave that even the finder of the tin of sardines seemed to think that his success had been eclipsed

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[1] *Times* May 21 1957

[2] B C G Vaccination Against Tuberculosis Conquest pamphlet no 2 Price 3*d* from the Research Defence Society, 11 Chandos Street, Cavendish Square London W 1

The inevitable Job's comforter in the car behind told her companion in a loud voice about a friend of hers who had been fined $500 for having "been caught with a bottle of aspirin," and that "everyone knows that the Communists in the jungle are very short of drugs" My visions of a happy Easter weekend with my colleagues were fading Then the Gurkha said "Ini obat banya sallah, Tuan" I translated this literally as "This is very bad medicine, Sir" and was prepared to agree, abandon it, and go on my way, but apparently it was the possession of it without a permit that was so serious I had to be taken before the assistant district officer to have my fate decided

A long interview followed in which I was able to establish my identity as a medical practitioner by the production of a number of passes which authorise me to enter military areas and the harbour board area, and to inspect houses and buildings under the municipal ordinance, which I had regarded for years as nuisances because they clutter up my wallet and were never required Finally I was given a "Permit for the Movement of Goods between the hours of 6 A M and 7 P M" with everything on it deleted except item 17 "Drugs," and that was endorsed "2 Packets Samples"

This is my first experience of tranquillisers, and, as far as I am concerned, they did their best to upset the tranquillity of a lovely day I was careful to dispose of them before setting out for the return journey to Singapore

* * *

A discussion of the French cave-paintings led me to undertake a small study of wall-work in the West Virtually everybody has come to this fast-growing Calgary from some other place, and where local roots seldom go deep the citizen is rare indeed who can say that his grandfather was born here Therefore walls carry material that indicates the origins, ambitions, and masonic degrees of the people In this land where everybody can read-and-write but so few can truly read, it is plain that little Johnny will go far when his parents have posted by his bedside the certificates of progress at school from grade 1 to grade 2, and then that from grade 2 to grade 3 Only the other day I visited a small boy who lay in a big bed, at the head of which I saw the neatly framed certificate of the marriage of his parents

I am devoting a special section of my study to the offices of doctors In a Province where the Pioneer is a man of such stature in the community that he is almost a Senator, the sign of special note in the offices of the small and diminishing number of doctors who were here before the establishment of the Province in 1905 is the arms of the North West Territories on the *diplomas of* registration with the College of Physicians and Surgeons of pre-history On the other hand a non-pioneer doctor of my acquaintance shows to the world, by means of a small certificate on his wall, that he once attended a course in field hygiene with the R C A M C, and another has put up the citation of a mention-in-despatches during the campaigns of a decade and a half ago

* * *

Equality of opportunity has reached high levels in America All milk is delivered homogenised, now nobody can take the cream off the top

Letters to the Editor

STEATORRHŒA AND HYPOPARATHYROIDISM

SIR,—Dent et al[1] have recently noted secondary hyperparathyroidism in cases of osteomalacia caused by steatorrhœa, confirming Albright's view[2] of the relationship between the two conditions But there may be a connection between steatorrhœa and *hypo*parathyroidism Steatorrhœa usually causes a deficient absorption of phosphorus as well as calcium, and this may lead to a lowered serum-inorganic-phosphate level and osteomalacia The elevated serum-phosphate reported in other cases of steatorrhœa is, therefore, unexpected and needs an entirely different explanation

Bennett et al[3] described the syndrome of "idiopathic steatorrhœa" and remarked that in 5 of their 15 cases the serum phosphorus was above 5 mg per 100 ml, in 1 case it was 6 3 mg They offered no explanation, beyond the unqualified remark that secondary hypoparathyroidism might have been present

Colin Williams[4] reported a case of idiopathic hypoparathyroidism in a boy of 6 years with papillœdema and generalised moniliasis Steatorrhœa became apparent at the age of 5 Tetany with low serum calcium developed a year later when the serum phosphate reached 10 mg per 100 ml There was a good response to parathyroid hormone (Ellsworth Howard test) The duodenal juice contained normal amounts *of trypsin Renal functions were unimpaired Rickets* did not develop and the serum alkaline phosphatase was estimated to be 10 Bodansky units The patient's brother was said to suffer from the "cœliac syndrome"

Lowe et al[5] reported the findings in a young girl who had tetany from birth with low serum calcium and a high serum phosphorus level (up to 7 mg per 100 ml) She had steatorrhœa (with only 65% fat absorption) associated with anæmia, ecchymoses, increased prothrombin time, raised alkaline phosphatase, and low serum vitamin A Pancreatic enzyme production was apparently depressed, but aspirated duodenal juice was normal when the test was *repeated later* There was no response to injection of an active preparation of parathyroid hormone On the other hand there were none of the specific skeletal abnormalities associated with pseudohypoparathyroidism *Ectodermal dystrophies, of the variety* produced by prolonged hypocalcæmia, appeared later

Liefer and Hollander[6] reported the case of a man of 20 who had had idiopathic hypoparathyroidism for ten years, and "diarrhœa" for eleven years They diagnosed steatorrhœa (no fat balance data are given), with normal vitamin A tolerance, normal glucose tolerance, and normal pancreatic enzymes The serum inorganic phosphorus in several estimations lay between 5 and 12 mg per 100 ml The response to parathyroid hormone was good The urine calcium output was around 200 g in twenty four hours, with a serum calcium of only 5 9 mg *Salmonella panama* was isolated from the patient's stool and biliary tract Addison's disease developed later

Salvesen and Böe[7,8] *describe a boy of* 8 who had had moniliasis of skin, nails, and mouth from the age of 6 months He had steatorrhœa, with 82 g of fat in a single day's stool The serum calcium varied from 5 0 to 8 4 mg per 100 ml and the inorganic phosphorus from 5 45 to 6 5 mg, with a single reading of 10 2 mg Though no further evidence is produced in favour of a diagnosis of idiopathic hypoparathyroidism, the well known association of the *condition with* moniliasis makes this diagnosis very probable *Candida albicans* was isolated from the stool, and moniliasis of the small intestine was suggested as the cause of the steatorrhœa

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1 Davies D R, Dent C E, Willcox A *Brit med J* 1956 ii 1133
2 Albright F Reifenstein E C The Parathyroid Glands and Metabolic Bone Disease London 1948
3 Bennett T I Hunter D Vaughan, J M *Quart J Med* 1932 1 603
4 Colin Williams C *Pediatrics Springfield Ill* 1950 5 998
5 Lowe C U Ellinger A J, Wright W S Stauffer, H M *J Pediat* 1950 36, 1
6 Liefer E Hollander W *J clin Endocrin* 1953 13 1264
7 Salvesen H A Böe J *Acta med scand* 1953 146, 290
8 Salvesen H A Böe, J *Acta endocr Copenhagen* 1953, 14 214

A patient discussed in a conference [9] had hypoparathyroidism, and no parathyroid tissue was found at autopsy Steatorrhœa was mentioned as an incidental finding

MacGregor and Whitehead,[10] while examining the evidence for two separate parathyroid hormones, remarked on 2 cases of steatorrhœa with tetany and with failure to respond to parathyroid hormone In 1, a man of 30, the serum calcium was 6 2 mg and serum inorganic phosphorus 6 3 mg per 100 ml There were 11 g of fat per day in the stool The intravenous parathormone (Ellsworth-Howard) test was negative, and there was no response to intramuscular parathyroid extract (150 *U S P* units a day for four days)

Our own patient [11] was a woman of 32 with a recent history of steatorrhœa and tetany The serum calcium was initially 6 6 mg per 100 ml She had the signs of idiopathic steatorrhœa (clubbed fingers, anæmia, tetany, abnormal small gut pattern and flat glucose-tolerance curve), but she had a gross deficiency of pancreatic enzymes and persistently raised serum phosphorus (4 1–6 7 mg per 100 ml) The high serum-phosphorus was combined with a low urine phosphorus output, but normal renal glomerular function Later tests proved that there was a greatly increased tubular reabsorption of phosphorus, characteristic of hypoparathyroidism There was no response to an active parathyroid extract (Ellsworth-Howard test), though there were none of the physical stigmata of pseudohypoparathyroidism Later, amenorrhœa (associated with a low urinary excretion of follicle stimulating hormone) and uterine atrophy developed

The association of steatorrhœa with the features of hypoparathyroidism is surely too common to be fortuitous Since either alone can produce tetany with low serum calcium, the combination might easily be missed if not specifically investigated, and hence may well be more common than appears Nevertheless, the cases reported do not produce a uniform picture In some the steatorrhœa is the outstanding condition, with biochemical features of hypoparathyroidism discovered accidentally, in others the hypoparathyroidism is outstanding, with the steatorrhœa apparently of less importance Furthermore, the type of hypoparathyroidism differs in its response to parathyroid extract, though in no case are the characteristic skeletal defects of typical pseudohypoparathyroidism reported Lowe et al [4] suggest that in their case the low serum calcium level led to continued excessive parathyroid hormone production This caused constant stimulation of the renal tubules till these eventually became refractory They adduce no evidence for this hypothesis, which could not account for the hypoparathyroidism in cases with a good response to parathyroid extract

Salvesen and Böe [8] suggest that intestinal moniliasis accounted for the steatorrhœa in their patient Certainly this could not apply to most of the others Analysing 85 cases of "sprue" (i e, presumably idiopathic steatorrhœa),[7] they found that the majority had a serum-phosphorus within the normal range In 22 cases the phosphorus was low, and all these had bony decalcification, in only one was the serum phosphorus abnormally raised (a very different incidence from Bennett's 5 out of 15) They suggest that the serum phosphorus would be expected to be low in all cases, if the parathyroids were responding properly to the lowered serum-calcium Consequently they believe that most patients with steatorrhœa have a relative parathyroid insufficiency, and they suggest that this is due to the malabsorption of some substance necessary for the normal maintenance of good parathyroid activity Unfortunately they produce no evidence for the existence of such a substance As mentioned above, other endocrine secretions have failed in this syndrome—pituitary gonadotrophin in one case, and those of the suprarenal cortex in another Addison's disease and true hypoparathyroidism are occasionally seen in the same patient, quite apart from the condition under discussion

I can think of no good explanation for this association of steatorrhœa with hypoparathyroidism, but believe that it is sufficiently well documented to be considered a definite "syndrome" If all patients with steatorrhœa had their serum-phosphorus estimated, and all patients with hypoparathyroidism had their fat absorption estimated, we might learn more about this "new syndrome"

I should like to thank Prof J F Brock Prof F Forman, Prof G C Linder, Dr R Hoffenberg and Dr E Dowdle for their interest and help and Prof C E Dent for drawing to my attention the case of Salvesen and Böe

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W P U JACKSON

SENIOR REGISTRARS AND CONSULTANT APPOINTMENTS

SIR,—Dr Hubble's letter of May 11 is specially valuable in that it throws the limelight on the basic problem of the senior registrars For years it has been one of the objects of the Registrars' Group to show that the ratio between senior registrars and consultants is too high and that this improper ratio has been worked out on a supposed need for competition This has always meant that the numbers in training should be fixed above the estimated needs, no serious thought has been given to the fact that this means delay beyond bearing for many whose abilities match up to the available posts but who seem to exist at the present time only to provide "committee fodder" It would be completely rational to allow only just as many senior registrar posts (in each specialty) as would fill the expected consultant vacancies—based on the assumption that the average senior registrar held his post for the expected four-year period Take then a specialty and imagine that twelve posts are to be advertised in 1937 If in fact there were just twelve fourth-year senior registrars available and if all the appointments were made by one committee on the same day, then truly the last post would be filled by default This sort of situation seems to be envisaged by those who demand competition and wastage In fact no such thing happens, the twelve posts are advertised at intervals throughout the year and by the time the last appointment is made in December, there is a new crop of well qualified men ready to compete on level terms with the last of the original twelve, there may even be some second or third year senior registrars to swell the short list, there may be some in their fifth and sixth years and there may be some university lecturers who have never featured on the senior registrar establishment

There is nothing fixed about an absolute length of training for any individual in any specialty, and there will always be adequate competition to allow a selection committee to exclude anyone who despite the passage of proper time interval does not match up to the job There is now and always has been a clear case for a simple adjustment of the ratio between senior registrars and consultants and the creation of a few more consultant posts at the expense of some senior registrar posts which could then disappear In terms of finance and in terms of specialist work this could almost be a paper transaction within the service, but it would be a move which would bring sanity into the situation and reassurance into the lives of many senior registrars and their families It is not enough, however, that the Minister of Health and his advisers should understand this viewpoint, the drive to appoint more consultants and to adjust the ratio must come through the established consultants who, like Dr Hubble, see the need for extra appointments and are prepared to push what may sometimes be unpopular opinions in this matter If this demand does not come the Ministry will for some time remain unconvinced of the position

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[9] Case records of the Massachusetts General Hospital (case 40361), *New Engl J Med* 1954 251 442

[10] MacGregor M E Whitehead T P *Arch Dis Childh* 1954 29 398

[11] Jackson W P U Hoffenberg R Linder G C Irwin L *J clin Endocrin* 1956 16 1043

I must agree with Dr Hubble, that senior registrar appointments at non-teaching hospitals do not promote professional progress, but only when these appointments are *wholly* at non-teaching hospitals Nothing should be allowed to interfere with the senior-registrar posts where experience is gained both at teaching and non teaching hospitals during the normal four-year *tenure*

Finally, I agree that "assistant consultant" status *should not be contemplated* as a compromise There is no real place for such a post in the National Health Service, and although one can understand the plight and urgency of some of its advocates its effect on their own future and on that of the hospital service as a whole might be disastrous

It would not take much in the way of agreement between the Joint Consultants Committee and the Ministry to set the whole matter to rights with fairness and speed, without prejudice to any other negotiations on pay, conditions of service, or junior hospital staff Those of us whose influence is limited to writing to the journals will wish luck to Dr Hubble and his like as they continue to plug away at committees and colleagues

Royal Albert Edward Infirmary
and Dispensary, Wigan
R M FORRESTER

CHRONIC BRONCHITIS AND SMOKING

SIR,—Dr Harley Williams (May 18) does not like the methods adopted by Dr Lennox Johnston in his efforts to stop people smoking—perhaps Dr Johnston's psychopathology exercise is of little value Personally, I do not like this approach either, but I do raise my hat to his tenacity and enthusiasm

Of all people who should discourage young people from smoking and encourage smokers to smoke less, surely Dr Williams should be a pioneer—can he tell us what he has done and what he hopes to do in this connection ? May I suggest that he would contribute something really worth while if he persuaded many of the consultant chest physicians to set a good example how can these men who see the results of smoking ignore the warnings so blatantly ?

That Mr Dunhill (May 18) is amused at the efforts of those who are trying to discourage smoking is understandable but one of these days the Minister of Health and *his department may be forced to take action* to protect the public from the ill effects of smoking And Mr Dunhill may be less amused when the full effects are felt of a campaign which is now being worked out

Many of us are not concerned with the axe the cigarette manufacturers have to grind , our only concern is the health and welfare of the millions of people who are ruining their health by the pernicious habit of smoking

T W HURST

Standish,
Wigan

Hon Treasurer,
National Society of Non Smokers

SIR,—Your three correspondents, Dr Harley Williams Dr Lennox Johnston, and Mr A H Dunhill, whose letters appeared last week, illustrate the variability of the assessment of the enjoyment of smoking

Mr Dunhill quotes the plain statement that smoking is enjoyable, Dr Harley Williams qualifies this by saying that *to smokers* smoking is a pleasure Dr Lennox Johnston says that his own assessment of the enjoyment of smoking is negative So is mine, and one of the deplorable factors in smoking is that so many smokers overlook the fact that smoking is repugnant to most non smokers It inhibits their attendance, not only at cinemas and theatres where smoking is allowed, but also at more important places, such as scientific meetings, and make even ordinary social relationships rather trying How far the non-smoker suffers medically from the smoker's smoking yet remains to be assessed, but it certainly does not contribute to the non-smoker's joy of living

Mental Hospitals' Group Laboratory,
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W W KAY

THE Rh BLOOD-GROUPS

SIR,—To answer the letter of Dr Renton and Dr Hancock (April 27) certain little known facts must first be discussed

Early in our studies on the blocking test [1] we found that highly agglutinable erythrocytes are hard to block, while less agglutinable cells are more easily blocked Accordingly, if the Rh positive cells used as test cells for titrating sera are old, lower titres will be obtained in the agglutination test but higher titres in the blocking test Conversely, more agglutinable erythrocytes, such as fresh cells of type Rh_z, or other fresh cells homozygous for the Rh_0 factor (such as cells of types $\mathrm{Rh}_1\mathrm{Rh}_1$, $\mathrm{Rh}_2\mathrm{Rh}_2$, and $\mathrm{Rh}_1\mathrm{Rh}_2$) give higher titres in the agglutination test, but give lower titres in the blocking-test because such cells are difficult to block

Lack of familiarity with this principle has been responsible for serious errors in medicolegal and anthropological blood grouping work, because the sera available commercially for testing for blood factors rh′ and rh″ are mostly prepared from anti-Rh'_0 and anti Rh''_0 sera, to which anti Rh_0 blocker has been added With very agglutinable cells *the blocking* effect may fail , weak false positive reactions can result and may be misinterpreted

Thus in a recent medicolegal case involving Negroids an expert appointed by the court reported an exclusion involving the factor rh′ In repeat tests, his report could not be confirmed, since the mother, child, and putative father all proved to belong to type Rh_0 Presumably *the two parents* were both of genotype R^0r, while the child was of genotype R^0R^0, and failure of complete blocking of the child's cells gave rise to false positive reactions with the anti rh′ serum, which had been prepared in the usual way by blocking anti Rh'_0 serum In another similar case the putative *father* was type Rh_1 and the mother type Rh_0, but the child's blood gave weak reactions with the anti rh′ serum used for the test This was obviously a false positive reaction since control rh′ positive cells gave much stronger and clearer reactions with the same serum, and repeat tests with antiserum to which additional blocker was added proved that the *baby's type* was Rh_0 instead of type Rh_1, as the preliminary tests seemed to indicate Of course, this pitfall can be avoided by the use of pure anti rh′ sera obtained from type Rh_2 individuals and of pure anti rh″ sera obtained from type Rh_1 individuals, but such monovalent sera are available only in *limited* amounts

Another striking example of mistakes resulting *from this* pitfall is provided by a study of blood type distribution among western Apache,[2] where the following distribution is reported

Rh Hr types	*Number*
CDe/CDe	16
cDE/cDE	4
CDE/CDE	2
CDe/cDE	130
CDe/CDE	47
cDE/CDE	16
CDe/cDe	7
cDE/cDe	6
Cde/cdE	2
CdE/cde	0
Cde/cde	1
Total	231

If these results were accepted literally, one would have to conclude that more than 25% *of the* individuals of this population were carrying the rare gene R^z Now, it is known that in Mongoloids and American Indians the most common gene by far is R^1 , gene R^2 is also present, and *though the* highest prevalence in the world of gene R^z is among Mongoloids, this *prevalence* rarely exceeds 5% Gene r is virtually absent, and almost all *individuals of types* Rh_1 and Rh_2 are of genotype R^1R^1 and R^2R^2, respectively Thus the use of poorly blocked anti-rh′ and anti-rh″ sera could cause a high percentage of these bloods to be misclassified as type Rh_zRh_1 or Rh_zRh_2, respectively I pointed this out in a letter to Dr B S Kraus, in his reply, he admitted the possibility of these errors in the tests, which were carried out in the field under unfavourable conditions

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[1] Wiener A S *Proc Soc exp Biol* N Y 1944 56 173
[2] Kraus B S White C B *Amer Anthrop* 1956, 58 1017

With respect to the questions raised by Dr Renton and Dr Hancock, our experience has been different from theirs The prevalence of so-called strong D has been much higher than only 5 in 653 If we consider only the rare type Rh_zRh_2 individuals alone, who (as Dr Renton and Dr Hancock admit) almost invariably give strong D reactions, this would already make up 2% for the minimum prevalence of this strong D The discrepancy in our experience might be explained if the bloods tested by Dr Renton and Dr Hancock were not all perfectly fresh After only one or two days' ageing, the blood-cells become less agglutinable so that the strong-D effect could readily be overlooked As I pointed out in a personal letter to Dr Renton, all his pedigree data can readily be explained on the basis of a gene dosage effect For example, the individuals whom he classifies as CDE/cde and cDE/cde seem to be *actually* of genotypes CDe/cDe and cDE/cDe respectively Measuring agglutinability like titrations, is a crude procedure, so variations in the titre may occur due *solely* to limitations of the technique, and this could account for occasional discrepancies in titration scores I should like to emphasise that while the possibility of "strong-D" *cells such as type* Rh^x *(–D–)* or carriers of gene R^{zz} is not denied, the evidence offered by Dr Renton and Dr Hancock was inconclusive, and the fallacious use of genotype symbols to represent phenotypes caused these workers to overlook other possible explanations for their observations

The designations anti-Rh_1 and anti-Rh_2 to which Dr Nicholas (May 4) objects, have not been used for over a decade, so that they can hardly be a source of confusion I am glad, however, that Dr Nicholas has called attention to my book published in 1943, which contains those obsolete symbols, because it also contains the first statistical data refuting the theory of linked genes, which was taken up again two years later by Fisher and Race (Incidentally, publications fifteen years old are not alone in containing ambiguities where C D-E is concerned, *every* current article by C-D-E workers contains errors and contradictions, which increase in number as time goes on)

The justification for the designation "International Rh-Hr Nomenclature" is that these symbols are used by *all* workers, including Fisher and Race, though the latter use the symbols under the transparent pseudonym of "shorthand" symbols

Dr Nicholas's response to my eight questions are not forthright answers It is impossible to acertain, for example, what is his exact position regarding the question of which of the 25 C D-E equivalents for Rh_1rh is the approved one, or what is the position of Fisher and Race regarding linked genes *v* multiple alleles, deletions, &c The difficulty is increased because what the C-D E paradoxers say often does not correspond with what they do In fact, their arguments and position shift as rapidly as a chameleon changes his colour I wonder, therefore, whether Fisher and Race endorse Dr Nicholas's response, or how would they answer my eight questions?

I should like to call attention once more to the tentative report of the committee on medicolegal problems of the American Medical Association, recommending that in medicolegal reports the correct Rh Hr nomenclature be used exclusively, and the C-D-E notations be avoided This report has now been revised, and the final report will shortly be published in the *Journal of the American Medical Association* When preparing this revised report, the committee took into account correspondence received from approximately 50 workers in the field, and could find no valid scientific reason to change the original recommendation This report will reach all practising physicians who depend on the *Journal of the American Medical Association* for an expression of approved standards in medical practice

Brooklyn, New York, U S.A A S WIENER

WILSON'S DISEASE

SIR,—May we comment on your leading article (May 11)? We think your statement that "there can now be no doubt that disordered copper metabolism is the underlying cause" of the disease needs amplification May it not be that the real underlying cause is some inherent biochemical abnormality permitting this disordered copper metabolism to develop? The disease is known to be genetically determined, and it is believed that genes are responsible, not for unit characters, but for unit biochemical processes (Haldane) It would seem justifiable therefore to suggest that hepatolenticular degeneration may be due to faulty genetic control of certain specific protein molecule(s) that normally enter into strong combination with copper, forming cæruloplasmin—the deficiency of which is such a striking feature of this disease The restoration and maintenance, therefore, of normal tissue levels of cæruloplasmin by parenteral administration of this enzyme seems an obvious goal once a supply adequate for prolonged treatment is available A start in replacement therapy of this kind has already been made by Bickel, though a longer period of treatment is necessary before the response can be evaluated The question arises of the disposition and disposal of the intrinsically administered copper, in addition to the problem of removing copper already accumulated, though it is conceivable that, with a sustained normal blood-level of cæruloplasmin, the disordered copper metabolism might readjust itself spontaneously Indeed, balance studies in three of our untreated patients showed an exact equilibrium and not a strongly positive balance, which may argue for a phased activity in this respect

A low serum copper level is not pathognomonic of Wilson's disease, for it may be found in the newborn and in some patients with the nephrotic syndrome Perhaps more significant is our recent finding of subnormal levels in some of the parents of our patients as well as in an unaffected sib, one father had serum-copper and cæruloplasmin levels strictly comparable with those of his daughter who died of the disease It cannot be ignored, then, that some additional factor(s) must co exist which tip the scale, turning a "potential" into an "actual" sufferer from the disease A thorough investigation of parents and families of patients may bring to light some new evidence to account for the anomalous situation now apparent When we can find out what mechanism prevents some individuals with low cæruloplasmin levels from becoming subject to the disease, then perhaps we may be a little nearer helping those not so protected

Considering therapeutic measures, you infer that the earliest possible treatment with dimercaprol (BAL) of biochemically proven cases is likeliest to succeed But, working in collaboration with Bickel (details in the press), we have seen the disease in a young girl progress during three years from the onset of symptoms to death, and at necropsy high tissue levels of copper were found despite protracted regular monthly treatment with dimercaprol, later interspersed with sodium calciumedetate ('Versene') No clinically satisfying improvement was seen in any of the patients we treated with various copper-removing agents, but it may be that the therapeutic attempts were not vigorous enough nor of sufficient duration, though seemingly successful in mobilising copper We found, as did A G Bearn (personal communication), that sodium calciumedetate could safely be given intramuscularly with excellent response, and in some patients the oral route was also effective

We are indebted to Dr P G H Goll for the determination of cæruloplasmin

Queen Elizabeth Hospital,
Birmingham

GILBERT HALL
F C NEALE

CARBUTAMIDE IN JUVENILE DIABETES

SIR,—Dr Engleson and Dr Lehmann [1] found carbutamide (BZ55) safe and useful in children, though Bertram et al [2] observed hypoglycæmic shock when it had been used for a long time

We have tested the drug in 16 patients between 6 and 13 years of age Their daily insulin need before the test period was between 12 and 64 units Carbohydrate metabolism was estimated from blood sugar curves determined before and after every meal, and at 12 midnight and 3 A M

To 3 children with recent diabetes, who had no tendency to acidosis and who had never received insulin, carbutamide was given for eight days in high doses—2 5 g (5 tablets) on the first day, and 1 5 or 1 0 g on each following day No beneficial effect on carbohydrate metabolism was noted

6 patients in full equilibrium with insulin were given, instead of the morning dose of insulin, 1–2 g of carbutamide Their diet remained unchanged The effect was related to the state of the carbohydrate metabolism observed during the insulin therapy

In 2 cases ketosis developed when insulin was stopped, and we were obliged to introduce insulin again In the 4 other patients there was no ketosis, but the drug did not reduce the blood sugar, on the contrary, increases up to 500–800 mg per 100 ml appeared—levels which had never been observed on insulin

In 5 cases we gave 1–1 5 g of carbutamide for five to eight days, combined with a moderate reduction of the dose of insulin Generally, the evening dose was reduced by 4 units to prevent hypoglycæmia at night

In 3 cases ketosis arose between the third and fifth days In 2 cases ketosis did not occur, but a favourable change could not be observed either, and on further reduction of the insulin dose the state became worse

In 4 cases the drug was given together with unchanged doses of insulin (In 2 patients, when the combined therapy had had no effect, the dose of insulin was raised to its original level) In 2 patients the dose was 1 5 g daily, while to the other 2 patients, together with the full dose of insulin, the dose of carbutamide given on successive days was 2 5, 2, 1 5, 1, 0 5, 0 5, 0 5, 0 5 (i e , 9 g in eight days) The drug had no effect on the variations of the blood sugar curve It did not influence carbohydrate metabolism, even in patients who received the drug together with the full dose of insulin

In the course of our experiments it was observed in some cases that in the morning the blood sugar was much under 200 mg per 100 ml, but during the day and at night it was extremely high The beneficial results reported by some observers might be ascribed to their determining only the fasting blood-sugar—i e , in the morning In several of our cases this was considerably reduced Sometimes only traces of sugar were found in the urine but at the same time diuresis was greatly increased, which means that the diabetic state remained unchanged

In our diabetic children the blood sugar level was not reduced by carbutamide, even in full adult doses, and a combination of carbutamide and insulin did not give good results

First Department of Paediatrics
Budapest University Medical School

L BARTA

FIBROSITIC PAIN

SIR,—The concept that fibrositic pain can be caused by localised areas of muscle in spasm—the so called myalgic spots or trigger spots—now seems to be conceded,[1] So too do the contentions that these areas can cause referred pain at a distance and that relieving their state of spasm can relieve such pain

I wish to record a clinical finding which may be of value to general practitioners During 15 years of concentration on the treatment of myalgic spots in the chronic rheumatic diseases, my case records have shown that the great majority of these spots responsible for fibrositic pain—more than 90% of them—are concentrated in a few well defined areas of the body When this is recognised it becomes much easier to locate the offending spots in cases where the source of the pain is not easily apparent

For convenience I have called these areas the "critical zones" There are four of them on each side in the shoulder girdle and two on each side in the buttocks

Critical Zones of the Shoulder Girdle

Zone 1 is the area above the spine of the scapula In my experience myalgic spots in that situation are often responsible for stiff neck, capsulitis of the shoulder joint, tennis elbow, and pain or stiffness in the wrists and fingers

Zone 2 is the area over the shoulder blade below the scapular spine Myalgic spots there can cause severe neuralgic pain affecting the wrists and fingers

Zone 3 is the area along the outer side of the shoulder blade and extending upwards There is commonly a myalgic spot in the upper extremity of the teres muscle, always present in long standing cases of capsulitis

Zone 4 is between the vertebral column and the mesial border of the scapula Though small in extent it may contain myalgic spots responsible for local pain, pain referred to the front of the shoulder joint, spasm of the chest muscles, deficient backward movement of the head, and pain, stiffness, and swelling of the fingers

Zones 2 and 3 are the areas in which myalgic spots can be responsible for Raynaud's phenomenon

Critical Zones of the Buttocks

A line drawn from the great tuberosity of the femur to the sacrum divides the buttock into two main zones

In the upper area, and in its outer portion will be found the spots responsible for pain in the upper part of the thigh, in the sacro iliac joint, and in the ankle joint

In the lower half of this zone may be found the spots causing intense neuralgic pain down the outer side of the thigh in long standing cases of arthritis of the hip joint Commonly they are situated over the tuberosity of the femur

Near the ischial tuberosity there is often a spot responsible for pain or stiffness in the knee joint

Myalgic spots responsible for pain or cramp in the calf muscles and for sciatic pain are often found in the midline of the buttock

London, W 1

LOUIS MOSS

NORMALITY OF AGEING

SIR,—Apropos Dr Rudd's article of May 4, I commend to your readers the following passage from Castiglione's *Il Cortegiano*, translated by Sir Thomas Hoby as *The Courtier* (Mine is the 1937 edition)

> "Old men commend the times past, and blame the times present, dispraysinge our doings and maners, and whatsoever they did not in their youth
>
> "The cause therefore of this false opinion in olde men, I believe (in mine opinion) is, for that, yeares wearing away, carry also with them many commodities, and among other take away from the bloud a great part of the lively spirites that altereth the complexion, and the instruments waxe feebly, whereby the soule maketh her effects
>
> "Therefore the meek flowers of delyte vade away in that season out of our harts, as the leaves fall from the trees after the harvest, and in steade of open and cleane thoughts, there

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1 Engleson G Lehmann O *Lancet* 1956 ii 786

2 Bertram F, Bendfeldt, E, Otto, H *Dtsch med Wschr*, 1955, 80, 1455

1 *Brit med J* 19[illegible], i 277

2 Savage O How to Live with your Rheumatism London 19[illegible], pp 46, 47.

entreth cloudie and troublous heavinesse accompanied with a thousand heart griefes so that not only the bloud but the minde is also feeble neither of the former pleasures receiveth it anything els but a fast memorie, and the print of the beloved time of tender age, which when wee have upon us, the heaven, the earth and such thing to our seeming rejoyceth and laugheth alwaies about our eyes and in thought (as in a savorie and pleasant garden) flourisheth the sweete spring time of mirth, so that peradventure it were not unprofitable, when now in the colde season, the sunne of our life (taking away from us our delites) beginneth to draw towarde the West, to close in in like case therewithall the mindfulness of them, and to finde out (as Themistocles saith) an arte to teach us to forget for the senses of our bodies are so deceivable, that they beguile many times also judgement of the minde

"Therefore (me thinke) olde men be like unto them, that sayling in a vessel out of an haven, beholde the ground with their eyes, and the vessel to their seeming standeth still and the shore goeth and yet is it cleane contrarie, for the haven, and likewise the time and pleasures continue still in their estate, and we with the vessel of mortalitie fleeing away, go one after another through the tempestuous sea, that swalloweth up and devoureth all thinges, neither is it granted us at any time to come on shore againe, but alwaies beaten with contrarie windes, at the end wee breake our vessel at some rocke"

London Hospital
Medical College, E 1 ALAN M BRAVERMAN

ATHEROSCLEROSIS IN THE BANTU

SIR,—In his letter of April 13, Dr Annand stated that the Bantu of South Africa are relatively free from atherosclerosis That this belief is fairly general is suggested by an editorial in the *South African Medical Journal*[1]

Such a view conflicts with the few satisfactory post-mortem records that do exist Possibly the most satisfactory of such records are those of Becker,[2] who stated that "the incidence of atheromatosis in the ascending period of life in the Bantu and Coloured subjects (of South Africa) is not far removed from that in other races, the incidence of the senescent type may be slightly less" Our findings are similar to those of Becker and we propose shortly to publish our records

It seems wrong, therefore, to claim that the relative freedom of the South African Bantu from coronary-artery thrombosis is attributable to a relative freedom from atherosclerosis We feel that one likely explanation for this relative freedom may be found in the changed physical and chemical characteristics of the Bantu blood, which in turn may be linked with some abnormality of liver function

Department of Medicine,
Department of Pathology,
Edendale Hospital
Pietermaritzburg, Natal J D WOODS
W LAURIE

PRIMARY HEPATIC CARCINOMA

SIR,—In your annotation of April 6 you claim that the incidence of primary carcinoma of the liver, judged by necropsy findings, has increased distinctly in recent years In support of this statement figures from the Mayo Clinic are quoted—to wit, in 1926 the frequency was 0 083% of 5976 necropsies, contrasted with the finding in 1947 of 0 19% of 16,303 necropsies

Applying the χ^2 test to the incidence-rates and the number of necropsies it can be shown that the absence of a real difference between the given rates of 1926 and 1947 has a probability of more than 7% In addition, the true incidence of a disease cannot be properly represented by necropsy material Therefore, it appears that the quoted figures do not justify the conclusion that the incidence of primary carcinoma of the liver has increased

Veterans Administration Hospital
Swannanoa N C U S A OSCAR KANNER

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[1] S Afr med J 1957 21 352
[2] Becker B J P S Afr J med Sci 1946 11 97

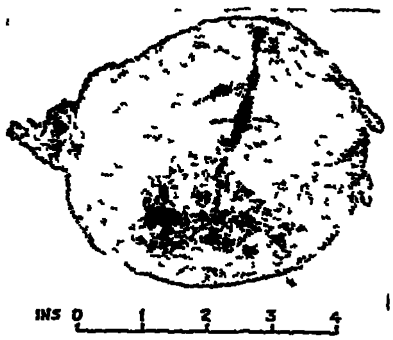
RUPTURE OF THE PREGNANT UTERUS

SIR,—Mr Higgins (March 23) has called attention to rupture of the pregnant uterus resulting from previous curettage, a condition which is probably more common than would appear from the literature Curettage is commonly done by junior residents—often people holding their first gynæcological appointment—and it is important that this hazard be more widely recognised

I should like, for this reason, to report the following two cases

CASE 1 —A pregnant woman aged 37 had had seven full-term pregnancies with easy, spontaneous deliveries, and five miscarriages, the last in July, 1951 This miscarriage was apparently accompanied by considerable bleeding even after evacuation, and she was taken back to the operating-theatre, where an adherent piece of placenta was removed from the fundus with ovum forceps, with considerable difficulty

Four months later she became pregnant again, had an uneventful antenatal period, and was admitted at term in very early labour The history of the difficult evacuation was unknown at that time On examining this patient during a night round (done merely as some insurance against being called after returning home from an emergency, and not because any abnormality had been reported) I found a soft cystic swelling at the fundus of the uterus, judged to be the size of half a tennis ball, though the major part of the swelling seemed to be behind the xiphisternum The swelling was neither painful nor tender During a uterine contraction the swelling remained soft, but appeared to bulge slightly Uterine rupture was diagnosed Although the notes of the previous curettage were not at that time available, it was considered to be a likely ætiological factor



Uterus in case 1, showing large rupture at fundus Stitched incision is site of cæsarean section

The patient was in excellent condition and an immediate laparotomy was performed The placenta was being extruded through a hole, three inches in diameter, in the fundus of the uterus (see figure) There was a small amount of clot around the hole, but no free blood in the peritoneal cavity Satisfactory repair was unlikely, so a cæsarean section followed by hysterectomy was done The baby weighed 8 lb 6 oz and was vigorous from birth, and the mother had an uneventful puerperium

CASE 2 —A woman aged 37, para 3, had a normal home confinement at term in March, 1951 She was admitted to hospital two weeks later with a severe secondary postpartum hæmorrhage She looked exsanguinated and very shocked A blood transfusion was given and the uterus evacuated During the evacuation the curette was felt to pass through the fundus, and I was asked to see her Exploration of the uterus revealed a hole that would admit one finger At laparotomy there was a moderate amount of free blood in the abdomen and a small hole in the fundus of the uterus, the edges of which were bleeding There was no damage to other organs The hole was repaired with figure of eight sutures and the patient recovered uneventfully

She became pregnant again eighteen months later The antenatal course was uneventful until term, when she complained of considerable pain and tenderness in the fundus of the uterus at the site of the previous rupture There were no clinical signs of rupture other than the tenderness, but, as she was in considerable pain and very apprehensive, imminent rupture was suspected and a laparotomy was performed

The surface of the *fundus* was intact A lower segment cæsarean section was done A small area of the placenta was adherent over the site of the scar, which was slightly thinner than the rest of the fundus, but there was no evidence of impending rupture, of retroplacental hæmorrhage, or of anything else to account for her symptoms The baby was vigorous and the mother had an uneventful convalescence

The first patient, who had a large rupture, and who had not been given warning of the importance of hospital confinement following damage at curettage, was completely without symptoms Had the swelling on the fundus not been fortuitously discovered, there would have been a catastrophe In case 2 the uterus was intact, yet the patient had symptoms and a previous history which indicated laparotomy

From these cases, and the few others that have been published, it can be seen that many more cases will have to be recorded before we can assess the dangers of uterine damage resulting from curettage or draw the picture of impending and early rupture in pregnancies after such damage

Dudley Road Hospital,
Birmingham
EDWARD COPE

ANÆSTHESIA FOR FRACTURES OF THE FEMORAL NECK

SIR,—Referring to an article on Fractures of the Femoral Neck by Dr Murray and Mr Young (March 23), Dr Rollason (May 4) writes "In my experience it is unnecessary to raise the blood-pressure preoperatively or during operation in those patients who have had chlorpromazine as part of their premedication" I am sure that Dr Rollason is absolutely right, but in my experience it is unnecessary to complicate the anæsthetic by the addition of chlorpromazine

I had a "run" of fractures of the neck of femur between Feb 25 and March 6, all in women (1) aged 87, Capener nail plate, (2) aged 86, McKee nail plate, (3) aged 78, Smith-Peterson nail, (4) aged 69, McKee nail plate, (5) aged 91, Capener nail-plate, (6) aged 85, McKee nail plate, (7) aged 86, McKee nail plate All were premedicated with morphine and atropine one and a half hours before operation and two ampoules of 'Adrenoxyl' (1 5 mg) half an hour later

Anæsthesia was induced by a sleep dose of hexobarbitone and 60 mg suxamethonium bromide, and was maintained on nitrous oxide 8 litres and oxygen 2 litres per minute endotracheally, further suxamethonium bromide being given if the patient showed any signs of reflex movement

None of these patients had any infusions or transfusions, all recovered and are alive and well except no 4, who fell forwards over her knitting on the fourth day and died of a coronary thrombosis, they were all able to take nourishment by mouth on the day of operation, and read their newspapers the next day The blood-loss during operation was minimal owing to the adrenoxyl, which reduces the bleeding time and increases the capillary resistance, and by conserving the patient's blood abolishes the need for transfusions

This appears to me to be the ideal anæsthetic for major cases, and the addition of further drugs tends only to complicate the issue Incidentally if the adrenoxyl is not given in good time it can be given immediately before operation mixed with hyaluronidase

Amersham Bucks
J SHEGOG RUDDELL

RELATIVES IN HOSPITAL

SIR,—I was delighted to read your excellent article of May 11, which deals with an aspect of hospital medical work to which indeed scant attention is being paid

I think it can be claimed that a not unsuccessful attempt to deal with the many aspects of the problem has been made in the pædiatric sphere It is in relation to the adult patient that our failure is so grossly evident I think that you make one mistake and also that you omit to make one vital point

Firstly the mistake The wisdom and humanity needed to deal with the various anxieties and sorrows resulting from illness are not to be taught to young men at a university To attempt to do so could only encourage their seniors to continue the common and highly criticisable habit of deputing such duties to them

The omission If we are honest we will admit that for relatives in trouble there is only one man—that is, the doctor in charge of the patient, usually a consultant Any junior doctor at all is only second best Apparently, and in general, the modern hospital consultant does not think that care for relatives is part of his obligation—either to superintend or organise such care, or to take part in giving it himself in outstanding cases I think it is also very probable that regional hospital boards would hesitate before providing time for them to do such work I think, therefore, that you omit to point out the serious ethical lapse which we have allowed to grow, in treating a vital part of our obligation as an unimportant matter to be left to juniors

Until this is remedied—that is, until it is acknowledged much more generally that the care of patients' relatives is work of the highest importance requiring all the skill and experience and more, of which the best of us is capable—we may expect the press to carry complaining letters from perfectly decent people who feel that they are not being properly treated

Leasowe Children's Hospital,
Moreton Cheshire
J K CAMERON

L-NORADRENALINE THERAPY IN ACUTE RENAL FAILURE

SIR,—In his extremely practical article (May 11), Dr Mattingly has drawn attention to the value of vigorous noradrenaline therapy in hypotensive states complicated by acute renal failure He rightly emphasises with the help of a dosage chart, the need for using high concentrations of the drug, far in excess of those often recommended Therapeutic failures, when lower concentrations are used, lead to unjustifiable censure of this drug's capacity to restore the normotensive state The risk of tissue necrosis at the infusion site (to which Dr Mattingly also refers) appears to be considerably reduced by the use of local phentolamine as an antidote[1]

It would be convenient if the manufacturers would provide ampoules containing 16 mg and 32 mg of noradrenaline, for use where high concentrations are needed It would not then be necessary to open eight 4 mg ampoules and inject their separate contents into a 500 ml infusion bottle, each time a fresh one was needed In a case I reported,[2] *200 ampoules had to be opened*

Finally, in support of Dr Mattingly's experiences with acute renal failure, may I report 2 similar cases, which bore a striking resemblance to each other in *many* respects ?

Both patients were men, admitted within four days of each other, with a history of recurrent syncopal attacks and precordial pain of recent onset, in both cases the electrocardiogram on admission showed evidence of acute posterior myocardial infarction, with a pulse rate of about 46 a minute and nodal rhythm, both were shocked, with systolic blood pressures averaging 80–90 mm Hg, and in both, severe oliguria and uræmia developed

The 1st patient was completely anuric for twenty four hours after admission Noradrenaline was then started in conjunction with the régime of Bull et al[3] His output of urine gradually rose to normal over a period of a week, noradrenaline being needed the whole time to maintain his blood pressure, though in quantities not exceeding 8 mg *per* litre of infusion His blood urea reached a maximum of 262 mg per 100 ml on the fourth day after admission The 2nd patient passed only 90 ml of urine during the second twenty four period after admission, and a noradrenaline infusion was started and continued for four days (maximum strength 12 mg per litre) His urinary output reached normal about the fourth day, though his blood urea continued to rise to 198 mg per 100 ml on the fifth day after admission A further rise to 289 mg per 100 ml on the seventh day was thought to be due to melæna, which complicated his anticoagulant therapy Both patients were eventually discharged with normal renal function

Llanelly, Carmarthenshire
J DE SWIFT

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1 Zucker G *J Amer med Ass* 1957 163, 1477
2 de Swiet, J *Brit med J* 1955, ii 1253
3 Bull G M, Joekes, A M, Lowe, K G *Lancet*, 1949, ii, 229

CORTISONE AND IMMUNITY IN TUBERCULOSIS

SIR,—In your annotation of May 4 you state " these findings [i e , from animal experiments] also explain the lack of interference by cortisone with the efficacy of B C G vaccination In short, cortisone does not seem to impair acquired resistance in guineapigs "

Possibly, a few investigations carried out with another species—namely, the mouse—are of some relevance here This animal, by contrast with the guineapig, is virtually anergic towards tuberculin By prior vaccination with viable B C G given intravenously it can nevertheless be protected against a virulent laboratory infection, either by *Mycobacterium tuberculosis* var *hominis* systemically [1] or *M tuberculosis* var *bovis* intracorneally [2] Using the latter technique, it was found that the subcutaneous administration of cortisone acetate at the rate of 0 5 mg daily for 28 days, this period beginning with the corneal inoculation, resulted in a complete loss of that protection otherwise to be expected [3] Indeed, the corneal lesions in the cortisone-treated, vaccinated animals tended to be more severe than in unvaccinated controls

Mice are naturally endowed with some resistance towards tuberculous infections The experimental corneal disease, for instance, normally remains confined to the eye Yet, as Naguib and Robson [4] have shown, the giving of cortisone following inoculation leads to more rapid progress of the ocular lesion and, significantly, to systemic spread of the infection as well

Now that cortisone is being given much more readily to patients with tuberculous disease we must hope that, as humans, we have more in common with the guineapig in this respect and less with the mouse Otherwise, it seems, the "best-laid schemes of mice and men" will surely " gang aft a gley "

London, S E 1 **ROY GOULDING**

CÆSAREAN SECTION

SIR,—I know of a maternity hospital with slightly over 1000 annual admissions whose cæsarean section incidence in 1955 was 9 5%, nearly equal to the forceps rate, and in 1956 was 11%, slightly in excess of the forceps rate If similar situations exist in other parts of the country, and a prominent member of the Royal College of Midwives tells me that they do, then your leading article on cæsarean section (April 6) is opportune

The maternal mortality of 0 99% following cæsarean section reported by Marshall and Cox [5] for the years 1943–47, was more than 18 times as high as the maternal mortality (excluding abortions) for this country in 1955 (0 54 per 1000) It may benefit surgically minded obstetricians to reflect that if they lose only one mother in their first 183 cæsarean sections, their maternal mortality for sections will nevertheless be exactly 10 times higher than the latest published maternal mortality for the country

Professor Baird (April 27) says it is fortunate that cæsarean section is seldom indicated in young women, because it is prejudicial to further childbearing , but this seems to be a minor consideration with older women because " few primigravidæ over 30 years of age have a second child " In case others share this false belief, I offer the following information A few years ago in our practice, I questioned 1000 women regarding their pregnancies 133 did not have a child before the age of 30 Of these 133 mothers, 17 out of 32 who began to have children at thirty, had further offspring At later ages the figures were as follows

9 out of 19 who began at thirty-one
10 out of 18 who began at thirty-two
9 out of 18 who began at thirty-three
5 out of 12 who began at thirty-four
6 out of 13 who began at thirty-five
3 out of 7 who began at thirty six
2 out of 3 who began at thirty seven
2 out of 4 who began at thirty eight
2 out of 2 who began at thirty nine

2 of the women who began at thirty-six years of age had 4 children apiece Of older women, 2 who began their family at forty, 2 who began at 41, and 1 who began at 43 did not have further offspring Nevertheless, out of the total of 133 primiparæ who were 30 years or over, 65 or 48 9% did have two or more children

The forceps incidence in primiparæ rises progressively with age, but the steady deterioration of uterine function, which occurs after 25, according to Professor Baird, is essentially a primiparous condition As only 7% of secundiparæ who required forceps in their first confinement, require them again,[6] the defect in uterine function is apparently remedied by one vaginal delivery On the other hand, cæsarean section is likely to maintain this uterine dysfunction, and to ensure the need for a repeat cæsarean section in any mother over thirty, who is courageous enough to risk another pregnancy

Reading **K D SALZMANN**

CLINICAL THERMOMETERS

SIR,—Your correspondents need only look in the late Prof Samson Wright's *Applied Physiology* to find an explanation of the term " half-minute " on clinical thermometers In a footnote on p 468 he states that a half-minute is the standard time taken for the thermometer to reach equilibrium under standard conditions These not being applicable in the human body a longer period of time is necessary to reach equilibrium and accurately record the body temperature

No doubt if the thermometer were placed in blood it would reach the temperature in the requisite half-minute

London E 9 **T SUSSMAN**

SURGEON'S " PRIVILEGE "

SIR,—" A cup of tea for the doctor " was traditional long before tea-breaks became one of the greatest hindrances to industrial production in this country In cottage, council house, and castle a cup of tea was the inevitable termination of any medical rite, a privilege both to offer and receive May I add a little detail to the general terms of the letters from Mr Capener (May 4) and Miss Judge (May 11) ?

When we first heard that we had to pay, I took with me a flask of tea and a bun on those afternoons when I had long outpatient clinics Later, when a nominal charge of *1d* for a cup of tea was imposed, my wife rebelled at preparing the flask two or three times weekly I protested that " it was the principle I objected to,' but I was told that to pay *only 1d* for a cup of tea was the best bargain I should ever obtain from the National Health Service, and I had to submit

I have now a collection of receipts for *2d* upwards, including one for *6d* the account for which was sent to me by post and forwarded because I was on holiday I could not resist paying it by return of post and by postal order

At last it was realised that the book keeping was not worth the trouble, and now to satisfy the auditors a token payment of *2s 6d* a year is made for all liquid refreshments This is an even better bargain, but still ridiculous

Harrogate **T. G REAH**

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[1] Dubos R J Pierce C H Schaefer W B *J exp Med* 1953 97 207
[2] Goulding R Thesis University of London 1956
[3] Goulding R *Tubercle* (in the press)
[4] Naguib M Robson J M *Brit J Pharmacol* 1955 10, 387
[5] Marshall C M Cox L W Transactions of the 12th British Congress of Obstetrics and Gynæcology 1949 p 30
[6] Salzmann, K D *Brit med J* 1955 ii 17

PRIVATE PRACTICE GROUP

SIR,—Last summer a number of private practitioners, intent on preserving and extending the institution of private practice, met in London They decided to make themselves the nucleus of what they hoped would become a substantial group, and deputed to an acting executive the task of encouraging its growth

All known private practitioners in Great Britain were approached, many responded with enthusiasm and these now form, with the original nucleus, a Private Practice Group

The Group believes that on the continuance and prosperity of private practice must depend, to a great extent, the well-being of the profession and the quality of medical service rendered to the whole body of citizens, whether through private or public channels It further believes that, unless those in private practice defend its interests and speak up for it, no one else will, and doctor and citizen may one day wake to find they have lost by default one of those precious "free institutions"—that of seeking and giving medical advice and help privately, without the participation of the State

The Group's immediate aims are

1 To press for the right of private patients to receive drugs on the same terms as patients treated under the National Health Service

2 To consider again the possibility of "opting out"

3 To press for more, and less costly, private beds

4 To inquire into and, it is hoped, to promote insurance schemes to cover general medical attention

These aims are intended to supplement, but in no way to conflict with, those of the profession as a whole

It is obvious that the Group would not exist unless its members felt that private practice had become something of a Cinderella It has no wish to be or become a "splinter group," and it is approaching the organisation committee of the B M A with a view to receiving recognition

Meanwhile, the Group desires to increase its membership from among those who believe and have an interest in private practice, although, as general practitioners or consultants, they work also in the National Health Service

There is no subscription, but secretarial expenses have so far been met by donations of a half to one guinea by members

The members of the Acting Executive are L W Batten (acting president), I J Brock (acting treasurer), A E J Etheridge (acting secretary), 73, Fitzjohn's Avenue, London, N W 3, and W Russell

London, N W 3 JOHN ETHERIDGE

PREVENTION OF BEDSORES IN PATIENTS NURSED AT HOME

SIR,—As the geriatric services develop, skilled home care for the aged becomes increasingly important Bateman[1] described a new régime for the prevention of bedsores in the elderly bedridden patient in hospital he concluded that the new method was at least as effective as the old, and that much labour and time was saved I decided to instruct one district nurse in the new technique, and encourage general practitioners and the nurse to select suitable cases for a controlled trial

A letter was sent to each practitioner in the selected area, inviting his cooperation The district nurse was then requested to contact the practitioner, to find out if he agreed to the patient being included in the trial When he agreed, the procedure was as follows

A silicone barrier cream was smeared thinly and evenly on all the pressure points twice daily for a week and then once daily

The skin was washed with soap and water as infrequently as possible Once or twice a week, or when they became fouled, the pressure points were washed with warm water only, and carefully dried

The patient was urged to change his position in bed at least five times daily

As additional measures, the family doctor was asked to prescribe ascorbic acid 50 mg t d s and tolazoline 25 mg t d s The latter, besides being a cardiac stimulant, dilates peripheral blood vessels and thus improves the blood supply of the skin

23 patients were thus treated Most were elderly, and many in poor general condition, but the results were very good (in some cases broken skin healed despite poor general condition)

Result	*No*	*Remarks*
Excellent	17	Condition of pressure points satisfactory throughout trial or improved
Fair	2	Condition of skin over pressure points improved, but bedsores developed later (1 patient would not take ascorbic acid and tolazoline because of vomiting, the other refused them)
Not assessed	4	2 died and 1 admitted to hospital within a few days of starting treatment, 1 refused to coöperate
Total	23	

The number of cases treated with silicone barrier cream in this survey is small and there are no controls, but the results are very satisfactory and it is proposed to introduce this method throughout the county with the cooperation of general practitioners The treatment not only saves a great deal of unnecessary suffering in bedfast patients but also reduces the time spent on the treatment of pressure-points and obviates the labour of treating patients by the usual method of washing and rubbing with spirit The three district nurses who have had experience of the new method praise it highly They also report that elderly patients who are free of bedsores show a quick improvement in their general condition

Dr Bateman emphasised that ascorbic acid and tolazoline are an integral part of the treatment This is supported by 2 cases in our own small survey in which improvement ceased when the patient did not take the tablets

Our sincere thanks are due to the general practitioners in the Rhyl area for their ready cooperation in this trial, and to the three district nurses for carrying out the trial and recording their findings

County Health Offices,
Mold, Flintshire

G W ROBERTS
F M WILLIAMS

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[1] Bateman I J A *Brit med J* 1956 i 554

RELEASE OF HISTAMINE IN URTICARIA PIGMENTOSA

SIR,—I was very interested in Dr Hamrin's preliminary communication (April 27) and in Dr Calnan's letter (May 11)

In studying a series of cases of urticaria I have found that, although true allergy to salicylates leading to urticaria occurs, in addition it is not uncommon to find that salicylates will affect the degree of an existing chronic urticaria This is usually seen when the patient takes acetylsalicylic acid as an analgesic, but in these cases the same effect can be obtained by giving sodium salicylate The response depends on the dose of salicylate and on the degree of urticaria at the time of administration Thus in a patient with chronic urticaria acetylsalicylic acid gr 5 may produce an exacerbation but have no effect at a later stage when the urticaria is in a milder phase Similarly, a patient showing no response to gr 5 may get an exacerbation when the dose is increased to gr 20 As suggested by Dr Hamrin and Dr Calnan, it seem possible that salicylate acts in such cases by liberating histamine

I hope to report further findings later

Bristol ROBERT P WARIN

Medicine and the Law

A Capital Murder

THE new defence of diminished responsibility under section 2 of the Homicide Act, 1957, was first raised at the trial of Shirley Campbell at Leeds Assizes last month In that case the defence succeeded, the accused being found not guilty of murder but guilty of manslaughter as required by section 2 [1]

The defence was raised again—this time unsuccessfully—at the trial at Newcastle last week of Ronald Patrick Dunbar, a labourer aged 24, on the charge of the capital murder of an 82-year-old widow and unlicensed moneylender [2] It appeared from Dunbar's own statements that he had broken into the woman's house, for the second time within a week, to rob her, and that he killed her with blows of a bottle on the head when she woke and, he thought, recognised him

Called as a witness for the defence, Dr. Robert Orton, a consultant psychiatrist, said that Dunbar was an inadequate psychopath This view was not accepted by Dr Ian Pickering, senior medical officer at Durham Prison, who was called by the prosecution. In his opinion, the accused was not a psychopath, he had an intelligence quotient of 112

In reply to cross-examination, Dr Pickering said that there were variations in the type of psychopathy but not in degree Psychopathy was an abnormality of personality which could be regarded as an abnormality of mind and could impair mental responsibility Dr Pickering agreed that, if a man were rightly said to be a psychopath, the only remaining question would be whether the abnormality of the mind would substantially impair his mental responsibility for the act in question.

Dr Pickering told the judge that he would expect a psychopath to show remorse This man had not, unless giving himself up to the police was a sign of remorse

Dealing with the effect of section 2 of the Homicide Act, the judge told the jury that it had not been put into the Act as a soft option If the case came within section 2, the jury would say so If it did not, they would not return a verdict within the section merely because the alternative was something somewhat grim

The jury returned a verdict of guilty of *capital murder*—the new term for those categories of murder still punishable by death—and Dunbar was sentenced accordingly The case may serve as a reminder that, if the section is pleaded, the onus of proof is on the defence

Death after Adder-bite

A boy of 14 collapsed and died a few minutes after he had been given serum as treatment for an adder-bite At the inquest last week,[3] a pathologist gave the cause of death as cardiorespiratory failure due to anaphylactic shock following snake bite treatment, and he added that " if the serum were not given at the earliest possible moment, it would have been nothing short of criminal neglect " The coroner, recording a verdict of death by misadventure, said that every step had been taken and it was very unfortunate that the condition arose which caused the boy's death The evidence indicated that nothing had been left undone which could have avoided the ultimate result After the boy collapsed oxygen was given and the heart was massaged After starting to beat again, the heart gradually stopped and further efforts to stimulate it were unsuccessful.

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[1] See *Lancet* May 4 1957, p 938
[2] *Times* May 17 1957
[3] *Ibid* May 18, 1957

Obituary

WALTER PERCEVAL YETTS

C B E , D Lit Lond , M.R C.S.

Dr Yetts, who died on May 14 held the chair of Chinese art and archæology in the University of London and he will be remembered chiefly for his work on these subjects But his work as a doctor should not be forgotten, for he served efficiently for many years in the Royal Navy and at the Ministry of Health

He was born at Reading in 1878, the son of A M Yetts, and was educated at Bradfield College and Lausanne University He qualified in 1903 from St. Bartholomew's Hospital, and the same year entered the Royal Naval Medical Service In 1904 he was Admiralty gold medallist for naval hygiene. His visits to Chinese ports aroused his interest in Chinese art and he learned the Chinese language before he retired from the service in 1912 with the rank of staff surgeon In 1913 he was appointed acting medical officer to the British legation in Peking, and in the 1914–18 war he served in the R A M C as temporary major and deputy assistant director of medical services Embarkation After a year as deputy commissioner of medical services at the Ministry of Pensions, he was appointed, in 1920, a medical officer of the Ministry of Health, where he worked in the section dealing with sanitary administration in relation to infectious diseases

In 1927 he resigned from the Ministry to give all his time to teaching lecturing, and writing on Chinese art. His distinction in this field was recognised by his appointment in 1930 to the newly founded lectureship on Chinese art and archæology at the School of Oriental Studies in the University of London Two years later he became professor of Chinese art and archæology He occupied the chair until 1946 when he retired with the title of professor emeritus He was the first to make Chinese archæology a subject of academic study with organised courses for postgraduate degrees and diplomas

As a sinologist Yetts won many distinctions He was awarded the D LIT of London University in 1934; he was a vice-president of the Royal Asiatic Society, chairman of the China Society, corresponding member of the Vereeniging van Vrienden der Aziatische Kunst (The Hague), and honorary correspondent of the National Library of Peiping (Peking) His contributions to the literature of his subject were important His book on *Chinese Bronzes* was published in 1925, and he was also the author of six volumes in the *Eumorfopoulos Collection Catalogue* and of *Ritual Bronzes of Ancient China* (1936) His books and articles were illustrated by beautiful drawings and reproductions of inscriptions and were notable for their comprehensive bibliographies.

A S MacN writes

Yetts was a pleasant colleague, somewhat reserved in manner, and with no great liking for the restrictions of a Government office, although he performed his duties conscientiously and well His knowledge of Chinese was a great asset He was often consulted on international health work relating to China and always chosen to escort distinguished Chinese medical visitors in their tours of English hospitals and health centres But his real interest lay in Chinese art, especially in the bronzes and jade of the prehistoric period His years of retirement were spent at Chesham Bois, Bucks where he was always glad to welcome old students friends and former colleagues His chief recreation was painting in water-colours a taste which he shared with his wife, an accomplished artist

Professor Yetts married in 1912 Gwendoline Mary, daughter of the late Mr D Hughes, F.R.C S

HAROLD GUYON TRIMBLE

M D

Dr H G Trimble, associate professor of clinical medicine at Stanford University, California died on May 13 at the age of 60. He had recently been elected to the board of regents of the American College of Chest Physicians and was head of the board of examiners for its fellowship He was a member of the National Tuberculosis Association and the American Trudeau Society and he was chairman of the research committee of the California Medical Association He had come to Europe regularly since 1950 and each year had spent some time in this country attending conferences and visiting institutions and clinics for diseases of the chest. In 1954 he was awarded the Varrier Jones gold medal and he gave a lecture in London on a statistical analysis of the present-day treatment of pulmonary tuberculosis He addressed the British Tuberculosis Association in Bristol last year on pneumoperitoneum therapy

Two of his English colleagues, C W L J and M M N, write

Harold Guyon Trimble enriched the lives of all those with whom he came in contact His kindly bearing and his readiness to help were well known among his many friends all over the world and in this country in particular He was only this week to have been elected as honorary life member of the British Tuberculosis Association in addition to his vice presidency of the South East Metropolitan Tuberculosis Society The mode of his death—he was shot by a patient near his consulting room—adds to the tragedy of his passing His reputation as a physician and as a man of deep knowledge and interest in his subject had spread far from his home country, and his reputation in Europe and in the Far East was one of great scholarship and humanity

Diary of the Week

MAY 26 TO JUNE 1

Monday, 27th

ST MARY'S HOSPITAL MEDICAL SCHOOL, Paddington, W 2
5 P M Dr S Udenfriend (Bethesda U S A) Clinical Studies Relating to Tryptophan Metabolism
INSTITUTE OF PSYCHIATRY
5 30 P M (Maudsley Hospital, Denmark Hill, S E 5) Prof H G K Weston Brink (Utrecht) Some Investigations Concerning Vitamin B_1 with special reference to Brain
MANCHESTER MEDICAL SOCIETY
9 P M (Medical School, University of Manchester) *General Practice* Dr H S Barber Management of Arthritis in the Home and in Hospital

Tuesday, 28th

ROYAL COLLEGE OF PHYSICIANS OF LONDON Pall Mall East, S W 1
5 P M Dr F P Lee Lander Rest and Pulmonary Tuberculosis (Mitchell lecture)
ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, W C 2
5 P M Mr R T Turner Warwick Lymphatics of the Breast in Relation to the Spread of Carcinoma and its Treatment (Hunterian lecture)
ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W 1
8 P M *Medicine* Dr M C G Israëls Dr Rosemary Biggs, Prof J V Dacie Some Blood Disorders
UNIVERSITY COLLEGE LONDON Gower Street, W C 1
5 15 P M Prof P Balint (Budapest) Nervous Regulation of Renal Function
INSTITUTE OF DERMATOLOGY *Lisle Street, W C 2*
5 30 P M Prof C A Keele Cutaneous Pain and Itch
ROYAL STATISTICAL SOCIETY
5 30 P M (Westminster Medical School Horseferry Road S W 1) *Medical section* Dr J H Edwards Some Aspects of *Cigarette Poisoning*

Wednesday, 29th

INSTITUTE OF DERMATOLOGY
[illegible] 30 P M Dr R W Riddell Differential Diagnosis of Fungous Infections of the Skin
INSTITUTE OF DISEASES OF THE CHEST, Brompton S W 3
5 P M Dr P D Arcy Hart Place of B C G Vaccination in an Established Tuberculosis Service
INSTITUTE OF NEUROLOGY National Hospital Queen Square, W C 1
5 30 P M Prof G Schaltenbrand (Würzburg) Myographic Analysis of Spasticity and Rigidity

Thursday, 30th

ST MARY'S HOSPITAL MEDICAL SCHOOL
5 P M Dr Udenfriend Metabolism of Phenylalanine, Tyrosine, and Adrenalin
GUY'S HOSPITAL MEDICAL SCHOOL London Bridge, S E 1
5 P M Dr William Evans Conditions that Mimic Heart disease (Carbutt memorial lecture)
INSTITUTE OF DERMATOLOGY
5 30 P M Dr H J Wallace Skin Diseases of the Vulva
HONYMAN GILLESPIE LECTURE
[illegible] P M (University New Buildings Teviot Place Edinburgh) Mr J A C Fleming Radiation Injuries in Clinical Practice
UNIVERSITY OF ST ANDREWS, Queen's College, Small's Wynd, Dundee
5 P M Prof Russell Fraser Diagnostic Procedures in Bone Disease

Friday, 31st

ROYAL SOCIETY OF MEDICINE
5 P M *Epidemiology and Preventive Medicine* Prof C H Stuart Harris Dr W Wood Dr J O H Tobin Dr John Knowelden Poliomyelitis Vaccination in 1956
ST MARY'S HOSPITAL MEDICAL SCHOOL
5 P M Prof W J Hamilton The Early Ovum
GUY'S HOSPITAL MEDICAL SCHOOL
5 P M Sir John Cockcroft F R S Atomic Energy and its Biological Implications (Eason lecture)
POSTGRADUATE MEDICAL SCHOOL OF LONDON Ducane Road W 12
10 A M Prof F A R Stammers Mechanical Factors in Post gastrectomy Complications and Syndromes
MEDICAL RESEARCH SOCIETY
5 30 P M (London School of Hygiene Keppel Street W C 1) Dr Stanley F Bradley (Columbia University) Circulatory Adjustments to Postural Changes

Notes and News

UNIVERSITY APARTHEID

WE have lately discussed the intention of the government of the Union of South Africa to take over the Durban medical school from Natal University [1] In a second report [2] Prof I Gordon, dean of the medical school, sets out subsequent developments

Although a technical difficulty in the Union Parliament has delayed that part of the Separate University Education Bill which deals with the separation of the Durban medical school from the University of Natal, there is no change in the intentions of the government The medical school will be dealt with in due course The Bill as first published provides for the establishment of "Bantu" and "non White" university colleges, from which the Durban medical school is in no effect distinguished In these colleges the minister of education will have the right both to limit numbers and to reject candidates for admission The minister has the power to appoint, promote, transfer, or discharge any member of the staff, this power may be exercised by any deputed officer of his department for posts designated by the minister In the interests of economy and efficiency he may discharge any member of the permanent staff The council for each college will be appointed by the governor general, the principal and the senate by the minister At the recommendation of the secretary of his department, the minister may punish misconduct by reprimand, by imposing fines up to £100, by reduction of salary and of grade, or by discharge from the service Such penalties may be applied to misconduct committed before the staff member, through this Act, became a servant of the State department Misconduct includes adverse public comment on the administration of any government or provincial department It is misconduct "to propagate any idea or take part in or identify himself with any propaganda or activity or act in a manner calculated (i) to cause or promote antagonism amongst any section of the population of the Union against any other section of the population of the Union, or (ii) to impede, obstruct, or undermine the activities of any Government department" As Professor Gordon pointed out to the minister, such a provision would place the staff at the mercy of any official who chose to interpret teaching on the social origins of disease as calculated to cause racial antagonism (For example, in the African widespread malnutrition contributes to a high incidence of cirrhosis of the liver, and the migratory labour system and poor living conditions to the prevalence of tuberculosis and syphilis, these diseases are far less common among the more fortunately placed Europeans)

In the face of this, by secret ballot 29 of the 31 full time members of the medical school staff indicated that they would resign when the Bill was enacted, while all 26 of the part time staff able to attend a meeting stated that in this event they also could not continue teaching This unrest was to some extent expressed by a deputation from the South African Medical and Dental Council to the minister The minister seemed unable to recognise any ground for anxiety or protest, and indeed he thought it the duty of the dean "to lead the staff towards a realisation of their responsibilities to the government and the country" As the medical school was heavily subsidised by the State, he thought the government was entitled to have a large say in its control He said that there was no intention of changing the status of staff, who would remain professors and lecturers There would be no reduction in salary, and he could not understand why the staff felt that they would lose prestige if they became Civil Servants Fears about the provisions for discipline were groundless—the staff would have "to deal with reasonable men who would act with justice, in all circumstances"

Despite these assurances, vigorous protest has been made not only in Durban, but by departmental heads in the Cape Town medical faculty, and by the Students Medical Council and the Medical Graduates Association of the Witwatersrand University The federal council of the South African Medical Association has expressed its grave concern Twenty six heads of departments in British medical schools wrote jointly to applaud the vigorous opposition to the threat to academic liberty and freedom of thought

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[1] *Lancet* March 30 1957 p 675

[2] Further report on the government's intended action to remove the *faculty of medicine from the University of Natal*, with Preface by Prof I Gordon. Durban Medical School May 4, 1957

As yet there has been no shift in government policy, and the academic staff at a meeting on May 2 steadfastly resolved that they can give no assurances about retaining their posts, "because we believe that we will be unable to carry out our academic and professional work and fulfil our responsibilities to our students under the conditions which will be established for the higher education of African, Indian, and Coloured persons when the Separate University Education Bill of 1957 is enacted."

CONGRESS IN RUMANIA

From May 5 to 11 a National Congress of Medical Sciences of the Rumanian People's Republic was held at Bucharest. The invitation of delegates from all over the world gave the conference an international flavour. Twenty-seven countries were represented, and the British participants were Dr F. Dudley Hart, Dr B. H. Kirman, Dr A. MacPherson, Dr Bernard Schlesinger, Mr P. G. Shute, and Dr Denis Williams.

Prof. C. I. Parhon, the 84-year-old honorary president of the R.P.R. Academy, and formerly President of the Republic, opened the proceedings. The congress was divided into four sections devoted to physiological, rheumatic, neurological, and epidemiological problems. It soon became apparent that acute rheumatism in childhood is still prevalent in Rumania, but on the whole it is milder than the type which was so common in England in the past. Infective hepatitis is also widespread at the moment. On the other hand it seems that malaria has been virtually eradicated—an achievement which must cause considerable satisfaction to Mr Shute, whose researches in Rumania before the war played no small part in it. In the section of neurology stress was laid on conditioned reflexes and on endocrinological factors. The Bucharest Institute for Endocrinology is a pioneer in this field.

The conference was valuable in enabling medical men from all over the world to pool their ideas, but even more so in bringing them together. In commenting on it one of the British party says: "To be able to discuss China and England with a professor from Peking who had never heard of the National Health Service, to walk back to the hotel with doctors from East and West Germany and obtain an idea of their respective views and ways of life, and to compare medicine in England and Rumania with the colleagues we met—all this helped us to step over the dividing frontiers. Preconceived ideas begin to waver and a way is laid along the precipitous path towards international friendship and peace."

BRITISH EMPIRE CANCER CAMPAIGN'S RESEARCH UNIT IN RADIOBIOLOGY

In 1954 the British Empire Cancer Campaign received a donation of £25,000 to provide additional laboratories for the study of the effects of X rays and other ionising radiations on living cells, and the new laboratories were opened at the Mount Vernon Hospital, Northwood, by the Duke of Devonshire on May 20. The research unit in radiobiology which will work there is under the direction of Mr L. H. Gray, PH.D., formerly senior physicist to the Mount Vernon Hospital. The other permanent members of the team are Mr J. W. Boag, D.SC., Mr D. L. Dewey, PH.D., Alma Howard, PH.D., and Dr O. C. A. Scott. At the moment five other scientists from abroad—2 from the United States, 2 from Canada, and 1 from New Zealand—are working at the unit.

Answers to the fundamental problems concerning the action of radiation on living cells are urgently needed, and knowledge is particularly scarce about the early stages of irradiation damage which precede the changes visible under the microscope. The new unit will focus its attention on these early stages, partly because they undoubtedly hold the key to an understanding of what follows and partly because it is at the very earliest stages that there is the best chance of controlling the nature and extent of the damage caused by radiation. One method of studying early effects is to deliver all the radiation energy to the cell in the shortest possible time and to measure the chemical changes which take place in the cell or in isolated cell components at the instant of irradiation and immediately afterwards. For this purpose the unit has an electron pulse generator designed by Metropolitan Vickers, which can deliver electrons in very intense bursts. Cells exposed to the beam from the generator can be given any desired amount of radiation, up to a limit exceeding anything previously attained in a single pulse lasting only about two millionths of a second. Special methods will be used to examine the changes in the cell during and after exposure by means of flashes of light also lasting only a few millionths of a second. These studies bear closely on the use of oxygen to increase the power of X rays in the treatment of malignant disease, since oxygen is believed to augment radiation damage by participating in chemical reactions of extremely short duration.

The new laboratories have been specially designed to meet the research requirements of the unit. A single-storey section of the building includes two rooms with thick concrete walls, one housing the electron pulse generator and the other a 200,000-volt X-ray apparatus. Both machines, as well as the analytical instruments which measure the changes in the cells, are operated from a control bay between the two rooms. Another two-storey part of the building contains laboratories and offices, and a large room which serves as library, staff room, and conference room. The laboratories, which have a total floor area of 5500 sq. ft., were designed by Messrs. Waterhouse and Ripley.

GUILD OF HEALTH

A conference of 21 doctors and 28 clergy was held at Hoddesdon, from April 29 to May 2, under the auspices of the guild. A study group considered coöperation between doctors and clergy, and reached these conclusions:

Individual doctors and clergy should continue to approach each other for spontaneous coöperation over problems of their daily work.

There is a need for informal discussion-groups of all engaged in work with the sick. Means should be developed for the exchange of opinion and information between all such groups and other bodies studying similar problems.

Local church communities should so develop themselves as to provide a healthy environment which will both tend to prevent breakdowns in health and to aid the rehabilitation of the recovering sick. The importance of this kind of development in "working communities" such as schools, large factories, hospitals, and universities must be noted.

Doctors have a responsibility to participate in this process both as individual members of the community and as possessing special experience of health problems and techniques.

Coöperation of doctors with the church community can be of particular value in preparation for the critical stages of development—e.g., for marriage, childbirth, and the young family, puberty, middle age, and old age.

People in transition from one stage of development to another or from sickness to health often need to be members of small groups within the larger framework of the community, and the development of such small groups to meet particular needs is to be encouraged.

It is necessary for clergy to have a better understanding of the medical approach to healing, and for doctors to have a better understanding of the spiritual significance of healing. Plans should therefore be discussed for providing medical study courses for the clergy, and theological study courses for doctors, at teaching-school level. Whether such training should be before or after graduation or both requires consideration.

B.M.A.'s SCOTTISH HEADQUARTERS

On May 14, Dr A. H. Hall, president of the British Medical Association, officially opened the reconstructed Scottish House of the association at 6–7, Drumsheugh Gardens, Edinburgh. The reconstruction was begun in 1954. The hall has been improved and enlarged and now provides handsome accommodation for over 300 for meetings of the association's Edinburgh division and other Edinburgh medical organisations, and for Scottish B.M.A. conferences. There is now a comfortable members' common room, a dining room where members and guests can have lunches and teas, and a reading room. The common room has a bar under a club licence. The office accommodation for B.M.A. staff has been virtually doubled, and the Medical Insurance Agency now has rooms on the third floor.

Dr Hall, in declaring the building open, traced the history of the association's premises in Edinburgh from the rooms in Rutland Square, rented in 1909, to the handsome new house. He forecast that the new and enlarged premises would enable the association to discharge better than ever before its duties in furthering scientific, educational, medico-political, and social activities.

University of London

Dr P. M. Daniel, senior lecturer at the Institute of Psychiatry and honorary consultant neuropathologist at the Maudsley and Bethlem Royal Hospitals, has been appointed to the university chair of neuropathology at the Institute.

Dr Daniel studied medicine at the University of Cambridge and at Charing Cross Hospital where he held the T. H. Huxley scholarship. After qualifying in 1942 he held house appointments at Charing Cross. Soon afterwards he was appointed senior research officer in the department of pathology at the Radcliffe Infirmary and he was one of the team which made a special study of the renal circulation and described what is familiarly known as the Oxford shunt. In 1948 he was awarded the John Hunter medal of the Royal College of Surgeons of England for his share in this research and for the discovery of afferent nerves and muscle spindles in the external ocular muscles He has done experimental work on the circulation through various organs, and also on various problems in neuropathology and comparative pathology including a study of scrapie in sheep which we published last October In 1949 Dr Daniel received from the University of Oxford the degree of M A and in 1955 the degree of D M He remained at Oxford until he took up his present appointment

On April 10 the following degrees were conferred

M D—J H Evans P K Thomas

University of Oxford

Our list (May 18) of recipients of the degree of D M should have included the name of R T Turner Warwick

University of Sheffield

The title of reader in social and industrial medicine has been conferred on Dr John Pemberton, at present senior lecturer in social and industrial medicine Mr J A Griffiths has been appointed part time instructor in anæsthetics, and Dr R E Church clinical teacher in dermatology

University of Colorado

Dr J D L Reinhold, assistant to the director of the department of child health at Guy's Hospital, London, has been appointed assistant professor of pediatrics in the university from July 1

British Association of Urological Surgeons

The annual meeting of this association will be held at the Royal College of Surgeons, Lincoln's Inn Fields, London, W C 2, from June 27 to 29

Beit Fellowships for Medical Research

The following elections have been made

Fourth year fellowships (£1000)

B T Donovan PH D Lond To study the hypothalamic mechanisms underlying the regulation of the onset of puberty and the mechanisms regulating the onset of œstrus, at the Institute of Psychiatry, Maudsley Hospital London

D S H W Nicol M A, M D Camb To continue his investigations of the chemistry and pharmacology of peptide fractions of insulin at the Dunn Institute of Biochemistry, University of Cambridge

Junior fellowships (£800 a year)

G A J Goodlad PH D Glasg To study the effect of the presence of a tumour on the protein metabolism of the host, at the department of biochemistry University of Glasgow

I Oswald, M A M B Camb For human electro encephalographic studies of the rôle of the emotional significance of conditioned stimuli in determining their arousal value during sleep and the mechanism of inhibition of responses to them, at the Institute of Experimental Psychology, Oxford

I C Roddie M B, B SC Belf To study the rôle of high and low pressure receptors of the vascular system in the regulation of the human circulation, at the department of physiology, Queen's University Belfast

S Varadarajan, M A Madras, PH D Camb For a comparative study of nucleotide metabolism in cancerous and normal tissue, at the department of radiotherapeutics, University of Cambridge

Pauline M Meadow, B A Oxfd PH D Lond To study the structure and mode of synthesis of bacterial cell walls, with special reference to their amino acid and amino sugar components, at the department of biochemistry, University College, London

Anglo-French Medical Bursaries

In the exchange with the Ciba Foundation, bursaries for 1937 have been awarded by the Institut National d'Hygiène to the following

Dr G A Collie Kohbabka (general practitioner Harlow) Dr F A L da Cunha (consultant obstetrician and gynæcologist Oldham and Ashton groups of hospitals), Dr R J T Gardiner (general practitioner Belfast) Dr T H Morgan (senior orthopædic registrar Nuffield Orthopædic Centre Oxford), Dr W R Probert (senior registrar thoracic surgery Sully Hospital) Dr J T Shepherd (reader in physiology Queen's University, Belfast), and Dr I McG Stewart (consultant physician Blackpool and Fylde hospitals)

More Blood-donors Wanted

On May 15, in launching a drive for over 100,000 new blood donors, Mr Dennis Vosper, the Minister of Health said that there were over 643,000 civilian donors in the National Blood Transfusion Service, but to meet developments in techniques an effective panel of 750,000 donors was needed Last year over 803,000 donations of blood were given—the largest figure ever recorded and an increase of 44,000 on 1955—and 120,000 new donors gave their blood for the first time Mr Vosper was speaking at a showing of a new film, *Blood Is Life*, which tells the story of the organisation of the service The film (two reels, running for 17 minutes) has been made by the Central Office of Information for the Ministry of Health It is intended for use in local recruitment campaigns

Anglo-French Meeting in London

A joint scientific meeting of the Royal College of Surgeons of England and the Académie de Chirurgie de Paris will be held from May 30 to June 1 at the college Papers and films will be presented by French surgeons, and the rest of the programme will be devoted to relaying by closed circuit television, in colour, surgical operations from the main theatre of St Bartholomew's Hospital to the great hall of the college This will be the first occasion in this country on which colour television has been used for a medical programme of this sort Attendance at the meetings on May 30 and 31 is by invitation, but, if seats are available, any doctor will be welcome at the meeting on Saturday, June 1, at 10 A M, when a Dupuytren's contracture will be operated on by Sir Archibald McIndoe and a cardiac operation performed under hypothermia by Sir Russell Brock Applications for seats should be sent in writing as soon as possible to the secretary of the college, Lincoln's Inn Fields, W C 2

Louis Rapkine Association

The second annual meeting of the British section of this association was held on May 6 under the chairmanship of Prof A V Hill, F R S The Abbé Breuil gave a talk on the cave paintings of Rouffignac in the Dordogne which was illustrated by slides showing some of the paintings and rock carvings of mammoths, horses, ibex, and rhinoceros found in the caves

The association was founded last year in memory of the French biochemist, Louis Rapkine Membership is open to British and French doctors and research workers in the biological sciences who have been awarded scholarships or bursaries to enable them to visit the other country Information about the association can be had from Dr G E Wolstenholme, Ciba Foundation, 41, Portland Place, London, W 1, or from Miss A M Vidal Hall, scientific office, French Embassy, 22, Wilton Crescent, S W 1

Faculty of Ophthalmologists

The following have been elected officers of this society for 1957–58

President Mr L H Savin, immediate past president, Dr John Marshall vice presidents Mr L G Mackie and Prof G I Scott hon treasurer, Mr A McKie Reid, hon secretary, Mr E F King

Islington Family Planning Clinic

A photograph of the late Dr Joan Malleson was unveiled at this clinic on May 22 Dr Malleson was one of those who helped to found the clinic in 1934, and as clinic consultant she was associated with its work until her death last year

Award for Malaria Research

At a sitting of the World Health Assembly on May 15, Dr Paul F Russell, of the Rockefeller Foundation, was awarded the Darling Foundation medal and prize for his work on the control of malaria

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Appointments

BOWEN, L W M B Lond D P M senior assistant psychiatrist Saxondale Hospital Radcliffe on Trent

FYNNE, MARGARET M B Dubl, D P H senior M O for mental health, Derbyshire

HAIGH, R D M B Leeds D P H, D OBST M O H and deputy principal school M O Bolton

HAMPSON, FRANK D M Oxfd consultant pathologist Reading area department of pathology

HANNAH R H, M B Edin F R C S E consultant neurosurgeon United Liverpool Hospitals

MCCULLOUGH ISABEL M L R C P I D C H, D OBST senior maternal and child welfare M O, Derbyshire

MCDONALD MARY G M B Aberd D P H M O, mobile clinic North Riding of Yorkshire

SERJEANT, J C B T D M B Edin F R C S senior casualty officer West Cumberland group of hospitals

Liverpool Regional Hospital Board

BURROWS M M M B Belf, F F A R C S, D A consultant anæsthetist St Catherine's Hospital Birkenhead

HOPKINS C A, M B Lpool, M R C P tuberculosis M O Liverpool and district eastern H M C area

LAMB W R, M B Dubl F R C S F F A R C S consultant anæsthetist St Helens and Warrington groups of hospitals

The Hospital for Sick Children Great Ormond Street London:

ABERDEEN, JOHN M B Melb, F R C S D C H senior surgical registrar thoracic unit

GARDNER D C M B Lond house-surgeon orthopædic and plastic departments

GUHA S K M B Calcutta resident registrar, ear, nose, and throat department

SCOTT J I M B Camb F R C S surgical registrar

WILSON F P M B Adelaide, D C H house physician

LEUKÆMIA *

RONALD BODLEY SCOTT
M A, D M Oxfd, F R C P
PHYSICIAN TO H M THE QUEEN, PHYSICIAN TO
ST BARTHOLOMEW'S HOSPITAL

CHRONIC MYELOID LEUKÆMIA

CHRONIC myeloid leukæmia is in many ways the most sharp cut of all the leukæmic syndromes It is marked by a great increase in the granular leucocytes of the peripheral blood, which are frequently to be numbered in hundreds of thousands per cubic millimetre, the least mature are scanty, and the majority fall into the grade between the myelocyte and the fully segmented neutrophil In almost every instance there is splenomegaly, often of massive proportions

Nevertheless, it is only one member, although the most common, of a group of disorders in which proliferation of myeloid cells is the characteristic feature This proliferative process may affect almost exclusively one cellular series in *myeloid leukæmia* it is the granular cells, in *polycythæmia rubra vera* it is the erythroblastic tissue, in *essential thrombocythæmia* it is the megakaryocytes In addition to these relatively "pure" proliferations an infinite gradation of intermediate forms may be distinguished, and the hyperplastic process may affect reticulin-forming cells, fibroblasts, and osteoblasts with progressive fibrosis or formation of new bone within the medullary cavity This medullary sclerosis may be the most prominent feature of the disease from its onset, and for this type the term *myelosclerosis* is reserved Its accompaniments are outstanding splenomegaly and a leuco-erythroblastic type of anæmia without significant leucocytosis In other instances medullary fibrosis accompanies the changes of chronic myeloid leukæmia (Hutt et al 1953) or supervenes on those of polycythæmia vera, of which it forms one of the recognised terminations In a third variety it is associated with a blood picture presenting the features both of polycythæmia vera and chronic myeloid leukæmia, although the totals of red and white cells seldom reach the levels attained in the "pure" forms of these disorders For this variant the term *chronic erythromyelosis* is used, and in these patients radiological evidence of intramedullary new bone formation is usually obtainable This syndrome deserves more general recognition, for it is usually accorded the diagnosis either of chronic myeloid leukæmia or of polycythæmia vera, but it is of much more indolent course than the former, and the radiological changes separate it from the latter

Besides these five clinical pictures (table VI) which stand out from among the innumerable variations of the myeloproliferative syndrome, chronic myeloid leukæmia itself may be subdivided into four types The first, or classical form, is that previously mentioned, the other three are chronic neutrophil (Weil and Sec 1932), eosinophil (Dittrich 1952), and basophil (Joachim 1906) leukæmia The last is an extreme rarity, of which I have seen no example The others are uncommon I have experience of 3 cases of the chronic neutrophil form and 2 of the eosinophil form All are marked by the presence of a great preponderance of mature segmented cells, respectively neutrophil, eosinophil, and basophil in granulation In my limited experience their course is longer than that of classical chronic myeloid leukæmia

TABLE VI—THE MYELOPROLIFERATIVE SYNDROMES

Syndrome	Cells affected			
	Granular cells	Erythroblasts	Megakaryocytes	Reticulin-forming
Chronic myeloid leukæmia	+ + +	–	+	+
Polycythæmia rubra vera	+	+ + +	+	+
Essential thrombocythæmia	–	–	+ + +	–
Primary myelosclerosis	–	–	+	+ + +
Chronic erythromyelosis	+ +	+ +	+	+ +

This lecture is concerned only with the classical variety of chronic myeloid leukæmia, and the phrase is used hereafter in this sense Exact figures for the relative frequencies of the other variants of the myeloproliferative syndrome are not available, but a rough assessment suggests that polycythæmia vera is almost as common as chronic myeloid leukæmia, while for every 100 cases of chronic myeloid leukæmia there are about 10 of chronic erythromyelosis, 15 of myelosclerosis, and 3 of idiopathic thrombocythæmia

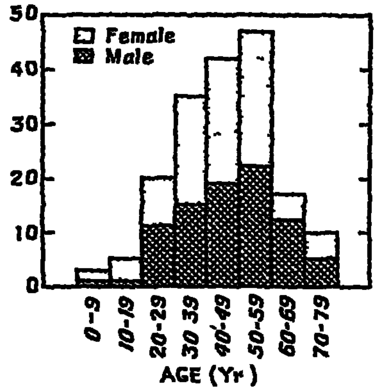

Fig 4—Age of onset of symptoms in chronic myeloid leukæmia

Incidence

The general incidence of chronic myeloid leukæmia was considered in the first lecture The insidious onset often makes it difficult to fix the date of the first symptoms, and all attempts to estimate with precision age incidence and length of survival are open to this objection In about 70% of patients the first symptoms appear between the ages of 30 and 60 In the present series the ages of onset are shown in fig 4 The mean age in males was 46 5, in females 44 6, and for the whole series of 179 patients 45 1 These figures are very similar to others published—e g, 43 6 (Shimkin et al 1951) and 44 (Ledlie 1953) There is a suggestion that the age incidence is tending to increase

In the present series females were affected slightly more frequently than males, the proportions being 52 2% and 47 8% respectively Thirty years ago males were apparently more liable to chronic myeloid leukæmia than were females A series of 116 cases collected between 1910 and 1939 was composed of 61% males and 39% females (Shimkin et al 1951) This increase in the incidence in females has been noted by other workers (Ledlie 1953)

The Clinical Picture

Initial Symptoms

The onset of symptoms in chronic myeloid leukæmia is so stealthy that few patients can recall with accuracy when they first began to feel ill Undoubtedly there is a long period, which may extend to four years, during which health is unimpaired, although the blood will show changes characteristic of the disease Occasionally chance decrees that the blood is examined during this "pre clinical" phase, and there are many reports describing the unfolding of the disease picture while the patient has been under observation (Wintrobe and Hasenbush 1939)

The commonest initial complaint is of tiredness, weakness, and disinclination for effort, it was a salient feature in nearly two thirds (58 2%) of the present series (fig 5) Next in order of frequency were the discovery of the splenic tumour by the patient (44 1%), abdominal pain (41 3%), and loss of weight (40 1%) The abdominal pain is usually referred to the left hypochondrium and often described as a sensation of weight or dragging *It is* clearly occasioned by the massive splenomegaly Less frequently

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* The second Lettsomian lecture for 1957 delivered before the Medical Society of London on Feb 13 The first was published on May 25 and the third will appear next week

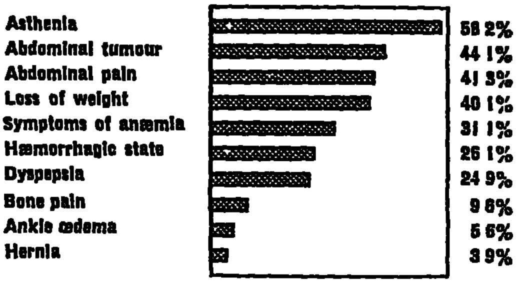

Fig 5—Presenting symptoms of chronic myeloid leukæmia in 177 patients

the first symptom is sharp pain, aggravated by respiration, and referred to the tip of the left shoulder It is presumably the result of splenic infarction with perisplenitis Loss of weight may be sufficient to cause the patient to seek advice, in several of our cases it exceeded 3 st in six months It must be related to the raised basal metabolic rate, which has long been recognised as characteristic of chronic myeloid leukæmia (Riddle and Sturgis 1927)

Somewhat less frequently than those already described, the initial complaints include such symptoms of anæmia as palpitation and dyspnœa (31 1%), digestive disturbance (24 9%), and spontaneous hæmorrhages (26 1%) The dyspepsia is usually accompanied by distension, flatulence, and loss of appetite Vomiting is uncommon, but noted in a few patients The frequency of spontaneous hæmorrhage at the onset of the disease is much higher than is generally believed At this stage the platelet-count is seldom reduced and the explanation of the hæmorrhagic state is obscure

In the third group of early symptoms are several which are interesting—though uncommon In about 1 case in 10 (9 6%) bone pain was of sufficient intensity to bring the patient to the doctor In the majority there was ill-localised aching in the bones of the legs, but in 3 it was referred to one hip-joint In 2 of these the radiological changes suggested ischæmic necrosis of the femoral head, in the 3rd an osteolytic lesion of the upper end of the bone was demonstrable Œdema of the legs was noted by a few patients (5 6%), in only 2 or 3 did this appear to be the result of thrombophlebitis, although venous thrombosis is a recognised opening symptom in the disease There was amenorrhœa in about 6% of women in whom the disease began during the reproductive period of life Priapism is well documented (Scheuer 1911) but uncommon as an initial event, it occurred in only 3 of the 86 males in this series

A final symptom, which has a practical importance, is the sudden appearance of a hernia or a uterine prolapse A hernia was the initial event of the disease in 3 9% of this series, and a uterine prolapse in 4 of 35 women over the age of 50 Common sense suggests that increase in pressure within the abdomen may precipitate such mechanical disturbances Certainly, if the occasional surgical catastrophe is to be avoided, the sudden appearance of hernia or prolapse demands careful examination of the abdomen to exclude splenomegaly

Initial Physical Signs

The physical signs of chronic myeloid leukæmia to be found at the first interview are compounded of anæmia, loss of weight, a hæmorrhagic state, and enlargement of the spleen, liver, and lymph nodes (fig 6) Pyrexia, usually intermittent, and commonly reaching 100–101°F at night, is present in about 1 patient in 3

Anæmia is variable but rarely intense Loss of flesh is the rule and in some instances profound, but all variations in habitus, from normal nutrition to emaciation, were represented in the present series A hæmorrhagic state is a presenting sign in about 1 patient in 4 It is seldom severe at this stage of the disease, and its manifestations are usually limited to spontaneous bruising, scattered petechiæ, and, more rarely, either hæmaturia or rectal bleeding A possibly related phenomenon is leukæmic retinopathy, marked by venous engorgement, with diffuse retinal œdema, hæmorrhages, and circular white exudates with surrounding hæmorrhagic halos This was noted in 11 4% of our patients when they were first seen

Enlargement of the spleen is almost constantly found at the first examination In this series it was lacking in only 2 4%, and in 72 5% the lower pole was felt below the level of the umbilicus Enlargement of the liver, on the other hand, is more variable In fully a third (34 8%) the liver was not palpably increased, and in only another third (30 9%) did its lower border extend more than 3 in beyond the costal margin

In the initial stages of chronic myeloid leukæmia significant enlargement of lymph nodes is uncommon In only a quarter (26 9%) of the present series was it judged to exist In the great majority of these there was very slight generalised lymphadenopathy In but 5 patients did it exceed this grade in 4 of them it was localised to one or two groups and moderate in degree, and in only 1 was it sufficient to occasion complaint In this patient, a woman aged 44, the presenting symptom was painful enlargement of cervical lymph-nodes, each of which measured 2–4 cm in diameter Early and significant lymphadenopathy has long been known to portend a rapid course and is to be regarded as a prognostic sign of sinister import (Weil and Isch-Wall 1930)

Less Common Clinical Features

Chronic myeloid leukæmia differs from other forms of leukæmia in its tendency to run a uniform course with symptoms which are familiar and relatively few Some less common features, however, are observed from time to time

Apart from purpura, cutaneous lesions are uncommon In only 2 of the present series did the skin present specific infiltrations, and in both these consisted of grey blue cutaneous and subcutaneous nodules widely scattered over the chest and abdomen Such lesions have been described occasionally by other authors (Paul and Limarzi 1942), they are generally considered to be of evil portent, and the truth of this belief was supported by both the present cases Herpes zoster is not rare (Wile and Holman 1940) and was noted in 7 of this series In 2 it was generalised

Skeletal infiltrations are usually regarded as uncommon in chronic myeloid leukæmia (Silverman 1948), but they were noted in 12 (6 7%) of the present series—3 of which have already been mentioned In 4 there was subperiosteal infiltration with some destruction of bone at the upper extremity of the femur or humerus, in 1 there were multiple chloromata of the skull, and in 1 similar tumours,

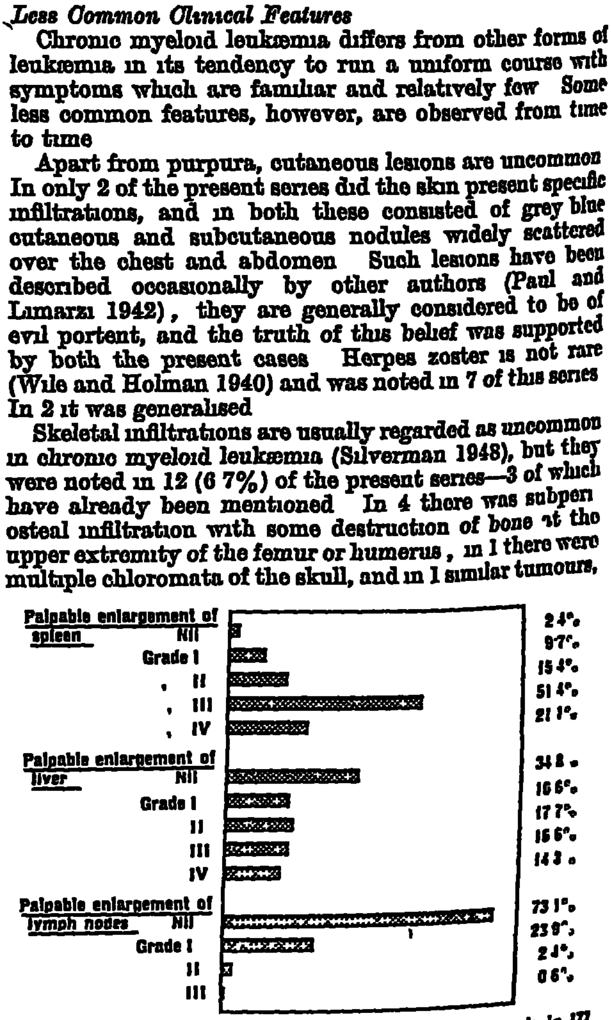

Fig 6—Presenting physical signs of chronic myeloid leukæmia in 177 patients

but lacking the green colour, were found on the ribs 1 patient had extensive osteolytic lesions of the upper ends of the humeri. In 2 patients solitary bone tumours were found—in one (who sustained a pathological fracture) at the lower end of the femur and in the other at the upper end of the tibia This variety is rare, and only 3 examples have been recorded in recent years (Townsend 1939, Minimi and Scardigli 1951, Nesbitt and Roth 1955) Swelling of, and effusion into, the knee-joints was observed in 1 patient and similar affection of the wrists in 1 other These articular lesions have been shown to depend on leukæmic infiltration of the synovial membrane (Bedwell and Dawson 1954)

Symptoms due to infiltration of the cardiovascular apparatus are exceptional, but pericarditis has been reported (Bierman et al 1952) In 1 of the present series pericardial effusion was a presenting feature, it disappeared after irradiation of the spleen, and the patient survived nearly three years in good health Pericardial effusion was noted also during the course of the illness in 1 patient with chronic neutrophil leukæmia

The frequency of dyspepsia has already received comment, but a neglected, although not uncommon, symptom is diarrhœa, which disappears with treatment of the leukæmia 3 patients in the present series developed massive ascites in 2 it followed infarction of the spleen, and in the 3rd, in whom its onset was accompanied by hæmatemesis, the cause was thrombosis of the portal vein

Associated Diseases

Associated diseases were infrequent in this series It has been suggested that peptic ulceration is common in chronic myeloid leukæmia (Wintrobe 1956), but here it was noted in only 7 patients Urinary calculus might well be expected, but it occurred in only 3, and gout in only 1 Apart from terminal pneumonia, intercurrent infection is strangely uncommon, but pulmonary tuberculosis was found in 6 of this series, in 1 of whom it assumed the miliary form This patient is of interest in that the miliary shadows disappeared under treatment with streptomycin, the leukæmia was controlled with busulphan ('Myleran'), and she lived for three and a half years after the double diagnosis was established In 1 patient tuberculous peritonitis complicated the disease

Pregnancy

6 of the 52 women in the childbearing period of life became pregnant during the course of the disease, 1 on two occasions All were delivered normally at full term, there was no maternal, and only one neonatal, death There was no evidence that the disease was made worse, and it is not an obligatory reason for termination of pregnancy (Allan 1954)

Blood Picture

As in all forms of leukæmia, diagnosis depends on examination of the blood, which, in the chronic myeloid variety is almost always characteristic and conclusive There is usually some anæmia, although in 10% of the present series the hæmoglobin level was above 80% on the first examination, in nearly half it lay between 40% and 60% The leucocyte-count is greatly increased, being between 100,000 and 300,000 per c mm in half the patients In 3 instances it exceeded 1,000,000 per c mm (fig 7) The increase is entirely due to an excess of cells of the granular series, from the neutrophil myelocyte to the fully segmented neutrophil Moderate increases in eosinophil and basophil cells are common, but myeloblasts and promyelocytes are scanty At this stage the platelet count is usually raised, sometimes above 1,000,000 per c mm Occasional normoblasts are often seen in the film

Treatment

The ease with which therapeutic remission may be obtained in chronic myeloid leukæmia separates it from other forms of leukæmia This characteristic does not appear to depend on an inherent tendency to spontaneous remission, for the usual course of the illness before the institution of treatment is one of steady decline In untreated cases phases of transient amelioration occur in only 6% (Minot et al 1924)

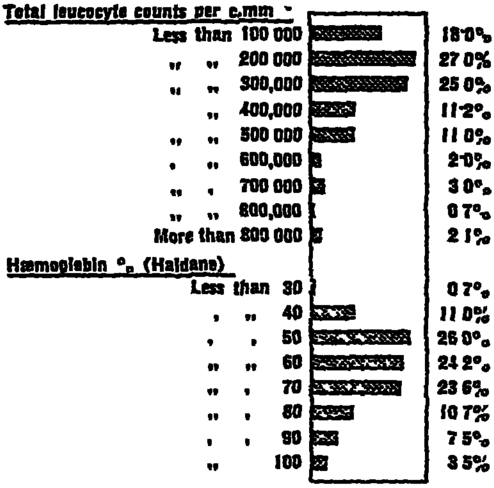

Fig 7—Initial blood-counts of 144 patients with chronic myeloid leukæmia

The first agent shown to have therapeutic effect was arsenic, in the form of Fowler's solution, and its use by Lissauer (1865) was the pioneer venture in the chemotherapy of malignant disease It held the field until displaced by the röntgen ray, applied first by Pusey (1902) in the United States and three years later in this country by Ledingham and McKerron (1905) Similar results were obtained with benzol (Korányi 1912), radium (Rénon et al 1913), mesothorium, and thorium X (Zadek 1933)

There was little further advance until about ten years ago, and in this past decade nitrogen mustard (Karnofsky 1948, Gardikas and Wilkinson 1951), urethane (Paterson et al 1946), radioactive phosphorus (Lawrence et al 1948), desacetylmethylcolchicine (demecolcine, 'Colcemid') (Moeschlin et al 1953), and 1–4 dimethanesulphonyloxybutane (busulphan, myleran) (Galton 1953a) have been introduced

It is impossible to review the use of all these agents, indeed many are now largely of historical interest only The three which require serious consideration are radiotherapy, demecolcine, and busulphan Of the remainder, radium and its relatives, nitrogen mustard, and urethane have no longer a place in the treatment of chronic myeloid leukæmia, and radioactive phosphorus has no advantage over conventional radiotherapy

Radiotherapy

Deep X ray therapy has been the mainstay of treatment in chronic myeloid leukæmia for fifty years Its advantages and drawbacks are well known In this series the great majority of patients have been treated by irradiation of the spleen The initial dose was usually 50r, and the total, depending on the rate of fall in the leucocyte-count, lay between 400r and 1200r, spread over one to three weeks Treatment has been stopped when the count has reached 15,000–20,000 per c mm, after which there follows a gradual drop to 8000–10,000 per c mm over the next three weeks Severe leucopenia has been observed only on three or four occasions The usual effects have been shrinkage of the spleen, disappearance of all general symptoms, and a return to apparently normal health Further courses of treatment have been dictated partly by recurrence of symptoms and partly by a rising white cell count In the absence of symptoms it has not usually been thought necessary to irradiate until the count exceeded 75,000 per c mm

The immediate results were excellent Remissions varied greatly in duration, from three months to as long, in 1 instance, as five years The mean is about nine months Second remissions are shorter and, as the disease progresses, they become less complete Eventually a state may be reached where there is massive splenomegaly and persistent anæmia but a leucocyte count of 20,000 per c mm or less forbids further irradiation More often the moment comes when the malignant process quickens its tempo the predominating cell becomes less and less mature until the blood is flooded with myeloblasts, the platelet count falls, and profound anæmia develops This myeloblastic crisis is the common termination of the disease

The place of radiotherapy in the treatment of chronic myeloid leukæmia is so well established that detailed discussion would be out of place Its disadvantages are the necessity for expensive apparatus and the inevitable succession of remission and relapse which this particular form of therapy imposes No attempts to make smooth the undulant pattern of this course have been fully successful

Demecolcine

Demecolcine (colcemid), an alkaloid isolated from extracts of *Colchicum autumnale* (Reichstein and Santavy 1953), was first shown to be effective in chronic myeloid leukæmia by Moeschlin et al (1953) In the present series it has been used in only 6 patients The practice was to begin treatment with an oral dose of 3 mg daily, this was cautiously increased to 5 mg after three or four days and, in some cases, to 7 mg or even 10 mg later

The fall in the leucocyte count may be precipitous and, if treatment is interrupted for more than three or four days, it may rise as rapidly as it fell, and further response be difficult to obtain

Side effects were common and included alopecia and generalised erythema Shrinkage of the spleen was slow and incomplete, the differential leucocyte count seldom returned to normal, and anæmia responded slowly

There is *no doubt that chronic myeloid leukæmia can* be adequately controlled with demecolcine (Leonard and Wilkinson 1955), but our experience did not encourage us to persevere with it Other workers have encountered even more severe reactions and have reached similar conclusions (Bousser and Christol 1955)

Busulphan

Busulphan (myleran) is a product of the Chester-Beatty Research Institute (Haddow and Timmis 1953) It was rapidly shown to have a virtually specific action on myeloid cells in laboratory animals and to be effective in the treatment of chronic myeloid leukæmia in man Reports testifying to its value have come from many countries (Consoli and Napoli 1955, Galton and Till 1955, Haut et al 1955, Pribilla and Stollberg 1955, Soares and Valente 1955, Blackburn et al 1956, Louis et al 1956, Schilling and Meyer 1956) It is now the routine method of treating this disease in my clinic and has been used in the last 23 patients

Treatment does not necessitate admission to hospital, the initial daily oral dose is 0 06 mg per kg body weight, usually equivalent to 4 mg Blood counts are made at first at intervals of a fortnight The leucocyte count falls slowly over four to six weeks and is followed by a rise in the hæmoglobin level and by shrinkage of the spleen A return to normal health is achieved in two or three months The dose is adjusted to that sufficient to maintain a leucocyte count of about 10,000 per c mm and a normal platelet count, and maintenance treatment is continued at this level (fig 8) Complete remission was obtained in all but 2 of our patients, and they had already become resistant to irradiation There are several in this series who have been maintained in complete remission for over fifteen months

It has been suggested that myeloblastic relapse may occur earlier in patients treated with busulphan than in those irradiated (Blackburn et al 1956) There is no solid support for this contention, indeed, the extreme variations in the course of the disease would make it difficult to obtain statistical proof At present busulphan is undoubtedly the most convenient means of treating chronic myeloid leukæmia It has the advantage, not possessed by radiotherapy, of maintaining remission until the disease is brought to a close by a final myeloblastic explosion and, so far as is known, its results compare favourably with those obtained by other methods

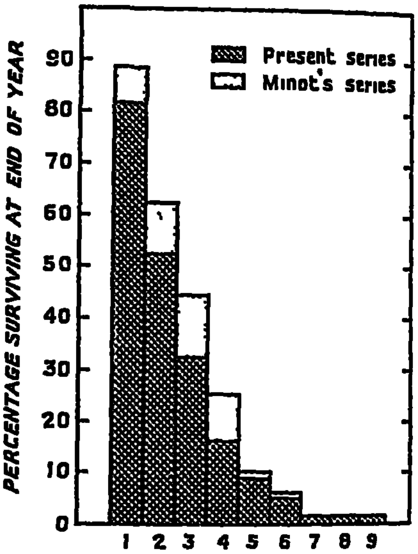

Fig 8—Survival of patients with chronic myeloid leukæmia 124 patients in present series compared with untreated series collected by Minot et al (1924)

When myeloblastic relapse takes place, busulphan is useless, and irradiation both ineffectual and dangerous The therapeutic problem becomes that of acute myeloblastic leukæmia, and the only drug of any value is 6 mercaptopurine In this series, it must be confessed, the results have been unsatisfactory *The leucocyte count* has always been reduced, but there has been little change in the appearance of the bone marrow, and no true remission has been obtained, although some clinical improvement has been evident In several patients the speed of the decline appears to have been slowed 6 Mercaptopurine will also control the disease satisfactorily in the early stage before myeloblastic relapse has occurred (Burchenal et al 1953)

Subsidiary Treatment

This discussion has concerned itself so far only with what might be called "specific" measures for controlling the leukæmic process The various subsidiary *forms of* treatment do not require detailed consideration

Blood transfusion is seldom needed until acute myeloblastic relapse has occurred, when it must be used to preserve a safe level of hæmoglobin while attempts are made to procure remission with 6 *mercaptopurine*

Splenectomy —Mention has already been made of the patient with severe anæmia, massive splenomegaly, and a leucocyte count too low for either irradiation or chemotherapy to be safe It seems probable that the anæmia in this situation is in part hæmolytic in origin (Galton 1953b), although clear cut evidence of excessive destruction of blood was not obtained in our patients

In 2 of this series, who reached this position of impasse, splenectomy was undertaken in one myeloblastic relapse took place three months later, the other enjoyed a complete remission for nine months before the final acute phase supervened This was marked, as observed by other workers in like circumstances (Laignel Lavastine A et al 1932), by striking enlargement of lymph nodes A 3rd patient, aged 8 years, underwent splenectomy at another hospital a year after the onset of the disease He Operation was preceded and followed by irradiation died ten years after his initial symptoms, and nine years after his splenectomy, from pulmonary infarction

Splenectomy in chronic myeloid leukæmia was first undertaken by Bryant (1866) of Guy's Hospital Both his patients died, and he concluded that the operation was theoretically unsound No-one would challenge this opinion of splenectomy as a definitive treatment, but occasionally circumstances may arise in which it will provide the patient with several more months of useful existence (Puorger and Aymon 1948)

Prognosis

Chronic myeloid leukæmia remains a fatal disease, but the duration of life from the first symptom shows remarkable variation In the great majority of cases myeloblastic transformation rings down the final curtain Only 39 of this series were examined post mortem, and in 23 this anaplastic change was the only cause of death discovered Bronchopneumonia was responsible for 4 deaths, tuberculosis for 4, pyelonephritis for 2, pulmonary embolism for 2, chronic cor pulmonale for 2, and coronary thrombosis and staphylococcal septicæmia for 1 each The relative rarity of terminal infection is noteworthy and contrasts strongly with its frequency in other forms of leukæmia

✓ It is impossible to foretell when myeloblastic relapse will occur, but its appearance always foreshadows the end In some patients this change has supervened only five months after the initial symptom, in others the interval has been as long as seven years In the present series the mean survival in 160 patients who have died was 32 4 months The variability is sufficient to deprive a mean figure of much value This length of survival does not compare favourably with those of other series, a selection of which in terms of months are 36 (Ledlie 1953), 37, 36, and 38 (Shimkin et al 1951), 42 (Krebs and Bichel 1947), 38 (Leavell 1938), 40 (Hoffman and Craver 1931), and 41 (Minot et al 1924) It is possible to explain some of this difference by the action of selection, the variation in the course of the disease, and the difficulty in dating its first symptom with precision It is safe, as a generalisation, to say that the mean survival from the first symptom in chronic myeloid leukæmia is about three years

There is little evidence that treatment prolongs the life of patients with this disease Fig 8 shows the proportion surviving at the end of each year, compared with a series of patients who received no irradiation, collected by Minot et al (1924) The two curves are almost identical, and the conclusion must be drawn that, as regards survival in this disease, there has been no improvement in the outlook during the past thirty three years

In any patient it is virtually impossible to foretell the course that chronic myeloid leukæmia will take In this series the survival is somewhat longer in females, with a mean of 35 2 months, than in males, for whom it is 29 5 months The disease lasted longer in the younger patients (table VII) It is perhaps justifiable to conclude that the prospects of long survival are better in young women than in old men

The outlook, moreover, bears no relation to the total white cell count when the patient is first seen, although the presence of a high proportion of myeloblasts naturally indicates the impending onset of acute relapse There is no difference between the duration of those who present with a hæmoglobin level below 9 g per 100 ml and of those with a lesser degree of anæmia Fever is usually, but not necessarily, an unfavourable sign, if it vanishes when the leukæmia is treated it is robbed of any evil significance The suspicion that survival is shorter in those whose spleens are of great size when first seen cannot be supported statistically, but the impression remains Outstanding enlargement of lymph-nodes in the early stages indicates a short course, and the specific skin lesions portend rapid deterioration Skeletal lesions are usually seen only in the later stages, but in the rare instances in which they are responsible for the presenting symptoms the progress of the disease is not necessarily rapid

TABLE VII—SURVIVAL FROM ONSET OF SYMPTOMS OF CHRONIC MYELOID LEUKÆMIA

—	No of patients	Mean survival (mos)
Total	160	32 4
Males	76	29 5
Females	84	35 2
Age at onset (yr)		
< 30	23	39 0
30–59	109	31 0
60–79	28	24 0
Date of treatment		
Before 1939	90	35 0
After 1939	70	30 0

Conclusion

It is impossible to contemplate chronic myeloid leukæmia with any feelings of satisfaction It is true that many new therapeutic agents have been devised, but its victims live no longer now than when our grandfathers treated them with Fowler's solution We may perhaps be justified in claiming that our methods preserve the patient's well-being and permit him to lead an active happy life for the greater part of his illness, although we are still unable to predict with any accuracy how long it will take to run its course

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DEATHS ASSOCIATED WITH STEROID-HORMONE THERAPY

AN ANALYSIS OF 18 CASES

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Most of the side effects and complications resulting from the use of cortisone and corticotrophin are not dangerous and cease when the hormone is stopped, but some complications have been serious and some fatal The fatal complications include infections, particularly "silent" pneumonia, which may cause rapid death (Page 1954, Jacobs and Clifford Rose 1955), septicæmia (Shaper and Dyson 1955), aplastic anæmia (Snively et al 1953), perforation of the ileum in regional ileitis (Sauer et al 1953), perforation of the colon in ulcerative colitis (Tulin et al 1952), massive gastro intestinal hæmorrhage (Gray et al. 1951, Sauer et al 1953), and hypersensitivity to corticotrophin (Hill and Swinburn 1954) Deaths have also been reported during the treatment of bronchial asthma (Savidge and Brockbank 1954), scleroderma (Lunseth et al 1951, Sharnoff et al 1951), and rheumatoid arthritis (Finck 1955) In addition, Salassa et al (1953) and Lewis et al (1953) have attributed deaths shortly after operation in patients previously receiving cortisone to adrenal insufficiency under conditions of stress

The published reports give the impression that cortisone and corticotrophin may have been unjustly blamed for some deaths, and this is likely to be the case when the disease under treatment is itself potentially fatal, and liable to similar complications during its natural history (for instance, perforation and hæmorrhage in ulcerative colitis) In view of this, details have been collected of all deaths during treatment with cortisone or corticotrophin at Guy's Hospital, in an attempt to decide whether the treatment was responsible, how death occurred, and whether it might have been prevented From 1949 until December, 1955, all patients receiving steroids at Guy's Hospital were under the supervision of the Department of Medicine, and during these years more than 400 patients received either one or both hormones Some of these cases were recorded by McGehee and MacLean (1954) Since December, 1955, when cortisone became available on prescription, many other patients have received treatment but the exact number is not known Dosage schemes have varied from short courses of corticotrophin by daily intravenous drip to maintenance therapy with oral cortisone, sometimes for as long as four years continuously The histories of 18 patients who died during treatment are available, but since some died at home or in other hospitals, accounts of their final illnesses are not always complete A necropsy was not possible in every case No death during substitution therapy for Addison's disease or hypopituitarism, or following adrenalectomy or hypophysectomy for carcinomatosis has been included

The accompanying table shows the cause of death—i e , fatal complication and details of steroid therapy in each of the 18 patients Steroid therapy was considered directly responsible for 9 deaths and probably for 2 more It cannot be blamed for 2 of the deaths, and it is unlikely to have been the cause of a further 2 In the remaining 3, the part played by cortisone or corticotrophin is more debatable

The Rôle of Infection

Infection caused most deaths in this series—at least 6 (and probably 7) out of 18

Man and laboratory animals are remarkably susceptible to infection whilst under the influence of cortisone or corticotrophin (Glaser et al 1951, Germuth et al 1952, Glaser and Loeb 1952, Mogabgab and Thomas 1952) This susceptibility has long been recognised in naturally occurring Cushing's syndrome (Cushing 1932), and in the 189 cases reviewed by Plotz et al (1952) death was due to infection in nearly half of the 114 in which a necropsy was performed

Thomas (1953) has pointed out that cortisone potentiates and enhances all known infections, and in mice and rats ordinarily non pathogenic organisms may be rendered pathogenic (Gledhill and Rees 1952, Le Maistre and Tompsett 1952) Thomas believes that cortisone acts directly on the cells of the reticuloendothelial system, since blockade of this system in animals, by injecting saccharated iron or thorotrast, produces effects identical with those of cortisone—namely, failure to clear injected cocci from the blood, dissemination of organisms that usually produce only local infections, and accelerated absorption of meningococcal toxin injected intradermally. There seems to be no evidence that cortisone either stimulates the growth of bacteria or increases their virulence in vitro The increased susceptibility and mortality result from depression of the host's defence mechanisms

Jawetz (1954) found that doses of antibiotics just sufficient to control infections in normal animals failed to protect animals receiving cortisone, but the infection could be overcome by increasing the dose, and bactericidal antibiotics were far more efficient than bacteriostatic ones, which had to be given in far larger amounts Jawetz explained this difference on the grounds that a purely bacteriostatic antibiotic will succeed only when the host's defence mechanisms are intact, and he believes that cortisone seriously interferes with those mechanisms It is doubtful whether Jawetz's work has any clinical application in the choice of antibiotics for, as he himself pointed out, the doses used clinically are far in excess of those actually needed in most ordinary infections

SUPPRESSION OF SIGNS OF INFECTION

One of the most disquieting features of many of the recorded deaths during steroid therapy is the suppression or masking of the symptoms and signs of infection Patients may appear well despite active infection, and Kass et al (1950) showed that blood and sputum cultures remained positive in patients with lobar pneumonia who were given corticotrophin, although fever subsided and great clinical improvement occurred This masking effect delays diagnosis and treatment, so that a sudden and often fatal collapse may be the first indication of infection

In the Guy's series, 2 patients collapsed suddenly, although the presence of a complicating infection was realised

Case 1—A woman, aged 23, had scleroderma, and cortisone was given in short courses (100 mg daily) during 1953 In 1954 she received cortisone (100 mg daily) almost continuously from June until August, when she was discharged to continue the same dose at home She had gained 20 lb She died in November and, according to her doctor, cortisone was stopped about ten days before her final illness She had a cold and mild bronchitis, and her doctor said she was "twice her normal size" As her condition was mild he did not visit again until called a week later, when he found some tachycardia but no pyrexia There were moist sounds at the left base and he diagnosed bronchopneumonia antibiotics were prescribed He was astonished to hear of her death twelve hours later, since he had certainly not considered her ill enough to warrant removal to hospital Necropsy was not obtained

Case 2—A man, aged 59, received cortisone (125 mg daily by mouth) for severe rheumatoid arthritis, but it had to be stopped after seven days owing to retrosternal pain Cardiac infarction was diagnosed, and confirmed by E C G Three weeks later, cortisone was restarted (100 mg daily) and his arthritis was much improved though he was troubled by slight bronchitis Ten weeks later a cough and sputum developed, and his temperature rose to 101°F A chest radiograph showed a wedge shaped opacity in the left lung Cortisone was stopped and penicillin and streptomycin started Twenty four hours later he collapsed and his blood-pressure was unrecordable , despite treatment by noradrenaline drip, he died five hours later At necropsy the left lower lobe was in the stage of red hepatisation There was a healed cardiac infarct The adrenals were macroscopically normal

ADRENAL FAILURE AS A CAUSE OF DEATH

This sudden collapse during steroid therapy has often been described, usually in association with acute infection (Page 1954, Jacobs and Clifford Rose 1955, Shaper and Dyson 1955) It was encountered in 3 cases in the present series (cases 1, 2, and 3) , and case 7 probably died in the same way

A similar collapse, postoperatively, has been reported by Salassa et al (1953) and Lewis et al (1953), and case 8 is probably an example

Case 8 —A woman, aged 67, developed intractable headache, and temporal arteritis was diagnosed She was known to have had attacks of diverticulitis, but after careful consideration, and because her symptoms were intolerable, prednisolone (20 mg daily) was started, with almost immediate relief Four weeks later perforation occurred and prednisolone was promptly stopped Four days later laparotomy confirmed a small perforation through an area of diverticulitis Twenty hours after operation she suddenly collapsed and, despite temporary improvement with intravenous hydrocortisone, death soon followed At necropsy there was no evidence of generalised infection and the peritoneum was quite clean

An almost identical sequence of events may occur in Addison's disease as a result of infection, trauma, operation, or other stress, and cortisone will protect a patient in such circumstances It might seem difficult to believe that a patient receiving large doses of cortisone and perhaps showing many of the signs of Cushing's syndrome can in fact be potentially adrenal deficient, but Thorn et al (1953) pointed out that this indeed can be the case, and that such a patient does not respond normally to stress A normal adrenal response to intravenous corticotrophin does not occur in a patient who has received cortisone for twenty days until the fourth day after its cessation (Renold et al 1952), and furthermore Calkins et al (1955) concluded that, in patients who had had cortisone for long periods, corticotrophin secretion was impaired for a similar time after withdrawal Nabarro et al (1955) warned that prednisone prevented the normal adrenal response to infection, and Ward et al (1953) stated that the normal adrenal response to stress was inhibited for days or months after hormone therapy They recommended large supplementary doses for patients undergoing surgery or when a severe infection developed, mentioning particularly the need for bigger doses after a perforation (see case 8) Salassa et al (1953) reported 2 deaths within twenty four hours of operation in patients who had had cortisone, and both deaths were attributed to adrenal failure The only abnormal post-mortem finding was atrophy of both adrenals Salassa et al examined the adrenals at necropsy in 42 patients who had had cortisone and found significant atrophy, particularly in patients receiving cortisone up to the time of death They believe severe stress may cause adrenal failure for as long as eighteen months after cortisone withdrawal, and recommend consideration of supplementary cortisone for all patients undergoing surgery in such circumstances

It is often difficult to be certain, in reported cases, whether hormone therapy was stopped, when infection or other stress occurred, and whether significant adrenal atrophy was found at necropsy In the 3 patients who collapsed as a result of infection in this series, cortisone had been stopped one week previously in case 1, twenty-four hours before the sudden deterioration in case 2, and on the day before death in case 3 In a case reported by Jacobs and Clifford Rose (1955) the daily dose of corticotrophin was increased from 80 mg to 120 mg when the patient was admitted collapsed and comatose with pneumonia Penicillin was also given, with dramatic improvement, only for relapse and death to follow two days after the withdrawal of corticotrophin, fifteen days after the initial collapse

Unfortunately the adrenals were not fully examined in every case in the Guy's series In case 2 the glands were not considered abnormal, and in case 3 they were reported as macroscopically normal In case 8 (a post-operative death) the glands were small (rt 6 5 g , lt 4 7 g), but no convincing microscopic changes were found Shaper and Dyson (1955) made no mention of the state of the adrenals in their 2 cases, but in Page's (1954) cases they were regarded as normal Jacobs and Clifford Rose (1955) considered that the adrenals of their patient who died after stopping corticotrophin were in a resting phase, and found severe atrophy and hæmorrhage in those of another who had had cortisone Evidence published in this country about adrenal atrophy in patients who have died suddenly is scanty and inconclusive, but reference has already been made to the work of Salassa et al (1953) in the United States

PREVENTION OF ADRENAL FAILURE

Surgeons are often reluctant to continue hormone therapy when operation becomes necessary, usually on the grounds of delayed wound-healing , but this risk has probably been overestimated, and, moreover, it seems unlikely to be much reduced by stopping cortisone only a day or two before operation Equally, physicians may feel bound to stop steroid treatment should infection occur Sudden withdrawal of cortisone, however, leaves the patient without endogenous corticotrophin, and though adrenal failure is not inevitable, the logical course is to continue cortisone or corticotrophin, often in much bigger doses, until the risk is past (Salassa et al 1953, Thorn et al 1953, Ward et al 1953, and Jacobs and Clifford Rose 1955) It may be necessary to increase the dose very considerably for a short time, perhaps to the equivalent of cortisone 300 or 400 mg daily, and whilst cortisone may be given intramuscularly to provide a depot, at least half the dose should be given orally in the early stages to ensure rapid absorption and action There is no reason to believe that adrenal failure is less likely in patients receiving corticotrophin, for, as Salassa et al (1953) have pointed out, it similarly depresses endogenous corticotrophin production It might seem logical to give corticotrophin to stimulate normal adrenal function when added stress threatens patients receiving cortisone, but it takes at least four days to get an effective response to corticotrophin in such patients Thus, patients receiving steroid therapy require increased doses of the appropriate hormone during periods of stress , and the need for large doses of antibiotics as soon as any infection is suspected cannot be overemphasised

Deaths Following Perforation

In 3 patients death followed intestinal perforation (see table) Perforation of the colon complicated ulcerative colitis in case 10 and diverticulitis in case 8 , and in case 9 perforation involved the terminal ileum affected by polyarteritis nodosa Though perforation usually occurs through a pre existing lesion in the gastro-intestinal tract, steroid hormones can produce peptic ulceration in previously normal persons , and though the exclusion of patients with an ulcer history from steroid therapy will diminish the chances of perforation, the risk remains

All 3 patients already had a gastro intestinal lesion Case 8 has already been discussed the presence of diverticulitis was known and steroid therapy was only started after careful consideration, but death was clearly the result of it

Case 9 —A woman, aged 57, received two courses of sulphonamide for tonsillitis Soon afterwards she became acutely ill with vomiting, diarrhœa, and purpura, and melæna followed Corticotrophin (40 mg daily) was started, and on the tenth day generalised abdominal pain and distension began This was attributed to a retroperitoneal hæmorrhage, and was treated with gastric suction and intravenous fluids On the fourteenth day corticotrophin was stopped and cortisone 200 mg substituted 100 mg was given on the next day During this time oxytetracycline was given intravenously, but she died on the sixteenth day At necropsy a perforation (1 5 × 0 5 cm) was found 30 cm from the ileocæcal valve The microscopic changes of polyarteritis were seen in the vessels at the edges of the perforation and in a large Peyer's patch which had ulcerated

The steroid's anti inflammatory action seems the likely cause of perforation, but it is hard to say that the ileum might not have perforated irrespective of therapy A third possibility is that cortisone or corticotrophin may produce areas of visceral infarction by causing intimal fibrosis and obliteration of the vessels in polyarteritic lesions Shick et al (1950) described such infarcts in the organs of 2 patients dying from polyarteritis, and Sharnoff et al (1951) reported similar changes in a patient who received cortisone for scleroderma Diffuse fibrinoid necrosis of the arterioles in a patient who died from jaundice and anuria whilst receiving corticotrophin for scleroderma was found by Lunseth et al (1951), and they thought this might be a change in immunological response induced by the hormone, though there seems little evidence for this The lesions at the edges of the perforation in case 9 have been carefully re examined but there is nothing to suggest diffuse fibrinoid necrosis It is considered that an already ulcerated and necrotic area of ileum perforated, and that cortisone hastened this, though it might have occurred in any case Presumably steroid therapy carries this risk of perforation in polyarteritis nodosa with intestinal lesions, but it would be unreasonable not to accept this risk in treating a disease so often fatal

IN ULCERATIVE COLITIS

Steroid therapy has never been regarded as a cure for ulcerative colitis, but remissions may be produced in a high proportion of patients, though relapse often follows withdrawal (Elliott et al 1951, Halstead et al 1951, Truelove and Witts 1955) Unfortunately perforation has been reported as a complication (Halstead et al 1951, Kirsner and Palmer 1951, Gray et al 1952, Tulin et al 1952)

Case 10 —A man, aged 75, had had diarrhœa (6 or 7 stools a day) for three weeks His condition rapidly deteriorated and, on admission, the motions contained blood and mucus Hb 70% Sigmoidoscopy showed an acutely inflamed hæmorrhagic mucosa Ulcerative colitis was diagnosed, and despite blood transfusion and antibiotics he grew steadily worse Corticotrophin was started by intravenous drip, the dose varying between 20 and 60 mg daily He improved strikingly, but after eleven days abdominal distension developed and a perforation was suspected He died on the twelfth day after a total of 420 mg Necropsy showed peritonitis, and a fresh perforation was found in the transverse colon The colon showed acute ulcerative colitis, with a little healing and fibrosis

Most of the reported perforations were in uncontrolled series, but in Truelove and Witts's (1955) experience perforation (2 cases) occurred in their control group, and there was none in patients receiving cortisone Had all their patients received cortisone, these 2 might well have been attributed to the hormone In fact, perforation is a natural complication of ulcerative colitis, though opinions differ as to its frequency Rice-Oxley and Truelove (1950) put it at 3 1%, which agrees closely with the 3 4% of Ranken et al (1935), though they say this is a conservative estimate Lahey (1951) considered acute perforation uncommon and Bockus (1944) regarded it as rare Crile and Thomas (1951), however, thought it was the commonest cause of death in acute toxic ulcerative colitis All seem agreed that it is a hazard of the acute, fulminating type, and rare in the chronic disease with considerable fibrosis Before cortisone was discovered, it was realised that perforation in ulcerative colitis presented grave difficulties in diagnosis, being characterised by distension, rather than pain and rigidity For this reason, and because it is so commonly fatal, its incidence may have been underestimated, and more information is needed upon its frequency in control and cortisone treated groups

It would perhaps be wrong to assume that steroids greatly increase the risk of perforation, but what increase there is is unhappily greatest in the acute rapidly progressive case—in which the need for cortisone is greatest Perforation is certainly not a new complication, and the masking effect of the steroid hormones adds to the existing difficulty of diagnosis

Gastro-intestinal Hæmorrhage

In 2 of the 3 patients who died from this cause no lesion of the alimentary tract had previously been suspected The third had ulcerative colitis

Case 11 —A man, aged 25, had diarrhœa with bloody stools a year before his first admission in 1954, and was found to have moderately severe ulcerative colitis He responded well to blood transfusions, but quickly relapsed and was readmitted six weeks later He was given corticotrophin (total 500 mg) and remission was obtained He remained well until three weeks before his final admission in April, 1956, when he became feverish and the stools contained blood and pus No improvement followed bed rest and blood transfusion, and cortisone was started (100 mg daily by mouth) Five days later his abdomen became distended, hiccups appeared, and he vomited Bowel sounds were absent on the seventh day Perforation was diagnosed, cortisone was reduced, and gastric suction instituted He improved slightly but on the eleventh day he had a severe bowel hæmorrhage, and died within twenty four hours Necropsy revealed no perforation, but the colon was extensively ulcerated and contained much blood

Although contributing greatly to the anæmia of ulcerative colitis, hæmorrhage is not usually so massive as to cause death Lahey (1951) regarded hæmorrhage as "not infrequent" and said it might be severe and uncontrollable He implied that it was commoner than perforation, and was a particular hazard in young patients with acute disease Truelove and Witts (1955) had one massive hæmorrhage in their cortisone treated patients and none in their controls Evidence as to its frequency is scanty Bockus (1944) stated it was very uncommon (0 5% in adults and 1% in children) Brooke (1954) also regarded it as unusual, but mentioned that it might occasionally be severe enough to warrant emergency colectomy Neither Hurst (1935) nor Rice Oxley and Truelove (1950) mentioned its occurrence

Massive hæmorrhage does not seem to have been reported as a complication of steroid therapy for ulcerative colitis, and it is impossible to decide yet whether such therapy carries this added risk

HÆMORRHAGE FROM STOMACH AND DUODENUM

Neither of the 2 patients who died after hæmatemesis and melæna had a history of peptic ulceration

Case 12 —A roundsman, aged 55, was admitted to hospital in 1952 He complained of weight loss, conjunctivitis, and chest and joint pains for eight months There was purpura over the legs and ulcers on both ankles Significant findings were Hb 52%, white count 12,000 per c mm (10% eosinophils) and albuminuria Skin biopsy suggested polyarteritis nodosa He was treated with corticotrophin for six weeks and later discharged much improved on cortisone 25 mg daily He relapsed and was readmitted in 1953 He was again given corticotrophin and improved In the four months after discharge he received cortisone intermittently, and deteriorated slowly He was readmitted in August, 1953, and received corticotrophin 30 mg intramuscularly and cortisone 75 mg by mouth daily After nine months he was discharged on corticotrophin 60 mg daily, but diabetes developed and he was admitted for stabilisation He now showed the typical appearance of hypercortisonism Two days after admission abdominal pain and melæna developed, and he became shocked Despite blood-transfusions, he deteriorated, and laparotomy showed an acute gastric ulcer Partial gastrectomy was performed, but further bleeding followed and he died twelve hours later At necropsy there was an erosion in the stomach remnant, and a smaller one in the jejunum The appearances suggested an acute erosive or hæmorrhagic gastritis No evidence of active polyarteritis was seen on microscopy in the removed portion of stomach, skin, lungs, heart, kidney, or muscles

Case 13.—A priest, aged 44, was admitted during 1954 with pemphigus vulgaris Blisters had appeared in the mouth eight months earlier and spread to the trunk and limbs they disappeared when he was given cortisone 100 mg daily for a month, but reappeared on withdrawal On admission there was blistering of the skin and loss of nails The mouth and gums were heavily involved and there was continuous dribbling of bloodstained saliva Cortisone was immediately started, but details of the early treatment are not available Though there was some response, gradually increasing doses were required By December, 1954, he was receiving 1 05 g cortisone daily (750 mg orally, 300 mg I.M) and this continued until Jan 5, 1955, when the oral dose was reduced Diabetes developed on Jan 18 when he was receiving 800 mg daily Insulin was started four days later, and two days after this there was profuse hæmatemesis and melæna four pints of blood were given. Further hæmatemeses followed and he died on Jan 28 $7^{1}/_{2}$ pints of blood had been given Two days before death the dose of cortisone was 650 mg After the initial hæmorrhage, when the Hb was 31%, the platelet-count was low On Jan 26, the platelets had risen slightly, and on Jan 27 the count was 30,000 per c.mm (Hb 39%) On the day of death, platelets numbered 50,000 per c mm and the Hb was 64% At no time was purpura observed Necropsy could not be obtained

Both patients were receiving high doses and showed signs of hypercortisonism Indeed, in both diabetes developed shortly before the hæmorrhage occurred In case 13 the dose was larger than any previously used at Guy's Hospital In case 12 there was a hæmorrhagic gastritis, and the jejunal erosion may have developed in the few hours' survival after gastrojejunostomy If so it would be interesting to know whether this was the result of a remarkably corrosive gastric juice from the stomach remnant or of diminished mucosal resistance due to corticotrophin Polyarteritis cannot be blamed in the absence of histological changes, and cortisone seems the most likely cause of death

There is no proof of the cause of hæmorrhage in case 13 The marked thrombocytopenia was originally suggested, but cortisone is usually considered to cause a rise in platelets, though a slight and variable depression may follow corticotrophin (Warren et al 1953), lasting up to forty eight hours and resembling the immediate fall after an operation Low platelet-counts have been recorded after massive gastro intestinal hæmorrhage (Desforges et al 1954) occasionally very low counts (50,000 or below) persisted if there was further bleeding Severe platelet depression may follow large transfusions for hæmorrhage (Krevans and Jackson 1955), and significant thrombocytopenia developed in 4 of 13 patients who received up to 5 litres of blood The same mechanism was probably responsible for the platelet depression in case 13 and it has not been attributed to cortisone In the absence of necropsy proof, and in view of the great similarity to case 12, death has been attributed to hæmorrhagic gastritis induced by cortisone

Hæmorrhage and perforation complicating ulcers reactivated or induced by steroid hormones are well recognised Gray et al (1951) showed that cortisone and corticotrophin might considerably increase gastric secretion and uropepsin excretion, in a patient who died from massive hæmorrhage from a duodenal ulcer, necropsy showed a hæmorrhagic gastritis Sauer et al (1953) recorded 3 cases of peptic ulcer, in 2 of which there was severe hæmorrhage These 3 patients had signs of hypercortisonism, but peptic ulcer may develop on comparatively small doses a patient developed both gastric and duodenal ulcers whilst receiving 50 mg cortisone daily (Davis and Zeller 1952) The increased gastric secretion (Gray et al 1951) is an attractive explanation for ulceration during therapy, but the doses used were extremely large, corticotrophin 120–160 mg or cortisone 200–500 mg daily These are comparable with the doses in cases 12 and 13, but far greater than in many reported cases of ulcer Hirschowitz et al. (1955) found no increase in gastric secretion in healthy students given 50 mg corticotrophin daily for six days, and in 1 an ulcer developed after five days A gastric ulcer also appeared in a student who had had small doses of steroid hormones intermittently (Hirschowitz et al 1956) This student had no increase in gastric acidity, and Hirschowitz et al consider that by no means all ulcers, either naturally occurring or hormone-induced, are the result of increased gastric secretion, but decreased mucosal resistance may play a more important part

The danger of peptic ulceration during steroid therapy lies in its liability to attack previously normal persons, and to cause hæmorrhage and perforation without warning Cases 12 and 13 resemble those of Gray et al (1951) in that they were having very large doses, but there is no evidence about their gastric secretion

Deaths from Other Causes

PULMONARY EMBOLISM

Case 14—A housewife aged 55, was admitted because of bronchial asthma, worsening in the previous six weeks There was slight cardiac enlargement, blood-pressure 160/110 mm Hg She had severe varicose veins Daily intravenous infusions of corticotrophin in glucose were given 30 mg for two days, 20 mg for four days, 15 mg for one day, and 10 mg on the last day Her asthma improved greatly, but the day after the last dose she complained of precordial pain, became pale and pulseless, and was soon dead Necropsy showed a massive embolus obstructing the main pulmonary artery The deep calf veins were thrombosed in both legs

There are conflicting reports of the effect of cortisone and corticotrophin on blood-clotting Cosgriff et al (1950) reported that the venous clotting-time and heparin-retarded clotting time were shortened, but there was no change in prothrombin-time, fibrinogen-B content, or protamine titration Monto et al (1950) found variable changes in coagulation, including in some patients an increase in circulating heparin during therapy Cosgriff (1951) encountered 48 thromboembolic incidents among 700 patients receiving steroid hormones and considered this incidence greater than expected, but Russek et al (1954) observed no complications in 100 patients treated with cortisone for various cardiovascular conditions, including angina pectoris and myocardial infarction

The incidence of thromboembolic complications during steroid therapy at Guy's Hospital has not appeared abnormal, and it is impossible to say whether the death in case 14 was due to corticotrophin An embolus shortly after a course of corticotrophin is interesting in view of the observation of Hume and Moore (1952) that thrombophlebitis was perhaps more likely to follow cessation of the hormone, and this might be analogous to the thrombophlebitis after surgical operations, when adrenocortical activity is lessening or has returned to normal Margulis's (1952) observation that circulating heparin increased during corticotrophin therapy and afterwards fell below normal may explain this If death is to be attributed to corticotrophin in case 14, this may have been the mechanism

HYPERSENSITIVITY TO CORTICOTROPHIN

Case 15—A man, aged 59, who had had ankylosing spondylitis for twenty-five years, was admitted for trial of corticotrophin He had had radiotherapy in 1936 *Bilateral sympa-*

thectomy was performed in 1946 for thromboangiitis obliterans. On admission, there was complete rigidity of the spine and neck, chest expansion was 1 in., and the temporomandibular joints were almost fixed. A few inconstant râles were heard at the left lung base. Because of his abject condition, corticotrophin was tried (25 mg. daily in glucose by intravenous drip). After two days, improvement was remarkable, and he could open and close his jaws normally, but during each infusion he complained of dyspnœa, and his temperature rose to 99°F. The dyspnœa became worse during the next two infusions and he produced a little tenacious sputum. Rhonchi and râles were heard over the chest. The symptoms subsided immediately the corticotrophin was finished, and none was given on the next day. On the sixth day, corticotrophin had to be stopped because of dyspnœa, and despite apparent improvement he was found dead twelve hours later. At necropsy there was slight right ventricular enlargement (heart 145 g.), a little free fluid was present in both pleural cavities, and the trachea and bronchi contained much tenacious mucoid sputum. There was no evidence of infection or of pulmonary œdema. The pelvic colon contained a small adenocarcinoma, without metastases, and there was a hæmorrhagic phæochromocytoma in the left adrenal gland.

Hypersensitivity to corticotrophin, occasionally fatal, has been reported (Feinberg et al. 1951, Wilson 1951, Brown and Hollander 1952, Stevenson 1952, Hill and Swinburn 1954). The sensitivity may be to pork or beef protein derived from the source of preparation or to the hormone itself. A previous dose or course of corticotrophin has usually been given and the reaction may be immediate or delayed (Thorn et al. 1953). The reported reactions include pruritus, angioneurotic œdema, or urticaria, particularly at the site of intramuscular injection, asthma and bronchospasm, and severe circulatory collapse, often with rigors and abdominal pain.

Death in case 15 seems undoubtedly due to corticotrophin, but the exact cause is less obvious. No skin rash was observed, and sensitivity tests were not performed. The picture suggested bronchial asthma, and there is little doubt that it appeared to subside each time corticotrophin was stopped. Pulmonary œdema from sodium and fluid retention in a patient with considerably diminished chest expansion was a possible explanation, but no rise in venous pressure was observed, and the necropsy findings did not suggest this mechanism. Whether the unsuspected phæochromocytoma in any way contributed to death is not known, but it seems unlikely. Death has been tentatively attributed to hypersensitivity to corticotrophin. This case emphasises Wilson's (1951) warning that the hormone should be stopped immediately at any sign suggesting hypersensitivity.

CARDIAC FAILURE

Case 16.—A housewife, aged 53, was admitted because of breathlessness for nine years and recent "blackouts" on exertion. She suffered from Raynaud's phenomenon, and had undergone bilateral cervical sympathectomy and amputation of the left 5th finger. She had signs of scleroderma. No cardiac enlargement was detected, but the pulmonary 2nd sound was increased, and the venous pressure was slightly raised. A chest radiograph showed fine reticulation over the lung fields and enlargement of the pulmonary artery and heart. Scleroderma with probable involvement of heart and lungs was diagnosed. Cortisone (100 mg. daily) was given, and the hands appeared much improved, but she was readmitted six weeks later in heart-failure. Cortisone was discontinued and treatment with digitalis and mersalyl started. She died in cardiac failure seven weeks after cortisone was stopped. Necropsy showed enlargement of the right ventricle and dilatation of the tricuspid ring. The pulmonary artery was dilated, and its walls showed plaques of atheroma. The lungs were tough but not grossly abnormal. A small ulcer was present in the stomach. Microscopical changes of scleroderma were seen in the skin, but not in the heart or in the lungs, which were emphysematous only.

This patient had pulmonary hypertension, presumably secondary to her emphysema, with the resulting symptoms and signs—e.g., effort syncope. In retrospect it is clear from the radiographs that the right ventricle and pulmonary artery had enlarged during the previous year and as cardiac failure developed within three weeks of starting it, cortisone must be assumed to be the precipitating factor. Since the fluid-retaining properties of cortisone and corticotrophin are so well known, few fatalities are likely from their use in patients with established or threatened failure. Although prednisone (Nabarro et al. 1955) and prednisolone usually cause less electrolyte disturbance, they may still precipitate failure and should be avoided when this risk is present.

RUPTURE OF THE AORTA

Case 17.—A schoolgirl, aged 15, was admitted for persistent pyrexia and indifferent health for a year. Seven weeks earlier her nose became red, painful, and swollen. Listlessness, sweating attacks, and remittent fever (99–102°F) developed. Both elbows became swollen and her appetite was poor. Several antibiotics had been given without effect. There was a red papular lesion over the nose, and slight faucial inflammation. The only other abnormal finding was an apical systolic murmur.

Investigations.—Chest radiograph normal. White count 15,800 per c.mm. (polymorphs 73%, eosinophils 1%). Erythrocyte sedimentation rate (Westergren) 135 mm. per hr. No L.E. cells in peripheral blood. Sternal marrow normal. Blood agglutination negative. Mantoux (1 in 1000 O.T.) negative. Stools normal. Serum-proteins, 6·6 g. per 100 ml. (albumin 3·0 g., globulin 3·6 g.); electrophoresis, diminished γ, but raised α_2 globulin. Muscle biopsy normal.

The rather imprecise diagnosis of "a collagen disease" was made and cortisone given by mouth (6·3 g. over twenty-six days). Symptoms were much improved and the pyrexia was abolished, but the E.S.R. remained high (118 mm. per hr.). On the twenty-sixth day of treatment she complained of vague chest pain and later severe substernal pain. At 5 P.M. she became pale and shocked, rapidly going blind. An electrocardiogram was normal. The signs suggested hæmorrhage but none could be detected. She died at 6 P.M. A fusiform dilatation of the descending thoracic aorta was found to have ruptured into the left pleural cavity. There were smaller aneurysms in the abdominal aorta and common iliac vessels. Many inflammatory cells were seen in the subintimal layer of the aorta, extending into the media near the aneurysms. The subintima of the coronary arteries contained similar lesions. The histological diagnosis was "an acute arteritis of unknown ætiology" affecting the aorta and main vessels.

The main problem here is to decide whether cortisone precipitated rupture of an already damaged aorta or was conceivably responsible for all the post-mortem histological changes. The possible production of fibrinoid necrosis by cortisone (Lunseth et al. 1951), and the sequel of visceral infarction in vessels affected by polyarteritis (Schick et al. 1950, Sharnoff et al. 1951) have already been discussed in connection with intestinal perforation. Severe mesenchymal reactions (with lesions indistinguishable from polyarteritis nodosa) have been observed in patients receiving large doses of steroid hormones for rheumatoid arthritis (Polley 1956). This girl clearly had a severe illness, compatible with a progressive arteritis, long before cortisone was given. Aortic weakening and dilatation had begun before treatment was started, for re-examination of the radiographs shows that, though the descending aorta appeared normal on admission, dilatation of the retrocardiac portion had begun seven days before cortisone was started, and was considerable on the last film, nine days before death. This change was not appreciated at the time. Cortisone may have precipitated rupture, but disorganisation of the vessel wall was so widespread that rupture appears to have been inevitable. This death was not, therefore, attributed to cortisone.

CHRONIC HYDROCEPHALUS DUE TO CYSTICERCOSIS

Case 18.—A man, aged 45, who had lived in India, was investigated for recurrent headaches with vomiting. Radiographs showed calcification in the limb muscles and an air encephalogram showed a shadow in the roof of the 3rd ventricle. Cysticercosis was diagnosed, and cortisone started because of the suggestion that the attacks might represent

DETAILS OF TREATMENT IN PATIENTS WHO DIED DURING STEROID THERAPY

Case no	Age and sex	Clinical diagnosis	Duration of steroid therapy	Dose at time of complication	Cause of death	Whether attributed to steroid therapy
1	23 F	Scleroderma	18 months Intermittent cortisone, usually 100 mg daily	100 mg daily Stopped 10 days previously	Infection (pneumonia) No necropsy	Yes
2	50 M	Rheumatoid arthritis	3½ months Cortisone 100 mg daily	150 mg daily	Infection (pneumonia) Necropsy	Yes
3	[illegible]4 M	Polyneuritis	11 months Corticotrophin 40–60 mg for 8 months Cortisone 200 mg daily for 3 months	Cortisone 200 mg daily	Infection (pneumonia) Necropsy	Yes
4	47 F	Polyarteritis nodosa	13 months Cortisone 150 mg for 7 months, 200 mg for 3 months Prednisolone 45 mg daily for 2 months	Prednisolone 45 mg daily	Infection (peritonitis followed by pneumonia) Laparotomy no necropsy	Yes
5	[illegible]6 M	Scleroderma	Cortisone 100 mg for 18 days 75 mg for 19 days	Cortisone 75 mg daily	Probably infection ? Septicæmia No necropsy	Probable
6	[illegible] M	Dermatitis of unknown ætiology	5 months Corticotrophin 30 mg daily and for last 2 months cortisone 200 mg daily added	Corticotrophin 40 mg cortisone 200 mg, both daily	Infection (bronchopneumonia) Necropsy	Unlikely (considered terminal event in the disease)
7	48 F	Scleroderma	Approx 2 months Cortisone 100 mg daily	Cortisone 100 mg daily	? Fulminating infection No necropsy	Probable No proof
8	67 F	Temporal arteritis	4 months Prednisolone 20 mg daily	Prednisolone 20 mg daily	Perforation of colon due to diverticulitis Post-op adrenal failure Necropsy	Yes
9	51 F	Polyarteritis nodosa	15 days Corticotrophin 40 mg daily for 13 days Cortisone 200 mg for 2 days	Corticotrophin 40 mg daily	Perforation of ileum Necropsy	Possible
10	75 M	Ulcerative colitis	12 days Corticotrophin (total 420 mg)	Corticotrophin 40 mg daily	Perforation of colon Necropsy	Possible
11	25 M	Ulcerative colitis	8 days Cortisone 100 mg daily	Cortisone 100 mg daily	Hæmorrhage from colon Necropsy	Possible
12	[illegible]5 M	Polyarteritis nodosa	1 year Corticotrophin and cortisone various doses	Corticotrophin 60 mg daily	Massive gastro-intestinal hæmorrhage Necropsy	Yes
13	45 M	Pemphigus vulgaris	Approx. 8 months Cortisone up to 1 g daily	Cortisone 750 mg daily	Massive gastro-intestinal hæmorrhage No necropsy	Yes
14	55 F	Bronchial asthma	8 days Corticotrophin 30–10 mg daily	Corticotrophin 10 mg daily	Pulmonary embolism Necropsy	Unlikely
15	59 M	Ankylosing spondylitis	3 days Corticotrophin 25 mg daily	Corticotrophin 25 mg daily	? Hypersensitivity to corticotrophin Necropsy	Yes
16	53 F	Scleroderma	6 weeks Cortisone 100 mg daily	Cortisone 100 mg daily	Congestive heart failure Necropsy	Yes
17	1[illegible] F	Acute necrotising arteritis	26 days Cortisone 150–300 mg daily	Cortisone 300 mg daily	Rupture of [illegible] Necropsy	No
18	[illegible]2 M	Cerebral cysticercosis	Approx [illegible]½ months Cortisone 1[illegible]0–300 mg daily	Cortisone 150 mg daily	Hydrocephalus from cerebral cysticercosis Necropsy	No

reaction to foreign protein, since the cerebrospinal fluid contained many eosinophils during these attacks. Later attacks were possibly improved by increasing the cortisone, but in one of these he became unconscious and despite ventricular puncture died. Necropsy confirmed the presence of cysticercosis.

There seems no reason to believe that cortisone in any way hastened or caused death, and it has not been held responsible.

Conclusions

Steroid therapy can be fairly blamed for 9 of the 18 deaths and was probably responsible for 2 more (see table). In 2 patients therapy has not been held responsible and it seems unlikely to have played a part in a further 2. In the remaining 3 death was quite possibly hastened or contributed to by cortisone or corticotrophin, for reasons already discussed. Of the 11 patients whose death has been attributed to steroid therapy 5 at least were suffering from diseases often fatal. 2 of the 3 patients whose death may have been precipitated by therapy were gravely ill, one with polyarteritis nodosa, the other with fulminating ulcerative colitis. It would be quite wrong, therefore, to assume that cortisone or corticotrophin was responsible in every case, and to do so would exaggerate the risks of steroid therapy. It is not possible to assess accurately the incidence of fatal complications, for though 11 deaths certainly resulted from treatment the exact number of patients receiving steroid hormones is not known (it is approximately 500). Even with accurate figures, such a crude incidence would be of doubtful value since it ignores the various diseases treated.

In this series fatal complications have not been related to size of dose or duration of treatment, though clearly the longer a patient receives steroid hormones the longer he is at risk. The minimum time for serious complications to appear is very short, and one of Page's (1954) patients died from pneumonia only seven days after starting corticotropin. Cases 10 and 11 (ulcerative colitis) had fatal complications twelve and eight days respectively after starting treatment. In cases 12 and 13 (death from gastro-intestinal hæmorrhage) very high doses were given for long periods, but severe hæmorrhage has been reported (Davis and Zeller 1952) after only 50 mg cortisone daily, and it would be unwise to draw any conclusions from these 2 patients.

Infection and gastro-intestinal perforation and hæmorrhage have been the commonest fatal complications as they have been in other published series It is hard to see how the risk of infection can be prevented, though patients with tuberculosis and perhaps other chronic infections should be excluded from treatment, save in very special circumstances Similarly patients with a history of peptic ulcer should be excluded, but steroid hormones can cause ulceration in some normal subjects, so that this complication cannot entirely be prevented Death could probably have been prevented in some cases in this series (particularly those due to infection, and the postoperative death) had the vital importance of continuing or increasing the dose of cortisone or corticotrophin during the period of stress been fully appreciated The masking effect of the steroid hormones will always make the detection of an infection difficult, and it is our practice to give large doses of antibiotics at the slightest hint of infection In cases of doubt such a patient is admitted to hospital for observation, and all patients are warned that they must immediately call in their doctor should any untoward malaise or symptom occur Even so, occasional fulminating cases, like those reported by Page (1954), are still likely to happen The patient away from home or who is admitted to another hospital after an accident runs an increased risk unless the need for extra cortisone is appreciated

The development of compounds similar in anti-inflammatory effect to cortisone will continue for prednisone and prednisolone it has been claimed that the unwanted action on fluid and electrolyte balance is much less than that of cortisone As Nabarro et al (1955) have warned, only the less important side effects are removed or diminished with these compounds, the serious ones of adrenocortical suppression and risk of infection remain This false security of prednisone and prednisolone may mean that they are more freely prescribed when there is no real need It is unlikely that compounds will be produced which retain considerable anti rheumatic and anti inflammatory properties without the risk of infective complications and without adrenal suppression

As with all other methods of treatment which have at first sight appeared miraculous, the limitations of the corticosteroid hormones are now being appreciated, particularly with regard to the possibility of serious complications But other forms of treatment have their risks, and it would be a great pity if the dangers of steroid therapy were overemphasised They must, however, be understood, and each physician may have his own ideas as to the best use of corticosteroids It is unwise to embark upon steroid therapy without adequate means for careful and regular supervision of the patient, and unless real benefit can be anticipated As Polley (1956) has recently put it, "For optimal therapeutic value, use of these hormones should be supervised by physicians who have familiarised themselves with its intricacies in the same thorough manner that they would consider necessary in undertaking any complicated medical or surgical treatment"

Summary

In 18 deaths associated with steroid-hormone therapy, infection was the commonest cause (7 cases), and gastro-intestinal hæmorrhage and perforation were each responsible for 3 deaths

Steroid therapy was considered directly responsible for 11 deaths, and probably hastened death in 3 more In 4, death was not the result of this treatment

There is a serious risk of adrenal failure in patients who encounter added stress during steroid therapy Under such circumstances, doses must be increased and antibiotics given in large amounts

Steroid therapy inevitably carries some risk, and regular and careful observation of all patients is imperative

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PLASMA-INSULIN AND INSULIN RESISTANCE

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THE plasma insulin level in man has been studied by Bornstein (1950), Bornstein and Lawrence (1951), Groen et al (1952), and Vallance-Owen and his colleagues (Vallance Owen and Hurlock 1954, Vallance Owen et al 1955) In all cases difficulty was caused by one of two factors with the technique used by one of us (J B) many laboratory animals either died during preparation or had to be rejected because of instability of their blood-sugar level , and the diaphragm technique used by other workers, notably Groen et al (1952), Vallance Owen and Hurlock (1954), and Randle (1956) lacks precision

An added difficulty in estimating plasma insulin is the fact that, in some diabetics, insulin antagonists can mask the presence of plasma-insulin (Bornstein and Lawrence 1951, Vallance Owen et al 1955, Field and Stetten 1956, Hampton et al 1956) Bornstein and Park (1953) and Randle and Young (1956) also found a labile inhibitor in the plasma of alloxan-diabetic rats

Attempts to simplify estimations by using small animals—e g , mice—are handicapped by the fact that glucose is injected together with plasma , thus the injection of 1 0–4 0 mg of glucose in 1 ml of plasma into an animal with a total blood volume of 1 5–2 0 ml may completely mask any fall of blood sugar level due to plasma insulin and will certainly decrease the observed fall

In view of these considerations we tried to concentrate insulin from plasma, thus freeing it from glucose and enabling us to give in a small volume the equivalent of much larger amounts of plasma The administration of such concentrates of insulin should then make it possible to design an assay using more stable animal preparations than before

We also hoped that, in the process of fractionation, the antagonists would either be destroyed or separated from the insulin fraction , but, since the nature of the antagonists was unknown, we could not plan to do so

We describe here the fractionation process and present the evidence that the fraction obtained contains insulin A study of normal, diabetic, and insulin resistant diabetics shows that the method used separates insulin from its antagonists

Methods and Material

In all the preliminary experiments insulin labelled with ^{35}S by sulphation according to the method of Stadie et al (1952) was added to the plasma to facilitate fractionation

The biological activity of all the fractions obtained was tested on the rat diaphragm at 200 mg of glucose per 100 ml by the technique of Brown et al (1952) A fraction was only considered active if the acceleration or inhibition observed was statistically significant ($P = 0\ 05$)

In all the cases freshly obtained normal human plasma was used, and clotting was prevented with heparin

Reagents

Analytical reagent (A R) absolute ethyl alcohol was redistilled

Sulphur free toluene (B D H) was found satisfactory If it was not available, toluene was freed from all sulphur-containing compounds by standard methods (Weissberger 1950)

A R grade *n*-butyl alcohol was repeatedly shaken with A R grade 5% sulphuric acid, refluxed with caustic soda and then redistilled, only the middle third of the fraction boiling between 117°C and 118°C being used

A R grade acetone was used throughout

It is essential to use reagents of the highest grade of purity because reducing substances in the solvents can inactivate insulin

Technique

To 1 vol of freshly obtained plasma were added 4 0 vol of ethyl alcohol, 0 4 vol of toluene, and 0 4 vol of *n*-butyl alcohol The pH was then adjusted with HCl to pH 1 5 (indicator paper), and the mixture was shaken for an hour Then the mixture was centrifuged, the supernatant fluid set aside, and the residue re extracted four times, for an hour at each extraction, with a solvent mixture consisting of 1 vol of 0 04 *M* sodium acetate, 4 0 vol of ethyl alcohol, 0 4 vol of toluene, and 0 4 vol of *n*-butyl alcohol, the pH being adjusted as before

The five supernatant fluids were combined, and acetone was added to give a final concentration of 83% acetone This precipitated all the protein contained in the extract

Experiments with added ^{35}S-labelled insulin showed that about 85% of all counts were present in this fraction (table I)

TABLE I—RECOVERY OF COUNTS IN PRIMARY EXTRACTION INSULIN LABELLED WITH ^{35}S ADDED TO PLASMA

Experiment no	Counts added	Counts recovered		% recovery	% counts in extract
		Extract	Residue		
1	21 950	19 600	3370	104 6	85 5
2	21 950	19 050	3220	101 5	85 5
3	24,000	20 132	2895	95 5	87
4	24 000	20,325	3870	100 8	84
Mean				100 6	85 5

The residue (residue A) and the extract were then dried in vacuo and stored

To test the biological activity of such extracts a fixed volume of 0 15 *M* saline solution (usually half the original plasma volume) was added, the pH adjusted to 2 5–3 0, and the mixture stirred for 30 minutes * The supernatant fluid was collected by centrifuging at high speed (8000 *g*) and the volume accurately measured to allow for correction in terms of original plasma volume The extract was then neutralised and incorporated in Krebs Henseleit buffer to give a plasma equivalent of 0 4 ml of original plasma per ml of buffer No glucose was found in the dissolved extract A considerable portion of the protein had been denatured and was insoluble (residue B) This was suspended in saline solution and tested on the rat diaphragm

Protein estimations showed that the extract contained about 2 5% of the original protein (table II), and all the insulin-like activity was contained in this extract (table III)

TABLE II—PROTEIN CONTENT OF INSULIN EXTRACTS OF PLASMA

Extract no	Total protein in sample (mg)	Extract protein (mg)	% extracted
1	69 0	1 014	1 47
2	61 0	1 268	2 08
3	66 5	2 290	3 44
4	61 0	1 960	3 22
Mean			2 55

Protein estimations according to method of Lowry et al (1951)

To determine whether the acceleration so obtained in utilisation of glucose was due to insulin or was non-

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* In earlier experiments the dry protein powder was stirred for a much longer time to bring a greater amount of protein into solution but much colloidal material became suspended, and this produced irregular results

TABLE III—ACTIVITY OF VARIOUS FRACTIONS OBTAINED FROM EXTRACTION PROCEDURE WHEN TESTED ON RAT DIAPHRAGM

Fraction	Change of rate of utilisation of glucose by rat diaphragm (mg per g per hr)	
	No of diaphragms	Change in rate ±S E M
Extract	45	+1 14 ±0 18
Residue B	14	−0 20 ±0 17
Residue A	28	−0 60 ±0 16

For effect of extract n = 44, T = 6 33, P <0 001
For effect of Residue A n = 27, T = 3 75 P <0 01
All results are expressed as either acceleration or inhibition of control rate

specific, extracts were prepared and divided into four parts One part was treated with alkali and one part with cysteine according to the technique of Sutherland and Cori (1948) After inactivation such inactivated extracts were dialysed against Krebs Henseleit buffer To avoid differences due to losses during dialysis, two remaining fractions were dialysed in parallel To prevent variations due to traces of cysteine or of alkali in the extract, *an identical quantity of these reagents was* added to Krebs Henseleit buffer, and this was then dialysed in exactly the same way as the extracts, and used for the incubation of the control hemidiaphragms Diaphragm experiments showed that both alkali and cysteine inactivated such extracts (table IV)

The technique of investigation thus established was applied to the study of insulin in the plasma of healthy people and patients with ordinary diabetes mellitus and with insulin-resistant diabetes mellitus

The method of study was the rat-diaphragm technique (Brown et al 1952) applied to crude plasma, the extract, and residue A

22 people were investigated by these methods 7 healthy adults, aged 23–37, 8 diabetics, aged 17–71, of whom 1 showed insulin resistance, and 7 patients in diabetic coma, including 4 with insulin resistance In all the cases 0 4 ml plasma or its equivalent was used

The sensitivity of the rat diaphragms to 1 milliunit (0 001 unit) of crystalline insulin was tested at intervals throughout the investigation

Results

The results are expressed as the change in glucose utilisation in mg per g of muscle per hr caused by adding the test substance to the buffer Table V shows that in all the cases where a statistically significant acceleration was observed as the result of adding crude plasma, a similar significant acceleration was seen when extract was used

It also shows that the residue from the extraction process never accelerated the utilisation of glucose by the diaphragm, and that in most cases a statistically significant inhibition was observed

The experiments on cases of untreated diabetes mellitus bear out findings previously reported (Bornstein and Lawrence 1951) that the patients fall into two groups those with and those without available plasma-insulin

TABLE IV—EFFECT OF CYSTEINE AND OF ALKALI ON ACTIVITY OF EXTRACTS

Extract no	Change in rate of utilisation of glucose by paired hemidiaphragms			
	No of diaphragms	Change in rate (mg of glucose per g)	S E M	P
1	8	+1 19	0 2	0 001
1A	8	−0 66	0 36	0 2
2	7	+1 61	0 34	0 01
2C	7	−0 14	0 31	

Extract 1A after treatment with alkali and dialysis
Extract 2C after treatment with cysteine and dialysis

It is of considerable interest that in no case of diabetic coma was "free" insulin found in the plasma, although, in some of these, very large amounts had been administered in the previous twenty-four hours In all such cases—i e, where insulin had been administered—the extract showed insulin activity Patients who had been stabilised on insulin showed insulin present in their plasma

Discussion

The distribution of radioactivity and biological activity after extraction, together with the fact that the extracts were inactivated by alkali and by cysteine, strongly suggests that the acceleration observed was due to insulin Strong support is lent to this view by the more recent finding (unpublished) of C W Baird and J Bornstein that such extracts depress the blood sugar level of adrenalectomised alloxan-diabetic mice Both the diaphragm experiments and the preliminary assays done on the prepared mice suggest that the plasma insulin level is about 1–2 milliunits of insulin per ml of plasma in healthy adults after a meal

TABLE V—COMPARISON OF EFFECT OF CRUDE PLASMA, EXTRACT, AND RESIDUE A ON RATE OF GLUCOSE UTILISATION BY RAT DIAPHRAGM

Experiment no	Sex	Age	Insulin in previous 24 hr	Change in rate of glucose utilisation (mg per g of muscle per hr) with S E M material added		
				Crude plasma	Extract	Residue A
Healthy people						
1	F	26	0	+1 6 ±0 32	+1 4 ±0 27	−0 6 ±0 21
2	M	37	0	+1 1 ±0 28	+1 2 ±0 31	−0 7 ±0 30
3	F	23	0	+0 9 ±0 11	+1 1 ±0 21	−0 2 ±0 18
4	M	34	0	+1 3 ±0 31	+1 0 ±0 28	−0 8 ±0 31
5	F	25	0	+0 9 ±0 26	+0 8 ±0 24	−1 7 ±0 19
6	M	28	0		+2 3 ±0 53	−0 4 ±0 50
7	M	23	0		+0 5 ±0 14	−0 7 ±0 20
Diabetes mellitus						
8	F	56	0	+1 2 ±0 26	+1 1 ±0 17	−0 3 ±0 13
9	M	37	0	+1 4 ±0 19	+1 3 ±0 11	−0 0 ±0 12
10	F	21	0	+1 7 ±0 11	+0 9 ±0 20	−1 0 ±0 23
11	M	17	0	+0 1 ±0 21	0 0 ±0 30	−0 4 ±0 31
12	M	29	0	+0 1 ±0 20	−0 1 ±0 10	−0 5 ±0 27
Diabetes mellitus (stable on insulin)						
13	M	43	70	+1 2 ±0 19	+1 0 ±0 39	−1 1 ±0 26
14[1]	F	71	24	+0 8 ±0 09	+1 0 ±0 16	−0 9 ±0 18
15[2]	F	38	300	−0 1 ±0 10	+1 2 ±0 22	−0 7 ±0 27
Diabetic coma						
16	M	69	0	+0 5* ±0 55	+0 3* ±0 33	−0 6* ±0 48
17	F	19	0	−1 2	+0 1	+0 1
18	F	58	1000	−0 2* ±0 27	+1 2 ±0 36	
19	F	73	400	−0 6 ±0 15	+1 1 ±0 31	0 0 ±0 21
20	F	52	3000	−1 1 ±0 26	+1 7 ±0 41	−0 9 ±0 26
21	F	29	0	−1 1	+1 1 ±0 12	−0 8 ±0 16
22[3]	F	71	8000	−0 8 ±0 20	+2 6 ±0 62	−1 6 ±0 28
Insulin (1 milliunit)						
a				1 9 ±0 39		
b				1 6 ±0 34		
c				1 1 ±0 26		
d				1 1 ±0 27		

In all experiments where standard error is given at least 6 diaphragms were used for the test Where S E M is not quoted only 4 were used owing to lack of material

Results marked with an asterisk were not statistically significant

[1] Patient stable on 24 units a day, insulin resistant 6 years previously

[2] Patient insulin resistant last dose of insulin 24 hr before test

[3] Patient insulin resistant before coma stable on 1000 units a day

0 4 vol of plasma or its equivalent was used in every case

The results obtained in the diabetics (table V) show that such patients fall into two groups those with and without available insulin, cases 11 and 12 being typical juvenile diabetics showing no insulin in either plasma or extract These two patients were later stabilised on 28–36 units insulin a day

Wrenshall et al (1952) have shown that the pancreas of most diabetics aged more than 25 contains insulin However, Bornstein and Lawrence (1951) and Bornstein and Trowbell (1951) found that, in patients with severe diabetes in this age group, the presence of insulin could not be demonstrated in crude plasma So far patients of this type have not been studied by the present technique, but case 21 strongly suggests that such patients may be secreting insulin masked by antagonists in the plasma This patient, a woman aged 29, was seen in coma after having omitted insulin for five days Her plasma actively inhibited the rat diaphragm, but the extract accelerated its utilisation of glucose to a degree seen in healthy people, thus indicating the presence of insulin

Cases 18–22 show that, in diabetic coma, insulin can be present in the plasma but is masked by an antagonist or antagonists, which can be separated by the fractionation process used It is of interest to speculate whether the antagonist is binding insulin in such a way that it is not available to the cell or the antagonist is acting on some enzyme system This masking of the insulin action confirms the results of Vallance-Owen et al (1955) and Field and Stetten (1956)

The nature of the inhibition produced by the residues obtained is of the greatest importance It is, of course, possible that such residues are inhibitors only because they contain toxic products arising from denaturation of proteins during extraction However, in case 22, intravenous injection of the residue in the same quantity as used on the diaphragm into each of a group of 20-g mice protected these animals against hypoglycæmic convulsion induced by a standard dose of insulin, thus suggesting that the effects observed may be due to a specific inhibitor If the effect of such residues is specific, it seems that, in healthy people, there is a balance between insulin and its antagonists in the plasma, and that this balance is upset when insulin resistance is present, whether the patient is in coma or not, as in cases 15–22

Furthermore there seem to be two kinds of antagonist one which is destroyed by extraction (cases 17 and 19), and another which is stable in this procedure (cases 15 and 20–22) It is impossible to state whether the labile antagonist is identical with that described by Bornstein and Park (1953), Krahl and Bornstein (1954), and Randle and Young (1956), but the stable fraction is probably the same as that described by Field and Stetten (1956)

Summary

A technique for extracting insulin from plasma is described

This technique, applied to diabetics, showed that, in diabetic coma, insulin can be present in the plasma, but its activity is masked by antagonists

The implications of the results are discussed

We wish to thank Dr Ewen Downie and Dr H P Taft for permission to study their patients, Miss J Hill for invaluable technical assistance, and the Australian National Health and Medical Research Council and Eli Lilly and Company for financial support

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DUODENAL ULCER

TREATED BY GASTRO-ENTEROSTOMY WITH VAGOTOMY

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In eight years, at the Royal Victoria Infirmary, I have treated 197 patients by vagotomy and posterior gastrojejunostomy according to principles previously described (Hindmarsh 1954) This series of 197 cases of duodenal ulcer comprises all those operated on at this hospital by this method except those treated in the past twelve months

Ætiology of Duodenal Ulcer

There is much evidence that the main factor in the causation of duodenal ulcer is the presence of unbuffered gastric acid combined with the free pepsin produced by psychic or nervous stimulation

The flow of gastric juice, under nervous stimulation, may in itself produce an ulcer This has been shown by work on dogs in which the œsophagus was dissociated from the stomach and anastomosed to the jejunum (Winkelstein et al 1956) The vagal nerves were kept intact and a considerable proportion of these dogs developed ulcers which had the same complications as duodenal ulcer in man and were pathologically similar to such ulcers

That peptic ulcer can be formed by unused secretion of gastric juice was shown in a case of reduplication of the bowel, when an ulcer developed on the antimesenteric border of the normal bowel just opposite the small communication connecting it with a gastric reduplication (fig 1) in a child, aged 3 years, admitted with generalised peritonitis from perforation of the ulcer

To Dragstedt and his colleagues belongs the main credit for introducing vagotomy as a means of reducing excessive peptic secretion, but a recent article emphasises the importance of avoiding the secondary effects of this operation (Oberhelman and Dragstedt 1955) The views expressed in that article are in accordance with my own clinical experience of combining vagotomy with gastro enterostomy

The Present Series

Selection of Material

The patients selected for this operation have been those (of whatever age) in whom chronic ulcer or scarring was demonstrated radiologically and confirmed by laparotomy The length of history was not considered important, because sometimes a chronic ulcer may be found after a very short period of symptoms Many of the cases, however, presented with symptoms which had been present many years—occasionally twenty-five or thirty Acute hæmorrhage—in which partial gastrectomy may save life—is a definite contra indication to this operation, but the need for emergency gastrectomy would diminish if more chronic ulcers were submitted to surgery at an earlier stage

Review of Results

Each patient was interviewed at the end of the first year and was later sent circular letters Of the 197 patients operated on, 1 died after the operation and 2 subsequently from cerebral hæmorrhage, and 1 was not traced, leaving 193 for review, all of whom have been reviewed in the last six months These were graded according to the scheme devised by Visick (1948), those without gastric symptoms being placed in grade I

If symptoms were present, their severity was assessed at an interview (see table) Grade II means that symptoms were slight, grade IIIS that symptoms were occasionally troublesome but controlled, grade IIIU that symptoms were troublesome and uncontrolled, and grade IV that the ulcer had definitely recurred Such assessment is always open to error because the grateful patients minimise their symptoms Those with symptoms were not included in grade II, however, unless the patient said that his symptoms were slight and did not cause any loss of work and his weight was steady Grade IIIS consists of patients who were much improved but lost work because of gastric symptoms, which were occasionally troublesome Loss of weight seemed *directly* attributable to the gastric operation in only 3 cases In 2 others pulmonary tuberculosis developed, and it was thought that loss of weight was due to the tuberculosis

The Operation

Most surgeons who have performed vagotomy by itself are familiar with its unpleasant side effects The most troublesome of these are flatulence with foul gaseous eructations, a sense of unpleasant fullness, vomiting, and very often diarrhœa Of a small series of 20 cases of duodenal ulcer which I treated by vagotomy alone, gastric ulceration occurred in 3 I regarded this as due to gastric retention and the symptoms were satisfactorily controlled when adequate drainage was provided by gastro enterostomy

In the present series of 193 cases the dual aim was to perform a complete vagotomy and to provide good drainage

Complete vagotomy—the first step—may be done without dividing the left coronary ligament to the liver, which can be drawn forwards to expose the gastrophrenic ligament The posterior (or right) vagus nerve is usually attached to the œsophagus by the small mesentery and is normally well defined The anterior (or left) vagus nerve, however, sometimes splits into two or three separate branches, occasionally an intramural trunk may also be present, which must be secured

The (posterior) gastrojejunostomy should create a large stoma extending from the lesser to the greater curve at the junction of the body with the antrum Adequate drainage of the antrum is essential, as has been shown by Oberhelman and Dragstedt (1955) using a more realistic kind of test-meal These workers found that gastric retention leads to oversecretion of hormonal gastric juices, and they report that many of the poor results of vagotomy and gastrojejunostomy have been associated with what they call high gastrojejunostomy—one not sited to drain a hypotonic antrum

Complications

The complication most closely related to the operation itself is gastric stasis, which may last several days A routine has now been developed which has almost eliminated it Nasal aspirations are discontinued at the first possible moment, usually twenty-four hours after the operation, and prompt feeding of semi solids by mouth is allowed in most cases on the third postoperative day The giving of solid food seems to stimulate gastric activity and to promote restoration of normal intestinal function

GRADING OF 193 CASES

Grade	Male	Female	Total
Satisfactory			
I	127	14	141 (73%)
II	31	3	34 (17%)
IIIS	12	2	14 (7%)
Total	170	19	189 (98%)
Unsatisfactory			
IIIU	0	2	2 (1%)
IV	1	1	2 (1%)
Total	1	3	4 (2%)
Grand total	171	22	193

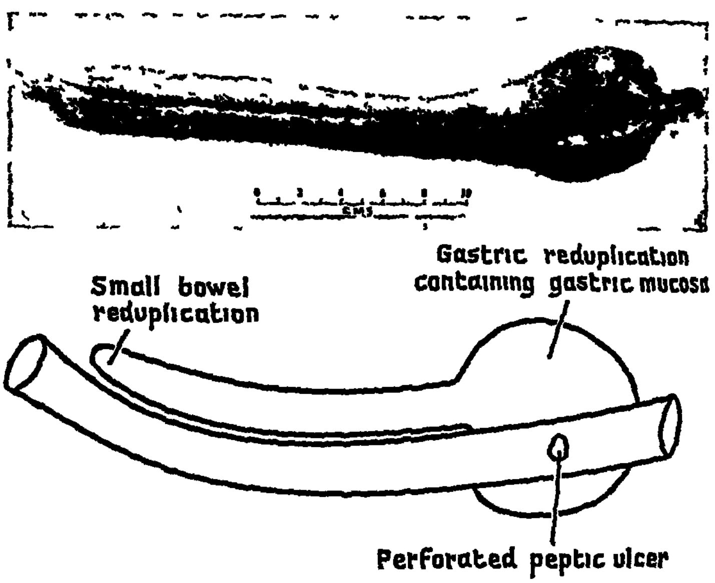
Gastric reduplication containing gastric mucosa
Small bowel reduplication
Perforated peptic ulcer

Fig 1—Reduplication of bowel with peptic ulcer

Gastric hypotonia can occasionally develop if the patient overeats immediately after discharge from hospital, 2 of the present patients ingested a very large meal within a fortnight of operation and had to be readmitted In these cases vomiting was the principal symptom The patients, however, settled down quickly under treatment with gastric aspirations and intravenous infusion

Occasional patients may have difficulty in swallowing for four to six weeks, but reassurance and the ingestion of semi-solid food during this period of difficulty allow the patient to thrive until the disability passes away

The symptoms of which patients complained at follow up were

Symptom	*No of patients complaining*
Pain	11
Diarrhœa	11
Symptoms of hypoglycæmia	3
Nausea and vomiting	6
Fullness and flatulence	10
Bilious vomiting	11

All these symptoms were slight except in 2 cases of bilious vomiting which necessitated entero anastomosis Radiography after a barium meal gave negative results (apart from continuing deformity of the duodenal cap) in all the patients with pain except 2 who had recurrent ulcers All the other symptoms were controlled by simple measures For example, the nausea complained of by 6 patients usually followed a heavy meal and was avoidable

Recurrences

The 2 recurrences are well worth describing because they show where the principles of the operation have been inadequately followed and have led to recurrence of the ulcer

Case 1 —A woman who was improved by the operation but a year after operation had fairly persistent pain *Radiography after a barium meal had been done twice in this patient*, but it was not until two years after operation that such radiography revealed a jejunal ulcer She was *admitted* for an insulin test meal, which indicated incomplete vagotomy, a finding which is useful in recurrent ulceration because it may indicate the cause of the recurrence The patient underwent exploratory laparotomy with a view to *partial gastrectomy* if necessary, but the anastomosis was satisfactory, with very little scarring, and no ulcer was found The lower end of the œsophagus was explored, and the anterior vagus trunk was found to be complete and was divided It is too soon to say whether this subsequent procedure has completely satisfied this patient

The other recurrence shows the danger of gastro-enterostomy which does not drain the gastric antrum satisfactorily Owing to some oversight, the anastomosis was placed rather high towards the fundus of the stomach and to the left of the usual site

Case 2 had symptoms of gastric retention in the immediate postoperative period This was clearly demonstrated by barium meal even of the ordinary type After three years he developed gastric ulcer, which was shown radiologically It was thought that his increasing pain was probably due to this, but in the interval, while awaiting admission, he had jaundice, which necessitated a further laparotomy, at which it was found that he had inoperable carcinoma of the head of the pancreas Owing to adhesions round the anastomosis it was difficult to ascertain whether there was any ulcer in the stomach Cholecystenterotomy was performed and the patient is now recovering from this operation

Mortality

The one postoperative death took place six years ago It happened before the full significance of potassium deficiency was recognised The patient had postoperative gastric retention which did not respond to the usual measures He died on the eighteenth postoperative day Necropsy did not reveal any technical failure but showed that he had lower-nephron nephrosis Such a fatal set of circumstances is unlikely to recur This single death gives a mortality of 0 5% in this series

Comment

The series is presented at this stage because I feel that the results to date of the standardised procedure of vagotomy combined with large stoma, drainage, and posterior gastrojejunostomy are encouraging This operation satisfies the requirements laid down by Oberhelman and Dragstedt (1955) If the principles of this operation are correct, and duodenal ulcer is due to the unbuffered action of gastric secretion, the probability is that, provided the operation is properly done, the results should be permanent The passage of time appears to show no deterioration in the proportion of satisfactory results (fig 2)

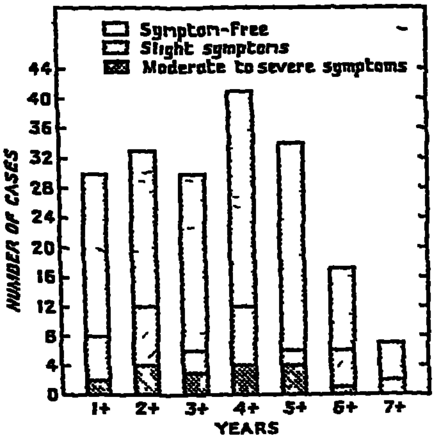

Fig 2—The vertical columns represent the number of operations per year The passage of time shows no deterioration in the proportions of satisfactory results

This series supports the view expressed by Lloyd Davies, reviewing the five year results of many British surgeons, that poor results of vagotomy and gastro jejunostomy tend to declare themselves early (Davies 1956) The better figures in the present series may well be due to the use of a standardised procedure in which the primary objective of the gastrojejunostomy has been drainage

The results of a few operations consisting of vagotomy and pyloroplasty for duodenal ulcer (not included in the present review) support the opinion of Lloyd Davies that this combination is not so satisfactory as that of vagotomy and gastrojejunostomy, the drainage is less adequate, and therefore the improvement produced by this operation is unlikely to be so permanent It is also undesirable to interfere with the duodenum in the presence of an active duodenal ulcer, and one of the great advantages of vagotomy and gastrojejunostomy is that the duodenum is left in situ and intact This is undoubtedly one of the main reasons why a lower mortality is to be expected from this operation

It is true that gastrojejunostomy alone may cure some cases, especially in the older age-groups Probably, in cases where this treatment proves satisfactory, the factors originally responsible for the ulcer have ceased to operate, through the passage of years or through changing circumstances By-passing a chronic ulcer would then prove efficient

It is not easy, however, to estimate how completely the patient's habits and mode of life have changed since the onset of symptoms The addition of vagotomy to gastrojejunostomy does little to increase the risk of the operation and deals permanently with the disordered physiology thought to be so important in these cases

The treatment of combined duodenal and gastric ulcer although infrequent, has been by gastrectomy, and I agree with Johnson (1956) that in these cases the gastric ulcer results from gastric retention In 1 case in this series, where a high gastric ulcer was associated with a duodenal ulcer, treatment was by vagotomy and gastro-enterostomy because removal of the ulcer would have meant almost total gastrectomy This patient has remained symptom free for more than three years

Summary

The results of vagotomy and gastrojejunostomy in 197 cases of duodenal ulcer are reported The patients were operated on by a standardised technique in a period of eight years

This review supports the opinion of Oberhelman and Dragstedt (1955) that, provided vagotomy is complete and drainage adequate the results will compare favourably with any other operation so far devised to treat duodenal ulcer

I acknowledge with gratitude the help of my secretaries, Miss D Brown and Mrs E Short, of Miss J Daniels for her diagrams, and of the house surgeons and nurses of wards 19 and 20 who have cared for these patients after operation.

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"   We do not know how to postpone our inevitable dissolution beyond our allotted span, but, by prolonging our flowing years, we may perhaps shorten our ebb of life There is too much talked today of rehabilitation, too little attention paid to habilitation, by which we mean enabling people still to continue in their daily lives without faltering by the wayside   The geriatricians, though they may have rescued many an old person from a paradise of bedfastness and placed them in a state of uncertain mobility, are not interested in the acuter illnesses of those on the verge of old age, and we are concerned that the very existence of this specialty should have created an artificial division between those in middle life and those who are past their prime There is much to be said for the system which *admits all* sick to one general hospital and will not allow the admission of old people directly to geriatric units   Acute infections these days, are as rapidly cured in the old as in the young, though recovery may be slower, there is however no reason why on that account the elderly should be denied their rightful place in a general hospital when they go down with acute illness"—Editorial in the *College of General Practitioners' Research Newsletter*, May, 1957 p 96

MALIGNANT GROWTH IN THE LIVER AND SERUM-VITAMIN-B_{12} LEVELS *

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High serum-vitamin-B_{12} levels have been found in acute liver disease (Rachmilewitz et al 1955, 1956) and occasionally in cirrhosis of the liver In acute hepatitis the serum-vitamin-B_{12} level rose in the acute phase of the disease, when disintegration of liver-cells was most pronounced It was therefore assumed that the injured liver cells released into the blood stream the vitamin B_{12} stored in the liver This assumption was supported by findings in dogs with acute liver necrosis induced by carbon tetrachloride Extremely high serum-vitamin-B_{12} levels (up to fourteen times as high as the normal level) were found in these dogs as early as 1–2 hours after the intraportal administration of carbon tetrachloride (Stein et al 1956)

The interrelationship between liver damage and a raised serum-vitamin-B_{12} level prompted us to estimate the serum-vitamin B_{12} levels of patients with neoplastic disease involving the liver

Methods

Vitamin B_{12} was determined microbiologically with the aid of a mutant strain of *Escherichia coli* as described previously (Grossowicz et al 1954, Rachmilewitz et al 1956) Only the total serum-vitamin-B_{12} was determined This was done in either of the following two ways (1) by diluting the serum 1 8 with distilled water, heating for 30 minutes at 100°C, and adding the heated mixture aseptically to the medium , or (2) by liberating the vitamin B_{12} from the serum-proteins by acid precipitation (0 6% acetate buffer , pH 4 6), autoclaving for 30 minutes at a pressure of 10 lb in the presence of cyanide (0 2 mg per ml of undiluted serum), and assaying the neutralised supernatant fluid

The serum-vitamin-B_{12} values of 35 healthy people ranged from 200 to 500 (mean 340) µµg per ml

Results

18 patients with various malignant tumours extensively involving the liver were investigated The malignancy and the hepatic metastases were diagnosed on the basis of clinical findings, biopsy at laparotomy, or necropsy findings In most of these patients the liver was heavily infiltrated with tumour tissue Mild to moderate jaundice was an accompanying sign in 8 patients In 16 of 18 patients the serum vitamin B_{12} level was found to be raised (640–20,000 µµg per ml) (see table) In cases 8 and 9 with malignant melanoma involving the liver the serum vitamin-B_{12} level was moderately raised (800 and 820 µµg per ml) In case 10, however, with a like tumour, the serum vitamin B_{12} level was excessively high (5800 µµg per ml)

The highest serum-vitamin B_{12} level (20,000 µµg per ml) was found in case 2, who had undergone total gastrectomy for cancer of the stomach When the level was estimated several months after the gastrectomy, the liver was extensively infiltrated with metastases causing jaundice

In case 16, with multiple myeloma, necropsy showed extensive amyloidosis of the liver causing flattening and displacement of the liver-cells by amyloid, and the serum vitamin-B_{12} level was raised at several examinations In 2 patients with multiple myeloma not complicated by amyloid the serum-vitamin-B_{12} level was normal

In case 15, a girl aged 19 with cancer of the ovary, the liver was heavily infiltrated with metastases, and

SERUM-VITAMIN-B_{12} LEVELS IN PATIENTS WITH MALIGNANT TUMOURS

With liver metastases

Case no	Date	Diagnosis	Serum vitamin B_{12} (µµg per ml)
1	April 15 1955	Cancer of stomach	920
2	Feb 13 1956	"	20,000
3	June 7 1956	"	1050
4	Dec 13 1956	"	1300
5	April 13 1956	Cancer of breast	4000
	April 30 1956		1800
	May 19 1956		1300
6	May 21 1956		640
7	May 20 1956	Cancer of colon	650
8	March 21 1955	Malignant melanoma	820
9	May 25 1956	"	800
10	June 29 1956	"	5800
11	Dec 14 1956	Hepatoma	470
12	Dec 4 1956	Hepatoma and cirrhosis of liver	4350
	Dec 7 1956		4650
13	Nov 14, 1955	Primary carcinoma of liver	1450
14	Dec 28 1954	Cancer of ovary	3000
	Jan. 7 1955		2100
15	March 10 1955		4800
16	Aug 1 1955	Multiple myeloma	1600
	Aug 9 1955		1100
	Aug 12 1955		1700
	Aug 20 1955		1200
17	Sept 16 1955	Hypernephroma	960
18	July 19 1956	Carcinomatosis primary unknown	500

Without liver metastases

Case no	Date	Diagnosis	Serum vitamin B_{12} (µµg per ml)
1	March 23, 1955	Cancer of stomach	250
2	Oct 17, 1955	"	400
3	Oct 17 1955	"	100
4	Feb 1 1956	"	410
5	March 23, 1956	"	200
6	April 11, 1956		200
7	June 5, 1956	"	100
8	July 1 1956	"	320
9	Feb 15 1956	Cancer of breast	235
10	Sept 19 1956		300
11	March 24 1956	Cancer of colon	400
12	July 12 1956	Cancer of colon and brain	390
13	Jan 21 1956	Neuroblastoma	300
14	Feb 15 1955	Fibrosarcoma of peritoneum	200
15	Feb 12 1955	Hypernephroma	310
16	May 5 1955	Myosarcoma of uterus	450
17	Dec 10 1956	Cancer of salivary glands	550
18	Jan 2 1957	Cancer of prostate	200
19	Jan 9 1957	Cancer of ovary	140

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* This work was supported by a grant from the Stela Glezer Memorial Fund Mexico City ,

histological examination revealed atrophy of the liver-cells adjacent to the tumour Her serum-vitamin-B_{12} level was 4800 μμg per ml

In case 12, with hepatoma in a cirrhotic liver and a raised serum-vitamin-B_{12} level (4350 μμg per ml), the entire liver was found at necropsy to be infiltrated with tumour tissue, but in case 11, with hepatoma and a normal serum-vitamin-B_{12} level (470 μμg per ml), the tumour was limited to a circumscribed area, leaving the rest of the liver intact

In 19 control patients with malignant diseases involving various organs but without evidence of liver metastases the serum-vitamin-B_{12} levels were normal (100–550 μμg per ml) (see table)

Discussion

These results show that invasion of the liver by a malignant growth is accompanied by a rise in the serum-vitamin-B_{12} level The invading tumour, by causing necrosis and/or displacement of liver-cells, allows vitamin B_{12} to escape from the liver into the blood Damage of liver-cells by virus (Rachmilewitz et al 1955, 1956, Kristensen 1956) or by carbon tetrachloride (Stein et al 1956) similarly raises the serum-vitamin-B_{12} level.

In liver disease, whether of viral or of chemical origin, the serum-vitamin-B_{12} level increases rapidly but only temporarily (lasting only 1–2 weeks in hepatitis and a few days in liver injury from carbon tetrachloride) and then falls rapidly to normal levels In cancer of the liver the process damaging the liver is more prolonged , hence a persistent rise of serum-vitamin-B_{12} level is to be expected Persistent rises were actually found in 3 patients (cases 5, 14, and 16) in whom estimations of serum-vitamin-B_{12} were repeated in the course of illness (see table)

That the neoplastic process per se is not responsible for the rise of serum-vitamin-B_{12} level is shown by finding normal levels in the controls with various malignant tumours but no evidence of liver metastases These findings suggest that *determination of the serum-vitamin* B_{12} may help the diagnosis of metastases to the liver in cases of malignancy Raised levels should be interpreted as an indication that the liver is involved Normal levels, however, do not rule out this possibility, because metastasising tumours not causing liver damage could be present in the liver without raising the serum-vitamin-B_{12} level

Vitamin B_{12} is not the only substance released from liver-cells affected by tumour Wroblewski and La Due (1955) reported that the level of glutamic oxalacetic transaminase in the serum was raised in virus hepatitis, carbon-tetrachloride poisoning, and malignancy with liver metastases However, whereas increased transaminase activity of the serum is found in destruction of various tissues, including heart muscle as in myocardial infarction (Wroblewski and La Due 1955), raised serum-vitamin-B_{12} levels are found only when the injured tissue is liver

The serum-vitamin B_{12} level is also much raised in myeloid leukæmia (Beard et al 1954 Killander 1954, Mollin and Ross 1955, Rachmilewitz et al 1957) Whether a mechanism common to liver disease and myeloid leukæmia is responsible or not for the striking rise in serum-vitamin-B_{12} levels in these two conditions remains to be elucidated.

Summary

Serum-vitamin B_{12} levels were determined microbiologically in patients with malignant disease

In 19 patients without metastases in the liver the serum vitamin-B_{12} levels were normal (100–550 μμg per ml) whereas in 16 of 18 patients with metastases in the liver the levels were raised (640–20,000 μμg per ml)

These and previous findings indicate that this rise in serum-vitamin-B_{12} level is due to release of the stored vitamin from damaged liver-cells

The rise of serum-vitamin-B_{12} level may be used to help the diagnosis of metastases to the liver in cases of malignancy

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CHILDREN IN HOSPITAL

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CHILDREN are usually given some kind of explanation by their parents before they go into hospital Are they then less fearful and anxious ? Mac Keith (1953) pointed out that children may have varied, bizarre, and sometimes frightening ideas about the hospital What they are told may be coloured by their parents' own anxiety about an operation, which is often based on incomplete understanding of the situation and is likely to confuse the child—the opposite to what was intended.

We assume that the nurses and doctors explain what is happening, and relieve these fears Are we justified in this assumption ? Should a simple explanation be given to children soon after they are admitted ? The following investigation was undertaken with a small group of children to discover more about their attitudes towards admission and operation, and to see whether a simple introductory explanation would result in less emotional disturbance

Method

The children were all admitted to the hospital for five days for the same operation—correction of a strabismus Those living more than twenty-five miles from Central London, and those with a history of previous operations, were not included The parents were interviewed, and the child's behaviour and personality before admission was assessed and classified under a number of headings (Cameron 1955) All the children were tested briefly by a psychologist

They were divided into two groups Group A was a consecutive series of 20 children who formed a " control"

AGE, SEX, AND INTELLECTUAL LEVELS OF THE TWO GROUPS OF 20 CHILDREN ADMITTED TO HOSPITAL FOR OPERATION

	—	Group A (control)	Group B (prepared)
Age (yr)	Mean	5 9	? 9
	Standard deviation	0 61	0 62
	Range	2 5–9 2	2 3–9 9
Sex	Girls	14	14
	Boys	6	6
I Q	Mean	107	100
	Standard deviation	1 9	19 8
	Range	71–127	60–140

group. Group B comprised 20 similar children, from the same social background, who were carefully matched with their opposite numbers in group A for the criteria shown in the accompanying table. In addition to facing the same experiences as the children in group A, these children were specially interviewed by myself on their first, third, and fifth days in hospital; they formed the "prepared" group. 12 children in group A and 13 in group B had a history of some disturbance before admission.

Evidence of disturbance after operation was derived from various sources.

(1) Disturbance in the ward was estimated from a daily record of behaviour made on a proforma by the ward sister.

(2) A week after leaving the ward, in conjunction with a clinical examination, the child's behaviour was re-assessed under the diagnostic headings described by Cameron (1955).

(3) Twenty-six weeks later this examination and inquiry was repeated.

There are well-known limitations to the validity of behaviour records for estimating anxiety and emotional disturbance in children, but the method presented here was the most suitable available. A child was designated "disturbed" when he showed disturbance in more than one major aspect of behaviour. The final assessment of whether a child should be classed as still disturbed was made by an independent person who had not observed the children.

The Ward

Each child was brought to the ward by one of the parents. The details for admission were collected, the parent then left, and the child was bathed and put to bed. This took about half an hour. The child wore hospital pyjamas. He was allowed to keep any special toy he might have brought with him. During this process he would already have passed through the care of several nurses.

Soon after his admission the ward sister came to him, and lightly bandaged his eyes for a few seconds, telling him that this was what it would be like after the operation. This brief contact should not be considered a preparatory explanation or interview, for no real opportunity was given for any discussion. The child seemed to accept it as another aspect of the bewildering process of coming to the ward.

Apart from an afternoon rest period, there was little formal discipline in the ward, and there were opportunities for play, tea-parties, and television. All types of surgical patients were nursed in the ward; one special section was occupied by a burns unit, where two or more naked, burned children were usually on view.

Next day premedication was given to the child in his bed. This was singled out from surrounding beds by having a red blanket placed over it. Parents were told that they could visit throughout the afternoon of the two days during which the child's eyes were to be bandaged, and thereafter each evening.

Preparation

Children in group B only were interviewed by myself soon after admission. This interview was unhurried and the child was encouraged to talk freely. Although it lasted only fifteen to twenty-five minutes, there did not seem to be any need for further time, and the child clearly appreciated the contact made with him.

A short while in a ward cannot help but make one appreciate that much of what is said to children (and for that matter, to parents also) is beyond their intellectual grasp, particularly if they are anxious and in strange surroundings. For this reason a few specific points were introduced into this conversation in a selected order using simple phrases which the child would be likely to understand. Questions which might increase anxiety were avoided as much as possible. The child was not suddenly asked who he was, or where he had come from; I opened the conversation by using his christian name, and then telling him that I knew about his home—the purpose of this, and indeed of the whole conversation, being to establish a close and meaningful contact with him as quickly as possible. I then told him that I was there to see that he was happy, and would look after him while he was in hospital. After this reassurance, a simple explanation was given of what was to happen. I told him when his parents were coming again (which I had found out beforehand), and how many days he would be in hospital. Questions were answered as truthfully, briefly, and simply as possible.

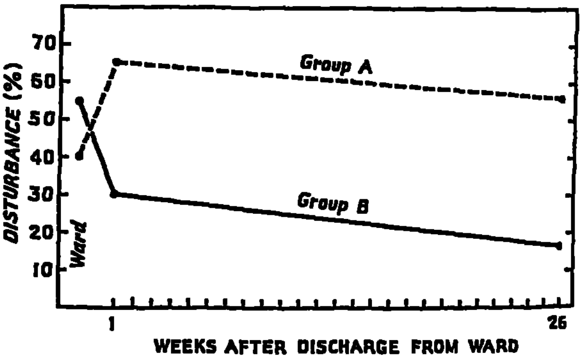

Fig. 1—Emotional disturbance in two groups of children admitted for operation.

The children were subsequently visited by me on the third and fifth days in the ward, for ten to fifteen minutes. They were encouraged to talk freely, and questions were answered.

Results

In group A, 8 children were "disturbed" in the ward and 13 at one week and 11 at twenty-six weeks after discharge. In group B the corresponding numbers were 11, 6, and 3 (fig. 1). The difference at twenty-six weeks is significant, and for this pair $\chi^2 = 5{\cdot}38$, P = just above 0·02.

When the pairs of children in each group were examined to see whether age played any part, it was evident that the children over 4 years had benefited considerably. The numbers in each group aged 4 years and more who were disturbed in the ward and at one and twenty-six weeks after discharge were respectively 7, 11, and 9 in group A (18 children), and 9, 4, and 1 in group B (18 children) (fig. 2). The difference at twenty-six weeks is significant, and for this pair $\chi^2 = 6{\cdot}7$, P = 0·01.

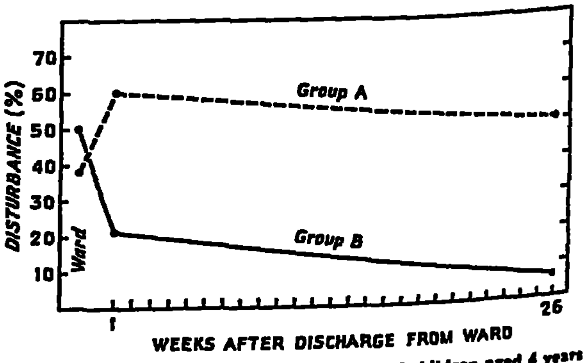

Fig. 2—Emotional disturbance in two groups of children aged 4 years or more admitted for operation.

The Children's Fears

Disturbances similar to those met with here have been fully described elsewhere (Jessner and Kaplan 1948, Prugh et al. 1953), and a detailed report would be out of place, but a few comments will illustrate the problems and responses encountered.

The parents of most of the 40 children had tried to tell them something of what to expect, but (except in 4 cases) these explanations were so incomplete, or so far from the truth, that they led to gross misconceptions in the child's mind. The parents of 9 gave no advice (4 in group A, 5 in group B). One said, "I couldn't bring myself to tell him—I was so afraid," and another, "I didn't know what to say, so I said nothing." 4 mothers told deliberate lies to avoid upsetting the children, saying they were going with them to the cinema or shopping, or going for a holiday.

A boy, aged 9 years, was trying hard to keep awake on the night of admission; his mother had told him the operation would be carried out while he was asleep. A girl, aged 8 years, refused to eat; she had been told something would be put into the food to put her to sleep for the operation.

Most children, when asked why they had come into hospital, said "for an operation," and then, asked what this was, said "don't know." A 7-year-old girl said, "I've never had an operation before in my whole life, so I can't tell you. I said to Mummy, 'Do they take your eye out?' and she said, 'No.' I said, 'Do they press your eye in?' and she said, 'No'; so I still don't know." This answer also illustrates a fear shared to some extent by all the children, fear that their eyes were to be removed, and that something important must be cut. A boy of 8 said, "They might cut it out—I don't know if they cut your eyes or not"; another of 6, "They take it out, turn it round, and cut it, and put it back"; and another, "I was one of the lucky ones, I got my own eye back."

All children over 4 were to some extent afraid of injections.

Fear was often projected on to animals or toys left at home; a pet would be said to be ill, or a favourite toy broken. As events in fantasy, these might be said to be under control, and therefore able to be brought at will to a safe and happy ending, in contrast to the uncontrolled events taking place in the ward, and in this indirect way the child was able to reassure himself about the future.

Some of the older children had repeatedly asked their parents what was to happen to them; others showed indifference or denied that they were going into hospital. In these instances their underlying anxiety appeared in other ways—general irritability, a readiness to be upset by trivialities, or temporary changes in eating and sleeping habits. Less often there was suppression and inhibition of previously disturbed behaviour. A girl, aged 7 years, on learning that she was to be admitted to hospital, became obedient, unusually quiet, and went out of her way to make sure her parents were pleased with her. We saw this reaction in 4 children in the ward, where they were clearly anxious to please as a cover for underlying insecurity, and some children reacted similarly on returning home.

There was sometimes a sudden flood of tears when the child realised what was to be talked about in the preparatory interview, or he would make comments on the ward, or reiterate a question such as "How long will I be here?" and then seem not to listen for an answer. This somewhat disheartening situation proved misleading. Tears were quickly followed by an apparent appreciation of what was happening, and the children gave surprisingly accurate accounts of the conversation to their parents.

Thoughtlessness on the part of the nurses sometimes led to increased anxiety. An 8 year old boy was moved to a more isolated part of the ward because he had been vomiting; he was given no reason for this and was intensely miserable. He said he had been "punished" for being naughty and for being a coward during the operation. This feeling of failure in relation to the other children was common. Children were intensely aware of their relationships with each other, and compared themselves in terms of bravery. Other children were often regarded as being punished when they were suddenly taken away for operation or investigations, the red blanket being cited as additional evidence for this. Sick children, particularly the burned children, were also a common focus for anxious fantasy.

35 of the 40 parents visited their children. The 5 who never visited (2 in group A and 3 in group B) happened to live near the hospital. They said to come would upset themselves too much.

Some of the mildly disturbed children in the ward became severely disturbed on returning home. They were either aggressive to their parents, particularly the mother and siblings, or over-dependent, following the mother about the house, and asking to be fed, bathed or dressed. Some of the most disturbed children in the ward were least so at home.

Six months after discharge, 14 children were still disturbed (11 in group A, and 3 in group B). 3 of these had not been disturbed at the one-week interview. They had been well behaved, quiet, and noticeably obedient for the first three weeks at home, and had then become restless and aggressive. These children may have waited until they felt secure at home before expressing their anxiety. As I have already mentioned, this situation is comparable to the over-compliant good behaviour shown by insecure children in the ward. Bedwetting and tics did not arise as complications.

Discussion

This investigation has two main interests: first, the extent to which these children were frightened and confused on admission; second, the lower incidence of disturbance after leaving the ward in the children who were specially prepared, coupled with the manifest relief and pleasure most of the children showed when they met a friendly adult who was not either doing something to them or asking questions.

An eye operation was chosen for this study because all the children would have the same hospital experience, and since the eye is a highly valued part of the body, it was thought that it would be a particularly disturbing operation. It might be argued that the results should not be applied to children admitted for other reasons; but this is not so, for the methods of thought which such a preparation aims to assist are common to all children of similar age and emotional development, whatever their physical illness.

Many of the children were told nothing, or very little by their parents when they were going into hospital, and some were even told direct lies; others formed alarming ideas based on what they had seen or heard, and here the "unpleasant" truth seemed less disturbing than their fantasy. They were helped considerably by the simple discussion and explanation.

The demonstration and talk, to be effective, must follow an extremely simple course, at the same time allowing the child adequate opportunity to express his feelings. There is a tendency to think of children, and to speak to them, as though they are either miniature adults at one extreme or uncomprehending animals at the other. But in fact a child of 4 years is quite different from a child of 6 years, and both are different in the range of their concepts and the form of their thought and emotion from an adult. They require accurate explanations—i.e., accurate in that they fit their own concepts—if they are to feel reassured.

These children clearly appreciated the contact made with them, and I think the main requirement of this preparatory interview was that the child should be left with a feeling that any fears were understood, and would be looked after, without his necessarily having had to express them in words

Unfamiliar and frightening surroundings and sights, and unsympathetic or thoughtless staff, increase the stress for the child, and it was interesting that in spite of having an experienced and understanding staff, much needless anxiety was caused by sudden changes in the ward routine, unexpected investigations, and a general failure to tell the children what was happening There was a tendency to treat children with little regard for their personal privacy, and to forget that they may be aware of what is going on around them and wish to understand it

Jessner and Kaplan (1948) have suggested that disturbed ward behaviour may be beneficial, as the child has been able to express his anxiety Certainly ward disturbance was common in the children who afterwards made a good recovery

The younger the child, the more dependent he is on his parents, and the more important is separation from the mother (Bowlby 1951), moreover, the less his skill in methods of dispelling fear, the more likely it is that these will fail him and that he will become emotionally disturbed It is a disquieting observation here that all the children under 4 years were still disturbed six months after discharge from the ward

One final comment I am not suggesting that every child should be interviewed by a psychiatrist before operation My clinical experience undoubtedly helped me in talking with these children, who were facing a critical time—left by their parents, in strange surroundings, and among strangers But this type of interview could be carried out by any person prepared to give the necessary time, to talk to the child in terms he can understand, and to allow him adequate opportunity to express his feelings Ideally, this person should almost certainly be one of the parents, and it seems advisable that they should be given some help in this task—if only by leaflet, letter, or a little briefing

Summary

40 children were admitted to hospital for an eye operation and followed up for six months Most of them were confused and frightened on admission Many had been told nothing, very little, or even direct lies, by their parents, and had formed alarming ideas about what was to happen

In a special interview on admission, the children were given a simple verbal explanation and reassurance A significant number of children aged $4^1/_2$ years and over benefited from this type of preparation

Many schemes of preparation have been recommended in recent years, some of them complicated This study suggests that the older child can obtain considerable benefit from a simple and systematic explanation opportunity to express his feelings, and the realisation that he will be understood and looked after while he is in hospital

I am indebted to the endowments committee of Guy's Hospital, who provided a grant which allowed the work to be carried out, Mr Frank Law and Mr O G Morgan, who kindly allowed me to see their patients, Miss S Cox, who undertook the psychological testing of the children, and the members of the staff of the department of child health for their kind coöperation

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GLOSSITIS AND THE PRE-ANÆMIC STAGE OF PERNICIOUS ANÆMIA

DIAGNOSIS BY SIMPLE METHODS

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ADDISONIAN pernicious anæmia is now regarded as a manifestation of vitamin-B_{12} deficiency, the development of anæmia being preceded by months or years of depletion of vitamin B_{12} in tissues and serum During this pre anæmic stage, the patient may complain of vague general ill health, and of symptoms, such as glossitis or neuropathy, suggesting vitamin B_{12} deficiency

It is the purpose of this paper to show that simple methods—gastric aspiration, bone marrow biopsy, and response to treatment with vitamin B_{12}—may establish the diagnosis of pernicious anæmia in the pre anæmic stage, once suspicion has been aroused by the presence of glossitis In the cases described the diagnosis was also confirmed by microbiological assay before treatment

Case-reports

Case 1 —A woman, aged 40, complained of soreness of the tongue of 8 months' duration The objective changes were gross, the tongue resembling raw beef Physical examination showed no abnormality, apart from the glossitis The peripheral blood was within normal limits hæmoglobin (Hb) 82% (=12 1 g per 100 ml), erythrocytes 4 31 × 10^6 per c mm packed cell volume (P C V) 39% Gastric aspiration revealed histamine fast achlorhydria, and the sternal marrow showed hyperplastic early megaloblastic erythropoiesis The diagnosis of vitamin B_{12} deficiency was confirmed by microbiological assay, the serum vitamin B_{12} being 40 µµg per ml (normal 100–900 µµg , mean 360 µµg) Parenteral administration of vitamin B_{12} caused complete subjective and objective improvement in the glossitis, but did not alter the blood levels

Case 2 —A woman, aged 76, complained of soreness of the tongue of a year's duration The tongue was smooth and, at the tip, red Physical examination was otherwise unrevealing The peripheral blood was normal (Hb 99%, P C V 42 5%) Histamine fast achlorhydria was found, and sternal marrow biopsy disclosed hyperplastic early megaloblastic erythropoiesis The serum vitamin B_{12} was 45 µµg per ml Parenteral vitamin B_{12} abolished the glossitis

Case 3 —A woman, aged 66, complained of glossitis for 5 years and dyspepsia for 2 Her tongue was smooth but not red There were no abnormal physical findings, and the peripheral blood was normal (Hb 104%, P C V 45%) Histamine fast achlorhydria was noted and the sternal marrow showed hyperplastic early megaloblastic erythropoiesis Barium meal examination and follow through were normal The serum vitamin-B_{12} was 120 µµg per ml Parenteral vitamin B_{12} relieved the glossitis but did not affect the dyspepsia

Discussion

Vitamin-B_{12} deficiency should be suspected in every case of glossitis where no other obvious cause is found It is still a common misconception that normal peripheral blood excludes such a diagnosis and renders further investigations unnecessary, though Ungley (1952) has reported a case of glossitis without anæmia but with a low serum-vitamin-B_{12}, and Mollin and Ross (1954) have shown that vitamin B_{12} deficiency can be demonstrated by microbiological assay in non anæmic patients

How commonly glossitis in non anæmic patients is due to vitamin-B_{12} deficiency is not known, for only one other comparable case has been reported (Ungley 1952), but the syndrome may not be rare, for the three cases reported here are half the cases of glossitis without anæmia seen in a year in a general medical unit These demonstrate clearly that the diagnosis can be established in the pre-anæmic stage In view of recent reports (Bastrup Madsen 1956a, Victor and Lear 1956) that the neurological lesions due to vitamin-B_{12} deficiency may progress even when the blood is normal, it is obviously desirable in such cases to begin treatment as soon as possible

In our patients the bone-marrow erythropoiesis was hyperplastic and undoubtedly megaloblastic, but the abnormality was not frank, and the abnormal cells were those described by Dacie and White (1949) as intermediate megaloblasts Mollin and Ross (1953) have shown that erythropoiesis becomes megaloblastic when the serum-vitamin B_{12} falls to about 80–120 µµg per ml At this borderline level the epithelial manifestations of vitamin-B_{12} deficiency, such as glossitis and cheilosis may precede the transition from normoblastic to megaloblastic erythropoiesis, in such cases there may be an abnormality in the maturation of the white-cell precursors (Bastrup-Madsen 1954, 1956b) but, unless erythropoiesis is megaloblastic, the more elaborate techniques of serum-vitamin-B_{12} estimation by microbiological assay or absorption studies with radioactive vitamin B_{12} are necessary to confirm or refute the diagnosis

The treatment of such patients does not differ from the treatment of those with established pernicious anæmia Glossitis has been observed in cases of pernicious anæmia in therapeutic remission maintained on 100 µg of vitamin B_{12} intramuscularly each month, and larger doses, as recommended by Davis (1957), should be given Failure to respond to treatment renders a diagnosis of vitamin-B_{12} deficiency untenable

Summary

Three cases of glossitis in non-anæmic patients are reported The diagnosis of vitamin-B_{12} deficiency was suspected from the demonstration of achlorhydria and of early megaloblastic change in the bone marrow It was confirmed by microbiological assay and by the response to treatment with vitamin B_{12} The value of gastric aspiration and bone-marrow biopsy in the detection of vitamin-B_{12} deficiency in non-anæmic patients is emphasised

I am grateful to Dr J A W McCluskie for his advice and criticism It is a pleasure to thank Dr D L Mollin, of the Postgraduate Medical School of London, for his most generous help and for the serum vitamin-B_{12} estimations

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ATHEROSCLEROSIS IN A HÆMOPHILIAC

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The narrowing of the coronary arteries which may occur in atheroma is attributed by Duguid (1946, 1954) to the deposition of fibrin on the endothelial surface of the vessel wall In his view the other appearances which characterise the atheromatous plaque, such as fibrous thickening of the intima, and fatty infiltration, follow this primary event Thus Duguid writes "The only process likely to reduce its [i e, the artery's] lumen is one arising in the lumen itself, such as thrombosis or embolism, and we may therefore take it that, where a coronary artery is narrowed by a fibrous thickening of the intima, thrombosis is the most likely factor" (Duguid 1954) He admits that there may be a second type of lesion not preceded by intimal thrombosis As he says, "there are in fact, two forms of atherosclerosis—one in which there is narrowing, and which is consequently a highly dangerous condition, and another in which the tendency is rather in the opposite direction" He believes that the latter has little importance in the pathogenesis of ischæmic heart-disease In Duguid's view the fatal factor may be "some thrombogenic influence, more powerful and generalised than mere local damage to the vessel walls" (Duguid 1954)

We report here a case in which extensive atheroma of the coronary arteries and aorta has developed in spite of lifelong hæmophilia

Case-report

Retired storekeeper, aged 73 [hospital no A 34249] When a child he noticed that he bled excessively after cutting his finger When 25 years old he bled for a week after a tooth had been extracted Shortly afterwards he gave up cricket because of hæmorrhage into his knee joints From that time he remained well, except for a tendency to bruise easily, until 1928, when he passed blood in his urine for a week Ten years later, at the age of 54, he again had hæmaturia In view of a prolonged clotting-time ($11^{1}/_{2}$ minutes) and a normal bleeding-time hæmophilia was diagnosed Between January, 1945, and his death in March, 1957, he was admitted to hospital nine times with hæmorrhage from the alimentary tract and had to have blood transfusions on four occasions

Between these episodes of hæmorrhage his health was good until 1954, when he began to have retrosternal pain on climbing stairs, it was relieved by rest and with nitroglycerin. In 1955 the frequency of the attacks on exertion increased

There is no history of consanguinity The patient's maternal grandfather "bled to death" at the age of 67, and also two first cousins 24 and 28 The two sons of the patient's married daughter bleed easily and one is a proved hæmophiliac

Clinical and Laboratory Findings

On admission on Jan 6, 1957, he weighed 183 lb No clinical evidence of anæmia, petechiæ, or ecchymoses The tissues around both knee joints were hypertrophied, and crepitus was palpable on moving these joints Cardiovascular system sinus rhythm, blood-pressure 150/80 mm Hg, apex-beat impalpable, first and second heart sounds audible, no systolic or diastolic murmur Respiratory, alimentary, and central nervous systems normal While dressing and undressing the patient had two typical attacks of angina pectoris

Examination of the blood showed Hb 103% (14 9 g per 100 ml), white cells 11,200 per c mm, platelets 210,000 per c mm, coagulation-time $15^{1}/_{2}$ minutes (Lee and White), clot retraction nil, prothrombin time 12 seconds, prothrombin consumption 100%, Wassermann reaction negative The total blood cholesterol was 240 mg per 100 ml The α lipoproteins were 32 mg per 100 ml (13%), and β lipoproteins 243 mg per 100 ml (87%) by the Cohn microfractionation method no 10 A thromboplastin generation test gave the following results

	Patient (sec)	*Patient + normal serum (sec)*	*Patient + 50% normal $Al(OH)_2$ plasma (sec)*	*Patient + 50% hæmophiliac aluminised plasma (sec)*
2 min	60	100	43	160
3 min.	37	70	22	90
4 min	30	36	18	
5 min	26	33	14 5	39

On X ray screening of the chest, the left ventricle was seen to be prominent and the aorta unfolded No calcification was visible in the coronary arteries or in the aortic valves Parallel linear calcification was clearly visible in the abdominal aorta, and there was a trace of calcification in the aortic arch

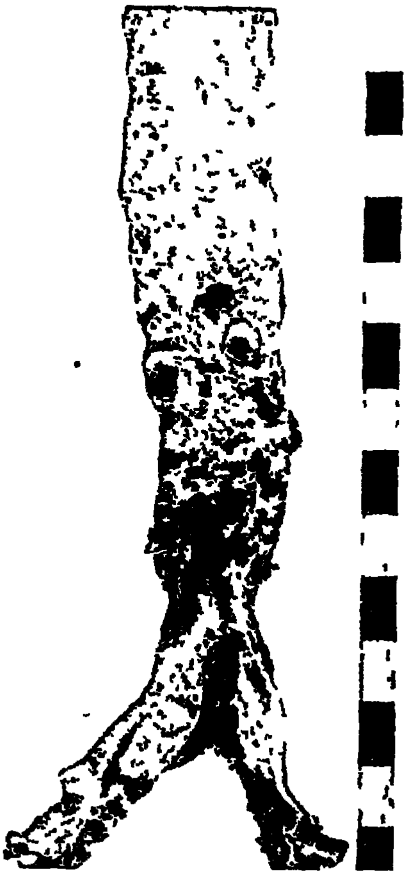
Electrocardiography on April 10, 1955 had shown sinus rhythm, P–R and QRS intervals normal, QRS complex normal, and horizontal RS–T depression of 1 5 mm in V4 and V5, and of 1 0 mm in I II, and V6 These changes are highly suggestive of myocardial ischæmia

Post mortem Findings

After another admission to hospital for melæna on March 10 the patient died on March 13 in spite of blood transfusion We are indebted to Dr P S Andrews, of the Bland Sutton Institute, for his report on the necropsy

The body was obese (weight 170 lb) and the skin pale The heart was enlarged from left ventricular hypertrophy and weighed 500 g the muscle showed ischæmic fibrosis of the septum and the lateral wall of the left ventricle The coronary arteries were atheromatous and calcified, the lumen being narrowed and tortuous but no recent occlusion was present The aorta showed early atheromatous yellow streaks in the thoracic part and calcified ulcerated atheroma in the abdomen (see figure). The major branches as well as the cerebral arteries were also atheromatous.

An apoplectic cyst was present in the left putamen. The kidneys showed nephrosclerosis. The immediate cause of death was hæmorrhage into the lower ileum, for which no local cause was found.



Aorta with atheromatous lesions (inch scale)

Discussion

Our patient had two attacks of hæmaturia and at least nine of melæna, and no adequate local cause for these was found. He also had hæmarthrosis and excessive hæmorrhage from minor trauma, as well as a lifelong tendency to bruise easily. Clinically he appeared to have moderately severe hæmophilia.

The results of the hæmatological investigations confirm a disorder of coagulation. The thromboplastin-generation test indicates conclusively that there was a deficiency of antihæmophilic globulin, and therefore that the patient was a hæmophiliac. His past and family history is typical of hæmophilia.

To have reached the age of 73 is remarkable for a hæmophiliac, but it is fair to say that but for blood-transfusion he would probably have died earlier. His history suggests that his tendency to bleed may have become more pronounced in the past ten years.

In the ordinary course of events this patient would not have been thought liable to thrombosis. Indeed both clinical and hæmatological evidence suggest that he could not form a firm thrombus in bleeding vessels. It is therefore difficult to believe that "some thrombogenic influence" (as postulated by Duguid) was an important factor in narrowing his coronary arteries in later life, unless the deposition of fibrin, which Duguid believes to be important, takes place independently of the ordinary coagulation processes.

Summary

The case is reported of a hæmophiliac, aged 73, who had angina pectoris.

His myocardial ischæmia was due to atheroma of the coronary arteries. Extensive aortic atheroma was also found.

This case is discussed in relation to Duguid's theory of the causation of atheroma by intimal thrombosis.

We wish to thank Dr H. L. Marriott for permission to publish, and Dr J. N. Pattinson for the radiographic examination. The cholesterol and lipoprotein estimations were performed by Dr G. L. Mills in the Courtauld Institute of Biochemistry, Middlesex Hospital.

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CLICKING PNEUMOTHORAX SIMULATING MYOCARDIAL INFARCTION

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The diagnostic problem raised in this case was due to the association of very severe chest pain with an audible systolic click and electrocardiographic changes. Suspicion was at first aroused by the severity of the pain, which suggested myocardial infarction at an unusually early age.

Case-report

A man, aged 22, had had no illnesses except severe whooping cough at the age of 5, when he had bronchopneumonia and was ill for six weeks. He was very well throughout his military service and was playing tough rugby football four days before his pain began.

The pain started in the back of the left shoulder, and radiated to the left side and to the front of the chest. For ten minutes he did not pay much attention to it, but it soon became so acute that he took a taxi on his way home. It remained severe for only about half an hour. That evening Dr A. R. Kelsall noticed a loud click in the chest which was audible by the unaided ear. This synchronised with the heart beat and was best heard, by stethoscope, near the left sternal border. The click was particularly obvious when he was lying flat or reclining, but went when he stood up. When I saw him next day he had had no further acute pain, but only momentary twinges, particularly on taking a deep breath, or on sitting up after being flat, especially if he did not use his arms. He had had no hiccup, no dysphagia, and in fact no other symptoms of any sort. Dr Kelsall had taken an electrocardiogram which showed inversion of the T wave in leads 2, 3, and VF.

Examination

He looked well but a little pale. The heart rate was 68, the rhythm regular except for a very occasional premature beat, and the blood pressure 130/70 mm. Hg. The pulmonary second sound was accentuated and sometimes reduplicated. The exocardial click was harsh and loud, particularly halfway through inspiration. It was at its maximum just before the second sound, and hints of it were present during diastole. I could detect no clinical abnormality of the lungs or abdominal organs. The erythrocyte sedimentation rate and white cell count were normal. In the electrocardiogram which I took the T wave in lead 2 was flat, and so were the P waves; this was associated with considerable bradycardia, which I took to be nodal. The T wave was inverted in leads 3 and aVF, but no Q waves were present in either lead. The T waves were also rather lower than normal in leads V6 and V7. I was not quite happy about the left lung in the anteroposterior radiograph. The markings suggested to me the possibility of slight cystic or emphysematous change.

Diagnosis

I decided first of all that he had not had a myocardial infarction, and secondly that the sound was exocardial and not pericardial. The most probable explanation was that some adhesions had formed around his lung at the time of his whooping cough bronchopneumonia, and that the strenuous game of football had begun a tear at this point which caused an encysted localised pneumothorax. A pneumothorax can produce electrocardiographic abnormalities, and I thought that the changes in his electrocardiograms could be ascribed to this cause. I advised that he should stop at home for two weeks, being up and about, and that he should then have a further week of greater activity.

Five Weeks Later

He remained symptom free and in a state of increasing eagerness to resume his club football. At my re-examination five weeks after the first, he said that he felt perfectly fit. He was free from aches or pains and had not been short of breath. He had not noticed any more of the audible clicking from his heart area.

I could find no clinical abnormality. The electrocardiogram had improved. The inversion of the T wave in lead aVF had disappeared. The T wave now was still inverted in lead 3 and flat in aVF; in both, it remained so on full inspiration.

He had also a wandering pacemaker (the P–R interval shortened to 0 05 sec but on full inspiration lengthened immediately to 0 12 sec, and in other parts of the tracing it was normal at 0 18 sec) Radiologically the heart was normal in size and shape The transverse diameter of the heart by orthodiagraph was 13 5 cm and that of the chest 30 0 cm

Thus his heart was normal The T-wave inversion was regarded as postural, particularly as no Q waves were visible in leads 3, aVF, or V7 His pneumothorax had healed

Dr Clifford Hoyle said that the chances of recurrence were in the neighbourhood of 10 to 1 against, and thought that from the pulmonary point of view he might resume his football I felt that this course would be safe from the cardiological aspect Should there be a recurrence, no permanent damage would be done

Additional Radiological Information

Dr Horace Post reported on the X-ray films taken within twenty-four hours of the onset of symptoms He could see no cystic or emphysematous lesion, no air in the mediastinum, nor any minor pneumothorax (though the postero anterior view did not cover the periphery of the left base) There were some old right basal pleural adhesions and old, very minor, peribronchial thickening in the right lower lobe, but no evidence of any tuberculous infiltration The heart and aorta were normal

Discussion

There are two points of diagnostic interest The first was the very loud systolic click, and the second the changes in the T wave in leads 2, 3, and VF in the electrocardiogram The more important of these, and the one giving the most definite lead, was the loud audible systolic click There is no other intrathoracic condition which can give rise to such a loud noise, and the diagnosis of small local encysted pneumothorax near the heart seemed to be inevitably correct, even though the films failed to reveal it No myocardial infarction could possibly give rise to this clinical picture On the other hand the T-wave changes, particularly those in lead 2, in association with very severe chest pain, provided graphic and visible evidence pointing in a somewhat sinister fashion to a possible posterior myocardial infarct in a young man

The clinical picture of clicking pneumothorax has been well painted by Scadding and Wood (1939), who append a considerable bibliography

They quote 4 cases of spontaneous pneumothorax and 2 of artificial pneumothorax with loud clicking sounds coming from the left chest In 2 of their 4 spontaneous cases the click was easily audible by the unaided ear In all cases either the sound or the pain or both were influenced by posture All their 4 cases were in males between the ages of 16 and 26 In only 1 is there record of an electrocardiogram, and in that case the changes were those of the Wolff-Parkinson White syndrome

Electrocardiographic changes can be produced by pneumothorax, usually, it must be admitted, as a result of changes in the axis or in the degree of rotation of the heart secondary to the presence of air in the pleural cavity Spontaneous mediastinal emphysema is another condition in which chest pain, exocardial sounds, and electrocardiographic changes have been recorded In more than one such case the suspicion of myocardial infarction has been raised

Pain was present in 6 out of 9 such patients in the series of Aisner and Franco (1949), it can be very severe It is usually to one side or other of the midline but may be central It does not last more than a few days The systolic click in Aisner and Franco's series was audible or felt as a creak by the patient in 4 of the 9 cases It does not appear to have been as loud as the clicking sound mentioned by Scadding and Wood or noticed in the present case In several of the recorded cases this click has been noticed, both by the patients and by the physicians, to vary considerably with posture Electrocardiographic changes were mentioned by Aisner and Franco, who referred to changes in the T waves and S–T segments Holoubek's (1953) patient suffered a sudden collapse with the development of auricular fibrillation and shock The S–T segment was elevated in lead 1 and depressed in leads 2, 3, and 4R These abnormalities were no longer present next day Miller (1945) reports a case in which pain, shortness of breath, and electrocardiographic changes raised the suspicion of an organic cardiac cause Here there was pain, shortness of breath, loud exocardial sounds varying with posture, and flattening of the T waves in lead 1 with S–T elevation in leads 2 and 3 These changes subsided after twelve days

Spontaneous pneumothorax and spontaneous mediastinal emphysema can clearly have a common origin—indeed they often coexist Of 39 cases of spontaneous mediastinal emphysema recorded by Fagin and Schwab (1946), 21 had definite evidence of spontaneous pneumothorax also In the present case the symptoms and signs thus seem to be due to a combination of these two lesions, the pneumothorax being so small that it was not detected by skilled radiologists, and the spontaneous mediastinal emphysema localised in such a way as to have given rise to electrocardiographic changes

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Fagin I D Schwab E H (1946) *Ann intern Med* 24, 1052
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Preliminary Communication

AUTO-ANTIBODIES IN ADDISON'S DISEASE

THE recent work of Witebsky and his colleagues [1] [2] has shown that immunisation of rabbits by rabbit thyroid tissue results in the development of organ specific antibody, accompanied by pathological changes in the animal's own thyroid gland Roitt et al [3] have demonstrated, by the precipitin test, anti-thyroid antibody in the serum of cases of Hashimoto's disease We present evidence here that the association of auto-antibody with thyroid disease may be an illustration of a wider phenomenon, insofar as the same principle may apply to adreno cortical atrophy in some cases of Addison's disease

MATERIALS AND METHODS

Extracts of human organs (liver, kidney, brain, thyroid, and adrenal) were prepared from post mortem material obtained within three hours of death and also from thyroid and adrenal tissue excised surgically Suitably sized pieces of the various organs were frozen, finely sliced, and extracted with saline solution in a mechanical shaker The extracts, freed of most of the suspended tissue fragments and lipoid by centrifugalisation, and diluted when necessary to reduce anticomplementary activity, were used as antigens Tests for antibodies were performed by the complement fixation reaction as follows

0 1 ml of the patient's inactivated serum was incubated at 37°C for 1 hour with 0 1 ml of antigen and 3 hæmolytic doses of guineapig complement 0 5 ml of 3% suspension of sheep cells sensitised with immune horse serum, was added, and examined for lysis after a further period at 37°C Sera showing anticomplementary activity were discarded

Sera were examined from patients with Addison's disease (10 cases), Hashimoto's disease (18), thyrotoxicosis (13), and Simmonds's disease (2), and from 55 patients in general medical and surgical wards who were not regarded as having any specific endocrine disturbance In 2 of the cases of Addison's disease there was evidence of tuberculosis The results are summarised in the accompanying table

Fixation of complement observed in these tests cannot be attributed to ABO blood group incompatibility of serum and tissue extract Tests were performed with several specimens of each tissue extract, and it was found

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[1] Witebsky E Rose N R *J Immunol* 1956, 76, 408
[2] Rose N R Witebsky, E *Ibid* p 417
[3] Roitt I M Doniach D Campbell P N, Hudson R V *Lancet* 1956, ii, 820

RESULTS OF TESTS FOR ANTIBODIES

Case no	Diagnosis	Antigen		
		Thyroid	*Adrenal*	Liver, &c
1	Addison's disease	++	++	–
2	Addison's and Hashimoto's disease	++	++	–
3–8	Addison's disease	–	–	–
9, 10	Addison's disease and tuberculosis	–	–	–
11, 12	Simmonds's disease	–	–	–
13–25*	Thyrotoxicosis	+ or ++	–	–
26–43	Hashimoto's disease	+ or ++	–	–
44–98	Various other diseases	3 + or ++, 52 –	–	–

– = Complete lysis + = Partial lysis ++ = No lysis
* Selected cases (vide infra)

that the degree of complement fixation varied with different thyroid and adrenal extracts In cases 1 and 2 the titres of the sera for complete inhibition of lysis varied between 0 and 16 with different adrenal extracts even with the weakest reacting extracts, however, partial inhibition of lysis was observed, whereas all the other sera were completely negative with all the adrenal extracts

DISCUSSION

In an investigation still in progress we have found that the serum of almost all cases of Hashimoto's disease and of approximately 50% of cases of thyrotoxicosis contain complement fixing antibodies reacting with thyroid extract In the present investigation, sera chosen for this property (cases 13–43) did not react with adrenal extracts We therefore conclude that cases 1 and 2 possess, in addition to thyroid antibody, an antibody to adrenal tissue It is uncertain whether this latter antibody plays an important part in the destruction of the adrenal cortex in idiopathic Addison's disease, but we present below evidence which inclines us to this view

Wells[4] drew attention to pathological changes in the thyroid gland in cases of idiopathic Addison's disease—namely, diffuse lymphocytic infiltration, formation of lymphoid follicles, loss of many of the thyroid acini, and eosinophilia of the epithelium of the surviving acini These changes, which appear similar to, but less pronounced than, those of Hashimoto's disease, were infrequent and slight in tuberculous Addison's disease Similar findings are reported by Sloper[5] Wells noted that the adrenal cortical atrophy in his idiopathic cases was accompanied by lymphocytic infiltration and regenerative foci of enlarged eosinophilic cortical cells He concluded that the changes in the thyroid and adrenal cortex were of the same nature, and attributed them to the long-continued action of a toxic agent The demonstration of both adrenal and thyroid antibodies in cases 1 and 2 supplies a possible explanation for Wells's observations As illustrated by cases 44–98, complement fixing antibody to thyroid extract is sometimes present in patients without overt thyroid disease when opportunity has presented, we have carried out subsequent post mortem examination of such unexplained positive cases, and have observed in the thyroid gland changes similar to those observed by Wells in idiopathic Addison's disease There is therefore some evidence that the presence of complement fixing antibody to thyroid extract is not unaccompanied by pathological changes in the thyroid

The work of Witebsky and of Roitt provides evidence that antibody to thyroid tissue is responsible for the changes of Hashimoto's disease By analogy, we infer that the antiadrenal antibody may be responsible for progressive destruction of the adrenal cortex in idiopathic Addison's disease We suggest that some cases of Addison's disease are prone to form both adrenal and thyroid auto antibodies, the latter antibody accounts for the histological changes usually present in the thyroid gland, and when particularly strong is detectable by the precipitin test and explains the coexistence of Hashimoto's disease and Addison's disease as in our case 2 The negative results of complement-fixation tests in cases 3–8 do not rule out these conclusions, for it may well be that cessation of adrenocortical destruction is accompanied by disappearance of the anti adrenal antibody, just as precipitating anti-thyroid antibody is frequently not detectable in the serum of cases of Hashimoto's disease after surgical removal of the major part of the thyroid gland Alternatively, some or all of our cases 3–8 may have tuberculosis of the adrenal glands, or it may be that auto antibody is only one of a number of agents which may affect adrenocortical destruction, and operates in only a proportion of cases of idiopathic Addison's disease

We acknowledge with pleasure our indebtedness to the physicians and surgeons who have willingly coöperated in providing us with specimens of blood, surgical material, and access to their case records, and to Prof D F Cappell for advice and criticism This investigation was assisted by a financial grant to one of us (J R A) by the Department of Health for Scotland

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Medical Societies

ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE

Laboratory Aspects of Amœbiasis

A MEETING of the society on May 16, with the president, Prof R M GORDON, in the chair, discussed the laboratory aspects of amœbiasis

Dr C A HOARE remarked that the ætiology of amœbiasis still needed elucidation, and that account must be taken of the fact that two races of *Entamœba histolytica* existed—the large race which was pathogenic, and the small race which was not pathogenic, was found only in the lumen of the bowel, and did not invade the tissues Parts of the life cycle of the small race were not yet known

Group Captain W P STAMM reviewed the methods of diagnosis currently used He agreed that the small race was non-pathogenic He had nothing good to say about the complement-fixation test, conscientious direct examination of specimens was as good as anything The view that any abdominal complaints associated with the presence of *E histolytica* in the fæces were invariably due to amœbiasis was to be deplored A series of 181 Pakistani aircraft apprentices had each had 3 consecutive stools examined every year for three years, 101 apprentices were found to be positive at least once, yet only 1 had symptoms severe enough to bring him to hospital for treatment of amœbiasis Moreover, a carrier rate of 6% was found in 724 symptomless ex overseas patients About 50% of Europeans with amœbic hepatitis or liver abscess had no demonstrable *E histolytica* in their stools

Dr R A NEAL discussed virulence, making the point that the kitten, commonly used in experiments, was so susceptible that the results might give an exaggerated impression of virulence Young rats were better, and a method of scoring on the basis of ulceration of the cæcum of infected rats had been used In this way, strains from acute cases were found to be virulent, and strains from carriers were non-virulent Virulent strains maintained in culture lost much of their virulence, but this could be restored by liver passage Investigation of various strains, in association with bacteria of different origins and species, had indicated that, though the presence of bacteria was essential for the amœbæ, it was the amœbæ themselves that were invasive and responsible for the lesions But the difference in virulence between strains of the large race from acute cases and carriers suggested that the large race itself was represented by two types Infection of man with the virulent type must pass through a quiescent phase when the disease did not arise, to ensure survival by the production of cysts

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[4] Wells H G *Arch Path* 1930 10 499
[5] Sloper, J C *J Path Bact* 1953 66 53

Dr G **Woolfe** described the process of screening large numbers of compounds in the search for new amœbicidal drugs In vitro tests in capillary tubes containing the amœbæ in culture medium with dilutions of the drug determined those which were amœbicidal in high dilution, and these were chosen for in-vivo/in-vitro tests, in which the drug was given by stomach-tube to young uninfected rats These were killed five hours later, and the cæcal contents tested for amœbicidal capacity by the in-vitro method In-vivo tests were then carried out in weanling rats

In the discussion Dr J D **Fulton** suggested that culture was perhaps more useful in diagnosis than was sometimes thought, and that the complement-fixation test was helpful in extra intestinal amœbiasis

Prof A W **Woodruff** said that, in amœbiasis, the clinician relied heavily on laboratory diagnosis, and he referred to the many occasions on which courses of anti-amœbic treatment were given without secure diagnosis, with resulting neurosis

Dr H C **Trowell** commented on the difficulty of diagnosis even if the laboratory report was positive The presence of the amœbæ was not enough—there must be clinical evidence of illness which could be attributed to that infection Almost every African in Uganda was a carrier Neurosis was much commoner than true amœbiasis

Lieutenant Colonel J H **Walters** raised the question whether persons passing cysts but having no bowel trouble should be given anti-amœbic treatment There was danger, he thought, in leaving them untreated, since liver abscess often developed in patients with no history of former attacks He therefore thought it unwise not to treat carriers of cysts—which might be virulent

Brigadier J S K **Boyd** recalled the old rule that, if amœbæ were found which were actively motile and contained red cells, the diagnosis of acute dysentery could be made, and in that condition they would be found if looked for carefully

Sir **George McRobert** emphasised that the patient should not have had anti amœbic treatment before the laboratory examination, since it would eliminate cysts Clinicians accepted emetine bismuth iodide as the best drug now available, but they were not satisfied with it

New Inventions

A METHOD OF DETERMINING THE pH OF THE BLOOD AT THE BEDSIDE

Until recently the determination of the pH of the blood has been a laboratory procedure A sample is withdrawn and removed to the laboratory, where it is transferred into the glass electrode system which is kept at room-temperature After determination of the pH at room-temperature, correction is made to body-temperature with the aid of tables [1]

By means of the system described below, in which a pH electrode is contained in the plunger of a syringe, it is now possible to measure blood pH at 37 5°C at the bedside The apparatus has been constructed in such a way that it is suitable for use in the wards, and readings of the pH of the blood can be made at the bedside at five-minute intervals

A sample is taken directly into the syringe electrode, and this is connected to the rest of the electrode system, all of which is kept in a water-bath at body-temperature In this way one can follow the changes in the pH of the blood in metabolic disorders, in respiratory or renal failure, under changing experimental conditions, and during anæsthesia The advantage of measuring the pH at body-temperature is evident

THE APPARATUS

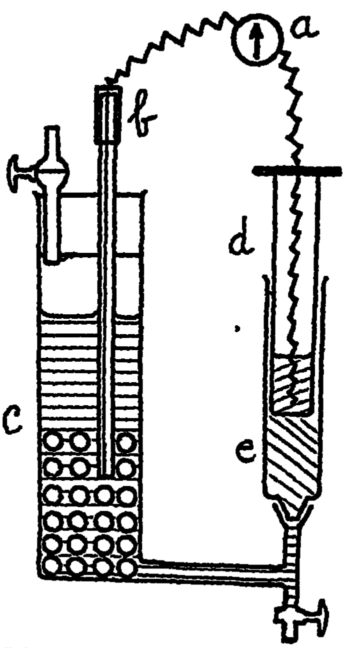
The electrode system consists of a glass U tube with unequal limbs, of which one is 10 0 cm long and 1 5 cm in internal diameter, and the other limb is 1 cm long and has the internal dimensions of a female Luer joint At the lowest point of the U-tube is a drainage tube 1 cm long bearing a glass stopcock The long limb of the U tube is filled with a supersaturated solution of potassium chloride, into which dips the calomel reference electrode supported in position by a rubber bung which fits into the top of the long limb The rubber bung also supports a small glass stopcock, which when opened to the atmosphere allows potassium chloride solution to flow from the long limb into the short limb If the stopcock is closed, the flow of potassium chloride ceases The syringe electrode which has a male Luer tip fits directly into the short limb of the U tube

The electrode system is held on a 'Perspex' support which can be raised or lowered into the water bath

The water bath is a perspex box measuring 20 × 20 × 15 cm It has a removable lid, and the electrode system can be lowered into the bath through a hole in the lid Other holes in the lid allow a thermometer, a thermostat, a 300 watt immersion heater, and a stirrer to dip into the water Further holes support test tubes which contain standard buffer solutions, potassium chloride, sterile heparin and saline solution, and sterile distilled water, which are kept at body temperature

TECHNIQUE OF MEASUREMENT

The water bath is kept permanently at 37 5°C The pH-meter, which is battery operated, must be switched on one hour before any measurements are made



Scheme of apparatus a, pH-meter, b, calomel electrode, c, supersaturated potassium-chloride solution d glass electrode, e barrel of syringe

The syringe electrode is washed out three times with buffer solution and then half filled with this solution The plunger is maintained in position by a small rubber band, which can be slipped along the plunger after all bubbles of air have been excluded The U-tube is raised from the water-bath, and the syringe electrode is fitted into the short limb before the electrode system is lowered into the water-bath It is allowed to remain there until the temperature of the buffer reaches 37 5°C, after which the meter is adjusted to this standard buffer solution

The electrode system is then raised, the syringe is disconnected, and the buffer solution is discarded A small glass stopper is fitted into the short limb of the U tube, which is then lowered into the water bath to keep it at the correct temperature until a sample of blood has been collected

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[1] Rosenthal T B *J biol Chem* 1918 173, 25

The syringe electrode is flushed several times with the heparin saline solution, which has been kept immersed in the water bath, and the dead space of the syringe is filled with this solution to prevent clotting A sample of blood is then withdrawn through a Riley needle The U tube is raised from the bath, the sample is fitted into the short limb, and the electrode system lowered again into the water bath The whole manœuvre is carried out as quickly as possible, to minimise loss of heat

The pH falls as the blood warms up to 37 5°C over two or three minutes It then remains steady for some time before metabolic changes in the blood lower it Once equilibrium has been reached, the sample can be discarded, the syringe electrode washed out, and the short limb of the U-tube flushed with a little potassium chloride solution from the long limb The whole process, including standardisation if necessary, can be repeated on another sample

The pH of the blood can be measured to an accuracy of ±0 02 of a pH unit

PRECAUTIONS

The heparin saline solution should contain very dilute heparin because this substance has a considerable buffer capacity and, when used at full strength, lowers the pH of the blood A solution of 1 ml of heparin in 200 ml of physiological saline solution prevents clotting and does not affect the pH of the blood

To avoid contamination, the electrode system must be washed out with several flushings of each solution

With battery operated meters, the battery must be kept at full strength if the meter is to remain stable For this purpose a trickle charger is incorporated in the apparatus

The thermostat and heater may give rise to electrical interference, which may upset the pH meter All electrical components should be earthed, low voltage relays used, and a suitable condenser fitted to suppress the spark which flashes when the thermostat switches on and off

An induction motor should be used for the stirrer because brush motors set up electrical interference

This apparatus is obtainable from Electronic Instruments Ltd, Lower Mortlake Road, Richmond, Surrey

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Reviews of Books

Pediatric Cardiology

ALEXANDER S NADAS, M D, F A A P, assistant clinical professor of pediatrics, Harvard Medical School, physician, Sharon Cardiovascular Unit, Children's Medical Center, Boston, Mass Philadelphia and London W B Saunders 1957 Pp 587 84*s*

THE appearance of the first complete textbook on heart-disease in children indicates the important place in medicine that this subject now holds

Most of the excellent works lately written on congenital heart-disease have looked from the viewpoint of the physician who normally deals with adults Dr Nadas, however, is a pediatrician as well as a cardiologist, and his book clearly reflects both these loyalties, which enhances its value as a practical treatise His observations are based solely on personal experience and not on information obtained by other people This approach has many advantages, but it does mean that some fields are not as widely covered as others, thus, more space might have been given to the surgery of certain conditions in infancy, in view of the high mortality of congenital heart-disease in the first year of life

In a preface Dr Nadas says he is writing for the pediatrician, the general physician, and the medical student There is much, however, which will interest the cardiologist, and the chapter on the electrocardiogram in childhood is of particular value Though the main emphasis is on congenital heart disease, the section on acquired disease is excellent, especially the chapter on rheumatic fever, which assesses very fairly the use of steroid therapy There is a well illustrated chapter on phonocardiography, but not everyone will agree with the interpretation of the nature of the first heart sound

In the accounts of congenital heart disease, clinical description is prominent and the essential hæmodynamic changes are shown in simple diagrams

A chapter on anæsthesia for children with heart disease will be a great help to those who must take decisions on this difficult question

Dr Nadas's father was a writer, which may be one reason why he has managed to make a book so full of facts both amusing and extremely readable

Treatment of Fractures

Vol II 5th ed Prof LORENZ BÖHLER M D director of the Accident Hospital and professor of accident surgery Vienna Translated from the 13th German edition New York and London Grune & Stratton 1957 Pp 1508 123s

VOL I of the new translation of the 13th German edition of this classic work appeared last year (see *Lancet*, 1956, ii, 1141) Vol II covers the injuries of the lower limb as far as the knee, and fascinating reading it makes It is in the femur especially that Böhler has had to modify his originally strong feelings against open fixation of fractures But metallic fixation is far from foolproof, and his accounts of the complications of maltreatment are as dramatic as ever This is an inspiring book, the illustrations are better than in the first volume, and in the text only the section on slipped upper femoral epiphysis is not fully satisfying

The Breasts and Breast Feeding

HAROLD WALLER, M B, F R C O G, formerly pædiatrician to the British Hospital for Mothers and Babies and the Poplar Hospital London Heinemann Medical Books 1957 Pp 56 7*s* 6*d*

IT is fortunate that Dr Waller, who had devoted much of his life to the study of human lactation, should have written down shortly before his death this brief but comprehensive account of his findings First published as a chapter in a textbook of obstetrics, Dr Waller's work now appears as a book He explains how failure of lactation is commonly caused by a period of over distension of the mammary gland and he goes on to describe the antenatal care and the management of the onset of lactation which have been evolved at the British Hospital for Mothers and Babies to avoid this hindrance The account is characteristic of Dr Waller, with its modest but fastidious use of language, its consistent logical teaching, and the impelling force of independent long, and patient clinical observation For these virtues it should remain a classic

Human Blood Coagulation and its Disorders (2nd ed Oxford Blackwell Scientific Publications 1957 Pp 476 42*s*)—Into the second edition of their book, Dr Rosemary Biggs and Dr R G Macfarlane have assimilated the discovery of the Christmas factor and other changes in knowledge about thromboplastin The general arrangement remains the same but the whole text has been revised in detail, at the small cost of 70 extra pages It is interesting to see that the theory of blood coagulation is now presented by a single diagram and apart from Christmas factor only "prothrombinase" is new A glossary of terms is a useful appendix The revision is so extensive that those who own the first edition will want to replace it by this excellent successor

Nursing and Diseases of Sick Children, for Nurses (6th ed London H K Lewis 1957 Pp 726 50s)—Edited by Prof Alan Moncrieff and Dr A P Norman, this textbook is written by many teachers at the Hospital for Sick Children, Great Ormond Street In tune with the modern emphasis on keeping children out of hospital the new edition contains more about the normal child, nursing at home and social and preventive medicine The comprehensive account of the medical and surgical treatment of children in hospital ranges from cupping and leeches to procainamide

THE LANCET

LONDON SATURDAY, JUNE 1, 1957

Consultant and Specialist

In the nine short years since the start of the National Health Service the work of hospitals has changed remarkably. Medical progress has led to contraction of some specialties, such as tuberculosis and hospital pædiatrics, and to expansion of others, such as cardiac surgery; but these changes, striking in themselves, have been overshadowed by the generally increased demand traceable to the disclosure, through the health service, of the population's full need for care.

In many hospitals the medical staffs do not suffice to meet the new demands. The teaching hospitals, in their privileged and largely protected position, are in no acute difficulty; but elsewhere the story is different. The public were quick to note the upgrading of peripheral hospitals and have responded by attending these instead of travelling, as once they would have done, to the teaching centre. In trying to fulfil their new responsibilities the peripheral hospitals are impeded by deficiencies not only in staffs but also in buildings and equipment. These deficiencies are related; for, as is seen from our survey on p. 1133, the appointment of much-needed surgeons, pathologists, or physicians may have to await the completion of new operating-theatres, laboratories, or wards. Nevertheless, it would be quite wrong to suppose that additions to clinical staff must all be deferred until new buildings have gone up. With ingenuity most busy outpatient departments could manage a few more sessions a week; and so could some operating-theatres. Nor is there any lack of suitable people for the work: in the main clinical subjects, and in some others, too many competent doctors are competing for what few consultant posts there are. The main difficulty lies elsewhere. Many clinical consultants find that their need for help does not extend over the whole range of their work: thus the physician might get along well if relieved of some of his outpatients, and the general surgeon if some of the operating were taken off his hands. A hospital authority, however, can hardly create a fresh consultant post for such restricted work; and, even if willing, it may be unable to do so because of lack of the beds and of the junior staff, including perhaps a registrar, needed to place a new consultant on a par with his colleagues. There is one way, and perhaps only one, in which such work can suitably be done without creating new units—namely, by the appointment of assistant physicians and assistant surgeons. The need for these is emphasised by the march of events in the many hospitals where it is proving impossible to find new senior registrars.

Noting that when it comes to applying for a consultant post, senior registrars in peripheral hospitals are at a disadvantage compared with their teaching-hospital contemporaries, registrars are shunning the non-teaching hospitals; and the consultants in these hospitals are having to undertake work that might be done by a junior colleague. Such a situation would be partly avoided if all senior registrars divided their time between teaching and non-teaching hospitals under a joint-appointments scheme. These schemes provide diversity of experience and ensure that no senior registrar who participates disqualifies himself for advancement simply by not working in a teaching hospital. But though in a few regions such a scheme is operating satisfactorily, in others, which seem to be more numerous, a scheme tentatively started has run into difficulties and has even had to be abandoned, because of incomplete understanding and possibly suspicion between the two hospital authorities or because of the reluctance of senior registrars appointed to the teaching hospital to move to the periphery. We believe that the country should be surveyed region by region to define the causes of success and failure, and to see whether in fact these schemes can possibly be extended; for in regions where there is no hope of their being operated successfully the appointment of senior registrars to peripheral hospitals should be discontinued, and the sooner this is done the better.

The new grade of assistant physician and surgeon might be expected to attract both senior registrars and S.H.M.O.s. For most it would be a step on the ladder to a consultant post (a step at a point where some senior registrars are at present being thrown off into mid-air), but others would be content to remain at this level. (One of the faults of the existing arrangement is that those who wish to make a career in one of the main clinical subjects, but may not even want to become consultants, are denied the opportunity.) The clinicians in this specialist grade would have a few beds; but they would be responsible to a consultant. Their remuneration should, we suggest, be spread over a wide scale, starting near the top of the present S.H.M.O. scale and stretching, with continuing service, well into the consultant's reaches.

To create a specialist grade of this kind would be to return to realities—to recognise the facts as they are today and as they were long before the National Health Service was thought of. The Spens Committee, so wise in many ways, ignored one big fact when it left no place in its scheme for the many doctors in our hospitals who are neither trainees nor consultants, but are certainly specialists; and, though the gap has been filled by calling them hospital medical officers, their morale has been damaged because even the most senior are paid less than a young consultant and because even the most junior feels himself out of the running for a consultant post. The Spens Committee was wrong, too, when it presumed that in an organised service the senior registrar would become a consultant about the age of 32, soon after finishing his formal training, or, if not, would (and should) find work elsewhere—in general practice or outside the N.H.S. Whereas in the old days the future consultant, in his 30s, often had to be content with small and miscellaneous appointments, through which, gaining experience, he worked his way up to major responsibilities, the Spens Committee prescribed an immediate long leap for everybody—with removal from the hospital service as penalty for anybody who could not jump the widening chasm. Because it has been so obvious that the hospitals need them, the majority have not in fact been asked to pay this penalty; but they have undergone, and are still undergoing, grave hardship; and because they are denied promotion the hospitals are often denied the full help they could give. Over six years ago we remarked[1] that senior registrars were doing advanced work satisfactorily, "and it seems a little odd to tell them that they must forthwith stop doing it because, now that their training is over, our principles forbid us to offer them anything less than the consultant posts they cannot get"

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[1] *Lancet*, 1950, ii, 749.

Beneath the reluctance to face this situation has lain an undercurrent of fear that if a grade of specialists were created the Ministry of Health might ruthlessly swell its ranks with the aim of securing cut-price consultants Such a fear is surely baseless It would be for the profession to agree by negotiation on the ratio of specialists to consultants[2], and thereafter professional bodies would ensure that the agreement was observed The picture of a conscienceless group of Civil Servants riding roughshod over a supine medical mass is out of keeping with facts Our representatives have had no difficulty in securing the strict observance of the agreement for limitation of S H M O posts, and there is no reason why they should be less successful with those for specialists The proposal to introduce a specialist grade deserves fresh and unprejudiced attention

Antibiotics and Sore Throat

ANTIBIOTICS are expensive and not without risk Should they be used routinely in the treatment of sore throat ? Every doctor with a child of his own that has had an acute pharyngitis will know what a temptation it can be to give penicillin or one of the newer antibiotics; and will feel himself in sympathy with WHEATLEY,[3] who favours giving rather than withholding these agents Yet in this country four studies on the natural history and therapy of acute febrile sore throat—two in general practice [4 5] and two in military personnel [6 7]—do not on the whole support such a policy They show that the majority of such sore throats settle down, untreated, in a few days, that streptococci can be recovered from only about half to two-thirds of the patients, and that sore throat associated with β-hæmolytic streptococci cannot be reliably distinguished on clinical grounds alone from other sore throats Penicillin can shorten the illness a little but is really necessary, it seems, only for severe cases and those with such immediate complications as otitis media or sinusitis The compelling argument, in theory at any rate, for the "blanket" policy of treating all sore throats promptly with penicillin arises not from these considerations but from the danger of delayed non septic complications (rheumatic fever, nephritis), which can be prevented by adequate treatment of the preceding sore throat but once they have arisen are not susceptible to radical cure and may cause serious invalidism and shorten life Does this theory hold good in practice ? In over 400 cases of sore throat associated with β-hæmolytic streptococci that were seen in general practice,[4 5 8] or under similar conditions,[6 7] and that were not treated with penicillin, rheumatic fever ensued in not a single instance The mildness of such sore throats is confirmed by BRUMFITT and SLATER's[7] observation that only 17% of untreated cases of proved group A β-hæmolytic streptococcal infection showed a significant (two-tube) rise in antistreptolysin titre It is difficult not to conclude that penicillin is needed only for severe cases and those with septic complications But this conclusion seems to conflict with that of the American Heart Association, which has issued a report on this subject, from the point of view of preventing rheumatic fever and bacterial endocarditis,[9] compiled by a committee composed of experienced and authoritative workers

The report summarises the symptoms and signs of the typical case of streptococcal sore throat, which should be treated with penicillin "on sight", but many cases are not typical, and accordingly the committee suggests that throat-swabs should be cultured more extensively The prevention of rheumatic fever demands the eradication of streptococci from the throat—not just their suppression The bactericidal penicillin (rather than the bacteriostatic sulphonamides) is the drug of choice, with the less effective broad-spectrum antibiotics reserved for patients who are hypersensitive to penicillin Of the possible penicillin preparations, the committee favours administration of the injectable long-acting benzathine penicillin G, or procaine penicillin with aluminium monostearate in oil, for at least ten days Penicillin by mouth is also effective, but only if the patient cooperates, and thus the committee does not recommend this route The committee proposes that, where a previous history of rheumatic fever is clearly established, chemoprophylaxis should be given in all seasons throughout the rest of the patient's life, to prevent streptococcal reinfection For choice the committee would inject each month 1,200,000 units of benzathine penicillin G, or, *failing this, it would* give by mouth each day 1 g of sulphadiazine or 500,000 units of penicillin G

Outstanding work on the relation of group A β-hæmolytic streptococci to rheumatic fever has been done by the members of this committee, and particularly by RAMMELKAMP and his associates[9] at Fort Warren Consequently the American Heart Association has been campaigning widely for chemoprophylaxis to prevent rheumatic fever, and in the U S A some would now regard it as negligent not to give a patient known to have had rheumatic fever antibiotics continuously But many doctors would feel uneasy about the committee's recommendation—it might almost be termed a life sentence—that antibiotics should be administered throughout the lives of patients who have had rheumatic fever Furthermore many would demur at the committee's implied recommendation that all sore throats known or suspected to be due to group-A β-hæmolytic streptococci should be treated with antibiotics, at least until a throat swab has been cultured These policies are based on the following premises[10] firstly, that approximately 3% of hæmolytic streptococcal throat infections are followed by rheumatic fever, irrespective of the age of the patient, secondly, that rheumatic heart disease can be prevented by preventing first attacks and recurrences of rheumatic fever, and thirdly, that the benefits of life long chemoprophylaxis warrant its risks That rheumatic fever follows infection of the throat by a group A β hæmolytic streptococcus in a susceptible subject must now be taken as proved

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[2] *Ibid* 1951 i 1277

[3] Wheatley D *Ibid* Jan 19 1957 p 161

[4] Landsman J B Grist N R Black R, McFarlane D Blair W Anderson T *Brit med J* 1951 i 326

[5] Chapple P A L Franklin L M Paulett J D Tuckman E Woodall J T Tomlinson A J H McDonald J C *Ibid* 1956 i 705

[6] Bishop J M Peden A S Prankerd T A J Cawley, P H *Lancet* 1952 i 1183

[7] Brumfitt W Slater J D H *Ibid* Jan 5 1957, p 8

[8] Fry J *Ibid* Jan 26, 1957 p 211

[9] Rammelkamp C H Breeze B B, Griffeath, H I Houser H B Kaplan M H Kuttner A G, McCarty M Stollerman G H Wannamaker L W *Mod Conc cardiov Dis* 1956 25 365

[10] Mortimer E A, Rammelkamp, C H *Circulation*, 1956 14 1144

The statement that 3% of such infections will be followed by rheumatic fever rests mainly on the extensive work at Fort Warren, and it is not at all certain that conditions there reflect those in general practice

Fort Warren, an Air Force base and a reception centre for new recruits, receives a constant stream of young men. Epidemics of streptococcal disease have arisen when one of the new arrivals has been a carrier of virulent organisms. In a classical experiment the Fort Warren workers found that only 2 cases of rheumatic fever occurred in 1178 patients with acute streptococcal sore throat treated with depot penicillin whereas 28 cases occurred in 1168 untreated controls [11] Subsequent work with other forms of penicillin or other antibiotics gave much the same results.

Impressive and valuable as this work is, it is based mainly on epidemics of streptococcal infection in a highly selected population in specialised surroundings Its results cannot be applied directly to endemic sore throat seen in general practice without ignoring an important ecological difference BRUMFITT and SLATER [7] noted that there may be differences between epidemic and endemic streptococcal infections; and the Fort Warren group [12] have themselves reported changes in the virulence and infectivity of group-A β-hæmolytic streptococci associated with the chronic carrier state Nevertheless they believe that the apparent variation in the incidence of rheumatic fever with age or with geographical, seasonal, or economic factors, is secondary to the effect of these factors on the distribution of the streptococcus Where the spread of the organisms is made easier, rheumatic fever will be more common, but the proportion of streptococcal throat infections which are followed by rheumatic fever will remain 3% On the other hand, SASLAW and STREITFELD,[13] working in Miami, Florida, where rheumatic fever is uncommon, found that group-A β-hæmolytic streptococci could be isolated from the throats of a large number of school-children once or more often over several years About half of the positive throat swabs were associated with significant rises in the serum titre for antistreptolysin O, suggesting that a true infection (rather than commensalism) was present in at least half the cases From this they deduced that the expected number of cases of rheumatic fever in the population they were studying should have been 212, if the 3% figure were universal. In fact none were reported.

There can therefore be no hard-and-fast rule that 3% of streptococcal infections are followed by rheumatic fever BYWATERS [14] believes that the normal rheumatic-fever rate after sporadic streptococcal sore throats in school-children in the London area is about 0·1%, but the rate may rise to as much as 10% during epidemics Nor can one assume as does WHEATLEY, that the decline in the incidence of rheumatic fever and of streptococcal diseases generally is due to the more widespread use of antibiotics This decline started decades,[15] and possibly centuries, before the introduction of penicillin although doubtless the antibiotics have hastened it in recent years. Furthermore, the relation of rheumatic fever to rheumatic heart-disease may not be as close as is commonly thought It has been regularly found that only 40–60% of those with rheumatic heart-disease on clinical examination or at necropsy have a history of rheumatic fever or of chorea WILLIUS [16] could find no relationship between the number of attacks of rheumatic fever and the severity of the heart-disease judged by the duration of life It is probably true that, on the whole the more severe and numerous the attacks of rheumatic fever the greater the chance of severe rheumatic heart-disease but the correlation is not close WEINSTEIN et al [17] from a seven-year follow-up study of 167 cases of scarlet fever treated with penicillin, conclude that treatment may suppress the clinical manifestations of rheumatic fever but not the subsequent valvular deformities (This work has been criticised by MORTIMER and RAMMELKAMP [10] mainly on the score of internal inconsistency.) It would be ridiculous to suggest that rheumatic heart-disease is unrelated to rheumatic fever but clearly it would be equally wrong to assume that all rheumatic heart-disease would be prevented by abolishing overt rheumatic fever

In its recommendation for chemoprophylaxis of streptococcal infections in rheumatic subjects the American committee is not absolutely unyielding:

> "Although recurrent attacks of rheumatic fever occur at any age, the risk of recurrences decreases with the passage of years Some physicians may wish to make exceptions to instituting prophylaxis in certain of their adult patients particularly those without heart disease or who have had no rheumatic attacks for many years"

Some have found that a useful working rule is to continue chemoprophylaxis for five years after the last attack of rheumatic fever or until puberty, whichever is the longer period The risk of recurrence after this period is reduced, although it still remains Against this must be set the risks of continuous medication, which include sensitisation to antibiotics, the development of resistant organisms and (because of the intramuscular injections) enhanced severity, if not enhanced likelihood of poliomyelitis On the scale of a life-span chemotherapy may have other dangers of which we still know nothing long-continued administration of sulphonamides to rats and mice is associated with the development of cancer in strains of animals not normally susceptible to neoplasms and with the early onset of cancer in susceptible strains [18] The difficult, crucial experiment has not yet been done, and perhaps it cannot be done It would consist in a controlled trial of antibiotic treatment of sore throats as they present in general practice, with the results judged mainly by the subsequent development of rheumatic heart-disease Meanwhile, those who argue that all sore throats should be treated with antibiotics in order to prevent rheumatic heart-disease are relying on a chain of indirect evidence which is very suggestive but in which there are still serious gaps

The primary object in treating acute febrile sore throat in most patients in general practice is to alleviate the immediate illness Sore throats associated with fever and chills, nausea, headache, swollen glands in the neck, and, particularly in children, vomiting are likely to be streptococcal sore throats associated with cough hoarseness and sneezing are likely not to be streptococcal, but the distinction cannot be made with certainty A throat-swab should be taken if possible but the decision whether to administer an antibiotic must be made clinically, before the result of culture is known Exudate in the throat is not a reliable guide to the infecting organism, but it is a strong indication for swabbing because it may be diphtheritic There is little to gain from treating with antibiotics mild sporadic sore throats, even if streptococcal, but in nurseries, schools, and camps and barracks, where streptococcal infections may reach epidemic proportions, it is important to give effective antibiotic treatment as soon as possible to all with febrile sore throats, and if the epidemic threatens to become troublesome chemoprophylaxis should be considered for the whole group at risk Patients with a history of rheumatic fever or who come of rheumatic families, and those with signs of rheumatic heart-disease, must be specially protected In them, continuous prophylaxis is justified, and in addition upper-respiratory infections must be treated vigorously pending the result of a throat swab Of the various methods of treatment procaine penicillin G, at the rate of, say, a million units daily, is probably the surest and, if this treatment is going to be given, it must be continued for at least ten days A single monthly injection of benzathine penicillin G 1,200,000 units is a convenient but painful alternative which is favoured by the American workers Tablets of oral penicillin G are less effective because of irregular absorption, and the patient may forget to take his tablets Phenoxymethylpenicillin is still under trial, and is not yet to be recommended[19] There is little evidence that the various antiseptic lozenges, with or without local anæsthetics, now offered for sale do anything to influence the course of the disease or give more than moral comfort

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[11] Wannamaker L W Rammelkamp C H Denny F W *Amer J Med* 1951 10 673

[12] Dingle J H Rammelkamp C H Wannamaker L W *Lancet* 1953 i 736

[13] Saslaw M S Streitfeld M M *Amer J Dis Child* 1956 92 550

[14] Bywaters E G L *Lancet* 1956 ii 957

[15] *Ibid* Jan 5 1957 p 32

[16] Willius F A *Amer Heart J* 1927 3 139

[17] Weinstein L Boyer N H Goldfield M *New Engl J Med* 1955 253 1

[18] Hansen P B Bichel J *Acta radiol Stockh* 1952 37 258

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[19] Griffiths, J C, Gray, O P *Lancet* 1956, ii, 730

Annotations

RADIATION AND LEUKÆMIA

When, in 1955, at the Government's request, the Medical Research Council appointed a committee to examine the hazards to man of nuclear and allied radiations, one of the things about which more information was urgently needed was the ultimate effect of small doses of radiation The reported increase in the incidence of leukæmia in patients who had been irradiated for ankylosing spondylitis seemed a fruitful line of inquiry, and Dr W M Court Brown and Dr Richard Doll were asked to undertake a more extensive investigation of such patients than had hitherto been attempted Their findings were summarised in the white paper published in June last year[1] and a fuller analysis of their results is published this week[2]

In the short space of nine months the records of over 13,000 patients from 81 radiotherapy centres in Britain were investigated, the patients were followed up, the radiation received by the bone marrow was estimated, and the doses given to each patient over the period of survival were assessed The investigation was planned to include all patients treated for ankylosing spondylitis by means of ionising radiations during the years 1935–54, and to study further those cases in which leukæmia, aplastic anæmia, or myelofibrosis had developed In all, 72 patients have been reported as having both ankylosing spondylitis and one of these conditions—49 in the study series of 13,352 and 23 outside the series (including 8 not known to have had previous radiotherapy for their spondylitis) From national vital statistics, the numbers of deaths which would have been expected in the study series by Dec 31, 1955, were put at 2 9 for leukæmia and 0 3 for aplastic anæmia in fact, 28 deaths in the series were certified as attributable to leukæmia and 12 to aplastic anæmia Thus, the mortality from leukæmia among patients treated with X rays for ankylosing spondylitis was about ten times greater than the mortality in a normal population of the same age and sex distribution

A possible explanation is that patients with ankylosing spondylitis are more likely to get leukæmia than healthy people, irrespective of how they are treated Three findings, however, are against this Firstly, the distribution of the different cell types of leukæmia in irradiated cases was not the same as in untreated cases (the irradiation group contained a smaller proportion of lymphatic leukæmias) But this observation is based on the Registrar General's figures for cell types, which may reflect differing views on cytological classification Secondly, Abbatt and Lea's comparison[3] between irradiated and non-irradiated spondylitic patients suggested that there was no important association between leukæmia and ankylosing spondylitis irrespective of treatment Thirdly, a relationship has been demonstrated between radiation dose and incidence of leukæmia, and Court Brown and Doll hold that this is strong evidence that radiation plays a part in the causation of leukæmia, though it is conceivable that the liability to leukæmia varies among spondylitics in proportion to the severity of their disease

What is the nature of this relationship between dose and response ? An unequivocal answer to this question would have resolved many of the doubts concerning radiation hazards, but unhappily no clear cut solution has emerged, despite the most painstaking analysis of the known facts by Court Brown and Doll and those who helped them Their inquiry did not establish whether leukæmia could be produced by doses of radiation less than those commonly given in the treatment of ankylosing spondylitis Few patients received a mean spinal marrow dose of less than 250r, and the results give no direct evidence on the effect of doses of this order If the dose response relationship is curvilinear, a threshold may exist below which there would be no increase in the incidence of leukæmia Thus, small doses, such as those involved in diagnostic exposures, would not induce leukæmia Court Brown and Doll believe, however, that it is more reasonable to adopt the working hypothesis that there is no threshold dose They base this view on the linear relationship observed with the doses given to patients receiving only spinal radiation, and on the fact that when the mean spinal dose to the whole population of patients is considered the incidence also increases approximately in proportion to the dose at all but the highest levels If there is no threshold for the induction of leukæmia the situation is analogous to the induction of gene mutations by radiation, and the rate at which the dose is accumulated may not affect the proportional relationship Court Brown and Doll remark on the importance of using this quantitative relationship in as many ways as possible to test the "no threshold" hypothesis, and they refer to the findings of Stewart et al[4] which suggested that the risk of leukæmia may be greater in children who were exposed to diagnostic X rays in utero Discussing the leukæmia rate among survivors of the Hiroshima explosion, Court Brown and Doll conclude that, within the necessary limitations of the available data, the incidence is compatible with a linear relationship

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[1] Hazards to Man of Nuclear and Allied Radiations Cmd 9780 H M Stationery Office See *Lancet* 1956 i 999

[2] Leukæmia and Aplastic Anæmia in Patients Irradiated for Ankylosing Spondylitis By W M COURT BROWN and R DOLL M R C Special Report Series no 295 H M Stationery Office Pp 135 10s *6d*

[3] Abbatt J D Lea, A J *Lancet* 1956 ii 1317

[4] Stewart A Webb J Giles D, Hewitt D *Ibid*, p 447

One important implication of the no-threshold hypothesis is that any exposure to radiation over and above natural background, however small, must increase the risk of leukæmia, and it must therefore be supposed that some leukæmias have been induced by diagnostic irradiation, which, it has been variously estimated, in countries where radiodiagnosis is widely used, can add to the population gonad dose from 10 to 70% of the dose due to background radiation Similarly, fallout from nuclear explosions would be expected to add a smaller quota to the leukæmia figures As Court-Brown and Doll emphasise, however, this is not the only hypothesis which is compatible with the data Much more work must be done before the true dose response relationship is clear Indeed, inquiries of this pattern may not be capable of producing a firm answer, and investigations on a gigantic scale may be needed[5] The formidable amount of time and effort that must probably be expended to identify beyond doubt the effects of low doses of radiation are leading some people to wonder whether a nearer target should be the immediate aim It may be better to decide, as far as the present incomplete evidence permits, what is an acceptable risk to balance against the benefits of useful radiation, and then to do everything that can be done to reduce additional exposure from all sources to the "safe" level To wait until the dose-response relationship is fully explained may be to wait too long

THE WELLCOME TRUST

THIS is an age of trusts, if not of trust, but among the many and diverse bodies which support scientific research the Wellcome Trust is believed to be alone in drawing its income from a pharmaceutical business in which the trustees hold all the share capital This unusual situation has been created by the will of an unusual man Sir Henry Wellcome was the sole proprietor and autocratic director of the pharmaceutical manufacturing firm of Burroughs Wellcome & Co He was also a man of wide and discerning scientific interests, and the success of his business enabled him to support research to an extent probably unequalled by any other private citizen At first the laboratories, museums, and libraries which bore his name and drew on his purse were the private hobbies of the owner rather than part of a large commercial undertaking But in 1924, for administrative convenience, Sir Henry gathered them and his commercial interests together to form the Wellcome Foundation Ltd On his death all the shares in the Foundation passed to the Wellcome Trust The first five trustees[6] were nominated in his will, and they were charged to use the large and continuing residue of his estate to advance research The objects for which they were empowered to use the funds, though wide, were carefully set out in the will The emphasis was, naturally enough, on the subjects which specially interested Sir Henry, including pharmacy and pharmacology, tropical and veterinary medicine, and the history of medicine The trustees have no mandate to assist undergraduate or postgraduate education or to provide facilities for treatment

The first report[7] of the trustees nominally covers twenty years, but in fact ten anxious and strenuous years were spent in winding up a complicated estate, finding the funds to meet the heavy death duties, and setting in order the affairs of the Foundation on whose dividends the income of the Trust depends Even in these early years, which were further complicated by the difficulties attendant on a major war, the trustees found money and energy to support Dr Henry Foy's work on malaria and sickle cell anæmia in Greece and in Africa and to provide funds for the plant which supplied plasma and serum for all the civilian and most of the Service needs in this country from 1943 to 1945 Hard on these tentative beginnings they record the endowment of research chairs of clinical tropical medicine and of pharmacology in the University of London, and chairs of anæsthetics in McGill University and in the University of Pennsylvania Research fellowships to the value of £28,000 have been awarded through the Animal Health Trust and the Pharmaceutical Society, and the trustees themselves have spent some £15,000 on what they candidly describe as "unsystematic" awards mostly in biochemistry In 1955 they also introduced travel grants, including short-term grants for senior workers who wished to visit centres abroad for purposes connected with their researches The total benefaction of the Trust in the period covered by this report amounted to £1,170,164

Though the trustees have rightly put people before things, they have also provided some very expensive tools on permanent loan Electron microscopes have been bought for the Medical Research Council, for the University of Oxford, and for the University of Cambridge, which is also to receive a nuclear magnetic resonance spectrometer The libraries and museums of the three Royal Colleges in London and the Royal Society of Medicine are all receiving, or have received, substantial help, and many scholars and publishers have been enabled to print contributions to medical history One of the most important of these is the collected edition of Ehrlich's work

So far most of the Trust's benefactions have been made within this country, but the trustees are mindful that they are legally subject to no territorial limitations and that they draw their income from a world-wide trading organisation They are glad that they have lately been able to endow research posts in Canada and in the United States, the country of Henry Wellcome's birth

FOUL FOWL

APPARENTLY about two cases of psittacosis are recognised each week in England and Wales (The name "psittacosis" is used here without prejudice to cover all human infections due to this group of viruses which are not lymphogranuloma inguinale) This number is almost surely an underestimate, for the apparent geographical distribution of the disease seems to be related to the location of laboratories able to make the specific diagnosis About half the patients with psittacosis give a history of contact with budgerigars or other parrots, but there are three reasons for doubting whether this observation is of great importance In the first place these pets are far commoner than they used to be, and statistically their association with human infection may by now be negligible (Observations on the number of houses with budgerigars would be useful) Secondly, hens, ducks, turkeys, seafowl, various passerines, and pigeons have all been found to be infected and a few of these have been convicted of causing infection in man Lastly, it is common experience that some patients with psittacosis have had no traceable contact with birds of any kind

It has been thought that man is usually infected by inhaling feather dust or dried excreta. Except for finches and canaries (which are susceptible to infection) only psittacine birds share man's living-rooms in this country Nevertheless the amount of dust inhaled by the most ardent fancier and his family must be a trifle compared with that in the respiratory tract of a man cleaning out a chicken-house Infection in hens is probably rare Because of their numbers and semi domestic habits, pigeons have been suspected of causing some of the infections which cannot be traced to parrots Half the pigeons in Oslo show antibodies to psittacosis,[1] and figures of this order have been found in other towns This line of inquiry is worth pursuing and should be extended to pigeons kept for racing

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[5] Court Brown W M Doll R. *Ibid* Jan. 12 1957 p 97

[6] The present trustees are Sir Henry Dale O.M F R C P F R.S (chairman) L C Bullock Martin Price F C A Lord Piercy and Brigadier J S K Boyd F R C P F R S

[7] Wellcome Trust First report 1937–56 52, Queen Anne Street, London, W 1

When first seen in this country about 1930, psittacosis was a virulent disease apparently derived from newly imported parrots Importation was very soon forbidden, and thereafter the type of infection was on the whole less severe The disease had probably been present for many years but had remained undiagnosed until the severe infections called attention to its presence and provided material for specific diagnosis At the request of the pet trade, and because infection had by then been recognised in other birds, the ban on imported parrots was lifted in 1952—an act of administrative daring which was followed almost at once by several outbreaks of severe infections traced to imported parrots The ban was reimposed This experience suggests that the strain of virus current in South America (whence come most of these birds) may be more virulent for man than that endemic here, but we know of no experimental support for this idea That the more virulent strain has not become established is perhaps due to the fact that it is even more fatal for birds than for man

Psittacosis is not a grave danger to the public health, and treatment with some of the newer antibiotics has been successful, but it can be an alarming and distressing disease In our present state of ignorance prevention will not be easy Active immunisation is possible, but few except bird-fanciers are likely to ask for it Without examples plain to see it would be hard to persuade the public that any harm can come from a bird so elegant and amusing as the little parrots If pigeons spread the disease this will be one more reason for reducing their numbers, but so far they seem to have defied all methods designed for their annihilation in town and country Before we are compassed about with any more restrictions and prohibitions it would be wise to try to establish beyond doubt the source of the two infections which are detected each week

PLASMA-INSULIN ASSAYS

INSULIN-RESISTANCE has rather more possible causes than diabetes itself Resistance may be noted during diabetic ketosis or (in the absence of ketosis) in association with allergic manifestations or immune reactions, infections, non-ketotic acidosis, and endocrinopathies such as Cushing's syndrome and acromegaly Resistance to exogenous insulin may also be found in non diabetics, such as mentally ill patients given insulin shock treatment The mechanism of resistance in any one case is often hard to understand and to investigate, though there have been notable recent advances in laboratory techniques to apply to this problem We reviewed the immunological approach last year,[2] and the paper by Dr Baird and Dr Bornstein on p 1111 of this issue represents the most recent advance in the technique of measuring "insulin activity" and insulin antagonists in the plasma The presence of such antagonists in the plasma has been inferred ever since it became known that, after pancreatectomy, patients needed no more than 30–50 units of insulin a day to control their diabetes,[3] though the insulin requirement of many "ordinary" diabetics is much greater than this

The nature of these insulin antagonists has not been established, but it is apparent that they are of more types than one, some have a very protracted effect,[4] and (as Dr Baird and Dr Bornstein found) some are stable to heat and to extraction procedures, whereas others are labile to such procedures Their presence in plasma has greatly complicated the task of measuring insulin levels in blood, for it is a resultant of the action of insulin and of insulin antagonists that is measured by the two main methods of insulin assay—the rat hemidiaphragm method, in which glucose utilisation[5] or glycogen deposition [6] is measured in vitro, and the method of following the change in the blood sugar of alloxan diabetic, hypophysectomised, adrenalectomised rats after they have received injections of standard doses of insulin or of a test plasma [7] Such rats have proved too fickle for satisfactory insulin bioassays, and most effort is now being expended on the rat hemidiaphragm method Stadie et al [8] used this method and radioactive insulin to study insulin binding They found that insulin, labelled with either ^{131}I or ^{35}S, was firmly fixed by rat diaphragm after a short exposure, and despite many subsequent washings, and that the activity of the bound insulin was affected by other hormones such as those of the anterior pituitary [9] Accordingly isotopes were used to differentiate an effect on insulin-binding from one on the hypoglycæmic action of insulin In the application of the rat diaphragm method to assays of "insulin" in blood, there is good evidence that insulin is indeed being measured, but the evidence cannot be accepted as conclusive, in view of Randle's[10] work showing the effect of growth hormone on this system Groen et al [5] have shown that in dogs the "plasma-insulin" activity disappears after pancreatectomy, and that cysteine and glutathione, which inactivate insulin, also inactivate the hypoglycæmic material in plasma At least two proved cases of β cell tumours of the pancreas have been shown to have high "plasma insulin" activity,[5 11] and an increase in the "plasma insulin" of a normal fasting man has been measured in blood withdrawn a few minutes after insulin had been administered [12]

Baird and Bornstein now report a real advance in their work *on the separation of the* "insulin" fraction of plasma from the insulin antagonistic one by extraction By their results in patients they have confirmed the separation of diabetics into those with available plasma insulin and those without (the juvenile diabetics)[4] Plasma extract from a woman aged 29 who was admitted to hospital in diabetic coma had insulin activity, but this was masked in the whole plasma by an insulin antagonist demonstrated in the residue of the extraction procedure Such masking of insulin activity in the plasma by inhibitor substances was demonstrated in 3 other patients with diabetic ketosis, and confirms the findings of two other groups of workers [11 13] Baird and Bornstein's results in normal non diabetic persons indicate that even in them there is a balance in the crude plasma between the effects of insulin and those of its antagonists A relative excess of the antagonists, whatever they may be, could account for the high insulin requirement of some non ketotic diabetics

DR A G MAITLAND-JONES, consulting physician to the children's department of the London Hospital, has lost his life while fishing on the river Usk

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[1] Ulstrup J C, Nes s Chr *J Oslo City Hosp* 1957 7 33

[2] *Lancet* 1956 ii 452

[3] Goldner M G, Clark D F *J clin Endocrin* 1944 4 194

[4] Bornstein J Lawrence R D *Brit med J* 1951 i 739

[5] Groen J Kamminga C F, Willebrands A J Blickman J R *J clin Invest* 1952 31 97

[6] Marsh J B Haugaard N *Ibid* p 107

[7] Bornstein J *Aust J exp Biol med Sci* 1950, 28 93

[8] Stadie W C Haugaard N Vaughan, M *J biol Chem* 1952 199 729

[9] Stadie W C Haugaard N Vaughan M *Ibid* 1953 200

[10] Randle P J *Lancet* 1954 i 441

[11] Vallance Owen J, Hurlock B Please N W *Ibid* 1955, ii

[12] Vallance Owen J Hurlock B Please N W *Ibid* 1954 i

[13] Field J B, Stetten D jun *Amer J Med* 1956, 21 339

Reconstruction

CONSULTANTS AND SENIOR REGISTRARS
THE PRESENT AND THE FUTURE

THE number and distribution of consultants is causing anxious questions in the minds of medical administrators, whose quite recent assessments of needs have been confounded by the rapid but uneven march of medical progress, of some of the consultants themselves, who are in danger of being under-employed because of this progress, of S H M O s whose claim to better status is once more under review, and of senior registrars, whose difficulties in making the leap into consultant status are well known

How effectively, in fact, are the specialist services meeting needs, and should these services be substantially expanded or modified to meet today's demands, which differ from those of even a decade ago? Inquiry in various hospital regions suggests that there are more or less enough beds for the acute sick, though the beds are not always in the place, or in the specialty, where they are needed, that patients found to need immediate inpatient treatment receive this without delay, and that the delay in seeing *new outpatients* is causing more concern than the delay in securing their admission There seems at present to be no prospect of the appointment of many additional consultants, but the argument for recognising a new grade of "specialists" is increasingly difficult to refute

Hospital Buildings and Beds

If it is true that there are more or less enough beds for the acute sick,[1] two important reservations must be made The first is that out-of date hospital buildings must be replaced and the second that beds must be redistributed in the places and the specialties where the need is greatest

Buildings

With the long continued restriction on capital expenditure, some hospitals in which the acute sick are treated (and which even in 1939 were unfit for this purpose) have never been brought up to date These hospitals, which include some former poor-law institutions, urgently need to be partly or completely replaced Roughly speaking from scratch a new "acute" hospital can nowadays be built at a cost of £5000 a bed, and a new block at a cost of £3000 a bed, but an outdated building can often be made serviceable for some years at a cost of about £1000 a bed The price of putting up a new block represents only four years maintenance costs at £15 a bed per week, and, on the ground that we must spend more in order to spend less it seems clear that an extensive building programme should no longer be delayed The provision of suitable modern buildings bears closely on the number of consultants who can usefully be employed, for the appointment of additional consultants is commonly prevented by the lack in old buildings, of physical resources (operating-theatres pathology laboratories), and the consultant establishments cannot everywhere be brought up to the required level until these capital developments have been made

Redistribution of Beds

In almost every region hospital beds are not distributed in accordance with present day needs Often, owing partly to the dual origin of our hospitals, beds are too scattered (in one medium-sized town in the North a physician has beds in four different hospitals) beds may not be in the places where they are most needed (namely the new towns and the towns which have grown most extensively), and beds are not always distributed between specialties according to demand In the past ten years the pressure on beds for the tuberculous has declined sharply, and that on beds for patients with infectious diseases has continued to fall, and there is now much less call than formerly on beds for children These changes are not yet fully reflected in the division of beds between the different departments

The Consultant's Work

Several ill-defined factors govern the amount of work a consultant can undertake, and the sufficiency of establishments can be gauged by no single test

A consultant with a maximum part-time contract may put in 40 hours' work a week instead of his agreed 31½, and a review in one region has shown that some 90% of consultants do in fact work substantially longer than their contract requires Such people get through *more* work *than their* agreed *number of sessions* would suggest Then again, the amount of work that can be done depends on distances to be travelled and the number of hospitals to be visited, on cooperation with colleagues and help from registrars and on associated activities (a consultant on a regional board or management committee may need extra help during his tenure)

Beds

For a physician or surgeon working maximum part-time, a convenient dividing-line is the 40-bed mark, with, say three outpatient sessions a week By this far from accurate criterion, it seems that not many in the South are overburdened A few have substantially more than 40 beds, but these had such a number before the start of the service and, being well supported by registrars, are reluctant to forgo any now *In the North on the other* hand, it is commoner for clinicians to have beds in excess of 40 But here as in the South, there is no opening for many new appointments if new consultants are to have charge of as many beds as do their established colleagues

Waiting-lists

The extent to which a consultant is meeting the demand on him is commonly measured by the waiting list Yet a waiting-list is a worthless guide without knowledge of the hospital and the consultant

In one hospital a waiting list may be regarded as a disgrace, and its surgeon may almost abolish his list by making full use of the operating-theatres in outlying hospitals and (if a spirit of coöperation prevails) by borrowing beds from his colleagues and holding evening operating sessions His colleague up the road on the other hand, may all the time be adding diligently to his waiting-list in order to underline his claim for extra help At one hospital no patient's name may be put on the waiting list unless there is a reasonable chance of his being admitted within a couple of months, at its neighbour names may be entered on the list without regard for the likelihood of the patient being sent for in the next few years Hospitals with long waiting lists might have still longer ones if general practitioners had not wearied of seeing their patients wait and so begun to send new cases elsewhere Most waiting lists are inflated by perhaps 20-25%, and a further 10% or so of patients may be expected to refuse admission when the time comes[2] Nevertheless when full account is taken of local conditions as in the careful study by Professor Grundy and his colleagues[2] waiting-lists are useful indicators

Grundy et al found that in Cardiff at the end of 1954 four departments accounted for 93% of the patients who had waited two years for admission These departments were orthopædics, gynæcology, general surgery, and urology In other regions, too these departments together with those of the other "regional" specialties (plastic surgery, neurosurgery) have long lists, and it will be noted that each of these specialties requires an operating theatre The lists tend on the whole to be longer in the north than in the south of England In the larger specialties, except possibly orthopædic surgery and gynæcology, the lists are beginning to come down, and there is no delay in admitting patients who are in pressing need of treatment But the delay suffered by the remainder, although it may not threaten lives, may prevent the patients from working fully and cause distress Grundy et al, for instance, found that in a group of patients who were interviewed at home and most of whom had been over a year on a waiting-list, 21% had a medico social problem associated with the waiting period

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[1] See Studies in the Functions and Design of Hospitals London 1955 p 149

[2] A Study of Hospital Waiting Lists in Cardiff a report prepared for the board of governors of the United Cardiff Hospitals By F GRUNDY R A N HITCHENS and E LEWIS FANING

Outpatients

The pressure on outpatient departments continues to grow at much the same rate, partly no doubt owing to the growing resources for treating patients without admission to hospital,[3] and partly owing to the ever-increasing complexity of medical practice which calls more and more often for reference to hospital In the outpatient department clinicians are heavily weighed down—including those (such as many physicians) who have no great cares with their waiting list One physician in the Midlands owns regretfully that, despite his best endeavours, new patients rated by their doctors as urgent cases must wait for 3 weeks before their appointment falls due, while the remainder must wait 16 weeks Delay, though often less severe, seems to be the rule in nearly every other clinical field, and is causing more general concern than delays in admission from the waiting-list

Openings for Consultants

Senior registrars in general medicine, general surgery, and obstetrics and gynæcology are having the utmost difficulty in securing a consultant post, because vacancies are few For a consultant appointment in medicine 50 or 60 candidates may apply, for one in surgery 45 or 50, and for one in obstetrics and gynæcology 35 or 40 Competition is fierce in some of the smaller specialties, such as orthopædic surgery, plastic surgery, and neurosurgery, but it is never as massive as in the three main fields

The number of senior registrars who have completed four years' training varies greatly between different regions Whereas in some regions there are none or hardly any, in at least one there are a dozen in the three main branches (general medicine, general surgery, and obstetrics) to say nothing of the people who are holding research posts but hope to get consultant appointments later In one region it has been suggested that the senior registrars should be dismissed on the grounds that the younger generation, trained since 1945, can no longer be denied their opportunity, and that the remaining older men are never likely to secure a consultant post since they have applied again and again without being short-listed more than once or twice This does not exclude the possibility that such men are good enough to become consultants it simply suggests that, against the weight of exceptional competition, they may not gain advancement

Indeed what evidence there is suggests that the majority of these doctors are fully fit to be consultants In the region with a dozen who have passed the four-year mark a committee was set up to examine dispassionately their claims to a consultant's competence This committee, working with the help of senior university teachers, each of whom has a very high standard, found that anyhow ten of the twelve are suitable for a consultant post

Replacement

In the three main fields the openings consequent on death or retirement may be even fewer in the coming years than published figures[4] indicate, for, as the demand on some of the other specialties shrinks, their exponents will tend to revert to the main fields The specialist in tuberculosis is turning to other diseases of the chest, thus diminishing the calls on the general physician, and specialists in infectious diseases and venereal diseases, in which the work has decreased, may go back to general medicine To a lesser extent the same process may declare itself in surgery For instance, owing to the decline in tuberculosis, some thoracic surgeons are now more lightly employed, and, since the transition to cardiac surgery is sometimes denied to them they are tending to turn (quite gladly in the case of the older men, who received a general training) to general surgery

Expansion

Expansion offers slight but ill defined hopes Some regions, including a few which started with a good complement of consultants, increased the number of these rapidly after the appointed day, and now they need no more than one or two in each of the main field At the other extreme is a region which began with too few consultants and is still seeking to expand their numbers at the rate of about twelve a year—though it does not always succeed in this

The speed of expansion is regulated by four principal factors physical resources, the Ministry of Health, money, and the availability of suitable candidates

Physical resources —Obviously it is no use appointing a surgeon who will have no operating theatre, a physician who will have no outpatient facilities, or a pathologist who will have no laboratory At a rough estimate, it seems that about half the planned increase in consultants is held up by lack of such resources

Ministry of Health —The proposal for each new post has to be approved by a Ministry of Health committee, which includes representatives of the Joint Consultants Committee This seems to exercise its powers temperately in order to secure not only a sound use of money but also the best distribution of scarce skills thus an application from a regional board in the south of England for an additional radiologist may be refused on the ground that the North has a greater need of radiologists, who will not go there if they have the option of settling in the South But the committee cannot be acquitted of unwisdom at least two boards have been told that their proposal to set up a new post was turned down because the board would be unable to find a suitable person to fill it—an affront to the board's ability to decide when to leave a post unfilled

Money —The experience with money differs between different parts of the country In one region the need is mainly for consultants in specialties where candidates are few and not always good, and the board has decided not to allocate more money to make additional appointments until the quality of candidates improves In another region, where the number of consultants is growing year by year, money seems to be no serious obstacle In a third region money seems to be a very real obstacle

A board budgets for increased consultant staff by including the cost under developments in its revenue estimate A board that is granted less money under this heading than it has applied for must decide which development to forgo and in this one region where money is a main difficulty it is thought that expansion might proceed more certainly if the estimate for consultants formed a separate category from which the money could not be transferred to another heading

The candidates —Candidates are few and opportunities relatively many in anæsthetics, psychiatry, radiology, otology, ophthalmology, and to a lesser extent pathology, and the prospects seem bright, too, for the medical fearing the effects of repression had permitted them to smoke.

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[3] Newcastle Regional Hospital Board 7th report, to March 31, 1956 p 11

[4] Consultant and other specialist staff in hospitals See *Lancet* April 13 1957, p 785

Smoking Forbidden at School.—In only 5 schools was smoking forbidden. In 1, boys were caned if caught smoking—the youngest offender was aged 12. Several headmasters pointed out that smoking is very common in the teaching profession, and one remarked that boys have only to see the rush for pipes and cigarettes in "break" to realise that their masters do not seem to take much notice of warnings. Masters, like parents, may feel diffident about enforcing the rule. One headmaster had recently given up smoking to convince a boy in the VIth form that this could be done, but it had little effect on the boy.

Combating the Habit.—44 headmasters were in favour of giving factual information to boys on the ill effects of smoking, 7 were doubtful, and 3 were against it. In one school the doctor saw all the boys at least in their first and fourth years (ages 12 and 15) and spoke to them about the ills of smoking. In another school the Vth form boys suggested that advice should be given before 13, when many boys start smoking. It may be difficult to convince boys that the danger is personal and not remote in time, and any semblance of tendentious propaganda in its presentation must be avoided. One headmaster who is against this teaching said that many VIth form boys are willing to consider objectively problems of modern life, but few base their personal conduct on purely intellectual evidence. Another thought it unnecessary because in his experience smoking has been uncommon among boys for some years, but he was unique in this view. Those who doubted the value of instruction held that because of the example set by adults it is hard to influence the adolescent, more could be done by informal conversation between masters and boys, and the basic safeguard is stricter parental control and a more rigid enforcement of the law about the sale of tobacco. Several headmasters pointed out lectures by outside visitors could carry more conviction than advice from masters who are smokers.

BOYS' PUBLIC SCHOOLS

The replies from the headmasters gave the impression on the whole, that addiction to smoking is less serious in public schools though in one, where boys are punished if caught smoking, it is common outside the surveillance of the school. The age at starting is later—often 14–15—and many boys do not smoke at all until they have left school at 18. One headmaster said that on the whole there is less smoking by people in their teens now than ten years ago. In one school the boys are permitted to smoke under certain conditions, and probably not half of them do so. One headmaster said that the habit is formed at home during the holidays.

In one school of 640 boys, of whom 350 were over 16, about 6 smoked habitually before 17 and not many more between 17 and 18. At another school about two thirds smoked and had begun at 13½ on the average. One headmaster pointed out that few of the boys leaving for universities smoked.

Of 19 headmasters 12 were in favour of giving factual information to boys, 3 thought it would be of doubtful value, and 1 was not in favour. At one school two thirds of 70 boys leaving school thought instruction should be given at an early age before smoking is begun.

GIRLS' PUBLIC SCHOOLS

Replies from the headmistresses of 3 public schools suggested that the problem does not exist in these schools. As one said, "it is no longer considered clever to smoke."

I wish to thank the Marie Curie Memorial Foundation for permission to study and publish this information, and the headmasters and headmistresses for their help.

CENTRAL HEALTH SERVICES COUNCIL

EARLY last year the Minister of Health asked the Council's Standing Medical Advisory Committee[1] for guidance about the present need for welfare food supplements other than milk to the diet of expectant and nursing mothers and young children under 5. Requirements of vitamin D and the supply of orange juice to children between 2 and 5 were two points on which the Minister was particularly anxious for advice. Changes in the availability of foodstuffs as well as dietary studies in recent years had suggested that it might no longer be necessary to continue these supplements.

A subcommittee formed jointly with the Scottish Standing Medical Advisory Committee began to review this subject a year ago, and its final report is expected soon. An interim report showed that most of its members agreed with the conclusions reached by the British Pædiatric Association in 1952 that children between 2 and 5 received adequate amounts of vitamin C from a mixed diet and that the issue of orange juice should be restricted to children under 2. But a minority of the subcommittee thought that there were still circumstances where this supplement was called for and that it should continue. Additional information was being sought and a further report would be prepared.

Another interim report concerned the content of vitamin D in welfare foods. The subcommittee's view was that the present level of fortification should be reduced so as to minimise the risk of causing hypercalcæmia while still continuing to give protection against rickets. A reduced level of fortification was recommended for infant cereals, so that a child of 9 months taking the recommended amount of a cereal would receive therefrom 200–400 international units of vitamin D daily. Assuming that these recommendations were implemented, the subcommittee further advised that National cod-liver oil should contain an average of 100 I.U. per g. and National dried milk an average of 90–100 I.U. per dry oz. (In 1953 the Ministry of Food recommended manufacturers of National dried milk to add 500 I.U. of vitamin D, as calciferol per dry oz., so as to allow for a maximum deterioration of 44%, thus giving a minimum of 280 I.U. per dry oz. in the food as marketed.[2]) Consultations have begun between the Ministry of Health and the Ministry of Agriculture Fisheries and Food with a view to bringing the subcommittee's recommendations about vitamin D into effect.

In 1955 a subcommittee of the Standing Mental Health Advisory Committee began a review of the functions of the various authorities concerned with arrangements for the treatment and care of persons suffering from mental illness at all ages or from infirmity arising from old age, and the results of this inquiry are summarised in the council's report. The subcommittee saw need for a closer coordination between the authorities concerned, especially between individual workers, and referred particularly to the schemes at Oldham and Nottingham. Dealing with alternatives to treatment in mental hospitals, it suggested that if there were more health visitors, district nurses, home helps, and social workers to give domiciliary help and closer coöperation with general practitioners, many patients could be retained in the community. The public should be made more aware of the psychological problems arising from the increasing number of old people in the community who need help. While local authorities should take the lead in this matter, their health visitors and social workers needed the active cooperation of other persons and bodies in close touch with families and able to assist in the home care of the aged who have physical and psychiatric disabilities

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[1] Report of the Central Health Services Council for the year ended Dec. 31, 1956. H.M. Stationery Office. Pp. 20. 1s. 3d.

[2] See *Lancet*, 1956, ii, 136.

The Minister has accepted the advice of the council that no action should be taken on these recommendations pending the report of the Royal Commission on the law relating to mental illness and mental deficiency

GENERAL MEDICAL COUNCIL

IN his address to the council's 194th session on May 28, the president, Sir DAVID CAMPBELL, discussed the relations of Great Britain to other Commonwealth countries in the sphere of medical education and registration The General Medical Council, which in the autumn of next year would celebrate its centenary, had been the model for and indeed the mother of all the medical councils in the Commonwealth The statutes establishing them had been based on and have often copied verbatim the words of the British Medical Acts Their procedure followed our own closely, not only on educational but on ethical matters Sir David spoke of his recent visits to Uganda, South Africa, Malaya, and Hong-Kong The council while seeking to maintain a high standard of medical education, had always been ready to encourage new medical schools overseas by visitation and advice, and might sometimes perhaps have taken a temporary risk in granting recognition But the risk, if it existed at all, had always been well worth while It had led in every case to a striking improvement in the provision of facilities for education and in the standard of attainment There was more to be done, Sir David declared The council had by statute no responsibility for post graduate education Yet the position of the specialist staff in some of the countries he had recently visited was such that, though there were men holding senior medical posts in the medical services, there was a striking gap between them and the junior staff It was imperative, if the medical service in these countries was to develop on modern lines, that the gap should be filled by doctors trained locally as specialists in medicine, surgery, and midwifery, yet willing to submit themselves to any standard of examination demanded in this country And they were desperately anxious to do so On the basis of what he had seen, it would be a good thing, therefore, for this country and for the Commonwealth if bodies which grant higher qualifications were to follow the example of the General Medical Council and approve the medical schools of the Commonwealth countries with whom we had reciprocity as places where the candidates for their examinations could be trained

More than six years had passed, Sir David remarked, since the publication of the reports of the eight committees on medical auxiliaries appointed in 1949 under the chairmanship of Mr Zachary Cope The recommendations of the committees had been discussed by the Health Departments with interested bodies, and last October the Minister and Secretary of State issued a memorandum containing details of a provisional scheme for the statutory registration of chiropodists, dietitians, medical laboratory technicians, occupational therapists, physiotherapists, radiographers, remedial gymnasts, and speech therapists collectively referred to as " professions supplementary to medicine " It was proposed that the machinery should consist of a separate registration board for each of the "supplementary professions" and a coordinating council Observations on these proposals had been invited from many bodies, including the General Medical Council Proposals put forward at earlier stages had been considered at the time by the executive committee on behalf of the council and the committee had then made certain suggestions Since the new proposals appeared to cover the points made by the committee, it had not been thought necessary to offer any further observations

In England Now

A Running Commentary by Peripatetic Correspondents

MY mind was switched from Africa to a Surrey village by the remark of a speaker at a recent conference that the principle of Occam's razor did not apply to practice among African children, until at least three distinct diseases had been diagnosed in each child, one had hardly started On Thursday afternoons, which was his "no surgery" evening, my father used to take me on expeditions which sometimes finished up with a splendid tea at the Hautboy at Ockham, where William of Occam was born late in the 13th century On one occasion, after animadverting on the charge of a shilling a head—ninepence he thought would have been more appropriate for a tea which included cakes and what we called "real" strawberry jam—he told me about William and the follies of the schoolmen and the early monkish scientists I grew up with a picture of a man in a grey habit plucking out a hair and attempting to split it with a "cut throat" like the one my father used each morning, while his colleagues peered down primitive microscopes trying to count the number of angels dancing on the point of a needle

By the way, the *Oxford English Dictionary* has blunted the razor (why razor? because it cut away the undergrowth?) which it describes as the principle that "things not known to exist should not, unless it is absolutely necessary, be postulated as existing" The original instrument of Old Bill Occam—*Doctor invincibilis et venerabilis Inceptor*—had a keener edge—*Entia non sunt multiplicanda praeter necessitatem* Six words instead of sixteen

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The need for reform of the English language had never struck me with much force till Bill (now 5) started to read and write Like all children, he is essentially logical He spells as he hears, and darned good spelling it is *too*, much better than *ours*

We have a game that whiles away the tedious hours before the blessed release of bedtime I write down a series of words for him to read, usually making some sense, such as HOCKEY MAN HIT DADDY POOR LEG Then it's his turn, and he writes words for me to read Alas, my sense of logic has been so warped through the years that often I can't RASING KRRE (racing car) FAYS (face), PYLO (pillow), RABYT (rabbit) O K so far perhaps But what *about* SCRYRAL which turned out to be squirrel, and MYRA (mirror), and UGCL (uncle), not to mention FROT (I bet even the otorhinolaryngologists didn't recognise that one) He writes DJ for J as in DJI FI (and he's right of course) The usual nursery class spelling for train is CHRAN, and RALRA is his interpretation of railway With DRORYNGE he strikes a pleasantly medieval note, but at HRISI for Horsey I decided he'd given up trying, even I don't pronounce it that way

I am reluctant to pervert such admirably accurate descriptions of what he hears Surely *to do so* would discourage the developing scientific mind? Perhaps everyone would benefit from Speling Reform Kood it be that behaivyer dissorders arise sumtimes from speling tenshuns? Is the increase in neuroses, gastric ulcers, cardiovascular disease, &c, directly related to our higher and higher standards of literacy? There is a good case for another Royal Commission, and I hope that Her Majesty's advisers will have the sense to appoint Bill as chairman

* * *

Post-war travel started in earnest in 1947 and many a traveller, like myself, must *be renewing* his passport this year To me mine is a valuable document, of historical as well as of geographical interest

The first year I had it I went to America, the land of freedom and of vigilance My finger prints were taken before a visa was issued which cost $2 Those were the days when dollars were beginning to be precious, yet I got £500 worth for seventy days Yet another testimonial to American hospitality is that I used less than half I was advised to transfer the rest into dollars and then buy pounds back and make a big profit but I have always prided myself that I did not Formalities such as declaring I had not earned money and therefore was not owing income-tax had to be gone through before I could leave.

The next year, I went to Germany and had to have a special permit to visit the British military zone I went via the Hook and thence to Cologne Sept 5, 1948, the date of my passage through Holland did not mean much to me when I landed, but I soon discovered that the decorations all over the country were in honour of the golden jubilee of Queen Wilhelmina The German currency had been revised shortly before and the British non-smoker like myself could no longer win himself a welcome with cigarettes Money apparently presented no difficulties on the Continent until 1950, and as I sometimes took my wife and three children, I was often glad of the limit

I strongly dislike visas and cannot help feeling that countries like Finland could well dispense with them, for the 450 Finn marks (about 10*s*) is hardly worth the trouble of collection The stamps on my passport are surprisingly few, a 82 stamp, three Finnish stamps of 300, 100, and 50 marks and some Spanish ones, some stuck on top of the others My passport shows that Germany, the three Scandinavian countries, Holland, Italy, Switzerland, and France responded to the Foreign Secretary s plea "We request and require in the Name of His Majesty all those whom it may concern to allow the bearer to pass freely without let or hindrance and to afford him every assistance and protection of which he may stand in need " Her Majesty makes the same plea

* * *

Though my researches are not exhaustive, I have so far seen only two medical journals in which a substantial bulk of the reading matter consists of letters to the editor They are both weeklies published in London W.C Why, one wonders do so few doctors in the United States think it worth while writing to the *J.A M.A* and are there really no amused or angry Swedes to write to *Svensk Kem Tidskr* ? Yet woe betide the man who makes a rash remark in his letter to a London editor By return of air-mail post comes an admonitory letter from Minneapolis or Madagascar " It appears to have escaped the notice of Dr X, in his otherwise admirable paper, that I first pointed out the use of seaweed in psoriasis as long ago as —— " But one must admit that there is a certain gratification in knowing that someone in Porto Rico or Pennsylvania is sufficiently interested to question the validity of one's statements

But perhaps the most pleasing feature of the London correspondence columns is the hospitality offered to the most unexpected of esoteric subjects Where else to quote a recent example could one expect to read a discussion on the utility of the word *fax* ? We may rest assured that so long as the catholic nature of the correspondence columns is thus maintained so long will London W C, remain the commodious seat of learning that it is today

* * *

When we were at Blackpool last week doctor Pam ad another attack of er hassma so we called m sister s doctor in an' 'e said we ll 'av er right in a jiffy an' e gave er some little white tablets an next mornin she adn t a sign of it ad yer Pam ?

Nay I were right champion next day

Champion she was so I says to m sister (she s the one as 'ad everything taken out except a hovary) I says m doctor at ome would like to know the name of them tablets nothin' 'as suited our Pam so well so she says go to is surgery an' ask im so I goes along an' e were right nice an said they were called Katie s Own

Perhaps some peripatetic reader could give me a clue ?

* * *

Our hospital is near London and the medical staff, unlike the patients are mostly urban types This can lead to misunderstandings Our Medical Registrar on asking a patient his occupation received the reply ' I'm an artificial inseminator The Registrar was rather taken aback, but, after a moment, inquired brightly Oh do you work for Mr —— (the gynæcologist) in the fertility clinic ? ' The patient stolidly replied " No, Doctor I work in the cattle market "

Letters to the Editor

MEDICAL STAFFS OF MENTAL HOSPITALS

SIR —We are very interested in this correspondence In 1946 our own hospital, which then had a staff of 3 doctors, providing 2 outpatient sessions per week admitted 158 new inpatients In 1956 our medical staff of 7½ doctors (7 full time and 1 part-time) provided 23 outpatients sessions per week and treated 743 new inpatients

It could scarcely be claimed that mental hospitals were extravagantly staffed in 1946, but a comparison of our figures for that year with those for 1956 will show that, relatively speaking, we were very much less favourably placed to treat our patients in 1956, eight years after the inception of the National Health Service In presenting these bare figures no account is taken of the change in scope and character of psychiatric practice in 1956 as compared with ten years earlier, but this aspect of the problem was well emphasised by Dr Strauss and his colleagues in their letter of May 4.

We believe that our situation is not unusual, indeed we know that there are hospitals where the position must be much worse than in our own We consider the increase of medical staffs of mental hospitals to be a problem requiring urgent attention if British psychiatry is to march with the times

FRANCIS E PILKINGTON
ROBERT A BLAIR
JOHN M GILROY

Moorhaven Hospital
Ivybridge Devon.

HIRSCHSPRUNG'S DISEASE

SIR,—We have recently had under our care a lady of 67 who suffered from this disease in childhood and was operated on for its cure by Frederick Treves in 1897 In view of the advances which have been made in the understanding of the pathology and in the treatment of this condition, we wish to draw attention to Treves's description of this case, in which he expressed his views on the pathogenesis of the dilatation of the colon

Before his time, and indeed since his time as well the enlarged hypertrophied colon had been considered to be the site of the disease, until Swenson and Bill[1] expressed the view that the primary abnormality lay in the narrow normal-looking segment of bowel beyond the dilated portion Although his remarks have been overlooked it is evident that Treves appreciated this fact and based his treatment upon it In a remarkable anticipation of modern concepts he wrote[2]

> I venture to think that there is strong evidence to support the suggestion that all cases of ' idiopathic dilatation of the colon in young children are due to congenital defects in the terminal part of the bowel, that there is in these cases an actual mechanical obstruction and that the dilatation of the bowel is not idiopathic The marked hypertrophy of the distended gut suggests in the most emphatic way that there is an obstruction to be overcome and such hypertrophy is quite inconsistent with the conception of an idiopathic " dilatation of the bowel I am not aware of a previous instance of the treatment of this condition by a radical operation.

After a preliminary colostomy, Treves resected the colon below the splenic flexure, including the narrow segment and the rectum, and he anastomosed the transverse colon to the anal skin The patient has remained fit for many years living an unusually active life The bowels move twice daily, and there is good voluntary control On examination the anus is seen to be replaced by a patulous opening measuring 1 cm laterally by 3 cm anteroposteriorly, through which normal mucosal folds are visible Sphincter action is effected by voluntary contraction of the levatores ani

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[1] Swenson O Bill A H jun. *Surgery*, 1948 24 212
[2] Treves F *Lancet* 1898 i 276

In 1954 we operated for the relief of obstructive symptoms associated with X-ray appearances suggesting a neoplasm in the ascending colon At laparotomy the colon was found to be mobile and not greatly shortened There was some dilatation but no thickening of the bowel wall A sharp kink in the ascending colon had been caused by adhesions, their division relieved the patient's colic

The Royal Free Hospital,
London, W C 1

H DAINTREE JOHNSON
HAROLD DAVIS
J H EVANS

SIR,—Mr Cooling, in his letter of May 18, advocates State's[1] procedure, in preference to Swenson's, on two grounds—that the results of Swenson's operation are not as good as one would hope, and that it may cause impotence I think this is dangerous advice, for in State's operation part of the aganglionic rectum is left in situ It is all very well to say that the only theoretical criticism of it is that recurrence may follow, but Hirschsprung's disease may kill the patient, and one hardly needs any further objection Before 1948 the majority of sufferers died in infancy or childhood

The dissection of the rectum in Swenson's operation cannot be compared with the wide excision made in adults to remove cancer The essential principle in the rectal dissection in Swenson's operation is that it is made *on* the rectal wall The almost complete absence of bladder complications in the series from Great Ormond Street suggests that a proper dissection does not damage the pelvic nerves Swenson[2] reported that in the 4 adults on whom he had operated ejaculation had not been disturbed He also pointed out that, in 43% of his patients, the lesion extended only to, or just above, the pelvic peritoneal floor, and that such patients would not be helped by a resection above the pelvic floor, for little, if any, aganglionic bowel would be removed Many cases of severe Hirschsprung's disease have resulted from abnormal segments no longer than those which State left in situ One is less concerned about the children, not fully cured, who will grow up to manhood, as about the many who will not grow up

I felt that the results in the series I reported were quite encouraging There are many problems still, but our understanding of them is increasing By due attention to bowel training after operation, close surveillance for the first three years, and the prevention of complications, we can expect improved functional results The great majority of the cases I reported are achieving perfect function, and the results appear as they do because quite a number are taking an understandable time to achieve it

North Adelaide
South Australia

G G WYLLIE.

OVERDOSAGE OF VITAMIN D

SIR,—I was most interested in the case of renal colic and persistent hypercalcuria, without hypercalcæmia, following self-administration of vitamin D, reported by *Dr Freedman (March 30)*

In an experimental investigation,[3] in rats and rabbits, polyuria and hypercalcuria were the first signs of vitamin-D intoxication

The animals were given a daily dose of 20 000 I U calciferol per kg body-weight The increase in the urinary excretion of calcium was significant in the rats and highly significant in the rabbits As hypercalcuria developed while the blood calcium level was still normal (in the rats the serum-calcium level remained normal throughout the whole experiment, in the rabbits it increased slightly in the later phase), it must be considered a result of decreased tubular reabsorption of calcium The polyuria likewise points to a tubular disturbance, the increase of the urinary flow was significant in the rats and not significant in the rabbits In view of the very slight histological changes in the tubular cells of the rats at the end of the experiment, it seems possible that these disturbances, caused by calciferol, may arise before morphological changes in the tubular cells

Roodeschool Groningen,
Holland

H TAKENS

INFLUENZA

SIR,—Those who remember the 1918 influenza pandemic will recall its passage round the world westwards and perhaps see, with me, a possible, even probable, portent in current events in Malaya where influenza is raging

If the events of 1918 should be repeated we might expect a much more rapid westward spread and now is a moment to consider any action European medical authority might be able to take Today both air and surface human-movement control is relevant though I suspect effective isolation is impossible

London, S E 5

GRAHAM E MURPHY

FATAL CARDIAC ARREST WITH FLUOTHANE

SIR,—Unfavourable responses to a new anæsthetic should be reported at once, whether or not they can be satisfactorily explained I therefore report with regret a case of cardiac arrest during the administration of 'Fluothane,' although the data are insufficient to allow definite conclusions to be formed as to its cause

A man of 48 was undergoing partial gastrectomy for chronic duodenal ulceration, in other respects he was healthy As pre anæsthetic medication he was given papaveretum 10 mg and scopolamine 0 4 mg Anæsthesia was induced with thiopentone 500 mg, and was continued with fluothane vaporised from the ether container of a Boyle type II circle absorber and given with oxygen through a cuffed endotracheal tube For relaxation gallamine was given in two doses, each of 20 mg, separated by an interval of a few minutes Soon after giving the second dose, the vaporiser was turned to the sixth notch to obtain deeper anæsthesia, and respiration was assisted This was followed within a minute by a fall in blood pressure to an unrecordable level, and the pulse could not be felt Nevertheless, his appearance did not become alarming he remained a good colour and respiration was not arrested I turned off the vaporiser and washed out his lungs with oxygen, after which his blood pressure returned to its previous level Thenceforward fluothane was administered in small amounts with oxygen

Throughout the operation the blood pressure remained within normal limits and the patient's breathing was satisfactory, its volume and rate were normal and there was no tracheal tug At the end of the operation relaxation was insufficient to allow the abdomen to be closed To meet the difficulty I again turned the vaporiser to the sixth notch and assisted respiration Within one or at most two minutes the blood pressure fell At first, as before, the patient's appearance was not alarming, but after a few moments he became cyanosed and the pupils dilated This condition did not respond to washing out the lungs with oxygen The heart was exposed through an incision in the thorax and was seen to be at a standstill the ventricles were not fibrillating Cardiac massage restored the heart beat, but the period of circulatory arrest had unfortunately been too long to permit survival, the patient died ten days later without having regained consciousness

Reviewing the case, I felt that the most likely explanation of the accident was that, as a result of vaporising fluothane in a closed circuit, a high and lethal concentration had been reached unexpectedly soon If that was so, anæsthetists should be warned against using the anæsthetic in this way It was difficult, however, to rule out the possibility that fluothane like chloroform but unlike ether or cyclopropane, might be capable of arresting the heart at concentrations not much greater than those needed for satisfactory anæsthesia That it has adverse effects on the circulation is suggested by the fall in blood pressure, sometimes to very low levels, that has been repeatedly observed during administrations of the drug even when its concentration was being carefully regulated A case of non-fatal syncope has been reported by Johnstone[1], and I have heard it said that elsewhere a death has occurred, though it has not as yet been reported It should be remembered that Snow, who always insisted on the need for accurate control and limitation of the vapour strength of chloroform, reported in 1858, the year of his death, that he had given that drug to more than 4000 patients with but a single death, and that, he thought, was not attributable to the anæsthetic Those sponsoring fluothane, it seems, have the onus of proving that it is, in fact, safer than chloroform

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[1] State D *Surg Gynec Obstet* 1952 95 201

[2] Swenson O Sugarman H J jun *J Amer med Ass* 1954 154 651

[3] Takens H Thesis University of Groningen 1956

Department of Anæsthesia
St Thomas's Hospital S E 1
C A Foster

TRIAL OF 5-HYDROXYTRYPTOPHAN IN PHENYLKETONURIA

Sir,—The cause of the mental defect in phenylketonuria, hitherto unexplained, may be related to a 5-hydroxytryptamine (5 H T) deficiency[2] We are accordingly treating affected patients with 5 hydroxytryptophan, which readily passes the blood-brain barrier, to be decarboxylated to 5-H T[3]

The number of available patients of a suitable age-group is small, and we therefore appeal to doctors who may have phenylketonuric patients (aged 3 years or under) in their care for their help

If the relatives are agreeable to such a patient entering hospital for a period of up to six months for a controlled trial, we should be grateful if the doctor would communicate with Dr C M. B Pare, Maudsley Hospital, Denmark Hill, London, S E 5, for further details

Fountain Hospital, S W 17	B H Kirman
Maudsley Hospital S E 5	C M B Pare
Royal Free Hospital W C 1	M Sandler
St Thomas's Hospital S E 1	R S Stacey

NEONATAL DEATH AND ELECTIVE CÆSAREAN SECTION

Sir —Regarding the article by Dr Strang and his colleagues (May 11) I have no observations to make, other than to express my appreciative interest in it I would, however, like to comment on one point raised by Dr Brown (May 18) He implies that delayed ligation of the umbilical cord might allow continuance of fœtal oxygenation, thus helping to span the gap between delivery and the onset of neonatal respiration I believe that this is not so I have attempted to show[4] that once delivery of the child is completed, placental transmission ceases This is certainly true of such a rapidly transmitted substance as sodium bromide, and I imagine that it applies equally to oxygen I have long held that attempting to deliver oxygen to the fœtus via the mother cannot be proposed as a reason for allowing the child to be anchored to the operation field by its cord Unless it can be agreed (and about this there is still much debate) that a significant quantity of blood can be drained into the child by holding it below the level of the placenta—and furthermore that this is of value—then I can think of no argument against cutting the cord immediately, performing a rapid oral suction and straightaway transferring the child, in a head-down position, to the resuscitation table

St Mary's Hospital
Milton Portsmouth
J Selwyn Crawford

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[1] Johnstone, M *Brit J Anæsth* 1956 28 392
[2] Pare C M B Sandler M Stacey R. S *Lancet* March 16 1957 p 551
[3] Udenfriend S Weissbach H Bogdanski D F *J biol Chem* 1957, 224 803
[4] *Brit J Anæsth* 1956 28 146

HUMANE TECHNIQUE IN THE LABORATORY

Sir,—It gave me great pleasure to read in your issue of May 18 a report of the Ufaw symposium

There must be many medical men lovers of animals who have had an uneasy feeling that the number of animals used for research far exceeded those really necessary, yet most of us would dissociate ourselves from the biased propaganda of the Anti-vivisection Society It is good, therefore, to read the well-balanced views expressed by various speakers at the symposium

Reigate
T W. Preston

CHRONIC BRONCHITIS AND SMOKING

Sir,—I was very glad to read Dr Kay's letter of May 25 However, I want to mention another aspect of the difficulty—smoking in non-smoking compartments

Although the report of Sir John Charles adumbrates the possibility of total prohibition of smoking in public transport, the present position is unsatisfactory Many persons smoke in non smoking compartments and the paper labels are continually being defaced or removed Few junior railway officials show any attitude other than amusement The passenger has often to perform the duty laid upon the railway—the duty to maintain the non smoking compartment Many of the offenders are abusive and prosecutions are few I had trouble 5 days out of 6 in one week in January I have a "dossier" of many official letters but I still have trouble though, I think, less frequently

Are there any suggestions for further action? The constant coughing of smokers must surely be deemed a menace, apart altogether from carcinogens

Department of Pathology
Royal Hospital
Sheffield
J L Edwards

ÆTIOLOGY OF PRE-ECLAMPSIA

Sir,—In my letter (May 4), I defined tensile force, stress, and strain, in relation to uterine action I said that these factors did not exhibit abnormal values in patients with toxæmia of pregnancy and that they tended to have *lower* values than normal in cases of hydramnios and gross uterine distension These statements were based upon measurements made in a number of patients

These facts are now contradicted by Mr Sophian (May 18), and it would be useful to learn the basis of his figures It is noticeable that, with hydramnios, clinical impressions are often at variance with the measurements of pressure and strain

It must be realised that the pressures and strains found by measurement in patients with toxæmia are not different from the values found in normal patients

Sensory nerve-endings, except those reserved for chemical and thermal stimuli, respond to strain only Measuring devices also respond only to strain—i e, changes of length They may be specifically adapted to register changes of strain or to respond to excess strain Force, tensile stress, and pressure are words used to condense observations of strain into convenient language, "coat-hooks" for ideas based on observations of more than one strain

The term "myometrial resistance to stretch," which is used in the correspondence, is another way of saying linear elastic modulus or Young's modulus It is the ratio of stress to strain, and can only be determined by a number of separate strain measurements It is highly improbable that the body would organise a reflex based on the maximum or minimum values of such a complex concept as Young's modulus, even assuming that nerve-endings were available to measure pressure (bulk strain), curvature (differential strain), and linear strain simultaneously.

Obstetric Unit
University College Hospital
London
C N Smyth

WARNING OF IDIOSYNCRASY

SIR,—In hospital practice patients are often encountered who have an idiosyncrasy to a drug in common use, such as iodine, penicillin, or chloramphenicol Not infrequently the fact of the existence of a specific idiosyncrasy has been noted in the clinical records of previous hospital examinations, but that fact is often so tucked away in a mass of notes that it may well escape notice by a doctor subsequently examining these notes I have found that a simple and reliable way of bringing idiosyncrasy to the notice of anyone examining a patient's clinical records is for a rubber stamp to be used in wards and outpatient departments It should consist of a lined rectangle 2 by $2\frac{1}{2}$ in, with the word IDIOSYNCRASY at the top of the space

Whenever a hospital doctor discovers that a patient has an idiosyncrasy to any drug he should immediately arrange for that word to be stamped prominently on the front of the folder or on the cover of the clinical notes, and under the word IDIOSYNCRASY should be written the name of the drug or drugs It would be an advantage *if this entry were initialed* by the person making the record

This procedure should save many a patient from the unpleasantness or danger of a widespread dermatitis, or copious vomiting, or other consequence of the administration of a drug to which he is sensitive

Bristol, 9 D G C TASKER

CHRONIC CARBON-MONOXIDE POISONING AS A CARAVANNING RISK

SIR,—Coma due to breathing carbon monoxide in high concentration is, in general, readily diagnosed, and its residua are well recognised, but the possibility of chronic poisoning is less widely appreciated This may affect any one exposed to moderate concentrations over long periods (e g, garage workers and policemen on traffic duty in the "canyons" of New York City), and the following case shows the need to consider it, as a possible cause of obscure symptoms, when patients are living in caravans

A woman of 27 was referred by her family doctor with a month's history of general malaise, nausea, headaches, and dizziness twice she had had rotational vertigo severe enough to make her fall The intensity of symptoms had varied considerably, but they tended to grow worse and latterly she had had transient double vision

Seven years previously, when training as a nurse, she had had an episode of acute depression Three years later she had married a man with disseminated sclerosis, and she was now living with him in a modern luxury caravan on a farm She admitted to anxiety as to the possibility of her contracting disseminated sclerosis

Examination showed slight weakness of the right internal rectus muscle, and when she was admitted to hospital a week later because of more persistent diplopia and the onset of vomiting the right pupil was appreciably larger than the left Otherwise no abnormal signs were found, and investigations (including examination of cerebrospinal fluid and radiography of chest, skull, and nasal sinuses) showed nothing except a mild hypochromic anæmia After four days she was discharged symptom free At a follow up a month later her husband said that her improvement had lasted only a few days He had then sent her to her mother's home for a week and she had again been much better, but all her symptoms had recurred soon after her return to the caravan He had noted that these were more severe when she had cooked a meal at the gas stove

Inquiry showed that the cooking, heating and lighting in the caravan were by 'Calor gas' (butane), and that a few days before the patient's symptoms first appeared additional incandescent mantles had been installed to improve the illumination A sample of blood withdrawn at the clinic was later reported to show 25% saturation with carbon monoxide With more careful attention to ventilation and the use of fewer gas mantles the patient has regained her normal health

The purist may object to the term "chronic carbon monoxide poisoning" on the grounds that carbon monoxide is not a cumulative poison, but here the term seems fully justified A working principle for those whose occupations involve exposure to carbon monoxide is that they should spend at least two thirds of each day in an uncontaminated atmosphere in the case described above, the husband, who was away from the caravan during the day, remained well

The symptoms are in no way specific and the diagnosis is unlikely to be considered unless there is reason to suspect exposure to the gas Such suspicion should be aroused by the fact that a patient is using a caravan for permanent residence In these essentially primitive though often luxurious, holiday dwellings adequate ventilation without draughts is not easily obtained The installation of butane or solid-fuel heating and cooking appliances can hardly have been envisaged by the original designers

Lancaster G M BARRETT

MASSIVE THROMBOPHLEBITIS

SIR,—It was only recently that I read the interesting paper by Mr Catchpole (Feb 16) Four years ago I saw a similar case in which a patient died after nephrectomy for pyonephrosis The fact that exceptionally thrombotic occlusion of the *femoral* vein leads to a "blue leg" seems to be due to the usually concomitant arterial spasm which prevents the rapid immobilisation of a large quantity of blood in the lower limb When it is intense, this contraction can even produce a clinical picture closely resembling arterial embolism Only if this reflex reaction is entirely missing can the syndrome of "phlegmasia cærulea" result

Jugenheim Germany EDUARD MELCHIOR

"TO COMFORT ALWAYS"

SIR,—Last night I listened to one of the items in the wireless programme "To Comfort Always," nine tenths "blurb" wrapped *round one tenth* of misunderstood fact I do not suppose these well meaning people realise the enormous amount of harm they are doing, but aided by some others who call themselves psychiatrists they are increasing the number of mental patients In an address which you printed on May 18 the chairman of the Board of Control said that, whereas the number of psychotic stayed about the same in this country (about 130,000), the number of voluntary patients was going up "by leaps and bounds" This series should make it bound further

Why? Chiefly because mankind has been *looking* inwards, led into doing so by the psychiatrists and their silly dogmas But man's mental processes were formed in the million years of his entity *for the practical ends* of survival and propagation Looking inwards was harmful to him That is why men and women forget their childhood, as the psychiatrists themselves have frequently observed A classical example of this comes *from* Galton who found *a number* of intellectual men who scoffed at the idea that anyone could think in pictures, think visually, *though*, of course, they themselves had done so right up to early manhood at any rate To psycho analyse anyone is just as dangerous to him as to do a laparotomy on him—more so probably because it is a dissection of a more delicate organ—and *is only* very occasionally justified Sometimes the analyst leaves a dirty swab in the mind by suggestive questioning, as Freud did by *suggesting* to his female hysterics that they had been sexually interfered with by their fathers in early childhood [1] Later he realised this, but nearly all his followers have neglected the clue that stares them in the face—that the introspective are the least stable members of the community

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[1] Sargant W Battle for the Mind London 1957 p 159

But the culminating stupidity of this series was in the title of the last talk, "The Price of Progress", the idea being that the stresses of modern life are the cause of mental breakdowns But the valid stresses of life which dominated men's minds from earliest times have gone, and gone recently I remember the time when the threat of losing his job made a man blanch, for it meant that his family and he would starve, when a penniless existence in the workhouse was dreaded by most ageing people, when the fear of being physically hurt guided the young and religions kept their grip by threatening torture after death, eternal torture, stresses and fears which were also stays I am not saying that they are desirable, but that modern stresses are much less severe If the social animal man has not got reasons for fear, he will invent them by making up conventions and codes A man without fear degenerates, as is seen in those with power

"To Comfort Always" is the motto of the mother who spoils her child, spoils him for the rough and tumble that is life, to threaten, to punish, to stimulate, to deride, to inspire, to ignore, also have their place Mine is a lone voice in the wilderness, crying out not for the first time that much of our modern psychiatry is damned bad natural history and worse common sense

Beckley, Rye C G LEAROYD

TOWARDS SAFER CLOTHING

SIR,—Your leading article last week prompts me to record a disquieting personal experience

Some short time ago my younger son was in need of some new pyjamas I suggested to my wife that they should be made of flame proofed material and she attempted to buy them locally Few of the shops approached had ever heard of flame proofed material and none stocked it I consequently wrote to the advisory service of a national magazine devoted to household affairs A reply bearing the names of three large stores in the London area was speedily received Consecutive postal inquiries revealed that one store stocked flame proofed material and another had nightgowns, none had pyjamas made of this material Perhaps one of your readers can tell me where I can buy them ?

Cambridge. H J WOODLIFF

FIBROSITIC PAIN

SIR,—Dr Louis Moss (May 25) emphasises the concept that "trigger spots" can cause myalgic and fibrositic pain Although this may be conceded, it must not be overlooked that 90% of these pains are of psychological origin In states of mental conflict there is an increase of electrical potential which must "explode" some where Any part of the body can be involved and any slight injury creates a "fixation" This explains the multiplicity of remedies and their futility in so called "rheumatic" pains

London W 1 M W BROWDY

SALMONELLÆ IN REPTILES

SIR,—Dr Ruskin (May 11) suggests the abundance of lizards in the hot climate of Ibadan keeps down the fly population I hardly think this is the answer but rather the result of the hot sun killing the fly larvæ

In the past I have kept dozens of Agama lizards (*A planiceps*) in captivity, and flies whether alive or dead were never a favourite article of diet with them

Some years ago when I was working in Ghana (Accra) flies were a menace, yet lizards were far more prolific than in Ibadan, but of course the climate of Accra is very humid

University College Hospital
Ibadan Nigeria STANLEY F WOODWARD

METALLIC CORROSION IN ORTHOPÆDIC SURGERY

SIR,—In considering the effects of metals in orthopædic surgery, it is useful, in a practical world, to differentiate between corrosion that is surgically serious and corrosion that, by present standards, is not When "micro" methods are used to detect it, corrosion can be discovered (both in the metal and in the tissues) with almost all metals, including the "safe" metals S Mo and 'Vitallium,' and any surgeon who insists on complete freedom from all trace of corrosion has at present no recourse but to forgo the use of metal altogether

Where Dr Bowden and his colleagues, in their article last week[1] say that the use of mixed metals *is* by far the most important cause of corrosion I would be more explicit and say that, apart from extraordinary metals such as aluminium magnesium, &c,[2] all the serious corrosion ever seen can be accounted for by one group of steels, which corrode severely even without the stimulus of a dissimilar metal, and by one particular pair of stainless steels in combination The group of steels are ordinary steel (1936), vanadium steel (1936), and chrome steel (? 1946), and the stainless combination is the E M S (1954) × F S L combination (The dates given are when the steels finally ceased being sold) Capener's implied criticism[3] of F S L cannot be justified on the grounds of corrosion because, so far as my experience and my search of the literature goes, *no* authenticated case of serious corrosion in unmixed F S L has ever been described

The later paragraphs of the article by Dr Bowden and his colleagues are misleading, I believe, in so far as they imply that corrosion caused purely by metallic transfer (from screwdrivers, drills, &c) can give rise to serious trouble Although they established[4] that corrosion does occur from this cause, they never demonstrated it above the "micro" level and in correspondence with Wright and Axon[5] they acknowledged this fact Subsequently, however, they attempted to explain[6] the more serious clinical cases of corrosion quoted by Wright and Axon and the nine cases collected by Laing himself[7] on the metallic-transfer theory

Of this, I contend, they have not established a satisfactory proof The weakness of their argument lies in the link between the in-vitro and the clinical findings Laing thought that the metal in his clinical cases was S Mo, in which case his conclusion that the corrosion seen must be due entirely to metallic transfer would be justified But there is evidence to suggest that he fell into the trap of accepting the metal identification on trust The firm from whom the metal was probably purchased did not, in fact, start selling S Mo screws and bolts until after most of Laing's cases had been operated upon It is possible therefore that in these cases the corrosion was due to the E M S × F S L combination as it had been in Wright and Axon's cases

In order to establish a proper sense of proportion, I would elaborate a statement I made previously—namely, that at the Birmingham Accident Hospital we have made sure that we never use chrome steel (or any of the more antiquated steels) or the E M S × F S L combination and have not had any case of serious corrosion amongst the 2000 cases of internal fixation since this was done We have not changed over from

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1 Bowden F P, Williamson J B P, Laing, P G *Lancet* May 25, 1957 p 1081
2 Verbrugge J *J Bone Jt Surg* 1956 38A 1384
3 Capener N *Lancet* 1956 ii 1107
4 Bowden F P Williamson J B P Laing P G *Nature, Lond* 1954 173 520
5 Wright J K, Axon H J Bowden F P Williamson J B P Laing P G *Ibid* p 1186
6 Bowden F P Williamson J B P Laing, P G *Ibid* 1955 176 826
7 Bowden F P Williamson J B P Laing P G *J Bone Jt Surg* 1955 37B 676

ordinary steel screwdrivers and drills or taken special care to avoid attrition We *have* had a number of cases of minor trouble and these, but only these, might be attributed to metallic transfer

Birmingham J H HICKS

IMMUNOLOGY OF THYROID DISEASE

SIR,—It is to be regretted that your admirable leader last week on the new concept of thyroid disease makes no mention of the pioneer work of Loeb on tissue transplantation and organ specificity, a comprehensive account of which is given in his book *The Biological Basis of Individuality*

Loeb probably did more experimental work on this subject than any other investigator before or since—work involving transplantation of every variety of tissue and organ under almost any conceivable given set of circumstances Those of us interested in tissue transplantation are becoming more and more aware that Loeb has already anticipated most of the "original" work and new "theories" of today, many of which are, in fact, his ideas wrapped up in a more modern terminology Just as today the neurohistologist finds himself confirming Cajal's work of fifty years ago, much of modern grafting experiment is a repetition of the work of Loeb Had his book been published today, instead of 1945, it would in many ways have been regarded as the most up to date and authoritative work on the subject

Department of Anatomy,
University of Glasgow G M WYBURN

CANCER AND ATHEROSCLEROSIS

SIR,—I was much interested by your annotation of Feb 16 I think it would be useful to mention the original work of S G Zondek on malignant growths and essential hypertension[1] and on the inhibiting influence of essential hypertension on malignant growths and rheumatoid arthritis[2]

Hadassah Municipal Hospital,
Tel Aviv Israel I LURJE

IDENTIFICATION OF THE "FOURTH TYPE" OF POLIOMYELITIS VIRUS

SIR,—In January, 1956, the Russian virologists Chumakov et al[3] reported that they had isolated a new immunological type of poliomyelitis virus from the fæces of three children with bulbospinal poliomyelitis This they designated type IV poliomyelitis virus

The three strains were named AB IV, MK IV, and GZ IV The first two were isolated in monkeys (*Rhesus macacus*) in which they gave rise to paralyses and pathological anatomical changes which resembled those of poliomyelitis Brain and spinal-cord passage material from monkeys caused paralyses when injected into suckling mice, suckling hamsters, and suckling cotton rats as well as in adult cotton-rats Relatively high virus titres were found in most of the viscera of the suckling cotton rats On histopathological examination of the central nervous system, poliomyelitis like changes were found in the monkeys as well as in the cotton rats The strain GZ IV was isolated in adult cotton rats and in newborn mice, and had the same animal pathogenicity as the other two None of the strains were pathogenic for adult mice

The pathogenicity of the virus for monkeys and cotton rats was regarded by Chumakov et al as indicating that the virus belonged to the poliovirus group By extensive cross immunisation experiments on monkeys and cotton rats they were able to show that the strains were identical immunologically but that they were not identical with the poliomyelitis types I, II, and III

One of the strains, AB IV (brain material from cotton rat), was kindly sent by Dr Chumakov to the Department of Virus Research here for further study

The passage material was *inoculated into tissue cultures* of human embryonic lung No degenerative changes could be detected In spite of the pathogenicity of the virus for monkeys, it was suspected to belong *to the Coxsackie* group In suckling mice the typical flaccid paralyses were found After a few passages the material reached a titre of about 10^{-6}, and, by neutralisation tests with hyper immune sera against Dalldorf type strains A_1–A_{19} and B_1–B_6 it was found that the strains under investigation were immunologically identical with Coxsackie virus type A7

CROSSWISE NEUTRALISATION TESTS IN SUCKLING MICE WITH THE RUSSIAN STRAIN AB IV AND COXSACKIE VIRUS TYPE A7

—	Guineapig antiserum type A7	Rabbit antiserum strain AB IV (Russian)	Mouse antiserum strain AB IV (Swedish)
Virus strain AB IV	≧3·5*	2·2	≧3·5
Coxsackie virus type A7	≧3·5	1·6	≧3·5

* Serum titre expressed in neg log

This was confirmed by crosswise neutralisation tests (see accompanying table)

Histopathological examination of one of the mice with typical flaccid paralyses showed diffuse and very pronounced changes in the skeletal muscles The lesions were mainly necrotic and necrobiotic in nature No lesions were observed in the brain, cord, or other organs The histological picture of the muscles resembled in principle that associated with Coxsackie virus (subgroup A) infections in mice

The original Russian material was inoculated intracerebrally into cotton rats aged 8–9 weeks and 1 year Both groups of animals came down with flaccid paralyses after an incubation period of 5–7 days

Microscopic examination of a large number of muscle groups as well as viscera of cotton rats gave *negative results*, and no lesions could be found in the brain In the cord, however, limited and slight changes were seen in *all four* animals examined These changes were *localised to the grey* matter, in particular to the anterior horns, but in a few instances lesions were also found in the posterior horns In the *affected areas, necrotic and necrobiotic* ganglion cells were observed with destruction of the tigroid substance Apart from these changes, there were small accumulations *of inflammatory* cells, principally *polymorphonuclear* leucocytes

It therefore appears, from the Russian results and our own, that a virus strain immunologically *identical* with Coxsackie virus type A7 can produce a poliomyelitis like syndrome in monkeys A new observation is also the pathogenicity for adult cotton-rats

Habel,[4] who studied the Russian type IV poliomyelitis virus thoroughly, *could confirm that the agent* was immunologically identical with Coxsackie virus type A7 He performed a series of blind passages in tissue culture and found a weak *cytopathogenicity appearing* after 11 passages After 30 passages the changes were pronounced In this connection it may be mentioned that Svedmyr et al,[5] in cooperation with *Johnsson,*[6] *have* studied two Coxsackie type A7 strains which were isolated from fæcal specimens in tissue *culture* One of them was also isolated directly in suckling mice The cytopathogenicity to tissue cultures was *still* weak and irregular after fifteen passages

Horstmann and Manuelidis[7] observed ataxia, tremor, and weakness after inoculation of one of the Russian strains in monkeys They found lesions similar to those of poliomyelitis but somewhat *differently localised*

The question of the connection between the Russian strains and the clinical manifestations in the three children must be left open at the moment Attention can be directed to pathological electro-encephalograms observed by Johnsson[8] in three cases of meningo-encephalitis, in which Coxsackie virus type A7 was isolated During 1954 type A7 was isolated from about twenty cases of meningo-encephalitis or aseptic meningitis[9]

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[1] Zondek S G Tchetchik M *Brit J Cancer* 1953 7 418
[2] Zondek S G *Acta med scand* 1955, 152
[3] Chumakov M P Voroshilova M K Zhevandrova V I Mirova L L Itzelis I G Robinson I A *Vopr Virus* 1956 1 16
[4] Habel K Personal communication
[5] Svedmyr A, Melén B Kjellén L *Acta med scand* [illegible] suppl 316 20
[6] *Johnsson T Ibid*, p 33
[7] Horstmann D M Manuelidis E *Fed Proc* 1957 16 41[illegible]

Department of Virus Research
Karolinska Institutet School of
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Laboratory, and Department
of Pathology, Södersjukhuset,
Stockholm

TORSTEN JOHNSSON
CURT LUNDMARK

AUSCULTATION OF THE SKULL IN PAGET'S DISEASE

SIR,—The auscultatory physical sign of Paget's disease of the skull is said to be a bruit arising as a consequence of hæmodynamic changes

A far more frequent finding, however, seems to be an abnormal conduction of breath-sounds through the altered bone What is heard in fact sounds like bronchial breathing, this is absent over normal skulls

Provided this observation is valid, it seems very likely that it has been recorded before I have noted this abnormal breath sound conduction in about twenty patients with Paget's disease of the skull, and would be glad to learn of any reference to it or other experience of it

St Stephen's Hospital,
London S W 10

D HYWEL DAVIES

DIARRHŒA AFTER PENICILLIN INJECTION

SIR,—Diarrhœa is a feature of many allergies but is not often cited as a reaction to penicillin

A young woman was given penicillin (for the first time, she thought), for " fever " 3–4 hours later her temperature rose, the injection site became hard and red, and she had diarrhœa lasting 2 days 2 years later, when aged 27, she had " sinusitis " and was given procaine penicillin 300,000 units intramuscularly 5–6 hours later she vomited and had several watery stools in the course of a few hours Another injection, two days later, was followed by redness and induration at both injection sites, but no further diarrhœa No more penicillin was given 8 days later generalised urticaria appeared This settled after antihistamine treatment

It seems possible that diarrhœa may be an allergic reaction to penicillin

Kupat Holim
Giva time Israel

KENNETH KATTAN

TELEVISION AND MEDICINE

SIR,—In last week's annotation you say that the first colour television demonstrations of surgery in Great Britain will take place this summer As a matter of accuracy it should be placed again on record[10] that colour television of surgery was shown at the International Congress of Ophthalmology in 1950 at St Thomas's Hospital On that occasion British equipment, by Pye of Cambridge, was used throughout, a camera in the theatre transmitted the image to six receivers (one in the control room, one in the theatre, and four in the display room) It was in use almost every day for four weeks

You also say that " a medical student gains little from watching operations on a screen (as) is now appreciated by most British film makers " While few would quarrel with this statement if applied to undergraduate medical students, to whom you are obviously referring, it should not be allowed to go by default that surgical films are a most valuable means of teaching postgraduate surgery if one considers not one's own medical school, but the world as a whole as one's lecture theatre And surely it is the very merit of mass media visual techniques, whether television or film, that they can extend the ability for detailed observations beyond the restricted confines of the operating-theatre

London, W 1

G B STANFORD

Parliament

QUESTION TIME

Shortage of Radiographers

In answer to questions on this subject from nine members **Mr DENNIS VOSPER**, the Minister of Health, replied The number of radiographers in the hospital service in England and Wales at the end of 1952 was 2652 whole time and 199 part time The provisional figures at the end of 1956 were 3087 and 289, respectively There has been, therefore, a marked increase, but there is evidence to suggest that it has not been enough to meet the increased demand for X ray services A sample inquiry in four hospital regions a year ago indicated that there was a shortage of 16% on establishment, and that not more than half the annual loss was due to reasons other than retirement, marriage, or domestic reasons

Since then, in November last, the salaries were substantially increased and the staffing structure improved following an award of the Industrial Court The salary of the basic grade is now £420–485 per annum, and of the highest grade of superintendent radiographer £675–850 In my view, it is too early to assess the effect of these increases Meanwhile, I have asked hospital boards for information about the staffing of radiography departments and the intake of students in order to obtain a full up to date picture of the position The last return has just been received

Dr BARNETT STROSS Is the Minister aware that the number of X ray examinations taking place today are roughly twice as many as compared with those that took place before the National Health Service was instituted ? Does he not agree that the present grades of remuneration that he has quoted—for example, the £420 minimum scale—should be £650 if it were evaluated with the minimum grade before the war and brought up to that standard in accordance with the cost of living ? Will he promise to look seriously into this matter and ensure that the long waiting lists, evidence of which is to be found in the hospitals, and the fact that people have to wait weeks before they can be X rayed, are brought to an end ?—**Mr VOSPER** The situation is unsatisfactory, but the existence of a gap between demand and supply is not confined to radiography On the other hand, there has been an increase of no less than 50% since 1949 As for remuneration, this is not fixed by me but by the Whitley machinery, and in this case was settled by the Industrial Court only six months ago

Mr J C JENNINGS May I ask whether the Minister is not aware that there is a serious wastage of trained personnel in this service, and does he not agree that it is a very serious matter when trained personnel leave this service to take up positions with higher remuneration ?—**Mr VOSPER** It is true that there is a wastage, and I hope that one of the results of my inquiry may be to determine more closely the reasons for it

Mr ARTHUR BLENKINSOP Will the Minister keep in mind also the very considerable wastage of all kinds of other professional workers in hospitals, as well as radiographers ?—**Mr VOSPER** It is true that both the deficiency and the wastage apply to all medical auxiliaries and to many classes of people employed in the hospital service

Lieut Colonel W H BROMLEY DAVENPORT In view of the increased importance of radiography and the obvious anxiety of those employed in this service, will the Minister give every possible consideration to this matter ?—**Mr VOSPER** One other factor which the House must bear in mind is that this matter may be affected by the committee under the chairmanship of Lord Adrian which is investigating radiological hazards Therefore, the demand in future may not be as great as it is today

The Affair at Bath

Mr I J PITMAN asked the Minister if he was aware that the premises of the Royal National Hospital for Rheumatic

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[8] Johnsson T J A Virological and Clinical Study of Infections with Coxsackie Virus Uddevalla 1955

[9] Berglund A Johnsson T J Data to be published

[10] See *Lancet* 1950 ii 190

Diseases at Bath were in a state of decrepitude and danger by risk of fire, and, in view of the national service and importance of this hospital as a centre for the treatment of rheumatic diseases, what steps he intended to take to expedite the necessary work of reconstruction —Mr VOSPER replied I am aware that this hospital falls short of modern standards, and I am at present examining the proposal of the South-Western Regional Hospital Board that the project to restore it should be included in the programme of major building projects which are financed centrally Mr PITMAN May I ask the Minister to urge the national need in serving the whole country upon the regional hospital board whose responsibility is primarily regional —Mr VOSPER I have that in mind Of course, this is not by any means the only hospital which draws its patients from all over the country

Mr THOMAS WILLIAMS Is the Minister aware that this particular hospital received donations of nearly £90,000 to rebuild the hospital before the war ?—Mr VOSPER I do not think that that point is particularly material, the money has to come out of the same pocket, whichever way the financing is done The difficulty is that priorities have changed since this hospital was first put down for rebuilding and more urgent needs have arisen

Domiciliary Psychiatry

Dr DONALD JOHNSON asked the Minister of Health if he was aware that, as a consequence of the South West Metropolitan Regional Hospital Board experiment in domiciliary psychiatry in the Worthing area, the admissions to mental hospital in that area had decreased from 166 in the first quarter of 1956 to 64 in the first quarter of 1957, and, in view of the urgent need to relieve the present overcrowding in mental hospitals throughout the country, how soon he would be extending a similar service to the remainder of the country —Mr VOSPER replied I am aware of this experimental scheme, which resembles other schemes in operation elsewhere in this country in reducing the number of admissions to mental hospitals Its early results are promising, and I will watch its progress with interest, but it is too early to come to a final conclusion about it Dr JOHNSON Does not the Minister agree that this is the simplest and most effective way of curing the overcrowding in mental hospitals, and will he, when coming to a conclusion on the subject, expedite matters so as to introduce these experiments on the widest base possible ?—Mr VOSPER I have studied this scheme I think it is most promising but I am sure that its authors would be the first to agree that it needs more time before we can be quite certain as to its results Dr EDITH SUMMERSKILL Can the Minister say whether there are enough psychiatrists in the country to provide a domiciliary psychiatric service ?—Mr VOSPER It would not be possible to establish a scheme like this in every area of the country immediately, but, if successful, and if the Royal Commission recommends an extension, most certainly we will do what we can about it

Consultants, S H M O s, and Senior Registrars

The number of consultants, S H M O s, and senior registrars in the National Health Service in England and Wales in 1949 and in 1956 was as follows

—	December 1949	June 1956
Consultants	5190	6695
Senior hospital medical and dental officers	2000*	2534
Senior registrars	1400*	1107

* Estimated

Glasgow Tuberculosis Campaign

The clinical assessment of patients identified in the Glasgow mass X ray campaign is still proceeding On May 21, 947 persons had been admitted to hospitals for further investigation or treatment Another 100 people were due to go into hospital

Cost of Prescriptions

The average cost per prescription dispensed in England and Wales in February was 5s 7 87d From a sample it is estimated that the average cost for March was about ½d more than in February

Medicine and the Law

The General Practitioner in the Witness-box

BY A METROPOLITAN POLICE SURGEON

I HAVE attended almost all the London courts many times, and have often listened to other doctors giving evidence Some of them leave the witness box looking very unhappy, and the impression they have left on the court has been equally unhappy There seems to me to be one chief reason for this An expert witness giving evidence is supposed to tell the whole truth and nothing but the truth He should not show bias, and these doctors have

The commonest example is the "drunk in charge" case in which the doctor has been called by the defence His mental attitude on entering the witness box seems to be something like this

> I shall tell the truth, but if the wind of unadulterated truth seems to blow rather cold on my lamb of a patient (who is perhaps about to be shorn of his driving licence), I shall temper it the least little trifle

Entering a witness box in that frame of mind is dangerous It is, I believe, the chief cause of the trouble that general practitioners make for themselves in court, when they undertake as amateurs, to engage in a bout of verbal fencing with a professional

There are several ways in which a doctor can try to evade an awkward question *They are all bad*

He can discard all his scruples and tell a lie Here are examples of things I have heard stated on oath by three different doctors

> "He was perfectly sober when I examined him and could not have been under the influence of alcohol an hour and a half before that"
>
> "I examined him for the first time two and a half months after he was arrested At the time of the police surgeon's examination he was suffering from influenza The police surgeon failed to diagnose this"
>
> "He is a nervous man, prone to bilious attacks His stomach is so irritable that it could not retain enough alcohol to put him under the influence He would be sick first"

I have heard it stated in court that practically all the symptoms and signs of mild drunkenness, except the smell of the breath, can be produced by high blood pressure, low blood pressure, exhaustion, sleeplessness due to toothache, carbon-monoxide poisoning, aspirin poisoning, amphetamine poisoning, congenital derangement of the cerebellum, influenza, sinusitis, middle-ear disease, Ménière's disease, cerebral arteriosclerosis, mild surgical shock, and hypoglycæmia (it is true, of course, that an overdose of insulin can simulate drunkenness very closely)

Another way of trying to evade an awkward question is to break off the engagement by retiring behind a smoke screen of abstruse verbiage—a technique which is liable to be poorly received Another way is to give an answer, but not an answer to the question that was asked This is the sort of thing that can happen

> "Doctor, would having taken four aspirin tablets cause this man to be rude to the Inspector ?"
>
> "He must have had some reason for taking four aspirin"
>
> "Doctor! Would having taken four aspirins cause this man to be rude to the Inspector ?"
>
> "We have only the Inspector's word for it that he was rude"
>
> "Doctor!! Would, &c ?"
>
> "You can't just consider the aspirins alone You must include all the other circumstances"
>
> "Doctor!!! Would &c ?"
>
> "No"

"No" is the right answer Everybody in court except the expert witness knew that all the time

A very common pitfall, and perhaps the most ruinous of all, is to start to fumble and mumble, hunting about for an answer that is not too damaging and yet approximately true The result is usually deplorable Counsel knows at once that the witness is trying to hide something He leaps to the kill and keeps on leaping until he gets it

Damaging admissions *freely made* enhance the credibility of the rest of one's evidence enormously

My advice to the general-practitioner witness is this You are going to swear to tell the truth, the whole truth, and nothing but the truth Do not deviate from the terms of that oath You will not then leave the witness box looking, and no doubt feeling, a shattered wreck

Your patient may not be entirely pleased with your performance, but he can have no legitimate grievance Warn him beforehand that you are terrified of the witness-box and will on no account embark on any funny business

Obituary

HAVEN EMERSON

M D Columbia

Dr Emerson, emeritus professor of public health practice at Columbia University, a former health commissioner of New York City, and chief epidemiologist in the American Expeditionary Force in the 1914–18 war, died on May 22 at Greenport, Long Island, at the age of 82 His age and his appointments might suggest a serene retirement, but the spirit which had enlivened and made so effective his fifty years' work in the public-health service was still lively, and only a few months ago he was energetically denouncing those who opposed the fluoridation of civic water-supplies

He came of a family with a tradition of public service His father, Dr John Haven Emerson, was a nephew of the essayist and one of New York's first public-health physicians A few years after qualifying in 1899, Haven Emerson joined his father in this work and for the next fifty years he took an energetic, witty, and imaginative part in every measure to control communicable diseases and raise the hygienic standards of the people He treated the last case of cholera in New York, he helped to fight the 1916 poliomyelitis epidemic, he introduced mass radiography for the city's population, he early advocated and obtained the pasteurisation of the milk-supply He has been described, not without good cause, as a "superb and dedicated nagger in what the public barely knew to be the public interest"

His work in the 1914–18 war and later for the League of Nations widened his range of action His relief work in Germany and Greece led to his studies on diet, and crop deficiencies He was a man who was easily, and usefully, irritated to action, and his dislike of the illogical variations of national medical terminology led him to work for an international system

Not unexpectedly, with his drive and independence went a distaste for over-formality in administration and over-mechanisation in technique He once informed some of his more conventional colleagues that "the test of a doctor s skill is what he can do with his brains, his faith, and carbolic soap"

R H P, one of his many English friends, writes

A year ago I spent the day with Haven Emerson and his wife in their home at Greenport, Long Island He was as alert mentally and physically (apparently) as he had ever been Although as intolerant as ever of the "fuzzy minded nitwits who speak with authority concerning matters they do not understand" he was most tolerant of and gentle to all the trees shrubs and flowers on his fine estate At lunch over which he presided with his usual dignity, there was not an item which had not been produced on his farm

He was proud of his ancestors proud of his country, and proud of the achievements of public health Although ripe in years, his enthusiasm and his confidence in the success of the great fight for good health for all mankind might well be the envy of any health officer at the height of his career

Diary of the Week

JUNE 2 TO 8

Sunday, 2nd

UNIVERSITY COLLEGE HOSPITAL MEDICAL SCHOOL, University Street, W C 1
10 15 A.M Lord Amulree Medical Problems of Old Age (Clinical demonstration)

Monday, 3rd

MARLBOROUGH DAY HOSPITAL 38, Marlborough Place, N W 8
8 15 P M Dr D J West Hypnosis

Tuesday, 4th

UNIVERSITY OF LONDON
5 30 P M (London School of Hygiene and Tropical Medicine Keppel Street, W C 1) Dr M Ruiz Castaneda (Mexico) Diagnosis and Treatment of Human Brucellosis
INSTITUTE OF DERMATOLOGY, Lisle Street W C 2
5 30 P M Dr D I Williams Ectodermal Defects

Wednesday, 5th

ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street W 1
5 15 P.M *History of Medicine* Prof John Fulton (Yale) The Reception accorded Harvey s discovery during Harvey's life
INSTITUTE OF OBSTETRICS AND GYNÆCOLOGY
3 P.M (Hammersmith Hospital Ducane Road, W 12) Dr G I M Swyer Intersex
INSTITUTE OF DISEASES OF THE CHEST, Brompton, S W 3
5 P.M Dr Margaret Macpherson Pulmonary Collapse in Children
INSTITUTE OF DERMATOLOGY
5 30 P M Dr Henry Haber Benign Tumours of the Corium
MEDICO CHIRURGICAL SOCIETY OF EDINBURGH
8 30 P M (Royal College of Surgeons 18, Nicolson Street) Prof J H F Brotherson Some Observations on Accidents

Thursday, 6th

ROYAL SOCIETY OF MEDICINE
5 P M *United Services* Colonel T M Ahern Lieut Colonel R E Waterston Lieut Colonel R. S Hunt Mass Casualty Management
INSTITUTE OF OBSTETRICS AND GYNÆCOLOGY
4 30 P M (Chelsea Hospital for Women, Dovehouse Street S W 3) Mr L P LeQuesne Postoperative Fluid and Electrolyte Balance
NUFFIELD ORTHOPÆDIC CENTRE, Wingfield Morris Orthopædic Hospital, Oxford
8 30 P.M Prof M C Mensor (Stanford University California) Mobility Studies of the Lower Lumbar Spine in Relationship to Low Back Pain
UNIVERSITY OF ST ANDREWS
5 P.M (Queen's College Dundee) Prof G H Bell In Search of Pellagra

Friday, 7th

ROYAL SOCIETY OF MEDICINE
4 30 P M *Experimental Medicine* Dr Hugh Davson Dr Honor Smith Penetration of Drugs into the Cerebrospinal Fluid
POSTGRADUATE MEDICAL SCHOOL OF LONDON Ducane Road W 12
10 A M Mr H G Hanley The Modern Treatment of Renal Tuberculosis
ST MARY S HOSPITAL MEDICAL SCHOOL Paddington W 2
5 P M Mr Leslie Williams The Use and Value of X rays in Obstetrics
INSTITUTE OF NEUROLOGY, National Hospital Queen Square, W C 1
5 30 P M Prof G A G Mitchell The Innervation of Blood-vessels
INSTITUTE OF OBSTETRICS AND GYNÆCOLOGY
4 30 P M (Queen Charlotte s Hospital Goldhawk Road, W 6) Prof J Chassar Moir Diagnostic Radiology in Obstetrics

Appointments

BRYCE SMITH ROGER D.M Oxfd, F F A R C S, D A consultant anæsthetist United Oxford Hospitals
CROW K D M B Lond M R C P consultant dermatologist Swindon/Cirencester area hospitals
DUTTON W A W M B Brist, M R C O G, M M S A tutor in obstetrics and gynæcology Queen s University, Kingston, Ontario Canada
JENKINS, ANITA J M D Lond D C H D P H assistant M O H and school M O Swindon
JONES C T M R C S D P H deputy M O H, Mid Warwickshire joint sanitary committee
LAYLEE A M M B Lpool M O, Atomic Energy Research Establishment Harwell Berkshire
MATHEWS E T M B Birm F F A R C S part time consultant anæsthetist Midland centre for neurosurgery and United Birmingham Hospitals
PINKERTON PHILIP M D Edin, D P M consultant psychiatrist and lecturer (child psychiatry), United Liverpool Hospitals, and Royal Liverpool Children's Hospital
TERRELL J D M B Glasg D C H assistant M O, school health and child welfare services Worcestershire
WATTON R W M B Lond, D.P H assistant M O H and school M O Croydon

South-Western Regional Hospital Board
BENNETT, M O M D Lond F R C S M R C O G D M R T consultant obstetrician and gynæcologist Bristol Clinical area
CROSSLEY, JOHN M B Camb F R C.S M R C O G consultant obstetrician Bristol clinical area
TROTTER, J K M R C S F F A.R C S, D A consultant anæsthetist, West Cornwall clinical area

Notes and News

A SIMPLE PRECAUTION

YOUNG doctors in the London area should consider carefully the advantages offered by a little known but most helpful body—the Society for Relief of Widows and Orphans of Medical Men Founded in 1788, this society has a long record of good work, and even in these days of superannuation schemes its aid is sometimes invaluable to a doctor's dependants who find themselves in difficulties because of his death after a long illness or unexpectedly Such aid could be given more widely if more doctors would qualify for it by joining the society

For membership, the candidate must be a male registered medical practitioner who at the time of election is living within 20 miles of Charing Cross The annual subscription is 2 guineas for members under 35 on admission, 3 guineas for those aged 35–45, and 4 guineas for those over 45 A medical examination may be required, and relief is given only to widows and orphans of deceased members of not less than three years' standing The present income limit for eligibility for grants is £150 per annum, but the directors can consider cases in which it does not exceed £200 The society has resources of over £120,000, and last year it distributed £4130

The president is Sir Robert Young Inquiries about membership should go to the secretary, Dr J A Struthers, at 11, Chandos Street, Cavendish Square, London, W 1

WORLD HEALTH ASSEMBLY

AT the tenth World Health Assembly, the committee on programme and budget recommended a budget of just over $13,500 000 for 1958, and this figure was adopted by the assembly (the budget for this year is $12,550,000) The committee asked W H O to undertake a research programme on the epidemiology of cancer carcinogens in the environment would be studied and comparative statistics published W H O would also advise on cancer registration and definitions of nomenclature

The committee called for the training of health physicists and doctors in the public health aspects of atomic energy A course in health physics will be held in Zürich this year, and the disposal of radioactive wastes is being studied The World Federation for Mental Health has drawn attention to the mental and social factors involved in the use of atomic energy A proposal to appeal for a ban on atomic bomb tests was ruled out of order by the chairman, whose rule was upheld by a vote of the committee

The malaria fund stands at $123,800, but more money is needed It is estimated that malaria could be eradicated in some of the larger countries of Asia if $15 million a year were provided for five years The committee emphasised the need for research into mosquito resistance to insecticides, and the dangers of reinfection across frontiers

On the recommendation of the committee on administration, finance, and legal matters, the assembly asked Dr M G Candau to renew his contract as Director General for another five years

PROFESSIONS IN A CHANGING SOCIETY

Prof W MANSFIELD COOPER, vice chancellor of the University of Manchester, spoke on this subject in his address at the annual meeting of the Manchester Medical Society on May 1 Dr J F Wilkinson, the president, was in the chair

It was curious he said, that almost the whole of the literature on the subject was peripheral and took the essence of a profession for granted Perhaps the only way of approach was by a study of characteristics common to all the professions The first characteristic was that a profession must be 'learned" techniques might be essential, but they were the accidents not the essence of professional activity Secondly, the object of professional activity was never primarily material reward as was shown to some extent by a study of the right to sue in respect of fees and expenses in the two professions of medicine and law Perhaps the most serious development at the present time was the growth of pseudo learned vocations seeking professional status and seeking legislative recognition the object which was partly exclusion from or control of entry to the profession and thus the limitation of competition A study of American trends showed how very far this had gone

Professor Cooper then set out to define the circumstances in which a new profession might emerge in modern society To seek State recognition might solve certain problems but it created others, particularly in relation to the essential characteristic of professional autonomy Here the increasing dependence of the medical profession on the National Health Service produced problems of a quite acute character

A study of recent trends suggested that in a democratic society the professions must on the one hand attempt to interpret themselves intelligibly to that society but must on proper occasions resist popular clamour In medicine the situation looked brighter than it had a few years ago, for the courts, after a series of cases in which the patient had been successful, had become much more critical of actions against the medical practitioner and were obviously attempting to understand the difficulties in the path of the doctor

THE ROYAL SOCIETY

DINOSAURS' eggs sat beside a model of the insulin molecule at the society's conversazione on May 23 Demonstrations and exhibits of strictly medical interest seemed quite staid compared with some of the dashing affairs elsewhere For instance, what physician or surgeon could hope to produce results as impressive as those modestly displayed by Dr P W Brian and his colleagues, of the I C I Akers Research Laboratories, who had been studying the stimulation of plant growth by gibberellic acid? This substance, a metabolite of a fungus pathogenic to plants, can stimulate the growth of stem internodes and sometimes leaves in growing plants It has been shown to "reverse" genetic dwarfism in some plants The I C I team say cautiously that far more experience is needed before the practical significance of these effects can be assessed, but that did not prevent them from nearly raising the roof of Burlington House with their monster plants

Dr P A Merton, of the Medical Research Council's neurological research unit at Queen Square, very effectively demonstrated compensatory rolling movements of the eye in man He had persuaded some strong stomached friends to sit in a swing which then rotated about the line of sight Through a magnifying system, it was then possible to examine the eye and to note how it rolled in its socket in the opposite direction to the movement of the head so as to minimise the relative rotation of the image on the retina This accurate stabilising mechanism enables vision to remain clear even during violent exertions

The midwifery department of Glasgow University and the physics department, Western Regional Hospital Board Glasgow, explained the artificial respirator they have been using for newborn infants This is a servo respirator in which a baby's feeble effort to take a breath is detected, amplified and used to release a supply of air or oxygen from a cylinder The infant thus gets air when he wants it and his breathing is not dependent on his own perhaps feeble strength

Inherited differences in certain human serum proteins known as haptoglobulins were demonstrated by Dr A C Allison and Mrs W ap Rees, of Oxford When red cells are lysed in the circulation, the liberated hæmoglobin is normally bound to the haptoglobulins In most subjects hæmoglobin appears in the urine only when its level in the plasma exceeds the combining power of the haptoglobulins, i e, only after severe hæmolysis People without haptoglobulins are much more liable to hæmoglobinuria and therefore to iron deficiency

The striking coloured model of the insulin molecule was brought by Dr F Sanger, F R S, from the department of biochemistry at Cambridge (the dinosaurs' eggs came from the British Museum) Dr K M Smith, F R S and his colleagues at the Agricultural Research Council's virus research unit showed how X ray analysis and electron microscopy had been used to deduce the structure of plant viruses

MEDICINE AND THE HEALTH SERVICE

AT the annual meeting of the United Sheffield Hospitals on April 25, Dr E J WAYNE, regius professor of medicine in the University of Glasgow, spoke on the Changing Face of Medicine

Prevention, he said, is always less dramatic than the results of failure to prevent, just as a Major Road Ahead sign is less exciting than an ambulance and a tangled mass of wreckage Nevertheless the vastly improved health of the community today is probably to be attributed more to the prevention of disease than to the potent remedies which we now possess

Turning to the progress made in the administration of medical services, he pointed out that advances in medical scien are of little value to the community unless they can be made readily available through what has been called "medical engineering" In general practice the danger of the present position is that the patient is tending to regard the practitioner not as an adviser but as a person to give prescriptions and certificates or to refer him to a specialist if the illness is more than very minor While the quality of the hospital service has on the whole notably risen since 1947, Professor Wayne drew attention to the major problem created in most hospitals today by the disabled and often aged patient who cannot return to his own home "There are far too few suitable long stay hospitals for such persons, with the result that they fill the beds of hospitals expensively staffed and equipped for quite different purposes No business concern would tolerate this type of waste, which is equivalent to using a factory equipped for making precision instruments for the manufacture of tintacks Yet to a greater or less degree it is a feature of our hospital service in all parts of Great Britain"

It has been said that while money may not lead to happiness at least it enables one to be miserable in comfort In the same way, Professor Wayne said, the National Health Service enables sickness to be endured under better conditions by early treatment at home or by admission to hospital But, apart from dealing quickly with the acute infections and surgical emergencies it has not in a statistical sense greatly increased the general health of the community "One sometimes wonders," he added, "if we are getting an adequate return for the £50 million we spend annually on drugs Many of these are used to relieve comparatively trivial symptoms and the public might be just as well off without them"

University of Cambridge

On May 18 the following degrees were conferred

M Chir—R B McGrigor
M.B B Chir—G J Jewell
M.B—P D Mulcahy Mary E Jewell.

Pinsent Darwin studentship—Applications are invited for this studentship in mental pathology

Its annual value is £500, and the normal tenure is three years Applicants should write before July 1 to the secretary of the studentship Psychological Laboratory Cambridge stating their age and qualifications and the general nature of the research that they wish to undertake

Royal College of Obstetricians and Gynæcologists

At a meeting of the council held on May 25, with Sir Charles Read, the president, in the chair, the following were elected to the council

As representatives of the fellows W C W Nixon F E Stabler, T N MacGregor C H G Macafee
As representatives of the members T L T Lewis Robin Murdoch

Sir Russell Brain was admitted to the honorary fellowship

The following were admitted to the fellowship

P C Barkla T S M Barnett F A Bellingham, N B Capon, Daphne Wai Chan Chun Alexander Culiner W D Cunningham, J P O Erskine, Mary Evans W R Foote F D Johnston K T Macfarlane T A Macfarlane, G B Maughan Daw Yin May W G Mills Kripananda Mitra J G O Donoghue H E Pellew Percy Peltz D A Ranasinghe W J Rawlings R M Rome D W Sparling Dorothy M Stewart James Walker J F B Wyper

The following were admitted to the membership

D C Aird, G B Batchelor R A T Boland G D D Cable Mahomed Ismail Cassimjee J S W Chambers Probhat Kumar Choudhuri C A B Clemetson K I Digwood Ammud Fraler W J Garrett William Gault William Gavin Ivan Goldman C J Gooden, Bernard Kirsch Margaret A Lakeman E W Lillie H H McCrostie J G Markus A F B Matthews T T E Michael A B Miller Arun Kumar Mitra Jessie M B Muirhead A C C Pinion L J Rice Ray Richards T J Ryan G J W Stump Sarosh Meher Thanevala K F G Wilson Robert Yule

Scottish Society of Anæsthetists

The executive council of this society for 1957–58 is as follows

President Dr Robert Lawrie vice president Dr R N Sinclair, hon secretary Dr M Shaw other members Dr H B Wilson Dr J Straton Dr J R Kyles Dr H Fairlie Dr A C Forrester Dr A W Raffan and Dr W Christie

The society's prize for the best paper submitted by a registrar has been awarded this year to Dr D B Scott

Royal College of Physicians of London

On June 3, the first day of the celebrations of the Harveian tercentenary the college is holding a memorial service at St Paul s Cathedral at noon The service is open to all who care to go

University of London

On Nov 22 Sir Charles Lovatt Evans, F.R S, will be among those on whom honorary degrees are conferred He will receive the degree of doctor of laws

At a recent examination the following were successful

D.P M—H R Alderton A A Bartholomew, D T F MacSorley C M B Pare A C R Skynner, H J Walton

The following have passed the final examination for the degrees of M B, B S

Honours—D R Amies (c) London M A Barraclough (b, c) St. Thomas s Pauline M. Feavers (c) Royal Free Ann L M Field (c) Royal Free R B Fountain (d) St George's Maurice Gross (b), St Thomas s, Joyce R Harter (c) Charing Cross R O Hicks (d) Univ Coll Hosp M J McLoughlin (a) St Mary's, D I Macnair (d) Middlesex B L Pentecost (a b) St Mary's Michael Roburn (a), St Mary's Cicely M S Saunders (d) St Thomas s, Jan Schneider (c), London, J A P Trafford (c) Guy s A J Zuckerman (a, b c *university medal*) Royal Free

(a) Distinguished in pathology (b) distinguished in medicine (c) distinguished in applied pharmacology and therapeutics (d) distinguished in surgery, (e) distinguished in obstetrics and gynæcology

Pass—W J Adam, Mary M Adlington, E U Akpabio T G L Allum A J U Anderson R St J Angel E J Applegate A R Archer, Joan H Arthur Paul Atkins, Martin Austin, J B Baker, Elizabeth S Barker A G Barrow G P E Beaney, N J M Bebb, Irene D Bennett T W Benson M. C Berenbaum M. J P Berkley, Elsie E M Bickham B D Birt, T J Biscoe Dorothy M Blackburn P G Bond Rosemary Bond A R Bone, D J Bowen, R V Boyd J J Brand J M Bristow A F Broad A G Brown C L Brown, T J Bucher T M. Bull P G Burles C J D Burrell Eunice R Burton, W J Cannon Mary F Canvin Margaret T Challis J A Chalmers Zoë D Chamberlain D J M Chastell A M A Clark G M Clark R C Clark, R M Clark J A I T Clement J R Clough T D Cochrane, Jean R Colston Nina E C Coltart Christina M Comty, P L Constantine Angela R Cooke, S A R Cooke E J Coomey Mary Corbett, S R Costley Phoebe M Cotes M J Coucher D R Couchman G Cowburn J M R Cox R A Crawford W A Crawford, W A Cuthbertson J de B J Dade Jane B Davey N B Davey R C Davie D W Davies H G Davies, J A Davis Barbara C Dean I A A De Coutére Ann C Deuchar B P Dillon D M. Dingle B C Dixon Warren Anne C Doulton M P Dowdell M. J Dyer Elizabeth M Edmunds A J B Edwards Joan M Edwards P W Edwards P J Eisinger C D Evans Pamela F Fancourt J S Ferguson Barbara M. Fessey Elizabeth C Finn Hilary K J Fisher G N Flaherty, J G Flatman Evelyn C Foot R D Forbes Bruce Foster J A Fox A J V H French Valentine I French E S Garnett, J C Garnham, J R M Gibson Gay J Gillbrand M E Gloster Jeremy Goodchild C J Goodwill Paula J H Gosling Judith F Gould J N Graham Evans B D Grant Hilary J Gravei M W Greaves, David Greenwood J M. R Griffiths Olive M Grundy, Jean A Hagger D S Hall Dorothy L Hall J G Hall J G Hall A H Halstead D L Hamblend H W I Hannan D A Hanania Eileen Harris Rosalie M Harrison Bloom B P Harrold V J Hartfield, A G Harwood Michael Hatfield P G Hawker Doris I Hawkins Sally Haynes M R Heal Margaret M Healey D B E Hennessy P R Hewett Jennifer Hill Phyllis M Hill M N Hirons L J Hobbs Maureen J Hodgson Johanna C J Hogerzeil J J Holden Margaret B Howell P J W Howes, R C Hudson D C Humphrey Gillian A. L M Hunt, R F Hunt S W Hyams Ekpo Etim Inyang Hannah E Jacoby Margaret D Janes, P M Jeffreys P J Jennings B L Johnson A F Jones J D Jowitt A C Kaeser R C Kempster B R Kesby M. S Kessel D W Keys Kalya Kitiyakara Peter Knight D A Lammiman Patricia O Lane, Monica M Langhan, William Larkworthy M J Lavine D G Law R T B Lawrence Seymour Lazarus F I Lee Frances Lefford J H Lemon Ian Lewis Helen A Linn Ann V C Lloyd Mary K Lucas Ian McColl Gillian B McCullagh Terence McGovern, C A G Mackenzie C P Mansfield J F Mansfield William Manton R D Martin Nancy F V Matthews P A Mead Kanubhai Paragji Mehta D S Meldrum A B Milne Vinod Ratilal Mody D A Moore Katherine M. Moore F B Morgan R V Morris D H Morrish F H Muir R C Mulholland M R Munro B R P Murray Carmel L Myers Patricia M Neale Lotte T Newman Sally F Newton J R Nicholson K T Nicolson Ann M. Notley R E Owen D W Parsons D T Parsons D W Patient B W Payton Jean M Peacey P T Penny John Pimm Sylvia I Pinder, P C C Pitt Ann M Pocock Kristin S J Pool, D R Potter D A H Pratt V J Pratt Leslie Pringle Rena Danne Proud J D Raiman Vivian M Rakoff Rudra Rasaretnam Heather G Rawlinson R L Raymakers Joan M Read Jeanne D Reeve P R Riddle Elizabeth A Ridley R B Roberts David Robertson D S Robertson Marita R Rodan, J F Rogers Muriel E Rolfe C W Rutherford D H R Salter T D Sayer A M. Segal H G S Sergeant P F J Sewell P C Shaw, Mary P Shepherd A G Sherman Mary Sibellas S H Simonian G B Smith R. D Smith A G Smart R C Snelling M J Solan Janet M Spencely John Spencer R D L Spurring R H Stearn D S Stephens M A Sternberg J L Storey Pamela J Stow P E N Suter J F Tattersfield A R Taylor J F Taylor S A W Taylor M F Terry Audrey A Thomas Edith H Thomas J P D Thomas Susan Thomas W I T E Thomas C D Thompson, Elizabeth M T Thyne Janet E Timberlake P J Tomlin D A Treissman Angela M Tresidder John Tudor K B Tyrer R A Underwood Anne L M Wadlow, R M Wakeley D A Walk R. J C Walkey M T A Wallace, D C Wallbridge M P Walsh A P Warner Joyce Warner Christopher Wastell J S Waters R P Watkin D M Watson W F Watson Joyce M Watt Felice M Weber Gillian de M. L Weller P B Whatmore Anne M Wigley A D Williams G H Williams M J Williams S R Williams Anne M Wilson E H Wilson Judy A Wilson, Susan M Wilson R S Winwood B M. Woodward Trevor Woodward J W Woolley Judith M. Wright, N J L Wright, G B Wyatt D G Yetman D A Young

Sir James Walton Memorial

A library in memory of Sir James Walton has been installed in the committee room of the Gemmological Association The library contains some of the gemstones and gem minerals he collected and the gem testing instruments which he made

Hunterian Society

The subject for this society's 1957 essay competition is the Diagnosis and Management of Coronary Disease in General Practice The competition is open to all *general practitioners* Further details may be had from the hon secretary, Dr C W Kesson, 51, Harley Street, London, W 1

Experimental Research into Ageing

The trustees of the Ciba Foundation are offering in 1958 not less than five awards (£300 each) for investigations into the basic problems of ageing Entries must reach Dr G E W Wolstenholme, director of the foundation, 41, Portland Place, London, W 1, not later than Jan 1, 1958

World Federation for Mental Health

The annual meeting of this federation will be held this year at Copenhagen from Aug 11 to 17 The theme of the meeting will be Growing Up in a Changing World Further particulars may be had from the secretariat, 19, Manchester Street, London, W 1

Biology of Hair Growth

The British Society for Research on Ageing is to hold a symposium on this subject at 1, *Wimpole Street, London*, W 1, from Aug 7 to 9 under the chairmanship of Prof William Montagna Further particulars may be had from Mr G H Bourne, D SC, histology department, London Hospital, E 1

Banting Memorial Meeting

This meeting, which is organised by the British Diabetic Association, will be held in Oxford on Friday and Saturday, July 12 and 13 Prof H A Krebs, F R S, will give the Banting lecture, on intermediary metabolism in the diabetic organism, and *Prof C H Best*, F R S, will speak on oral hypoglycæmic agents The full programme may be had from the secretary general of the association, 152, Harley Street, London, W 1

Flour and Bread

The Nutrition Society is holding a symposium on this subject in the Anatomy School, Cambridge, on Friday and *Saturday, July 5 and 6*, under the *chairmanship of Sir Rudolph* Peters, F R S The speakers will include Dame Harriette Chick, D SC, Miss E M Widdowson, D SC, Prof R A Morton, F R S, Dr H M Sinclair, and Mr J R Nicholls, D SC Further particulars may be had from Miss D F Hollingsworth, c/o Ministry of Agriculture, Fisheries, and Food, Great Westminster House, Horseferry Road, London, S W 1

National League of Hospital Friends

Mr Dennis Vosper, the Minister of Health, speaking on May 24, at the annual meeting of this league, said that he would like every hospital to have its own special group of supporters Hitherto mental and mental deficiency hospitals had not been nearly so well befriended, but he was now glad to see that there had been exceptional progress in the formation of leagues of friends of mental hospitals Nothing could be more important because these hospitals were so often situated in old buildings, designed for another age in mental health, and located in remote districts Those who do work in association with mental hospitals would be aware of the enormous change in attitude and treatment which had taken place during recent years It must be our aim to convince the public that they should look upon a mental hospital as upon an ordinary hospital for the physically sick and he was sure that an active League of Friends could help towards breaking down remaining barriers Many people, he added, thought that with the advent of the National Health Service in 1948 voluntary work was no longer wanted in the hospitals of this country He did not believe that attitude was ever adopted by those in any way associated with the hospitals, and there could be nothing but tragedy if this should ever come to pass Perhaps it was not as widely known as it should be that in the past few years there had not been a decrease in voluntary work for hospitals but a most startling and welcome increase " Although the League of Hospital Friends are not mentioned by name in any Act of Parliament I, like my predecessors, regard them as essential partners in the health service '

Tuberculosis Conference in Glasgow

The British Tuberculosis Association and the Tuberculosis Society of Scotland are holding their annual conference in Glasgow from June 26 to 29 Further particulars may be had from the administrative secretary of the association, 59, Portland Place, London, W 1

Reciprocal Benefits

A convention on social security between the United Kingdom and Belgium has been signed It covers benefits for sickness, maternity, death, unemployment, old age, widowhood, orphanhood, and industrial accidents and diseases, and family allowances It will not come into operation until it has been ratified by both Governments

Calvert Memorial

On May 23 Sir Geoffrey Jefferson, F R S, unveiled a portrait of the late Cecil Calvert which his *medical colleagues on the* staff of the Royal Victoria Hospital, Belfast, are giving to the hospital In accepting it Mr Victor Clarendon, the chairman, announced that the hospital committee are to set up, from their "free funds," a Cecil Calvert research scholarship

Control of Chemical Additives in Food

This subject will be discussed at a joint meeting of the Food Law Institute of the United States and the food group of the Society of Chemical Industry, the Society for Analytical *Chemistry*, and the Association of Public Analysts, *to be held* at the Royal Institution, London, on Friday, July 26 at 10 A M Further particulars may be had from the office of the Society for Analytical Chemistry, 14, Belgrave Square, S W 1

Therapeutic Substances Act, 1956

By regulation, novobiocin, oleandomycin, spiramycin, prednisone, and prednisolone have been brought under the control of part II of this Act and from June 1 their sale and supply will be restricted

Since the provisions of part II of the Act apply to any preparation which contains a controlled substance, it appears *that the sale and supply of ' Sigmamycin,'* which is understood *to be a mixture* of tetracycline and oleandomycin, are subject to control

Latency and Masking in Viral and Rickettsial Infections

From Sept 4 *to* 6 the University of Wisconsin School of Medicine is holding a *symposium* on this subject to consider recent information on human, animal, and plant systems that bear on the interaction between host cell, infecting agent and the cellular environment The speakers from England will include Dr C H Andrewes, F R S, and Mr F C Bawden, F R S Further particulars may be had from Dr A S Evans division of preventive *medicine*, University of Wisconsin Medical School, Madison, Wisconsin, U S A

L C C Child-guidance Clinics

Besides using 20 hospital and other child guidance clinics the London County Council has established four child guidance units—at Earls Court, Battersea, Brixton, and Woodberry Down A report presented to the Education Committee on May 20 says that, during 1956, 516 applications were received for reference to these four units, and at the end of the year 130 children were awaiting a first interview and 63 had been interviewed and awaited treatment Though very urgent cases can usually be seen within two or three weeks, the waiting period for other cases is two to three months *for interview and* between three and eight months for treatment *After consultation* with the regional boards which provide the *medical staff* (but not the psychologists and psychiatric social workers) it is proposed that from Sept 1 the *unit at Earls Court* shall be *expanded and that a new unit shall be established at Queen's* Road Centre, Peckham, to serve part of south east *London*

Dr Hirotoshi Hashimoto president of St Luke's International Hospital Tokyo Mr Yoshisuke Kasai vice president of the Japanese Red Cross Society Mr *Toshikatsu Kuraki* chief of the planning section at the ministry of health and welfare and Dr Nobuo [illegible] assistant chief of the tuberculosis prevention section of the ministry are spending ten days in Britain studying the National Health Service in a programme organised by the British Council

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CORRIGENDUM *Wilson's Disease*—In the letter by Dr Hall and Dr Neale last week (p 1089), the last *sentence* of the first paragraph should have begun ' *Indeed*, balance studies in three of our patients ' We regret that we wrongly inserted "untreated" The authors stress that none of the balance studies was done during a period of active copper-removing therapy

PROGNOSTIC FACTORS IN MYOCARDIAL INFARCTION

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From the Radcliffe Infirmary, Oxford

Since the early reports by Obrastzow and Straschesko (1910), Herrick (1912, 1919), McNee (1925), and Gibson (1925), coronary thrombosis has become well recognised, and it now ranks as one of the more common causes for emergency admission to hospital. Probably the condition has truly become much commoner, but nowadays one reason for admission to hospital in many cases of this condition is the development of treatment with anticoagulants—a form of therapy best controlled in hospital.

We need to know whether the prognosis of this dangerous illness has been much changed by the use of anticoagulant therapy, and to define other factors which have a bearing on either the immediate or the long term prognosis. These questions are examined in the present study.

TABLE I—ANNUAL ADMISSIONS FOR CORONARY THROMBOSIS

Treatment-period	Year	No. of admissions	Total for period	Percentage treated with anti coagulants
I	1940	8	110	0·0
	1941	11		
	1942	7		
	1943	14		
	1944	18		
	1945	18		
	1946	15		
	1947	19		
II	1948	29	170	37·1
	1949	29		
	1950	51		
	1951	61		
III	1952	81	263	74·5
	1953	87		
	1954	95		
Total			543	

SOURCES OF DATA

The case notes of all patients with myocardial infarction admitted to the Radcliffe Infirmary in 1940–54 inclusive were analysed, together with those of a much smaller number of patients who developed the disease while in the hospital for other reasons. Only patients in whom there was no reasonable doubt about the diagnosis were included. In all cases the diagnosis was supported by electrocardiographic or necropsy evidence. A comparatively small number of patients who were admitted late in the illness (for example, because of congestive cardiac failure due to myocardial infarction two or three weeks earlier) were excluded in order to keep the clinical material as homogeneous as possible. After these exclusions, there were 543 admissions available for analysis. Some patients were admitted more than once and the number of patients was 506. We have chosen to treat each episode as a separate entity.

We have taken the arbitrary period of two months (eight weeks) as representing the acute attack. The subsequent fate of patients who survived the acute attack was discovered in all cases, except for a man who was admitted to the Radcliffe Infirmary in 1950 and was known to be alive in 1953, but whom we were unable to trace subsequently. With this solitary exception, it is known whether each patient was alive or dead when this study closed in January, 1956, and, if dead, the date of death and the certified cause. We are glad to express our thanks for information supplied by other hospitals and by family doctors. The patients themselves, their relatives, and their friends have all been very cooperative. The Registrar-General has been a valuable source of information. From the data obtained in these various ways, factors affecting long-term prognosis were assessed.

TABLE II—THE DAILY NUMBER OF DEATHS DURING THE ACUTE ATTACK

Time	No. of deaths	Average daily deaths
1st day	62	62
2nd day	13	13
Rest of 1st week	42	8·4
2nd week	35	5·0
3rd week	16	2·3
4th week	7	1·0
5th week	5	0·7
6th week	6	0·9
Rest of 2nd month	9	0·5
Total	195	

There were certain advantages in making this study in the Radcliffe Infirmary:

(*a*) It is the only general hospital admitting emergencies from the city of Oxford and a surrounding rural district.

(*b*) It is the main teaching hospital of the University of Oxford, the case notes are well kept and there is an efficient records department.

(*c*) The laboratory estimations on which the control of anticoagulant therapy is based are done under the direction of pathologists who are authorities on blood coagulation (Biggs and Macfarlane 1953).

PROGNOSIS IN THE ACUTE ATTACK

During the period under review, the annual number of admissions to hospital increased progressively, the chief rise being between 1947 and 1952, when anticoagulants began to enjoy a vogue in treatment. Before 1948 no patient was treated in the Radcliffe Infirmary with anticoagulants. In 1948, 4 patients out of 29 admitted were so treated, and in 1951, 36 out of 61 admitted. Since 1951, 3 out of every 4 patients have been treated with anticoagulants, and there has been little change from year to year. Throughout the hospital it has been usual to treat patients with anticoagulants unless there were contra-indications. We can therefore define three treatment-periods—1940–47, 1948–51, and 1952–54 (table I).

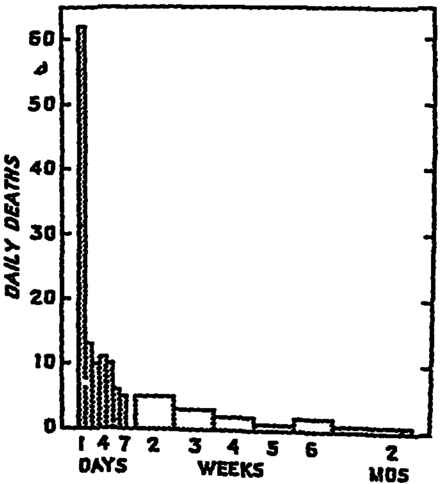

Fig. 1—Number of deaths during acute attack among 543 admissions. After first week numbers are expressed as average daily rate.

When bigger numbers of patients are admitted at the same time as a new treatment is coming into regular use, any results must be interpreted cautiously. A seeming improvement in prognosis may be attributed to the new

TABLE III—FATALITY RATE IN ACUTE ATTACK BY AGE AND SEX

Age (yr)	Men			Women		
	No of patients	Deaths		No of patients	Deaths	
		No	%		No	%
<40	10	1	10 0	0	0	0 0
40–	56	18	32 1	15	3	20 0
50–	119	37	31 1	30	8	26 7
60–	118	38	32 2	61	24	39 3
70–	57	31	54 1	58	21	36 2
80–	12	10	83 3	7	4	57 1
Totals	372	135	36 3	171	60	35 1

therapy when in fact it is due to the admission of less severe cases In making the analysis, we have therefore kept separate the groups of patients who were admitted in the three main periods of time, and have further subdivided them according to whether or not anticoagulants were used In presenting the results we have often fused these subgroups in the interests of brevity, but only after satisfying ourselves that no distortion is caused by so doing

Death in the Acute Attack

Among the 543 admissions, there were 195 deaths (34 9%) within two months of admission (table II) The outstanding feature is the high fatality during the first day, followed by a progressive fall in the average daily deaths until the end of the fourth week, when the curve of deaths flattens out and runs at a low level (fig 1) No less than a third of all the deaths in the acute attack took place on the first day in hospital The danger of this first twenty four hours is emphasised by the realisation that 1 patient in every 9 admitted died within this period This reflects the fact that the Radcliffe Infirmary receives a large proportion of its patients as acute emergencies soon after the actual infarction (The results obtained in different hospitals are difficult to compare because of differences in the proportion of patients admitted in the earliest and most dangerous stage of the disease)

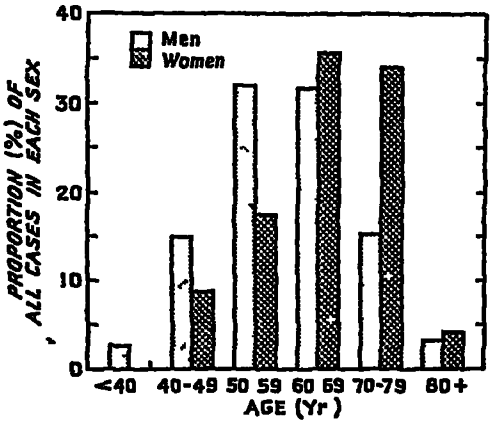

Fig 2—Percentage distribution of all cases in each sex by age

TABLE IV—FATALITY RATES IN FIRST AND SUBSEQUENT ATTACKS

—	No of patients	Deaths	
		No	%
First attack	455	170	37 4
Second or later attack	88	25	28 4

Early Deaths

In view of the large number of deaths soon after admission to hospital, it is convenient to separate off the deaths in the first forty-eight hours from the later deaths For several reasons, we have chosen the period of forty eight hours to cover what we shall refer to as "early deaths"

First, it is sometimes difficult to decide from the case notes whether a patient died exactly within twenty four hours or not, so that a small error arises from this "fringe effect", the error is less if the division is made at forty eight hours

Secondly, when considering the usefulness of anticoagulants, it is convenient to be able to eliminate the deaths in the first forty eight hours, to give a reasonable length of time for the treatment to be instituted and become effective

All deaths later than forty eight hours after admission have been called "late deaths"

Factors Affecting Prognosis in the Acute Attack

Age and sex—Coronary thrombosis is much commoner in men than in women, and there were more than twice as many men as women in this series (table III) On average, the condition arose in women at a later age than in men (fig 2) Two thirds of the men were admitted between the ages of 50 and 70, and two thirds of the women between the ages of 60 and 80 In each sex, the fatality increased with advancing years, but in each age group women tended to have a lower fatality rate than men (fig 3) There were therefore two opposing influences affecting the fatality rate by sex the women included a greater proportion of elderly subjects who were more liable to die, but in all age groups but one the women had a better chance of survival than the men These two processes counteracted one another so evenly that the net result was an almost exactly equal fatality-rate for men and women Because of this, in many of the succeeding sections the patients are treated as a whole

TABLE V—FATALITY RATE IN ACUTE ATTACK IN RELATION TO HISTORY OF ANGINA OF EFFORT

History of angina	No of patients	Deaths	
		No	%
Positive	217	81	37 3
Negative	326	114	35 0

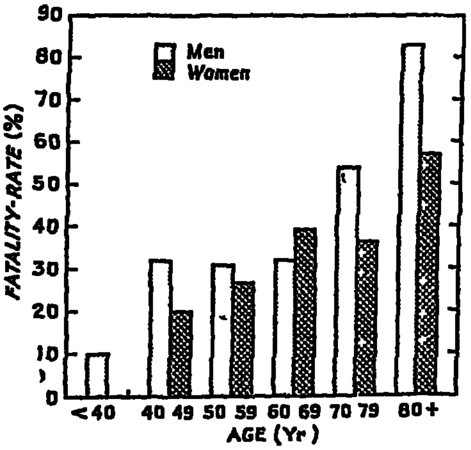

Fig 3—Fatality rates by age and sex

History of a Previous Attack

It is commonly held that a second or subsequent attack is more dangerous than the first attack of myocardial

TABLE VI—PRE-EXISTING HYPERTENSION RELATED TO FATALITY RATE IN THE ACUTE ATTACK

History of previous hypertension	No of patients	Deaths	
		No	%
Positive	180	57	31 7
Negative	363	138	38 0

TABLE VII—PREVIOUS BREATHLESSNESS ON EXERTION RELATED TO FATALITY-RATE IN THE ACUTE ATTACK

History of breathlessness on exertion	No of patients	Deaths	
		No	%
Positive	196	69	35 2
Negative	347	126	36 3

TABLE VIII—FATALITY-RATES AMONG PATIENTS DEVELOPING CORONARY THROMBOSIS AT REST AND ON EXERTION

Mode of onset	No of patients	Deaths	
		No	%
At rest	296	102	34 5
On exertion	181	54	29 8

infarction In 88 admissions in the present series there was a clear-cut history of a previous attack—treated at the Radcliffe Infirmary in 37 cases and elsewhere in 51 There was no appreciable difference in the mortality-rate between these 88 patients and those admitted in their first episode (table IV)

Previous Angina of Effort

No less than 40% of the patients had a history of angina of effort The two sexes were almost identical in this respect We have not counted angina of effort noticed for the first time in the ten days preceding the frank infarction leading to admission, for this may be a prodroma to the infarction In neither sex was the fatality-rate affected by a history of angina of effort (table V)

TABLE IX—SHOCK AND HYPOTENSION RELATED TO DEATHS IN THE ACUTE ATTACK (I.E, IN FIRST TWO MONTHS)

Shock and hypotension	No of patients	Deaths	
		No	%
Both	41	26	63 4
Shock alone	50	23	46 0
Hypotension alone	21	11	52 4
Neither	431	135	31 3

TABLE X—EARLY DEATHS (I E, IN FIRST FORTY EIGHT HOURS) RELATED TO SHOCK AND HYPOTENSION

Shock and hypotension	No of patients	Early deaths	
		No	%
Both	41	22	53 7
Shock alone	50	12	24 0
Hypotension alone	21	5	23 8
Neither	431	36	8 4

Previous Hypertension

A third of the patients were known to have been hypertensive before the onset of myocardial infarction By hypertension we imply a systolic pressure of more than 160 and a diastolic pressure of more than 100 mm Hg Hypertension was commoner among women patients (41 5%) than among men (29 3%)—a difference which is significant The fatality rate was unaffected by pre existing hypertension (table VI)

Previous Breathlessness on Exertion

More than a third of the patients had been breathless on exertion for at least some months This, too, had no effect on the fatality rate (table VII) There was no appreciable difference in mortality here between men and women

Mode of Onset of Infarction

It is often taught that coronary thrombosis usually begins when the patient is at rest In this series the circumstances of the onset were clearly specified in 477 instances In 181 of these, the infarction occurred during exertion, this made little difference to the outcome (table VIII) The proportion of cases in which the infarction developed during exertion was the same in men and in women

Shock and Hypotension

If patients arrived at hospital in a state of clinical shock or with hypotension, their prognosis was much worse than if they had neither We have accepted the statement of the admitting doctor that "shock" was present or absent, by hypotension is meant a systolic blood-pressure of less than 100 mm Hg In many cases these two features were combined, and the outlook was then even worse, nearly two-thirds of such patients dying (table IX)

TABLE XI—LATE DEATHS (BETWEEN FORTY-EIGHT HOURS AND TWO MONTHS AFTER ADMISSION) RELATED TO SHOCK AND HYPOTENSION ON ADMISSION

Shock and/or hypotension	No of patients	Deaths	
		No	%
Present	73	21	28 8
Absent	395	99	25 1

TABLE XII—LATE DEATHS (FORTY-EIGHT HOURS TO TWO MONTHS) RELATED TO DIABETES MELLITUS

Diabetes mellitus	No of patients	Deaths	
		No	%
Present	37	19	51 4
Absent	431	101	23 4

The increased fatality among patients admitted with shock or hypotension occurred solely in the first forty-eight hours (table X), the survivors of this period having the same prognosis thereafter as other patients (table XI, fig 4)

Diabetes Mellitus

Diabetic patients with myocardial infarction did badly The surplus of deaths among diabetics was solely among the late deaths (table XII)

History of Cardiac Asthma

A history of cardiac asthma had a bad prognostic significance—an effect almost confined to the late deaths (table XIII)

Evidence of Cardiac Failure

Any evidence of cardiac failure had a bad prognostic significance, for half of the patients with such evidence died The effect was almost confined to the late deaths, and was much the same whether the failure was of the right side or the left side of the heart (table XIV)

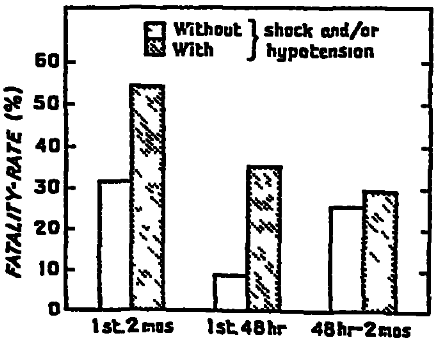

Fig 4—Fatality-rates in acute attack according to presence or absence of shock and/or hypertension

Arrhythmias

Cardiac arrhythmias were also of bad prognostic import, though not as serious as evidence of heart failure, the effect was confined to the late deaths

TABLE XIII—LATE DEATHS (FORTY-EIGHT HOURS TO TWO MONTHS) RELATED TO PREVIOUS HISTORY OF CARDIAC ASTHMA

Previous cardiac asthma	No of patients	Deaths	
		No	%
Present	26	10	38·5
Absent	442	110	24·9

TABLE XIV—LATE DEATHS (FORTY-EIGHT HOURS TO TWO MONTHS) RELATED TO EVIDENCE OF CARDIAC FAILURE

Heart failure	No of patients	Late deaths	
		No	%
Nil	325	61	18·8
Right sided	61	25	41·0
Left sided	82	34	41·5

(table xv) 17% of all admissions were complicated by arrhythmia Heart-block and ventricular tachycardia were unusual Multiple extrasystoles and auricular fibrillation or flutter were roughly equally common, and their prognostic significance also was equal Excluding deaths in the first forty-eight hours, of 38 patients with multiple extrasystoles 14 died (36·8%), while of 39 patients with auricular fibrillation or flutter 15 died (38·5%)

Cardiomegaly

The size of the heart was definitely stated in 307 cases If we take these as being reasonably representative, patients with gross cardiac enlargement (found clinically or radiologically) had a worse prognosis than those with hearts of normal size or only slightly enlarged The effect falls chiefly on the late deaths (table xvi)

Good risk and Bad risk Patients

We can define two groups of patients—a "good-risk" group who show none of the factors included in the left-hand column of table xvii, and a "bad-risk" group in which one or more of these factors is present (table xviii, fig. 5)

TABLE XV—RELATION BETWEEN CARDIAC RHYTHM AND LATE DEATHS (FORTY-EIGHT HOURS TO TWO MONTHS)

Cardiac rhythm	No of patients	Deaths	
		No	%
Sinus rhythm	385	89	23·1
Arrhythmia	83	31	37·3

TABLE XVI—RELATION BETWEEN HEART SIZE AND LATE DEATHS (FORTY EIGHT HOURS TO TWO MONTHS)

Heart size	No of patients	Deaths	
		No	%
Normal or sl enlarged	241	48	19·9
Grossly enlarged	48	16	33·3

Effect of Age on Prognosis in Relation to Good and Bad Risk

In an earlier section it was shown that the older age-groups were more prone to die than the younger In good-risk patients the fatality-rate increased with advancing age, whereas in bad-risk patients the fatality rate was not much influenced by age, being remarkably constant until the age of 70 This is equally true for total deaths and for deaths after the first forty eight hours (tables xix and xx, fig 6)

The proportion of good-risk patients was highest in the younger age groups (table xxi) Taking the series as a whole, the younger age groups had a better prognosis for two reasons

(*a*) They contained a bigger proportion of good risk patients

(*b*) The good risk cases had a better prognosis in the younger age groups

Effect of Anticoagulant Therapy

During the period covered by the present series, the outstanding change in therapy was the introduction of anticoagulants, which were being widely used during the closing years of this study It has been generally accepted that anticoagulants exert a highly beneficial effect on the course of myocardial infarction, and direct comparison of the patients in the present series who were treated with anticoagulants with those who were not so treated suggests that anticoagulants have substantially lowered the fatality-rate (table xxii) But when patients have not been allocated at random to one form of therapy or another, the results may be biased by selection in the choice of patients for treatment In the present series there is strong evidence that such bias has been introduced Tables xxiii and xxiv and figs 7 and 8 set out the fatality-rates for the three treatment periods and in relation to treatment Taking period i (when no anticoagulants were used) as the starting-point, the fatality-rates in periods ii and iii fall progressively among the patients treated with anticoagulants, *but rise progressively among the patients not so treated* The only likely explanation is that the patients not given anticoagulants included an increasingly high proportion with a bad prognosis Any direct comparison between the patients treated with anticoagulants and those not so treated is therefore invalid

With our present data, the nearest we can get to a fair assessment of the effects of anticoagulant therapy is to present the overall results for the three periods, which will show the net effect of the introduction and subsequent extensive use of anticoagulant therapy There has been some improvement in the overall fatality rate in period iii when anticoagulants were being extensively used (table xxv, figs 9 and 10), and the effect is entirely in the late deaths There is therefore prima facie evidence that anticoagulants have been beneficial, but the fatality rate remains substantial and even the improvement in late deaths is not statistically significant

Moreover, the composition of the three period groups must be considered, especially in relation to those factors

TABLE XVII—FACTORS ASSOCIATED WITH BAD PROGNOSIS IN THE ACUTE ATTACK

Factors associated with bad prognosis	Factors unassociated with bad prognosis
Associated with early deaths	Previous attack of myocardial infarction
Clinical shock on admission	Previous angina of effort
Hypotension on admission	Previous breathlessness on exertion
Associated with late deaths	Previous hypertension
History of cardiac asthma	Mode of onset of infarction (at rest or on exertion)
Cardiac failure	
Arrhythmias	
Gross cardiac enlargement	
Diabetes mellitus	

TABLE XVIII—DEATHS AMONG GOOD RISK AND BAD RISK PATIENTS

Group	Total deaths			Late deaths (early deaths excluded)		
	No of patients	Deaths		No of patients	Deaths	
		No	%		No	%
Good risk	152	26	17·1	142	16	11·3
Bad risk	391	169	43·2	326	104	31·9

which we have demonstrated as having an influence on prognosis. The three period-groups were closely similar in respect of the proportion of patients with recurrent attacks, previous hypertension, angina of effort, and breathlessness on exertion. The age-composition was also closely similar. With respect to the bad prognostic factors, the general picture is best seen from the proportion of good-risk patients in the various periods. Period III had the highest proportion of patients falling in the good-risk class (table XXVI).

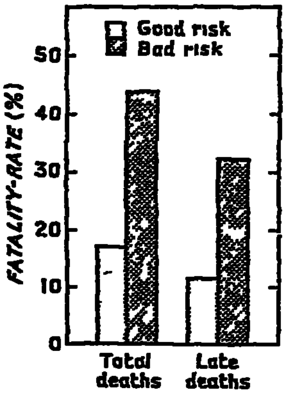

Fig 5—Fatality-rates in acute attack of good risk and bad-risk groups

This fact alone would account for some of the improvement in prognosis in period III. Whether it accounts for it fully can be seen by constructing a table in which the fatality-rates observed for good-risk and bad-risk cases in period I are used as the standard by which "expected" deaths are calculated for periods II and III (table XXVII). There were only 86 deaths in period III instead of the 96 which would be expected from the number of good-risk cases if anticoagulants had no effect, so some true improvement can be said to have taken place. The proportion of patients dying within forty-eight hours after admission was closely similar in periods I and III, so the improvement over expected values is to be found among the late deaths.

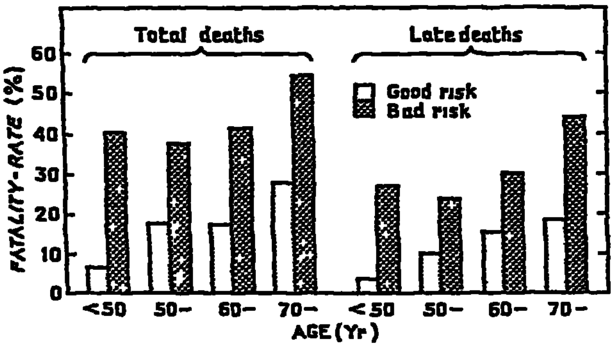

Fig 6—Fatality rates in acute attack among good risk and bad-risk cases related to age

We have made a further calculation on slightly different lines. From the total series, age-specific fatality-rates can be calculated for both good risk and bad-risk cases (tables XIX and XX). Then, for each period, the expected number of deaths can be estimated while taking account simultaneously of the number of good-risk and bad-risk cases in each age group. In effect, one is making a "null hypothesis" with respect to treatment and setting out the expected fatality rates on the assumption that treatment has not materially changed in efficacy and the only prognostic factors which matter are the age and numbers of good-risk and bad-risk cases in the successive periods. If anticoagulant treatment has revolutionised the outlook in the acute attack, the observed fatality-rates should differ sharply from expected rates, being worse than expected before the onset of anticoagulant therapy and better than expected after it was widely used. In fact there are some differences in these directions between observed and expected rates, but they are not large (table XXVIII). In other words, the data in table XXVIII agree with those in table XXVII in suggesting that anticoagulants have had only a small beneficial effect on the fatality of myocardial infarction in this hospital. The total saving of lives in period III, when anticoagulants were extensively used, was of the order of 10 lives out of 263 admissions.

TABLE XIX—TOTAL DEATHS RELATED TO AGE IN GOOD AND BAD-RISK GROUPS

Age (yr)	Good risk			Bad risk		
	No of patients	Deaths		No of patients	Deaths	
		No	%		No	%
<50	31	2	6.5	50	20	40.0
50–	56	10	17.9	93	35	37.6
60–	40	7	17.5	139	57	41.0
70–	25	7	28.0	109	59	54.1

TABLE XX—LATE DEATHS RELATED TO AGE IN GOOD- AND AND BAD-RISK GROUPS (EARLY DEATHS EXCLUDED)

Age (yr)	Good risk			Bad risk		
	No of patients	Deaths		No of patients	Deaths	
		No	%		No	%
<50	30	1	3.3	41	11	26.8
50–	51	5	9.8	76	18	23.7
60–	39	6	15.4	120	36	30.0
70–	22	4	18.2	89	39	43.8

TABLE XXI—PROPORTION OF GOOD RISK CASES IN EACH AGE GROUP

Age (yr)	No of cases	Good risk cases	
		No	%
<50	81	31	38.3
50–	149	56	37.6
60–	179	40	22.3
70–	134	25	18.7
Total	543	152	28.0

In view of this, it is of interest to examine the causes of death in the successive treatment-periods. The proportion of fatal cases examined at necropsy was about 70% in all periods. From a detailed examination of the necropsy reports, the salient point emerges that the widespread use of anticoagulants has been accompanied by a striking reduction in the number of deaths from pulmonary embolism. In other respects, there was no obvious difference in the immediate causes of death in the three treatment-periods.

TABLE XXII—DIRECT COMPARISON OF PATIENTS TREATED WITH ANTICOAGULANTS WITH PATIENTS NOT SO TREATED

Anticoagulants	Total deaths			Late deaths		
	No of patients	Deaths		No of patients	Deaths	
		No	%		No	%
Given	259	59	22.8	239	39	16.3
Not given	284	136	47.9	229	81	35.4

Before anticoagulant therapy became generally used, about 6% of the patients surviving the first forty-eight hours died from pulmonary embolism, whereas in the latest treatment-period only about 1% did so (table XXIX).

The final column of table XXIX shows estimated figures based on the assumption that the patients examined at necropsy were an unselected sample of the late deaths; we believe this assumption to be sound, because the usual reason for an absence of necropsy was that the relatives refused permission.

TABLE XXIII—TOTAL DEATHS RELATED TO TREATMENT-PERIOD AND USE OF ANTICOAGULANTS

Period	Patients given anticoagulants (%)	With anticoagulants			Without anticoagulants		
		No of patients	Deaths		No of patients	Deaths	
			No	%		No	%
I (1940–47)	0				110	44	40.0
II (1948–51)	37.1	63	17	27.0	107	48	44.9
III (1952–54)	74.5	196	42	21.4	67	44	65.7

The use of anticoagulant therapy has therefore saved about 11 lives which would otherwise have been lost through pulmonary embolism About 10 fewer patients died in period III than one might have expected from what had happened in period I The similarity between this improvement and the saving of life by protection from pulmonary embolism makes us conclude that the only substantial effect of anticoagulant therapy is to prevent death from pulmonary embolism

TABLE XXIV—LATE DEATHS RELATED TO TREATMENT-PERIOD AND USE OF ANTICOAGULANTS (EARLY DEATHS EXCLUDED)

Period	Patients given anticoagulants (%)	With anticoagulants			Without anticoagulants		
		No of patients	Deaths		No of patients	Deaths	
			No	%		No	%
I (1940–47)	0				92	26	28.3
II (1948–51)	39.5	60	14	23.3	92	33	35.9
III (1952–54)	79.9	179	25	14.0	45	22	48.9

Discussion

The most arresting feature of the present study has been the finding that extensive use of anticoagulant therapy has not made a dramatic difference to the fatality rate of myocardial infarction in this hospital It is true that some improvement has taken place since this form of therapy was introduced, but this can be accounted for by the nearly complete abolition of death due to pulmonary embolism There seems little doubt that anticoagulants are very effective in this respect The success of anticoagulant therapy in preventing pulmonary embolism is evidence that this form of treatment was being effectively administered in this hospital We therefore conclude that anticoagulants do not have any major influence upon the course of an established myocardial infarct per se, although they save some lives by removing almost completely the dangerous complication of pulmonary embolism

This conclusion does not go as far in support of anticoagulant therapy as that of its more enthusiastic advocates For example, Wright et al (1948, 1950, 1954) claimed that anticoagulant therapy with dicoumarol produced a significant reduction in fatality during the acute attack Their opinions have been widely acclaimed, for they are based on the results of a large scale therapeutic trial carried out under the ægis of the American Heart Association At first glance their results appear impressive, for the fatality among those treated with anticoagulants was 16%, as against 23% for a control group not receiving this treatment But there are certain disturbing elements in the design and conduct of their trial

TABLE XXV—OVERALL FATALITY-RATES IN THE THREE TREATMENT PERIODS

Period	Total deaths			Late deaths		
	No of patients	Deaths		No of patients	Deaths	
		No	%		No	%
I	110	44	40.0	92	26	28.3
II	170	65	38.2	152	47	30.9
III	263	86	32.7	224	47	21.0

The most important criticism is that it was laid down that patients admitted on an odd day of the month would be treated with anticoagulants, whereas those admitted on even days would not It should be a cardinal rule in any controlled therapeutic trial that a patient should first be selected as suitable for admission into the trial and then be allotted at random to one or other forms of treatment Any failure to insist on this creates the opportunity for bias In the case of Wright et al 's trial, the number of treated patients was considerably greater than the number of controls, the numbers being 580 and 442 respectively There are, of course, a few more odd days of the month than even days in the course of a year, but not nearly enough to account for this big disparity in numbers between the two groups Indeed, even allowing for the extra number of odd days in a year, such a big surplus of treated cases would happen by chance less than one in a thousand times, so we can take it that bias has entered into the allocation of treatment The authors themselves admit that, as the trial progressed, some patients were being put into the treatment group at the express wish of their relatives or private physicians

Tulloch and Gilchrist (1950) also presented evidence that anticoagulants were highly

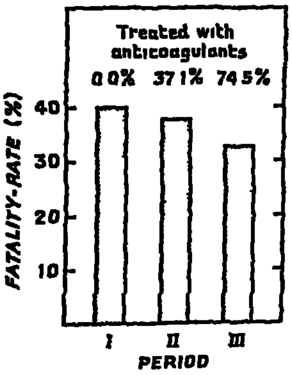

Fig 9—Overall fatality rates in acute attack in each period

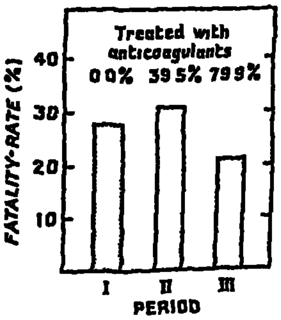

Fig 10—Fatality rates in acute attack, with early deaths excluded, in each period

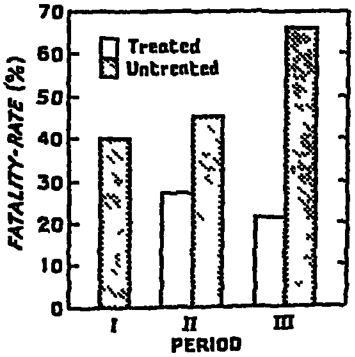

Fig 7—Fatality-rates in various treatment periods related to treatment with anticoagulants

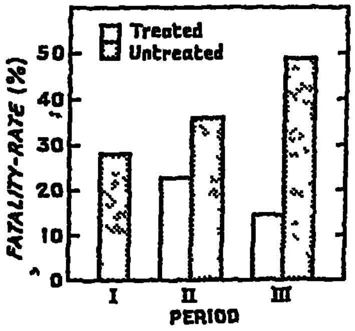

Fig 8—Fatality rates in acute attack, excluding early deaths, according to period and treatment with anticoagulants

TABLE XXVI—PROPORTION OF GOOD RISK PATIENTS IN EACH TREATMENT-PERIOD

Period	No of patients	Good risk patients	
		No	%
I	110	27	24·5
II	170	38	22·4
III	263	87	33·1

beneficial in myocardial infarction, those treated having a fatality-rate of 22·8%, as against 40·5% for the control group

Some of their patients were not given anticoagulant therapy because of some contra indication, but they do not mention whether equivalent patients were excluded from the control group In fact, their control group was larger than the treated group, and this may have been due to a failure to exclude similar patients from each group Our own data show that patients not treated with anticoagulants at a time when this form of therapy had become generally accepted had a very bad prognosis—considerably worse than the overall figure for the pre anticoagulant era In other words, if Tulloch and Gilchrist removed patients with a bad prognosis from their treated group and failed to remove similar patients from their control group, this would inevitably exaggerate the beneficial effects of anticoagulant therapy

A later paper by Gilchrist (1952) is open to more stringent criticism, for in this he has made a direct comparison of patients treated with and without anti coagulants over a period which begins well before the introduction of this therapy, passes through the "controlled" stage of 1947–49, and extends into 1951 when anticoagulants were being generally used except when specific contra-indications existed

TABLE XXVII—OBSERVED AND "EXPECTED" DEATHS IN THE PERIODS, USING PERIOD I AS THE STANDARD FOR CALCULATING EXPECTED DEATHS IN *GOOD-RISK AND BAD-RISK* CASES

Period	No of deaths	
	Observed	Expected
I	44	44
II	65	69·6
III	86	95·5

In effect, Gilchrist was comparing 87 patients treated with anticoagulants in 1950 and 1951 with 77 patients not so treated before 1947 But he does not mention how many patients were unfit for anticoagulant therapy, and in our data (tables XXIII and XXIV, figs 7 and 8) such patients had a bad prognosis By eliminating them from the period 1950–51, Gilchrist was bound to show an improvement even if anticoagulants had done nothing Thus selection of cases probably exaggerated the beneficial effects of anticoagulant therapy

TABLE XXVIII—OBSERVED AND EXPECTED DEATHS IN EACH TREATMENT-PERIOD

Period	Total deaths			Late deaths		
	No of patients	Observed deaths	Expected deaths*	No of Patients	Observed deaths	Expected deaths*
I	110	44	40·4	92	26	23·5
II	170	65	64·9	152	47	41·7
III	263	86	92·6	224	47	54·7

* Calculated on the basis of the age-composition and the number of good risk and bad risk cases in each age group

TABLE XXIX—DEATHS FROM PULMONARY EMBOLISM IN THE THREE TREATMENT PERIODS (*EARLY DEATHS EXCLUDED*)

Period	Number of patients (excluding early deaths)	Percentage of patients dying after the first 48 hours examined at necropsy	Deaths from pulmonary embolism in necropsy material	Estimated fatality-rate (%) from pulmonary embolism
I	92	73·1	4	6·0
II	152	61·7	6	6·4
III	224	74·5	2	1·2

From our own hospital, Loudon et al (1953) presented the results for the period January, 1948, to May, 1952, when anticoagulants were coming into vogue By making a direct comparison of treated and untreated cases they found a highly beneficial effect from the use of anticoagulant therapy The period they took was almost the same as our treatment-period II (January, 1948, to December, 1951) Our own results show a highly significant difference between anticoagulant treated and non-treated patients (table XXII), but we have been able to show that most of this effect is due to bias in the selection of patients for anticoagulant therapy This became more obvious as time went by, and in our latest treatment-period (1952–54), after we had excluded early deaths, nearly 50% of the patients not receiving anticoagulants died—a figure far in excess of that seen in period I before anticoagulants were introduced into this hospital (table XXII)

Schilling (1950) has also advocated anticoagulant therapy

In his hospital in New York, one admitting service treated patients with anticoagulants and the other did not Patients treated with anticoagulants did much better than patients not treated, but he does not compare the overall results for the two services, which would have given the net effect of anticoagulant therapy and would have removed the almost inevitable bias which is created if patients unsuitable for this form of therapy are excluded from one group and not from another Moreover, the figures for the two groups added together are slightly worse than the overall figures for the hospital during the preceding four years when anticoagulants were not in use

When we look closely at the evidence that anticoagulants exert a major influence on the course of myocardial infarction, it becomes plain that this evidence is not strong enough to deter us from the conclusion that the sole beneficial effect of this therapy is to eliminate death due to pulmonary embolism

Summary

In 1940–54 there were 543 admissions to the Radcliffe Infirmary because of acute myocardial infarction

In the acute attack (the two months after admission) there were 195 deaths (34·9%)

A third of these deaths were on the first day Thereafter the rate of dying fell off progressively

The presence of shock or hypotension or both when the patient arrived at hospital was associated with enhanced risk of death within forty-eight hours of admission

Among patients who survived the first forty-eight hours, a different set of factors was associated with enhanced risk of death during the rest of the acute attack These were a history of cardiac asthma, evidence of cardiac failure (either left or right ventricular), cardiac arrhythmia (including multiple extrasystoles), gross cardiac enlargement, and diabetes mellitus

Factors which have sometimes been supposed to be associated with a bad prognosis had no obvious association of this sort in the present series These factors were a previous attack of myocardial infarction, previous angina of effort, previous breathlessness on exertion, and previous hypertension Prognosis was likewise unaffected whether the onset was with the patient at rest or during exertion

Anticoagulant therapy was first used in this hospital in 1948 and was in extensive use by 1952 The overall effect of anticoagulant therapy on the fatality-rate has not been very great, and the improvement can be accounted for by the almost complete abolition of deaths from pulmonary embolism

(To be concluded)

LEUKÆMIA*

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CHRONIC LYMPHATIC LEUKÆMIA

THE two common forms of chronic leukæmia stand in sharp contrast: whereas the myeloid variety follows a stereotyped and constant pattern, the lymphatic may assume any one of a dozen disguises. There are differences too in their age and sex incidence and in their therapeutic response. In chronic myeloid leukæmia treatment may fairly be described as standardised, but, because of the vagaries of the disease itself and its frequent association with other maladies, the management of chronic lymphatic leukæmia demands high qualities of clinical judgment and therapeutic finesse.

Chronic lymphatic leukæmia can be defined only in descriptive terms. It is marked by proliferation of lymphoid cells throughout the blood-forming organs; the cellular elements are usually mature; in the lymph-nodes the proliferation is diffusely spread throughout the medulla, and the resemblance of each cell to its neighbour confers on the microscopic field an appearance of unrelieved monotony; destruction and infiltration of the stroma, the histological hall-marks of malignancy, are lacking (Robb Smith 1938). In many instances this lymphoid overgrowth is associated with a rising tide of lymphocytes in the peripheral blood, but in the early phases this epiphenomenon may be absent.

The difficulties of definition are of two kinds. First, the tissue changes described as characteristic of chronic lymphatic leukæmia may occur without the peripheral lymphocytosis which has often been regarded as a diagnostic sine qua non. Secondly, a great increase in the number of lymphocytes in the blood may be accompanied by tissue changes quite different from those of chronic lymphatic leukæmia.

When faced by the first situation, morbid anatomists have been accustomed to apply the label of "lymphosarcoma"; but, though some claim the ability to separate lymphatic leukæmia from lymphosarcoma without reference to the blood count, the majority believe it to be a distinction without a difference. In most instances the passage of time brings with it the typical blood picture of lymphatic leukæmia. Some would regard this sequence as deserving the title "lymphosarcoma cell leukæmia," but this term is as imprecise as it is inelegant (Hauswirth et al. 1948) and, if it must be used, should be reserved for the escape of primitive lymphoid elements into the blood stream which often marks the closing stages of reticulosarcoma.

The second source of confusion is the presence of a leukæmic blood picture with tissue changes other than those of leukæmia. This may occur in lymphoid follicular reticulosis (follicular lymphoblastoma) and in Hodgkin's disease. It is more easily understood in the first, where the cellular proliferation is lymphocytic, than in the second, where it is pleomorphic.

In recent years I have seen 3 examples of lymphoid follicular reticulosis accompanied by a leukæmic blood picture; it is a well recognised event and usually noted toward the close of the disease (Anday and Schmitz 1952). In one it appeared only in the terminal phase; in the second it was found when the patient first sought attention; and in the third it provided a transient episode during the course of the illness. In none was the leucocytosis in excess of 30,000 per c.mm., and in all of them the cells were large lymphoid elements of unusual appearance. Some workers would undoubtedly have called these cases lymphosarcoma cell leukæmia.

Several instances are recorded in which the tissue changes of Hodgkin's disease were accompanied by the blood picture of chronic lymphatic leukæmia (Gill and McCall 1943, Seife et al. 1951). I have seen one example of this curious combination in a male aged 56; at the initial blood count, twenty-eight months before his death, the lymphocytes amounted to 96% of 160,000 white cells per c.mm.

Thus the blood changes commonly regarded as pathognomonic of chronic lymphatic leukæmia may on occasion accompany tissue changes characteristic of some other disorder, and the tissue changes of chronic lymphatic leukæmia are at times unassociated with any alteration in the peripheral blood. Both these events are uncommon, and difficulties of diagnosis are not frequent.

Incidence

The general incidence of chronic lymphatic leukæmia was discussed in the first lecture; although statistical proof is lacking, most clinicians in this country would agree that it is the commonest type of leukæmia seen in practice today. It is likely that there has been a relatively greater increase in its incidence than in that of other types, for it was reported in 1929 that only 25 patients with this disease had been admitted to the wards of the London Hospital in the preceding sixteen years (Panton and Valentine 1929). There has always been a greater number of males affected than females, and, in the present series of 227 patients, males made up 67.4% and females 32.6%. These proportions may have changed in the past few decades: a small series collected in 1912–28 was composed of 80% males and 20% females (Panton and Valentine 1929); another, of about the same period, contained 74% males and 26% females (Minot and Isaacs 1924); and 137 cases collected between 1913 and 1947 were divided into 71.5% males and 28.5% females (Shimkin et al. 1953). There is some indication in these figures that the disease may be becoming more common in women.

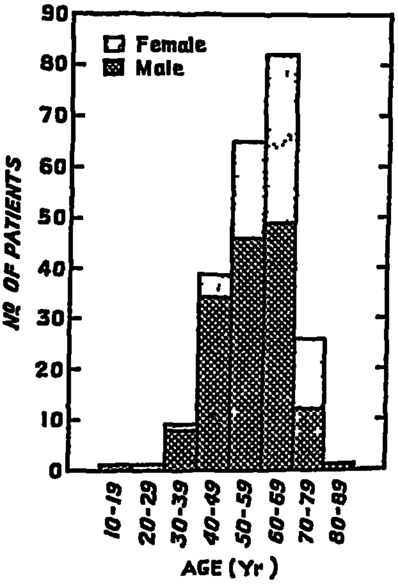

Fig. 9—Age at onset of symptoms in chronic lymphatic leukæmia.

In 80% of patients the first symptoms appeared between the ages of 40 and 70 (fig. 9). The mean age at onset for the whole series was 58.2, for males 56.0, and for females 62.8. There is little change in the overall mean from that of other published series, but for women the mean age of onset is some ten years older than in comparable collections of earlier date (Shimkin et al. 1953). This suggests that the increased incidence is particularly in elderly women.

Initial Physical Signs and Symptoms

The commonest reason for seeking medical advice is the chance discovery of enlarged lymph-nodes (fig. 10); this was the presenting complaint in 42.5% of the present

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* The third Lettsomian lecture for 1957, delivered before the Medical Society of London on Feb. 18. The first two lectures were published on May 25 and June 1.

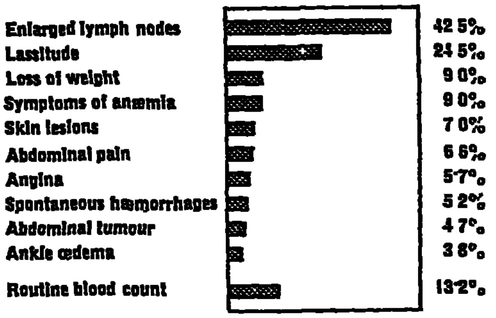

Fig 10—Presenting symptoms in 212 patients with chronic lymphatic leukæmia

series Next in order of frequency as an initial symptom was lassitude (24 2%), followed by loss of weight (9%), and symptoms of anæmia, such as dyspnœa (9 0%) A considerable proportion of patients (5 7%) complained of anginal pain, showing again how moderate anæmia will unmask myocardial ischæmia in the elderly Symptoms attributable to splenomegaly, so familiar in chronic myeloid leukæmia, are uncommon In only 6 6% was there abdominal pain, and only 4 7% had felt an abdominal tumour Œdema (3 8%) and spontaneous hæmorrhages (5 2%) were also rare

In a considerable proportion (13 2%) repeated infections brought the patient under observation This peculiar inability to withstand bacterial aggression is a feature of chronic lymphatic leukæmia and another point of distinction from the chronic myeloid variety It is a consequence of the immunological defect which marks the disease and of the long-recognised failure of its victims to produce antibodies on antigenic challenge (Howell 1920, Larson and Tomlinson 1953)

These recurrent infections are commonly of the respiratory tract, and the diagnosis is often first established when an attack of pneumonia or of purulent bronchitis brings the patient into hospital A smaller group have recurrent tonsillitis, in them considerable enlargement of the tonsils is usual. Repeated attacks of inflammation of unduly large tonsils in an elderly person should always arouse the suspicion of chronic lymphatic leukæmia In a still smaller number attacks of sinusitis furnish the overture to the disease

The other territory liable to bacterial invasion is the skin Impetigo, recurring cellulitis, and boils were all common initial complaints In addition to septic infection, however, other cutaneous lesions provide early symptoms In 3 these were specific leukæmic infiltrations (discussed below), but in 7 the illness began with an attack of herpes zoster This association is well recognised but remains unexplained (Gelfand 1951)

Finally, in 13 2% of this series the diagnosis of chronic lymphatic leukæmia was disclosed by a routine examination of the blood, usually because of some apparently unrelated illness Chance discovery of the disease in this way is increasingly common (Hougie 1956)

When the patient is first seen, the physical signs of the leukæmia fall into one of five categories (table VIII)

(1) The first is what may be called the "classical" form, in this, generalised enlargement of superficial lymph-nodes, moderate in degree, is usually associated with palpable enlargement of the liver and spleen In the present series the disease assumed this form in 73 2% of the patients in 86% of these the spleen could be felt, and in about an equal proportion the liver was enlarged

TABLE VIII—PRESENTING SYNDROMES IN 212 PATIENTS WITH CHRONIC LYMPHATIC LEUKÆMIA

"Classical" type	73 2%
Splenomegalic type	11 8%
Local tumour	7 3%
Specific skin lesions	0 8%
Blood changes only	6 9%

(2) The second category is the splenomegalic type these patients often complain of abdominal pain, and physical examination reveals massive splenomegaly of the order usually associated with chronic myeloid leukæmia, there is commonly a lesser grade of hepatic enlargement, and no superficial lymph-nodes are palpable In this series 11 8% of the patients presented in this fashion

(3) The third group includes those patients who display enlargement of the lymph-nodes of one superficial group or some other solitary tumour of lymphoid tissue The onset was of this pattern in 7 3% of our patients, in the majority one superficial lymph-node was enlarged, most commonly in one of the cervical groups In 2 patients there was an abdominal tumour, shown by laparotomy to be a mass of lymph-nodes, and in a 3rd lymphoid overgrowth in the pharynx

(4) Specific skin infiltrations, although not rare, are seldom the presenting manifestation, only 2 of our patients (0 8%) coming into this group

(5) Finally, in 6 9% no physical signs of disease were evident and the characteristic changes in the blood were the only leukæmic manifestations

Diagnosis

The diagnosis of chronic lymphatic leukæmia rarely presents great difficulty, and several of the pitfalls have already been discussed

Anæmia is seldom severe when the patient is first seen, in this series, the initial hæmoglobin level lay above 70% (Haldane), or 10 4 g per 100 ml, in over half the patients, it was below 50% (Haldane), or 7 4 g per 100 ml., in about a fifth (fig 11) In 10% the initial leucocyte count was below 10,000 per c mm and in nearly half between 20,000 and 100,000 per c mm Initial counts above 500,000 per c mm were uncommon and occurred in less than 5% In 85% the small lymphocyte dominated the cytological picture, this differs from that of normal blood in its more leptochromatic nucleus, the absence of azurophil granulation, and the thin rim of cytoplasm surrounding the nucleus Cells of this kind may amount to 99% of the circulating leucocytes Less commonly the predominant cell was a medium sized lymphocyte with a circular nucleus, clearly less mature than that just described but not approaching the lymphoblast in this respect Occasionally cells with indented nuclei or other bizarre features were seen There is little correlation between the cytology and the pattern the disease may be expected to follow The medium sized lymphocyte does not necessarily portend rapid deterioration, nor the small "mature" cell an indolent course Lymphoblasts are rare and the reversion to a more primitive cellular proliferation, so characteristic of the closing stages of chronic myeloid leukæmia, is most exceptional The

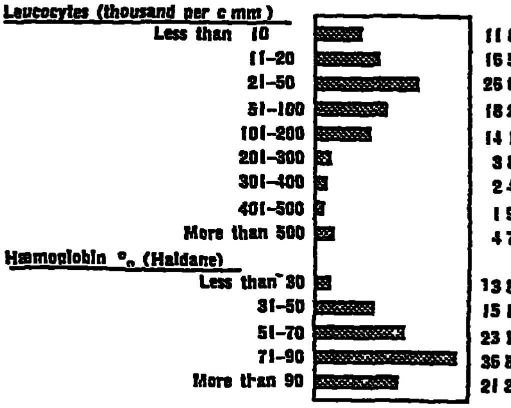

Fig 11—Initial blood-counts in 212 patients with chronic lymphatic leukæmia.

platelet count is usually normal until the stage of bone marrow failure

In almost every instance there is a constant increase in the total number of lymphocytes above 4500 per c mm , the accepted upper level of normal (Osgood et al 1939) There is, moreover, a lack of the pleomorphism which characterises reactive lymphocytosis Nevertheless diagnosis may remain uncertain when the total leucocyte count is not raised , in such circumstances a lymphoid proliferation in the bone marrow in excess of 40% of the total cell population is confirmatory (Scott 1939), although its absence does not exclude the disease In these patients biopsy of a lymph-node may provide conclusive evidence

Alterations in the serum-protein pattern have often been reported in chronic lymphatic leukæmia (Rundles et al 1954) The increase is usually in the gamma globulin fraction, but cryoglobulinæmia has been recorded (Schwartz and Jager 1949)

Less Common Clinical Features

The less common clinical features of chronic lymphatic leukæmia fall into two groups , those depending on leukæmic infiltrations in unusual sites, and those presumed to be the result of immunological disturbance

Infiltrations

Infiltrations have been recorded in every organ and tissue I shall draw attention only to the less rare, of which the present series affords examples

Cutaneous lesions have long attracted attention by their multiplicity (Gates 1938) 8 of the present series (3 8%) were affected 2 of them had generalised lymphoid erythrodermia of the *homme rouge* type , 1 had a violaceous infiltration of the cheeks , 1 had a more patchy erythrodermia , and in the remaining 4 there were blue or red nodular lesions around the orbit, on the forehead, or in the scalp

In the nervous system few abnormalities are to be recorded Facial palsy was observed in 2 patients, and paraplegia resulted from vertebral collapse in 1 Lymphomatous lesions of the conjunctiva were found in 2

Skeletal infiltrations were noted in about 5% The most common of these was an osteoporosis of the vertebral column, particularly in the lower dorsal and lumbar regions In these patients collapse of vertebral bodies was common In 1, as already noted, this accident led to compression of the cord with paraplegia , in 1 successive collapse of four vertebræ was observed The appearances are reminiscent of the diffuse decalcifying type of myelomatosis (Weissenbach and Lievre 1938) and were observed in 8 of this series This lesion may be regarded as the characteristic skeletal expression of chronic lymphatic leukæmia

In 1 case, which should perhaps be regarded as an example of plasma cell leukæmia, there were destructive lesions of most of the skeleton The peripheral leucocyte-count never exceeded 50,000 per c mm , and lymphoid cells made up 70–80% of the total From time to time a proportion of these were plasma cells, but bone-marrow puncture yielded typical lymphocytes, and the plasma-protein levels remained normal Another patient had rarefying lesions in the head of the tibia, suggesting tuberculosis

In the alimentary tract lesions were uncommon, but in 2 patients multiple lymphomatous polyps were felt in the rectum Ascites was often noted , usually an event of the final stages, at times it made its appearance early in the disease and caused great disability

Respiratory symptoms are common The frequency of infection has already been noted, and in 2 patients it led to empyema Massive mediastinal tumour is exceptional in chronic lymphatic leukæmia, although characteristic of one variety of the acute lymphoblastic type Nevertheless the mediastinal nodes naturally share in the general lymphadenopathy , sometimes they cause bronchial obstruction with subsequent infection Infiltration of the lung parenchyma is uncommon, but multiple lymphoid nodules have been recorded, often leading to obstruction and purulent bronchitis (Herold and Michel 1950) A miliary infiltration, closely resembling that of tuberculosis, was reported by Fleischmann (1909) but is of great rarity One instance was seen in the present series, in a man aged 43 The lesion appeared during the course of the leukæmia and was associated with rapidly increasing dyspnœa no evidence of tuberculosis was found and improvement was noted after irradiation

Serous pleural effusion is common and, like ascites, usually a feature of the later stages There were, however, 8 patients in this series in whom the earlier stages of the illness were associated with effusions into all three major serous cavities 6 of them were men under 50 years of age, and in all of them the disease was of the more rapidly progressive type with medium sized lymphocytes dominating the blood picture

Attention has already been drawn to the frequency of tonsillar enlargement and recurrent infection as an opening event Similar episodes are common during the course of the disease

A nephrotic syndrome was observed twice in this series No previous reports of this complication have been found

One patient was a woman of 71 years and the other a man of 57 , in both hyperglobulinæmia was noted early in the illness, but the urine was initially free from albumin Both cases were hæmatologically typical, with cells of the small mature type Œdema of the legs with purpura, but without thrombocytopenia, appeared eighteen months after the onset of the disease in the first patient, and five years after in the second At the same time heavy albuminuria, but no Bence-Jones proteinuria, was found The serum-protein levels at this stage were albumin 3 78 g per 100 ml and globulin 3 8 g in the first, and albumin 3 5 g and globulin 4 8 g in the second In both the proportion of gamma-globulin was greatly increased

Both patients sank and died of renal failure respectively six and five months after the first appearance of œdema The woman developed a nodular skin eruption which biopsy showed to be the result of amyloid infiltration, and necropsy revealed amyloid disease of her kidneys, liver, and myocardium This case recalls the amyloidosis occasionally associated with myelomatosis (Stewart and Weber 1938, Trubowitz 1950, Magnus-Levy 1952) and forms another link between this condition and chronic lymphatic leukæmia Necropsy of the other patient showed no sign of amyloidosis , there was lymphocytic infiltration in the kidneys with some hyaline change in the glomeruli In neither case did the cytology of the peripheral blood or of the bone marrow support a diagnosis of plasma cell leukæmia or of myelomatosis

Immunological Disturbances

The second group of less common clinical features are those that may be tentatively ascribed to the perverted immunity mechanisms characteristic of chronic lymphatic leukæmia These disturbances are reflected in changes in the peripheral blood The most common and the most important is auto immune hæmolytic anæmia An occult hæmolytic process has long been thought to underlie the anæmia of this disease (Brown et al 1951, Berlin et al 1954), but from time to time frank and unequivocal hæmolytic anæmia has been reported (Marchal et al 1934) It is only since the introduction of the Coombs test (Coombs et al 1945) that its frequency has been appreciated Rosenthal et al (1955) record 20 such cases

In these patients the direct Coombs test is positive and often provides a warning of impending hæmolysis , serum hæmagglutinins are often demonstrable, and indeed there is no difference between this type of auto-immune hæmolytic anæmia and the "idiopathic" variety (Dacie 1954). It has been suggested that the antibodies are derived from the pathological lymphoid tissue (Harris and Harris 1951, Wager and Chase 1952, Wiener et al. 1953). Undoubtedly this syndrome is very much more common than was believed even five years ago, and the reported incidence in this series, which is only 5·7% (12 cases), greatly underestimates its true frequency, for most of these cases have been recognised in the past five years. Hæmolysis of all grades of intensity has been encountered from that causing persistent moderate anæmia to that marked by a fall in hæmoglobin sufficiently precipitous to place the patient's life in jeopardy within a few days. A moderate rise in the serum-bilirubin level is the rule; the excretion of urobilinogen is increased; but reticulocytosis depends on the capacity of the marrow to respond to stimulation; and, as its function is usually impaired by lymphoid infiltration, figures in excess of 10% are rare. 3 of our patients died in the first hæmolytic attack; in others the process relapsed and remitted over periods lasting as long as six years. In 1 the spleen was not palpable, and, contrary to some opinion (Rosenthal et al. 1955), there was seldom any obvious parallel between its size and the severity of the hæmolytic state.

Thrombocytopenia due to similar causes undoubtedly occurs in chronic lymphatic leukæmia. In the present series there were 5 patients in whom purpura of this kind was the main cause for complaint. A low platelet count is, of course, the rule in the later stages of the disease, when it is evidence of bone-marrow failure; it is accompanied in these circumstances by anæmia, and examination of the bone-marrow reveals lymphoid infiltration with disappearance of normoblasts and megakaryocytes. In the patients in question, however, there was no anæmia and, although lymphocytes made up 60% or more of the medullary cells, megakaryocytes were present in adequate numbers. In only 1 of these patients was an agglutinin for platelets demonstrable in the serum, and in her case the Coombs test was also positive. It is difficult to avoid the conclusion that platelet auto-antibodies may be elaborated in like fashion to those active against red blood cells. A similar mechanism may be responsible for leucopenia in some cases of chronic lymphatic leukæmia, for leucocyte antibodies have been demonstrated in 1 instance (Andre et al. 1954).

The importance of appreciating this type of disturbance cannot be exaggerated, for its recognition provides an insistent call for specific treatment. Moreover the sudden appearance of anæmia or of thrombocytopenia is no longer to be regarded as the harbinger of death. 1 of our patients with hæmolytic anæmia lived six years in fair health after his first admission to hospital with a hæmoglobin level of 30%, and another lived eighteen months after a hæmolytic crisis which brought his hæmoglobin down to 18%.

Associated Diseases

It is no matter for surprise that many diseases common in the second half of life should occur in combination with chronic lymphatic leukæmia. Most of these are degenerative: ischæmic heart disease was present in 10% and essential hypertension in another 7·5%; 3 patients had diabetes mellitus, 2 gout, and 5 gall-stones; 5 had peptic ulceration and 5 prostatic enlargement. Chronic infection was rare, but 5 had pulmonary tuberculosis. Urinary calculi, which are stated to be a particularly common accompaniment (Weisberger and Persky 1953) were present in only 3.

The association with other forms of malignant disease has interested many authors (Morrison et al. 1944, Axelrod and Berman 1949, Bichel 1949). Beresford (1952) reported that 20 of 106 patients with chronic lymphatic leukæmia had other malignant lesions, although in 10 the cancer was of the skin or lip. In the present series 4·7% (10 patients) were known to have other primary tumours arising in the following sites: bronchus 3, breast 2, skin 2, and bladder, rectum, and tongue 1 each.

Treatment

The problems of treatment in chronic lymphatic leukæmia are quite different from those in the chronic myeloid variety. In myeloid leukæmia complete remission of limited duration can be confidently expected; but in lymphatic leukæmia it is unusual. Enlarged lymph-nodes may shrink, and the raised leucocyte-count may fall, but improvement in general health and repair of anæmia as a result of treatment, are rare.

The first decision the physician has to make is whether any treatment is required. In those patients in whom evidence of leukæmia is limited to lymphocytosis in the peripheral blood, therapeutic inactivity is the wise course. The same is true when there is only very slight lymphadenopathy and no significant anæmia; but when symptoms appear the patient will naturally enough demand treatment.

These symptoms may be the result of massive infiltrations in lymph nodes or other tissues, or such systemic effects of the disease as anæmia, loss of weight, and exhaustion. Undoubtedly irradiation remains the most effective means of disposing of lymphoid tumours; their radiosensitivity varies greatly, but a total fractionated dose of 1200r to any one superficial group will usually lead to satisfactory resolution of the mass. This treatment has little effect on the leucocyte-count, to lower which irradiation of the spleen is required; this measure may increase the radiosensitivity of superficial lymph-nodes and discourage recurrence in the irradiated areas (Levitt and Scott 1955).

The effect of radiotherapy on the general features of the disease is far less satisfactory. The lower the initial hæmoglobin level, the less good the outlook (Leavell 1938). In 51 patients after deep X-ray treatment the hæmoglobin level was unchanged in 32, it rose by more than 1·5 g. per 100 ml. in 7, and fell by more than 1·5 g. in 12 (Scott 1949). There are occasional exceptions in which irradiation initiates a general remission and the patient is restored for a spell to normal health. Radioactive phosphorus has little advantage over other forms of irradiation (Lawrence et al. 1949, Diamond et al. 1950).

When the symptoms are due to failure in general health without exuberant lymphadenopathy, it is rational to use one of the chemotherapeutic agents. Arsenic was much recommended in former years (Nägeli 1930) but has now been largely discarded; urethane produces temporary benefit in the occasional patient; but it is the nitrogen mustards and their derivatives which have come to occupy pride of place. Good results have been obtained with the 2-chlorethylamines (Wilkinson 1953), but sensitivity to these drugs is extremely variable in this disease. Their polyethylenimine derivatives, triethylene melamine (tretamine) (Rundles and Barton 1952, Paterson et al. 1953, Hambly and Robertson 1955), triethylene phosphoramide (Sykes et al. 1953), and triethylene thiophosphoramide (Shay et al. 1953, Leonard et al. 1956) have all been used, the first and third most extensively. Sensitivity is again variable; in most patients the leucocyte-count is reduced to normal and the lymph nodes and spleen regress, but repair of the general health is unusual. The most recently introduced and perhaps most effective drug is chlorambucil (γ-p (N,N di-(2 chloroethyl)amino phenylbutyric acid)). This is given in the daily oral dosage of 0·1–0·2 mg. per kg. body-weight for three to six weeks Toxic effects are uncommon, and reduction in leucocyte count and glandular masses is the rule, although, once again, significant gain in hæmoglobin is less frequent (Galton et al 1955, Altman et al 1956)

In the present series irradiation has been used largely for treating lymph node masses, of recent years it has been applied but rarely to the spleen Tretamine was used for two or three years with excellent effects on the white-cell counts, less on the lymph node tumours, and least on the hæmoglobin level and general health The greatest rise in hæmoglobin observed was from 7 4 g to 9 8 g per 100 ml, and this was on one solitary occasion In the last 18 patients chlorambucil has been used and the results have been similar to those obtained with tretamine, although somewhat better

In short, improvement in the hæmoglobin level, gain in weight, and recovery of general health are rarely obtained with radiotherapy or with chemotherapy It is an ironical reflection that these measures are most effective in the patients whose symptoms are so slight that the necessity for treatment is debatable

The onset of frank hæmolysis is an urgent indication for treatment with cortisone or corticotrophin Of 7 patients with auto-immune hæmolytic anæmia who were treated with steroid drugs the effect was miraculous in 5, and in the 2 others overwhelming infection was added to the hæmolytic state The remainder were observed before these drugs were available splenectomy was carried out in 1, who died with bronchopneumonia after the operation, 3 others died with uncontrolled hæmolysis, and in 1 patient blood-transfusion and splenic irradiation arrested the excessive destruction of blood on three separate occasions, before the process escaped from control to prove fatal after a course of five years

Auto immune thrombocytopenia is less easy to control, in the milder forms it improves either spontaneously or as a result of treatment with steroids Of our 5 patients 3 fell into this class, in the 2 others splenectomy was undertaken, with complete remission for seven months in one and with no effect in the other Occasional dramatic improvement results from cortisone in patients who, although anæmic, present no evidence of excessive hæmolysis, apart from a reduced survival of transfused blood

In addition to the 1 patient with hæmolytic anæmia and the 2 with thrombocytopenia, splenectomy has been carried out in 2 others in this series

In one the bulk of the organ made life intolerable, its removal three months ago has greatly increased the patient's comfort, although it is too early to judge of its effect on his disease

The other, a woman aged 45, presented with enlarged inguinal lymph nodes, biopsy of which showed the changes of lymphatic leukæmia The peripheral leucocytes numbered 17,000 per c mm, 78% of which were small lymphocytes, and 82% of the cells in films from bone marrow puncture were lymphocytes Four and a half years later there were bilateral pleural effusions and massive painful splenomegaly with a leucocyte count of only 2800 per c mm and a hæmoglobin level of 8 g per 100 ml After argument, I yielded to her entreaties to allow removal of her spleen Now, six years later, she is in abundant health, apart from an injury to her knee sustained while she was skiing last winter, there are no signs of disease, the hæmoglobin level is 16 3 g per 100 ml, the leucocytes number 4400 per c mm (lymphocytes 40%), and the bone marrow is normal

This observation confirms Galen s opinion that the spleen is an organ full of mystery, but it should not urge us to advise removal of that organ unless one of the accepted indications—uncontrollable hæmolysis, thrombocytopenia, and pain—exists (Fisher et al 1952, Reinhard and Loeb 1955)

Control of effusions into serous cavities has been very difficult In some patients wide field irradiation has been effective, and perhaps this is the most hopeful measure Injections of radioactive gold gave no benefit in 4 patients

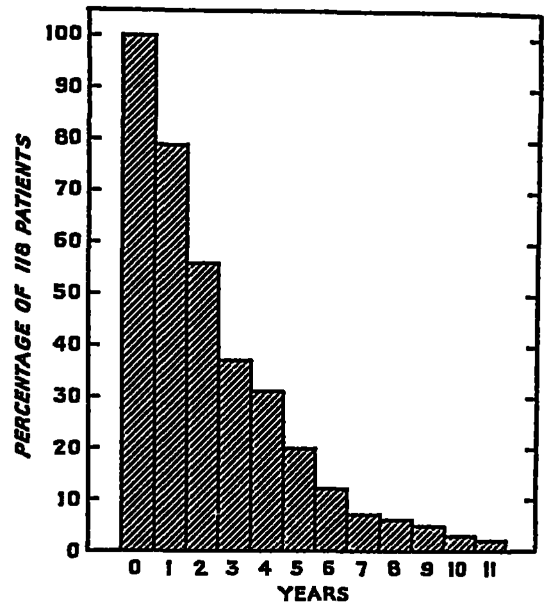

Fig 12—Survival from onset of symptoms of chronic lymphatic leukæmia

Prognosis

As one watches patients with chronic lymphatic leukæmia through their years of illness, it is possible to discern some pattern in the course of the disease Usually there is a period of reasonable health, during which the lymph-nodes and spleen increase slowly in size and the leucocyte count creeps upwards, although the hæmoglobin level and the platelet count are well maintained, then, with various degrees of abruptness, the advancing lymphoid infiltration determines bone marrow failure, the hæmoglobin level falls, a hæmorrhagic state appears, and, unless life is maintained by repeated transfusion, death follows rapidly from anæmia and exhaustion During the first phase radiotherapy or chemotherapy will lower the leucocyte count and cause the lymph nodes to regress, in the second phase treatment is seldom of avail At any time this course may be interrupted by the effects of infiltrations in such tissues as bone and skin, by infection, or by the appearance of one of the auto immune syndromes The length of the first phase varies from a few months to eight or ten years, and many of the older patients die with, rather than from, the disease (Marlow and Bartlett 1953) Rarely a patient appears to recover (Schott 1955) In this series, a woman of 80 died of bronchopneumonia ten years after the onset of chronic lymphatic leukæmia, at the time of her death there were no enlarged lymph nodes nor splenomegaly, and the blood count was normal

In the present series the mean duration of the disease in 118 patients known to have died was 36 7 months (fig 12) Survivals of 40 months in 30 untreated, and 42 months in 50 irradiated, patients (Minot and Isaacs 1924) again underline the fact that treatment has not improved the outlook in this disease

Envoi

When the third Marquess of Salisbury was Prime Minister, he is said to have dismayed his Cabinet by holding that to many important political questions there neither were nor could be answers Though it is sometimes tempting to translate this opinion to the sphere of medicine, and perhaps even to apply it to leukæmia we must remember that the science of them peutics is founded on the touchingly naïve assumption that there is an answer to every question it poses

In retrospect this review of leukæmia makes discouraging contemplation, the incidence of the disease is rising, its cause is unknown, and treatment seldom prolongs life, let alone preserves it Nevertheless those who have elected to interest themselves in the subject are inspired by the belief that answers will be found to the many problems it presents, and in the recent report from Harwell of the cure of experimental leukæmia in mice (Barnes et al 1956) the more sanguine have detected a gleam of light

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POSTOPERATIVE COLLAPSE DUE TO ADRENAL INSUFFICIENCY

FOLLOWING CORTISONE THERAPY

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UNTIL recently we took care not to operate on patients while they were still under corticosteroid therapy—a situation encountered particularly in cases of ulcerative colitis Cortisone was withdrawn before operation, in order to avert the postoperative complications it might cause But events have made us reverse this policy

One of us has lately recorded three cases of bowel disintegration following cortisone treatment (Brooke 1956b) In two of these the termination was the same though the patient's condition after operation was at first satisfactory, they collapsed after 18–24 hours Though their peritoneum had been much contaminated at operation, the interval before death seemed too short for infection to be the main cause of the collapse Moreover, soon afterwards a similar death followed an operation at which contamination was only slight

Case 1 —A woman aged 52, with ulcerative colitis, had received cortisone 50 mg t.d s for 2 weeks On her admission to hospital, cortisone was stopped, and aqueous intramuscular corticotrophin (A C T H) 20 units was given daily for 2 weeks This was withdrawn a few days before operation Her general condition was good and primary panproctocolectomy was performed, the operation was straightforward, though there was slight contamination The blood-pressure (B.P) remained normal until 7 hours later, when it suddenly fell Response to methedrine and noradrenaline was transient, and she died 13 hours after operation

In none of these patients did necropsy show any cause for the sudden collapse It seemed possible, however, that adrenal insufficiency might be responsible, though in case 1 the adrenals appeared normal both to the naked eye and after examination by conventional histological procedures, with a combined weight of 16 g (rather higher than normal, possibly because of the effects of corticotrophin) The right suprarenal of one of the patients previously reported (case 2, Brooke 1956b) had been found to be necrotic following thrombosis of its vein Salassa et al (1953) had reported deaths from adrenal insufficiency in patients with adrenal cortical atrophy following protracted cortisone therapy the adrenal cortex showed no obvious atrophy but definite histological changes Similar reports have come from Fraser et al (1952) and Lewis et al (1953), and Harnagel and Kramer (1955) recorded successful treatment with cortisone in a case of postoperative collapse following manipulation of the knee joint which required but 5 minutes' anæsthesia

Adrenal insufficiency therefore seemed a likely cause of death in our cases Administration of cortisone is known to produce adrenocortical hypoplasia and even frank atrophy through suppression of endogenous corticotrophin This cortisone induced depression takes several days to pass off, and even after the response to corticotrophin has been fully restored, it may be a very long time before the hypoplastic gland returns to absolute normality During this period, though the adrenal glands are capable of producing enough steroids for ordinary daily requirements, they may be unable to meet the additional requirements of severe stress During this period, which may last as long as 6 months to 2 years (Hench and Ward 1954), a major operation could have disastrous results With these facts in mind, we decided that in

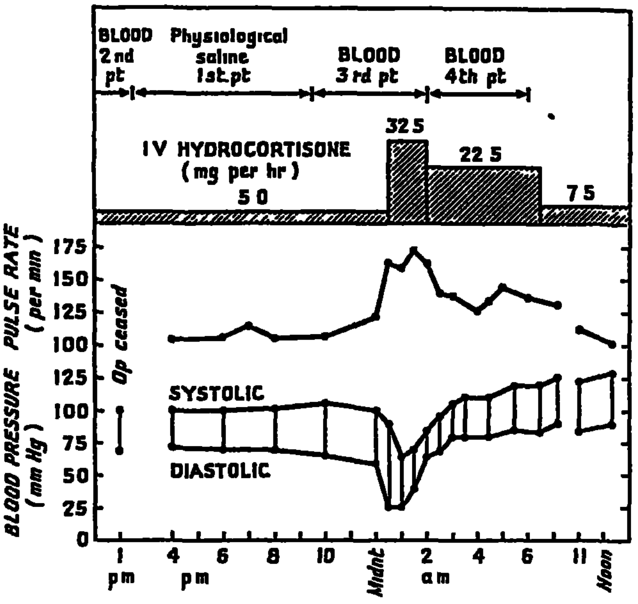

Fig 1—Case 2

operating on patients who have had a course of cortisone we would henceforth give corticosteroids over the operative period

Case 2—A woman aged 29, developed severe ulcerative colitis during the puerperium following the birth of her second child She did not respond to a course of cortisone (100–150 mg daily) lasting 6 weeks Therapy ceased 10 days before operation, but was recommenced 3 days before primary colectomy, with corticotrophin 20 units b d s, followed next day by prednisone 5 mg q d s, at operation, therapy was maintained with intravenous hydrocortisone 50 mg per pint of physiological saline solution Operation was uneventful Her condition and blood pressure (100/65) remained satisfactory until 12 hours later, at 12 30 A M, when she collapsed with a blood pressure of 75/30 She was then given hydrocortisone 50 mg intravenously followed, at 2 0 A M, by 100 mg No vasopressor drugs were administered, her condition improved with a gradual return of blood pressure to normal by 6 0 A M Convalescence remained smooth from 6 0 A M on the first postoperative day (fig 1)

This patient had collapse and hypotension, with no obvious cause, in a manner and at a time identical with those in our previous cases She was revived by cortisone treatment alone

Case 3—A woman, aged 43, was admitted as an emergency with perforation of the colon following 6 weeks of cortisone treatment Emergency ileostomy was followed by persistent hypotension (B P 94/70 mm Hg) This was unrelieved by the usual measures, but cortisone 100 mg initially, given intramuscularly, followed by 50 mg daily for 3 days with corticotrophin 10 units b d, restored and maintained her condition 11 days later colectomy was undertaken with a repetition of postoperative hypotension which was corrected only by a similar regime using hydrocortisone and corticotrophin While she was receiving these drugs, her abdomen burst on the 8th day after colectomy, it finally proved impossible to raise her blood pressure, which fell after resuture, and she died

Hayes and Kushlan (1956) report intractable shock in five of twelve patients previously treated for ulcerative colitis with corticosteroids In four, collapse attended operation, in the fifth it began with the induction of anæsthesia Treatment of shock with corticoids was successful, and the condition was avoided at subsequent operations by their administration before, during, and after operation But this state is not confined to ulcerative colitis in fifteen of twenty eight patients who received steroids at some time (for either ulcerative colitis splenic disease, or rheumatoid arthritis) shock refractory *to blood-transfusion followed an operation, whereas the* condition of twenty five who had similar diseases, but who had not received corticoids, remained satisfactory after undergoing operations (Hayes 1956) This has also been our experience

Case 4—A woman, aged 51, had received cortisone 100 mg daily for 5 weeks for acquired hæmolytic disease Treatment ceased at the time of splenectomy, she collapsed 24 hours later (B P 90/50) and responded to 50 mg cortisone intramuscularly followed by 25 mg, the blood pressure rising to 115/80

In our series seven patients have had shock due to adrenal insufficiency (table I), all three who received no planned course of corticoids to counter this died, whereas all but one of the remainder survived Since we have given corticosteroid cover immediately before during, and after operation, this form of postoperative shock has been conspicuous by its absence in eight patients severely ill with ulcerative colitis after previous corticoid therapy 10 operations were performed with uninterrupted recoveries following primary colectomy (5), primary panproctocolectomy (2), or excision of the rectum (3) One of the patients undergoing primary colectomy is of particular interest because though his blood pressure did not fall after this major operation, it fell after a minor operation undertaken subsequently when cortisone cover had been withdrawn

Case 5—A man, aged 41, was *admitted for surgery* 2 months after a course of cortisone followed by prednisone lasting a month Primary colectomy was performed under cortisone cover (table II) without incident, his blood pressure remaining steady throughout convalescence 17 days later just after corticosteroids had been withdrawn, a small skin

TABLE I—POSTOPERATIVE COLLAPSE IN PATIENTS RECEIVING CORTISONE THERAPY BEFORE OPERATION

Sex and age		Diagnosis	Duration of corticoid treatment	Cortisone preoperative total dose	Operative cover	Corticoids for post operative shock	Outcome
F	41	Ulcerative colitis	1 2–3 weeks	Not known	No	No	Died
M	[illegible]	Ulcerative colitis	Cortisone 4 weeks corticotrophin 40 u daily 5 days preop	5 25 g	No*	No*	Died
F	[illegible]	Ulcerative colitis	Cortisone not known, corticotrophin 20 u daily 14 days preop	Not known	No	No	Died
F	43	Ulcerative colitis	Cortisone 6 weeks	3 g	No	Yes	Initial recovery Survived colectomy 10 days later with cortisone and corticotrophin Died 9 days later following further operation for burst abdomen
M	[illegible]	Ulcerative colitis	Cortisone 4 weeks corticotrophin 40 u daily 4 days preop	9 g	No	Yes	Recovery despite subsequent rectal hæmorrhage and burst abdomen
F	51	Acquired hæmolytic anæmia	Cortisone 6 weeks	4 75 g	No	Yes	Recovery
F	29	Ulcerative colitis	Cortisone 6 weeks corticotrophin 40 u. daily 7 days preop	5 g	Yes	Yes	Uneventful recovery

* This patient received 100 mg cortisone during operation empirically, but at no time received steroids as planned cover or to counter final collapse

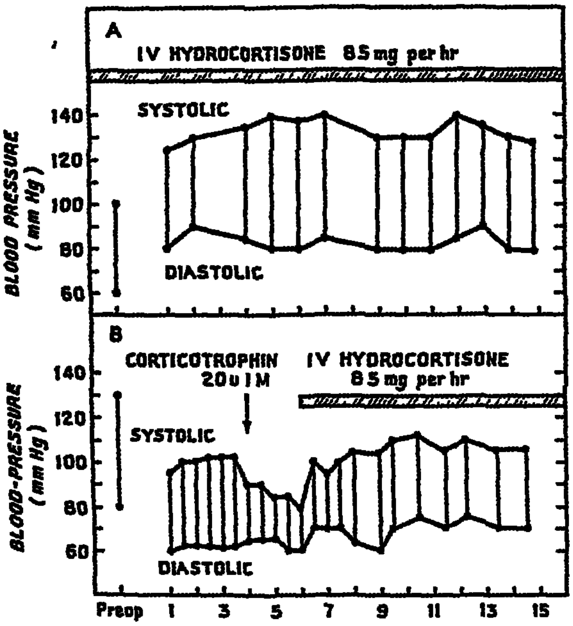

Fig 2—Case 5 A, primary colectomy and cortisone cover B, skin-graft to anal ulcer no cover

graft was applied under general anæsthesia to an ulcer in the anal area This was a minor procedure causing little or no bleeding, no further cortisone cover was given His blood-pressure following operation fell to 100/60, from a preoperative level of 130/80 4 hours later it had fallen to 90/65, and 2 hours after this to 80/60 At this point it was deemed advisable to institute steroid therapy, corticotrophin 20 u was given intramuscularly, and hydrocortisone intravenously by continuous drip, 100 mg in 12 hours Within 5 hours the blood pressure had stabilised at 110/70, and the patient's general condition was excellent The cortisone was gradually withdrawn over the ensuing days under corticotrophin cover with no further fall in blood pressure (fig 2) Subsequent excision of the rectum under corticosteroid cover was without incident

Hypotension without collapse has also been seen

Case 6 —A woman, aged 33, had had a course of cortisone during the 2 months before admission for surgery Primary colectomy was done 2 months after the end of the course, and though convalescence was uneventful, her blood-pressure (106/66 before operation) remained at about 100/70 for 24 hours, the possible reason for this was not appreciated at that time 6 months later she returned for excision of the rectum, her blood-pressure was then 140/80 Following operation, which was performed without difficulty and with little blood loss, pressure recordings on each successive day were 85/50, 95/60, 100/70, 90/45, 95/65 95/65, 96/50, and 100/65 They remained at 100/60 for a fortnight after operation Nevertheless, her condition gave no cause for concern, for she was never shocked She was found to be excreting only 1 mg of 17-ketosteroids in 24 hours which suggested adrenal atrophy, corticoids were, however, withheld, because a tuberculous pulmonary focus had developed between the two periods of admission

TABLE II—SCHEME OF CORTISONE AND CORTICOTROPHIN DOSAGE DURING OPERATIVE PERIOD

Day	Cortisone (hydrocortisone where stated)	Corticotrophin
O − 2	Nil	20 u i m i b d
O − 1	50 mg i m i 6 P M	20 u i m i b d
O	50 mg oral 6 A M 50 mg i m i with premedication Postoperatively hydrocortisone 100 mg i v by continuous drip in 12 hours	20 u i m i b d
O + 1	Hydrocortisone 150 mg i v by drip in 24 hours	20 u i m i b d
O + 2	50 mg i v by drip 12 noon, 25 mg 10 P M 25 mg	20 u i m i b d
O + 3	25 mg t d s	20 u i m i b d
O + 4	25 mg b d	20 u i m i b d
O + 5	25 mg	20 u i m i b d
O + 6	Nil	20 u –10 u i m i
O + 7	Nil	10 u b d
O + 8	Nil	10 u
O + 9	Nil	Nil

O operation i m i intramuscular injection i v, intravenously
All postoperative cortisone is given by mouth unless patient has ileus, &c Corticotrophin is given in an aqueous solution

The suggested dosage for prophylactic treatment is set out in table II The scheme is based on the fact that cortisone administered orally is most effective 4–8 hours later, intramuscularly, 8–12 hours later, and intravenously (as hydrocortisone), almost immediately but only for a short time Given intramuscularly, corticotrophin acts optimally 6–8 hours afterwards, but intravenously its effect is rapid and long-continued (Hench and Ward 1954) Especial vigilance is needed because patients treated thus are prone to gastric and duodenal ulceration, and to infection

Discussion

In ulcerative colitis, more than any other condition, surgical intervention is likely to follow a course of corticosteroids Postoperative shock due to adrenal insufficiency will therefore be seen mostly in patients with this disease In the Medical Research Council's trial of cortisone for ulcerative colitis forty-five patients (a fifth of the original group) ultimately required surgery (Truelove and Witts 1955) and fourteen died, giving a mortality of 32% as opposed to the overall mortality for surgery (Swinton 1956, Brooke 1956a) of 10–12% in the pre cortisone era Patients who do not respond to cortisone often deteriorate during its administration, and this must partly account for the higher operative mortality in the cortisone trial Truelove and Witts observed that most deaths took place soon after the initial operation, adrenal insufficiency may therefore have played a part in the high death-rate According to Salassa et al (1953), 5 days' administration of cortisone is enough to cause histological changes in the adrenal cortex Hench and Ward (1954) say that a total dose of 2 g is likely to induce frank atrophy, the M R C trial, when followed to the limit of 6 weeks, provided twice that critical dose In five of the seven patients of our series who had postoperative adrenal shock the dosage is known; all had previously received over 2 g cortisone (table I)

Before cortisone is given for any condition, the likelihood of surgery being required later must be considered, together with the increased risk if it is undertaken after cortisone By no means all patients who have received cortisone go into shock after operation, some have hypotension without shock (case 5), others show no ill effects Though tests have been devised for adrenal insufficiency (Hench and Ward 1954) it is difficult to predict which patients will become shocked, and therefore wise to perform any subsequent operation under the cover of corticosteroids

Salassa et al (1953) have said that adrenal insufficiency may persist up to 2 years after cessation of cortisone, in our case 6 it was still present after 8 months Post operative collapse may take place even in a patient under routine cortisone cover (case 2), in these circumstances more cortisone should be given intravenously in the form of hydrocortisone, for intramuscular injections are absorbed too slowly Signs of hypercorticism during the initial course of cortisone are an absolute indication for the provision of cortisone cover at a subsequent operation, since atrophic changes within the adrenal are to be expected in these cases (Hench and Ward 1954) When considering the advisability of treating a patient with cortisone, a factor to be weighed is the need to give cortisone again later if surgery should be required The risks of such cortisone cover for operations—i e, ulceration in the upper alimentary tract, greater likelihood of infection, and (in particular) septicæmia—will be by no means negligible

Summary

Patients who have received cortisone are liable to collapse when later submitted to the stress of operation subsequently There is evidence that this state of shock is the outcome of adrenal insufficiency due to atrophic changes within the adrenal cortex induced by cortico steroid therapy Death in three patients could be explained only on these grounds Shock was successfully treated in four other patients by the further administration of cortisone, though one eventually died

It is suggested that cortisone should be administered prophylactically to any patient undergoing operation who has had corticosteroid therapy within a year, and possibly two years, of the operation, cortisone cover should include the operation-period and be withdrawn during convalescence A scheme of dosage is proposed Since this scheme was followed, eight such patients have been treated without collapse in any

The complications usually associated with cortisone therapy must be expected while prophylactic cover is being maintained—especially a tendency to infection and septicæmia Such infections require larger doses of antibiotics than usual for their control

In any patient for whom corticosteroid therapy is contemplated, careful consideration should be given to the likelihood of operation being needed Operative risks are increased by antecedent administration of cortisone

We wish to acknowledge the assistance given by Dr W T Cooke in the preparation of this paper and for permission to record cases under our joint care We wish to thank Mr J C Edwards for permission to report case 3 and Dr E Bulmer for case 4

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PAGET'S DISEASE OF BONE

THE RADIOLOGICAL INCIDENCE

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Large series of cases of Paget's disease of bone (diagnosed radiologically) have been reported by Dickson, Camp, and Ghormley (1945), Brailsford (1938), and others, but there has been no report of the radiological incidence of the disease at differing ages Necropsy studies by Schmorl (1932) and Collins (1956) on unselected subjects over 40 years of age have shown an incidence of 3% and 3 7% respectively

In the ten year period 1947–56, 689 cases of Paget's disease have been diagnosed in the radiological department of the Central Middlesex Hospital Table I shows their age and sex distribution

TABLE I—AGE AND SEX DISTRIBUTION IN 689 CASES DIAGNOSED AS PAGET'S DISEASE

Age group	Men	Women	Total
25–24	1		1
35–44	11	7	18
45–54	27	13	40
55–64	111	57	168
65–74	192	86	278
75–84	104	45	149
85 +	17	18	35
Total	463	226	689

For the six year period 1947–52 it was possible to divide the 357 cases of Paget's disease discovered (245 men and 112 women) into two groups according to whether the diagnosis was made initially as a result of an examination which included the lumbar spine and pelvis, or as a result of examination of any other site There were 289 patients in the first group (204 men and 85 women) and 68 patients in the second group (41 men and 27 women) It is well recognised that, radiologically, the pelvis is the most fruitful area of examination for Paget's disease thus in the series of Dickson et al (1945) the pelvis was involved in 243 out of 367 cases and in that of Rosenkrantz et al (1952) it was involved in 60 out of 111

As a sample of the 69,783 patients radiographed during this six-year period 3000 X ray record cards were examined to see what proportion of patients of different sexes and ages had an examination involving the lumbar spine and pelvis area—including, for example, an examination of the urinary tract or a barium enema From the information thus obtained, it was possible to estimate the total number of patients in whom this area was examined

Table II sets out the age and sex distribution of the 289 patients in whom the diagnosis was made from examination of the pelvis and lumbar spine and in parentheses the estimated number of persons similarly examined in the same age group

TABLE II—CASES OF PAGET'S DISEASE OF BONE

Age group	Men	Women	Total
35–44	6 *(1466)*	4 *(1466)*	10 *(2932)*
45–54	7 *(1956)*	7 *(1466)*	14 *(3422)*
55–64	48 *(1675)*	16 *(1187)*	64 *(2562)*
65–74	88 *(1157)*	38 *(1047)*	126 *(2234)*
75–84	49 *(698)*	12 *(419)*	61 *(1117)*
85 +	6 *(70)*	8 *(70)*	14 *(140)*
Total	204 *(7052)*	85 *(5655)*	289 *(12 707)*

From table II the rate per 1000 persons at different age groups was calculated (table III) Only the last group, the 85+, is too small for any reliable information to be obtained from it

From table III it appears that the incidence in men alters little from 35 to 54 years but after 55 it increases rapidly to a steady high level which is reached in the decade 65–74, after 75 it shows little change In women the incidence under 55 years is surprisingly similar to that of men of the same age, but after 55 the increase is only to a rate about half that of men of the same age, except possibly in the 85+ group where the rate rises sharply to the male level

Taking the average of both sexes combined over the age of 45 years (279 patients with Paget's disease among 9775 examined) the incidence of 3 5% is surprisingly near that of Collins for subjects over 40 years of age

It is of interest that in the larger series of 689 cases of Paget's disease only 3 sarcomas were encountered—one in a man of 78 with extensive Paget's disease in the pelvis and both femora who had developed an osteolytic lesion of his

TABLE III—PAGET'S DISEASE OF BONE (RATE PER 1000)

Age group	Men	Women	Average both sexes
35–44	4 0	2 7	3 4
45–54	3 6	4 8	4 0
55–64	29 0	13 5	22 4
65–74	73 9	36 2	56 5
75–84	70 2	28 6	51 3
85 –	85 7	114 3	90 6
Average	28 9	15 0	22 8

right femur, another in a man of 56 with an osteolytic lesion in the right ilium who had Paget's disease limited to the pelvis, and the third in a woman of 58 who had an osteochondro-sarcoma of the sacrum as well as Paget's disease of the pelvis.

Summary

A consecutive series of 689 patients with Paget's disease is reported. In part of the series it was possible to correlate the number of radiographic examinations which included the lumbar spine and pelvis with the number of cases of Paget's disease so encountered.

The incidence of Paget's disease in both sexes was nearly equal below the age of 54 years but thereafter the male rate rose rapidly to a high level in the period 65–74 when it was approximately double the female rate.

Above the age of 75 the male rate showed little alteration. In women the rate appeared to rise sharply to the male level over the age of 85.

Sarcoma was encountered only 3 times in the series.

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SEASONAL INCIDENCE OF MEGALOBLASTIC ANÆMIA OF PREGNANCY AND THE PUERPERIUM

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MEGALOBLASTIC anæmia of pregnancy in the tropics is generally considered to be due to nutritional deficiency; patients often respond to vitamin-B_{12} therapy, although folic acid and other deficiencies are often present as well. The rôle of dietary deficiency in the ætiology of megaloblastic anæmia of pregnancy in temperate climates is, however, by no means so certain. If dietary deficiency is a significant factor, more patients might be expected to develop the disorder during the winter and spring than during the summer and autumn (see below). The present study was made to find if any such seasonal variation existed.

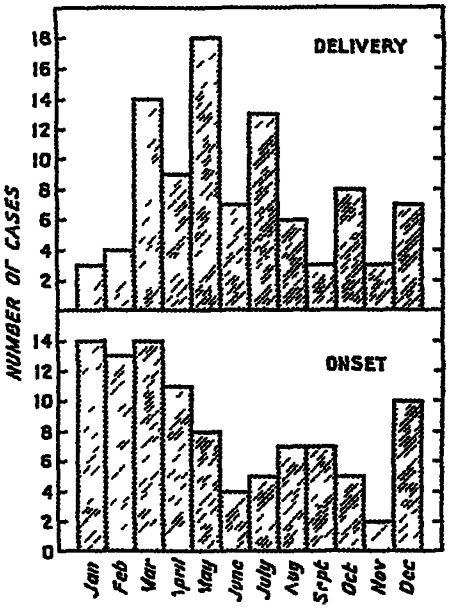
Methods

The hæmatological methods were essentially the same as those described by Thompson and Ungley (1951). In all the present cases megaloblastic erythropoiesis was found either by marrow biopsy, blood film, or buffy-coat smear (Goodall 1955). All the recent cases responded satisfactorily to folic acid; the treatments used in the earlier cases have previously been described (Thompson and Ungley 1951).

The date of delivery was always readily obtained. The date of onset of anæmia could not be determined with any accuracy in most of the patients; it could, however, usually be assessed to within about a month. Errors of a month, or even of two months, would not effect the main conclusions, for the onset of symptoms was always either about the time of delivery or, more commonly, about the 7th–8th month of pregnancy. Since full blood examinations have been made for some years on all patients attending the antenatal clinic in whom the Hb was less than 70%, the date of onset of anæmia could often be ascertained to within a month. Unfortunately, many patients were admitted late in pregnancy or in the puerperium, and the date of onset had to be assessed from the patient's symptoms and from data supplied by the family doctor. Soreness or ulceration of the tongue was a useful guide, especially when taken with the onset of symptoms such as general tiredness, loss of appetite, vomiting, pallor, and breathlessness.

Material

The case-records of 105 patients were available for this study: 36 from a general hospital, to which most of them were admitted in the puerperium, 55 from one maternity hospital, and 14 from another. In neither of the maternity hospitals was there any seasonal variation in the number of deliveries.



Monthly incidence of onset of megaloblastic anæmia and of parturition.

The 1st patient of the series was seen in 1933 and all available cases were included up to October, 1956. In recent years, since the clinical and hæmatological picture has become better recognised, most patients have been diagnosed during pregnancy, whereas most of the earlier cases were puerperal.

In 5 patients the dates of delivery are known, and these are included in parentheses in the accompanying table; it was, however, impossible to assess the date of onset of symptoms in these patients, and they have not been included in the main analysis or in the accompanying figure.

Results

The results are presented in the figure and the table, which show that there were significantly more deliveries in the six-month period from February to July inclusive than during the other half of the year. Since the onset of the disorder is commonly about two months before delivery, the table and the figure show a similar seasonal incidence but in an earlier six-month period. Thus the onset was in the period December–May in 70 patients and the period June–November in 30.

Discussion

The results are most readily explained by postulating that dietary deficiency during the winter months plays a significant part in the ætiology of megaloblastic anæmia of pregnancy. That such a factor is important in scurvy has been long recognised; indeed it was the possible analogy with scurvy that suggested the present study.

The richest animal source of folic acid is liver, the total folic acid content of 100 g. of beef liver being stated by

MONTHLY INCIDENCE OF ONSET OF MEGALOBLASTIC ANÆMIA AND OF PARTURITION

Month	Jan	Feb	Mar	Apr	May	June	July	Aug	Sept	Oct	Nov	Dec	Total
Delivered	3 (1)	4	14 (2)	12	18	7	13	6 (1)	4 (1)	8	4	7	100 (5)
Onset	14	13	14	11	8	4	5	7	7	5	2	10	100

[1] The figures in parentheses refer to 5 patients in whom the date of onset of anæmia could not be assessed.

the U S Human Nutrition and Home Economics Bureau (1951) to be nearly 300 µg

Fresh green vegetables are the most important vegetable source, the richest content being usually associated with the greenest leaves (Olson et al 1947)

Spinach, for instance, has a total folic acid content of 49–115 µg and a free folic acid content of 31–110 µg per 100 g when fresh

The total and free folic acid contents respectively of broccoli, brussels sprouts, and cauliflower are 33 9 and 8–14, 27 1 and 11 7, 29 1 and 8 5 µg per 100 g

Some beans—e g, dry Lima beans—contain 103 and 16 36 µg total and free folic acid respectively per 100 g Root vegetables are usually unimportant sources, and most fruit contains but little folic acid Some nuts and some breakfast cereals prepared from wheat—e g, wheat bran and shredded wheat—are quite good sources These values just cited are mainly derived from the U S Human Nutrition and Home Economics Bureau (1951)

The folic acid content of green vegetables and of meat (but to a much lesser extent that of liver) is mostly destroyed by cooking and canning (Cheldelin et al 1943, Hanning and Mitts 1949) Spinach is unusual in that it retains much of its folic-acid activity after canning, most vegetables retain their activity well on storage in refrigerators (Fager et al 1949) If liver is not frequently eaten, it is clear that much of the supply of folic acid must come from fresh green vegetables, which are unavailable in winter It may well be that in winter other dietary sources are inadequate to meet the increased needs for folic acid during pregnancy, and that deficiency results The vomiting, of which patients with megaloblastic anæmia of pregnancy so often complain, will decrease yet further the folic-acid intake

Day et al (1949) reported that, in megaloblastic anæmia of pregnancy, the urinary excretion of hormones was abnormal That these patients might produce an abnormal steroid which antagonises folic acid was suggested by Thompson and Ungley (1951) and Girdwood (1953, 1954) It is my impression that hæmatopoietic responses are poorer during pregnancy than in the puerperium, if this is confirmed it might support the hormonal idea, but it is difficult to explain on such a hypothesis the cases seen several months after delivery The hormonal theory could also explain the high incidence of twin pregnancies in the series There were ten sets of twins in the 100 cases, the expected incidence being about 1 in 80 births Increased demands for folic acid would also be expected, however, in twin pregnancy Again, a seasonal variation would hardly be expected if this hormonal antagonist theory were true No evidence has been produced to suggest that malabsorption plays a part in the ætiology of the deficiency (Badenoch et al 1955 Girdwood 1956)

The reason why patients with the disorder in temperate climates develop a predominantly, if not exclusively, folic acid deficiency is explained by Vinke and Van der Sar (1956), who point out that healthy people have a store of vitamin B_{12} which can supply their requirements for many months and sometimes for years The store of folic acid on the other hand, can supply the needs of the body for only about a month In a previously well-nourished person with increased demands for both substances and with a poor dietary intake folic acid deficiency becomes manifest much earlier than does a deficiency of vitamin B_{12} In a previously malnourished person with a low store of vitamin B_{12}, however, the deficiency is likely to be of both vitamin B_{12} and folic acid, this would obtain in patients developing megaloblastic anæmia in the tropics

The evidence presented here does not warrant the assumption that all cases of megaloblastic anæmia of pregnancy are due to dietary deficiency but it suggests that dietary deficiency is at least an important contributory cause It is interesting that the disorder disappeared from the wards of a maternity hospital in Montreal when an antepartum daily supplement of 4 5 µg of vitamin B_{12} and 3 0 mg of folic acid was given (Lowenstein et al 1955)

Summary

A study of 100 cases of megaloblastic anæmia of pregnancy has shown an increased incidence of the disorder during the winter and spring months This suggests that dietary deficiency is at least a contributory cause of the disorder

My thanks are due especially to Dr C C Ungley for allowing access to his case notes and to Prof H Harvey Evers, Mr W Hunter, Mr Linton Snaith, and Mr Frank Stabler for allowing me to study patients admitted under their care

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STAPHYLOCOCCUS AUREUS IN THE FÆCES OF HOSPITAL PATIENTS

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Patients with *Staphylococcus aureus* in their stools may be a source of ward cross infection (Brodie, Kerr, and Sommerville 1956) We describe here an investigation made to determine the frequency of fæcal carriers at St Bartholomew's Hospital, and we draw attention to a method of diagnosing acute staphylococcal enterocolitis

Methods

Nasal swabs and stools were obtained from patients in a medical and surgical unit (each having male and female wards) as soon as possible after admission and afterwards weekly when possible The nasal specimens were cultured on blood agar and incubated at 37°C overnight, the stool specimens were cultured on nutrient agar containing 7% sodium chloride and incubated at 37°C for forty eight hours Representative colonies resembling *Staph aureus* were tested for coagulase production, and single colonies of all coagulase positive strains were typed by the phage method The number of colonies of *Staph aureus* on the positive plates ranged between 1 and 40

Results

Of 196 patients, 194 had nasal swabs examined within three days of admission and 76 of these (39%) yielded *Staph aureus*, 142 had stools examined within seven days of admission with 32 (23%) positive

153 patients had more than one nasal swab tested 30% yielded *Staph aureus* on each occasion, 41% were

negative each time, and 29% had at least one specimen positive and one negative For the 112 patients with two or more stool specimens tested, the corresponding figures were 11%, 60%, and 29% respectively

Stool carriers had staphylococci in their noses significantly more often than non-carriers (see table) 79% of 62 patients with at least one stool positive had a positive nasal swab, compared with 45% of 109 patients who never yielded staphylococci in their stools 21 patients yielded staphylococci from their stools on more than one occasion, 16 of these (76%) were also persistent nasal carriers

ISOLATION OF *Staph aureus* FROM NOSES AND STOOLS OF INPATIENTS

—	Noses		
	+	−	Total
Stools +	49	13	62
Stools −	49	60	109
Not tested	9	16	25
Total	107	89	196

+ at least one positive specimen −, no positive specimen

There was an indication that the frequency of stool carriage increased with the time the patient had been in hospital

From 35 patients, staphylococci from both nose and stool were typed by the phage method 22 yielded strains of the same phage type in nose and stool on at least one occasion A further 5 had untypable strains in both sites 7 had two different staphylococci in the nose, and 1 had three Of 16 patients with strains of phage group I in the nose, 7 yielded the same type from the stools, with group II the corresponding figures were 6 and 4, and with group III 13 and 9

No relation was detected between nose or stool carriage and antibiotic treatment, nor were there detectable differences between men and women or between surgical and medical patients

Discussion

Our results confirm the findings of Brodie et al (1956) on the frequency of *Staph aureus* in the stools As with nasal carriage so with fæcal carriage some people seem to carry persistently, some intermittently, and some rarely in the fæces

Apart from the potential reservoir for ward infection, which is difficult to assess because so many of the stool carriers are also nasal carriers, this finding is important in relation to the diagnosis of staphylococcal enterocolitis Whether the patient's own staphylococci can cause this disease or whether the disease always results from cross-infection with another strain is not known, but in either case the fact that staphylococci are not uncommonly present in the stools of healthy people means that, by itself, a stool culture may be misleading in the diagnosis of enterocolitis—besides taking too long to be useful in the more acute cases We have seen about 30 patients thought to have staphylococcal enterocolitis, 1 died three days after an operation for partial gastrectomy, and the others survived with treatment or had relatively mild infections The initial laboratory diagnosis was made on the presence of clumps of Gram positive cocci in stained films of the stools, an appearance seen only once in a large number of stools from patients without staphylococcal enterocolitis More experience is needed to judge the full reliability of this examination, but for the present it seems to us that this simple and rapid test ought to be done as a routine for patients with diarrhœa after treatment with broad spectrum antibiotics

Our thanks are due to Mr M P Curwen, M.A, for help in analysing the figures, to the nursing staff of the medical and surgical professorial units for their help in collecting the specimens, and to Dr M P Jevons and Miss Joan Rippon, PH D, for the phage typing of the staphylococci

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AN IMPROVED METHOD FOR EXTRACTING OXYTOCIC AND ANTIDIURETIC HORMONES FROM BLOOD

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In a previous paper (Bisset, Lee, and Bromwich 1956) a method was described for extracting the hormones of the neurohypophysis from human blood When pituitary (posterior lobe) extract (P P L E) was added to blood and extracted, approximately one third was recovered A considerable part of the activity was lost in evaporating the extracts to dryness at 40°C Subsequent work has shown that this loss can be avoided by concentrating in a vacuum desiccator It has been found also that if the blood samples are centrifuged immediately after the addition of acid alcohol, and not left to stand for three or four hours, as originally described by Melville (1937), at least three quarters of the activity can be recovered in the supernatant

The method of extraction has now been improved by the inclusion of these two modifications P P L E, vasopressin, and oxytocin have been added to blood and extracted in order to estimate the recovery of activity obtainable with the new method

Methods

Collection of Blood Samples—Blood was obtained from the median cubital veins of human subjects, from the carotid arteries of rats under ether or ethanol anæsthesia, and from the femoral artery of a dog under pentobarbitone sodium

For the collection of human blood a *siliconed* glass syringe (Bisset and Lee 1956) was used, containing a trace of heparin solution (25,000 u per ml), and for blood from the rat or dog, a *nylon* syringe containing 50 u heparin in 1 0 ml of 0 9% saline

To 5 0 ml samples of blood was added either P P L E (' Pituitrin ') 100 mu, oxytocin (' Pitocin ') 100 mu, or vasopressin (' Pitressin ') 10 mu (preparations of Parke, Davis & Co)

Preparation of Extracts—The following is a description of the modified method which was used to prepare the extracts

(1) The blood was added to 9 vols of 80% (*v/v*) ethanol in a 'Polythene' beaker, and normal sulphuric acid added until the mixture was blue to Congo red

(2) The mixture was shaken vigorously and centrifuged at once

(3) The supernatant from (2) was concentrated by distillation in vacuo at a temperature not exceeding 50°C, until reduced to a volume of 10 ml or less The residue was centrifuged

(4) The supernatant from (3) was placed overnight in a vacuum desiccator containing enough phosphorous pentoxide to ensure concentration to about 2–3 ml Evaporation to dryness under these conditions is permissible

(5) The residue from (4) was taken up in distilled water and the solution dialysed in a ' Cellophane ' membrane (' Nojax '

RECOVERY OF ACTIVITY OF PITUITARY HORMONES ADDED TO BLOOD

Experiment no	Source of blood	Percentage recovery of activity	
		Oxytocic	Antidiuretic
1	Rat	73	83
2	,,	82	90
3	,,	58	60
4	,,	103	88
5	,,	50	54
6	Human	64	58
7	,,	60	47
8	,,	115	87
9	,,	86	52
10	,,	83	
11	,,	75	
12	,,	68	
13	,,		60
14	Dog	79	
Mean percentage recovery		77	68

casings 8/32) against running tap-water for forty five minutes The final extract was not neutralised until needed for assay

Assay of Extracts —Methods of assay were as previously described (Bisset et al 1956)

Results

The table shows the percentage recovery of activity of pituitary (posterior lobe) hormones added to blood In experiments 1–9, P P L E was added, in experiments 10, 11, 12, and 14, oxytocin, and in experiment 13, vasopressin The mean recoveries of oxytocic and antidiuretic activity from rat blood (experiments 1–5) were 73% and 75% respectively The corresponding figures for human blood (experiments 6–13) were 79% and 60% The recovery of oxytocic activity from dog blood was 79% The mean recovery of oxytocic activity for the whole series of experiments was 77% (S E ±5 01) and of antidiuretic activity, 68% (S E ±5 38) There is no significant difference between these means ($P > 0\ 1$) Under the conditions in which the experiments were carried out endogenous oxytocic and antidiuretic activity was negligible

In every experiment oxytocic activity was abolished by treatment of the extracts with 0 01 M sodium thioglycollate (van Dyke et al 1942) It was not thought necessary to apply this test routinely to antidiuretic activity, for assay by intravenous injection in the rat is almost specific for antidiuretic hormone (A D H)

Discussion

The introduction of two modifications in a method for extracting oxytocin and antidiuretic hormone from blood has resulted in an increase in recovery from about one-third to more than two thirds Experiment has shown that there is an initial loss of at least 10% of the activity during centrifugation of a blood sample, for only 90% of the total amount of fluid present in the sample is recovered in the supernatant Therefore any further loss of activity during concentration and dialysis of the extract does not exceed a mean of 20% Immediate centrifugation of the blood samples considerably shortens the time required for the preparation of extracts The hormones are stable in the supernatant which may conveniently be left overnight in the refrigerator and concentrated on the following day

The fact that there is no significant difference between the mean recoveries of oxytocic and antidiuretic activity from blood suggests that no extraneous factors are introduced in the extracts which might influence the response of the test preparations to oxytocin and antidiuretic hormone This is important in relation to estimating the ratios of endogenous hormones in blood under various conditions

Summary

An improved method is described for extracting oxytocin and antidiuretic hormone from blood

In a series of experiments in which posterior pituitary lobe extract, oxytocin, or vasopressin was added to blood and extracted, the mean recoveries of oxytocic and antidiuretic activity were 77% (S E ±5 01) and 68% (S E ± 5 38) respectively, compared with recoveries of about a third in the original method

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Medical Societies

ROYAL SOCIETY OF MEDICINE

Metals in Bone Surgery

A MEETING of the section of orthopædics on May 7, with the president, Mr STANLEY EVANS, in the chair, discussed the use of metals in bone surgery

Mr G K McKEE (Norwich) said that the history of the use of metals in bone surgery was not a happy one The use of unsuitable metals had marred the work of Lane and Lambotte, but interest had been revived by Smith Petersen's use of a stainless steel trifin nail in fractures of the neck of the femur

Two problems faced the orthopædic surgeon today —to prevent corrosion phenomena in his appliances and to determine indications for the use of different appliances These problems were closely related because the indications for the use of metal would increase as corrosion rate decreased when more suitable metals or metallic alloys were found

Tests were carried out to compare the relative rates of electrochemical attack on two different types of stainless steel and on the non-ferrous alloy 'Vitallium' If two different metals were in contact and were immersed in an electrolyte such as the body-fluids, one metal would become electrically positive to the other Cl ions in the electrolyte would migrate to the negative metal or anode and give rise to chemical attack Some metals, such as those under consideration, tended to form oxide films which had a high resistance to penetration by ions It had been established that the presence of molybdenum in an alloy was an aid to the establishment of a barrier film of oxide

If two identical metals were used to form the cell then no electrical potential difference was created between them, no current flowed, and there was no attack In practice it was virtually impossible to produce metal components of identical material Plates and screws, for example, would be produced from different metal stocks, and although of the same nominal composition there would inevitably be some slight differences Surface working during machining operations would itself create some degree of electrical potential It was this creation of a passive oxide film on the anodic metal that must therefore be the main barrier against corrosion

The recommendation was, therefore, that if stainless steel was used for internal fixation it should contain $2^{1}/_{2}$–$3^{1}/_{2}$% molybdenum The non ferrous chromium cobalt molybdenum alloys (vitallium or 'Vinertia') were quite free from corrosion Plates and screws made of the same stainless steel would corrode but less rapidly if they contained $2^{1}/_{2}$–$3^{1}/_{2}$% molybdenum The screw was anodic and therefore suffered greater attack than the plate Vitallium screws used with a stainless steel plate were not attacked, the plate, however, being anodic, did show some effects of corrosion

The most resistant type of stainless steel, known as F M B, appeared in practice to be quite satisfactory where the fixation was only temporary as in fractures and arthrodesis operations Where a permanent functioning insert was required, however, then the apparatus must be made up of a non-ferrous chromium cobalt-molybdenum alloy

Mr McKee described the development of an artificial hip joint The earlier model (1951) was in stainless steel It was satisfactory for several years but later failed because the steel corroded and the plate broke some 3½ years later Since then the apparatus had been redesigned for manufacture in an inert alloy, and it now appeared to be very satisfactory since no corrosion had occurred It was a complete replacement ball-and-socket joint for the hip, and was particularly indicated for hip-joint surgery when the acetabulum was grossly eroded It had, therefore, been used largely when failed acrylic prostheses had given rise to changes in the acetabulum

Mr John Charnley (Manchester) thought that electrolytic phenomena in metal appliances were of considerable importance only with long-term inserts Over short periods mechanical stress was a commoner cause of loosening Stress was a cause of corrosion too, because under its influence even high-quality steels suffered a deformation of their investing film of oxide The molecules of the film were wrenched apart and ionic penetration became possible

In the response of bone to metals, three situations deserved consideration when the inserted metal was not transmitting any stress, when it was transmitting stresses and was moving slightly, and when the metal transmitted stress without moving An example of the first case was the plate across a fracture which had united Such devices did not loosen on the contrary, they might be very difficult to extract because new bone gripped the holding screws very tightly And this was true of highly polished stainless steel screws as well as of matt vitallium ones An insert which was moving slightly under stress always became gradually looser Such a change was to be seen in a Steinmann pin pulling on a fractured femur. This loosening seemed to predispose to infection, as Hey Groves observed when he tried to fix experimental fractures with short plates which permitted a little movement in place of long ones When stress was transmitted to bone by a metal insert which was not moving, it did not excavate the bone about it Cortical bone was very resistant even to immense strains if they were of constant direction, as for instance when a compression clamp was applied across a joint undergoing arthrodesis, the device did not become loose Bone responded primarily to the application of stress by osteogenesis over a long period, continuous pressure induced remodelling, which was a balanced process of osteoclasis and osteogenesis

Mr J H Hicks (Birmingham) suggested that in the past inflammatory processes caused by corrosion of metal had not been adequately distinguished from those due to infection The changes induced by corrosion closely resembled those of bacterial infection and the granulation tissue at the site of an unsuitable insert often looked typical of infection, but the lesions proved to be sterile The common cause of such reaction was the use of corrodible steels some stainless steels provoked reactions sometimes even without contact with a dissimilar metal The use of these steels might give rise to unfortunate sequelæ which could not be prevented by any "no touch" technique, however rigid Once it was realised, however, that bone in the presence of metal inserts had no peculiar susceptibility to infection, it was logical to extend the benefits of internal fixation to compound fractures And it had in fact been found at the Birmingham Accident Hospital that extensive use of metal devices in securing open fractures had not been followed by an increase in the incidence of infections With the disappearance of the hazards of bad metal, the pre eminent problem was now that of skin necrosis and sloughing

Discussing some engineering problems in the design of metal inserts, Mr J M Zarek, PH D (King's College, London), pointed out that the resistance of metal to corrosion was influenced by the way in which it was polished The extent to which different screws changed could be related to the shape of their threads Areas where stress concentrations were high corroded early, particularly when screws and plates were not perfectly co apted to each other

Mr Norman Capener (Exeter) spoke of the desirability of standardising as soon as possible at least one acceptable combination of plate, hole, and screw

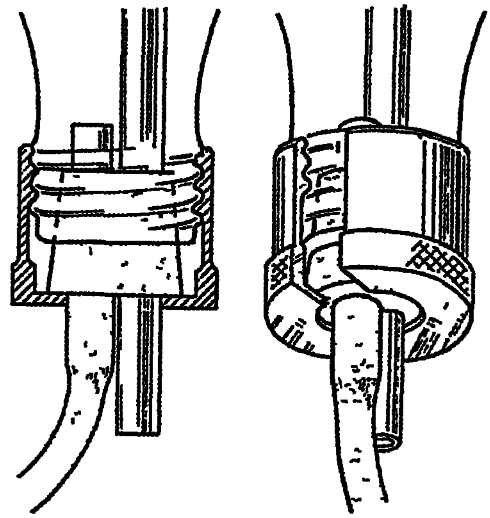
Dr J T Scales (Stanmore) described an investigation into the extent of corrosion in a large number of metal appliances Corrosion was commonly worst at the screw-countersink interface, and was conspicuously absent in chromium-cobalt molybdenum alloys

New Inventions

A SIMPLE METAL RETAINING CAP FOR THE STANDARD NATIONAL BLOOD TRANSFUSION SERVICE GIVING SET

The mantle of the standard blood-transfusion giving set is normally held in position by a rubber stopper inserted firmly in the neck of the glass bottle There is always a danger of the stopper slipping out, particularly in the operating-theatre if positive air-pressure has to be applied to the infusion to increase the rate of delivery

The usual method of preventing this is to tape the rubber stopper in position with adhesive strapping This is cumbersome, whereas the device described here is simple A small metal cap fits over the rubber stopper and screws on to the neck of the bottle The cap has a small round hole in its top through which pass the outlet and inlet tubes The hole is slightly smaller than the diameter of the rubber stopper, which is thus supported round its perimeter A small slit in the side of the cap allows it to be easily slipped over the rubber tubing Once the mantle of the giving set is firmly inserted into the bottle, the cap is readily screwed into position, preventing the rubber stopper from being dislodged



I am indebted to Mr E G Smith and Mr A T Smith, of the Guy s Hospital Medical School workshop, for making the cap, and to Miss M J Waldron, of the department of medical illustration of Guy s Hospital, for the diagrams The cap may be obtained from A Charles King Ltd , 27, Devonshire Street, London, W 1

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Reviews of Books

Movement of the Heart and Blood in Animals

An Anatomical Essay by William Harvey Translated by KENNETH J FRANKLIN, D M, F R C P F R S, professor of physiology, University of London Oxford Blackwell Scientific Publications 1957 Pp 209 17*s* 6*d*

THIS new translation from the Latin text of *De Motu Cordis* was first suggested by Prof John F Fulton as an appropriate contribution to the tercentenary of Harvey's death The idea commended itself to the president of the Royal College of Physicians and at his invitation Professor Franklin undertook the task Earlier versions were not sufficiently accurate for those doing either historical or experimental research upon the circulation The new translation and the Latin text are each preceded by a title page suggesting that they represent the text of the Frankfurt edition of 1628, whereas it is stated in the preface that the text used is the 1766 edition, presumably the *Opera Omnia*, published in London This edition was very carefully prepared, and at the end of the section containing the writings on the heart there is a list of 246 corrections made to the original edition [1] There are therefore differences between the Latin texts of 1628 and 1766

The translator and his sponsors at the Royal College are to be congratulated on a first-class book that will appeal to a new generation of readers Let them read for themselves Harvey's indignation at the old theories ("Good God! How do the mitral valves hinder the return of air and not of blood?") and the way in which he reaches his final statement

> "I am obliged to conclude that in animals the blood is driven round a circuit with an unceasing, circular sort of movement, that this is an activity or function of the heart which it carries out by virtue of its pulsation, and that in sum it constitutes the sole reason for that heart's pulsatile movement"

Surgery of the Anus, Anal Canal and Rectum

E S R HUGHES, M D, M S, F R C S, F R A C S, surgeon to outpatients, Royal Melbourne Hospital, Melbourne Edinburgh E & S Livingstone 1957 Pp 304 50*s*

A MEASURE of the esteem in which St Mark's Hospital is held is the speed with which its doctrines—anatomical, pathological, or clinical—become part of orthodox surgical practice Mr Hughes's book bears the stamp of St Mark's and cannot, therefore, be provocative or even novel, but it embodies much valuable research done by the author himself

With Goligher, he demonstrated the importance of the rectal mucosa in the initiation of bowel sensation—an important argument in the current controversy over restorative resection for high rectal cancer (Of the controversy itself the book contains a balanced and critical account and the description of the operations is admirable) Immediate skin-grafting after excision of anal fissures and fistulæ is another attractive proposition that Mr Hughes put forward some years ago Although the procedure may seem to transgress surgical principles, scepticism will be disarmed by the detailed and convincing way in which it is presented

Some readers will be disappointed when Mr Hughes disclaims sufficient experience to dogmatise on one or two difficult therapeutic problems (such as the management of high rectal fistulæ), but this attitude is the correct one and strengthens confidence in what Mr Hughes says elsewhere in the book Throughout his aim has been to guide rather than to pontificate and he dwells on the difficulties which the average surgeon may meet rather than on his own mastery

The most important criticism applies to most monographs whose subject is anatomically rather than functionally circumscribed—namely, the book cannot adequately deal with conditions which affect the region but show no respect for its boundaries Thus proctitis cannot be properly discussed without more fully considering ulcerative colitis and even familial polyposis of the colon and rectum may only be part of a more widespread disease

The historical illustrations with which the text is embellished are pleasing, but the biographical notes are rather less successful, and a critical survey of the growth of proctology might have been more illuminating Perhaps such a chapter may be added to future editions—for which there should be a steady demand

The Doctor as a Witness

JOHN EVARTS TRACY, professor of law (emeritus), University of Michigan Philadelphia and London W B Saunders 1957 Pp 221 30*s*

Professor Tracy is a senior member of the American legal profession and necessarily writes with a background of United States law His book shows clearly how the qualities required of an expert witness, and especially of the doctor, are the same under any legal system The types of legal proceedings in which the doctor may be involved are described, and the question of opinion evidence and the expert witness is examined in detail It is evident that in the United States preparation of a case is expected to be more thorough than is customary in Britain This work makes fascinating reading and can be recommended to any graduate in medicine or law

Simulium and Onchocerciasis in the Northern Territories of the Gold Coast

G CRISP, B SC, PH D, director, entomological unit, British Empire Society for the Blind London H K Lewis, for the British Empire Society for the Blind 1956 Pp 171 57*s* 6*d*

IN 1952 two teams of experts, one entomological and one ophthalmological, were sent to the Gold Coast by the British Empire Society for the Blind to work on the problem of onchocerciasis, then only recently recognised as one of the worst of the many community scourges of the hinterland Dr Crisp's entomological report is the first of the two to be published He gives a clear description of hard methodical work on all aspects of simulium ecology in the area He is almost overcautious in making deductions from the great amount of data he has assembled, for example, it was not *proved* that the fly's survival of the dry season takes place in adult form, but his experiments make it very likely The scientific honesty of Dr Crisp's writing is notable

To anyone working on simulium or onchocerciasis in West Africa the monograph is an essential guide Laymen interested in the subject or the country will find it understandable and easy to read Dr Crisp and the society are to be congratulated

An Atlas of the Commoner Skin Diseases (5th ed Bristol John Wright & Sons 1957 Pp 384 105*s*)—A new edition of Dr Henry Semon's book will be welcomed by those who often feel the need for a good atlas of common skin diseases It has been prepared in collaboration with Dr Harold Wilson 16 excellent new plates have been added to an already good set of illustrations Too much space has perhaps been given to the now comparatively uncommon disease, lupus vulgaris, including two plates illustrating the rarer form, lupus verrucosus The omission of molluscum sebaceum from the fourth edition has been remedied, but too little attention is given to squamous celled carcinoma, and the term 'epithelioma' is treated as synonymous with rodent ulcer Many new methods of treatment have been added but some of the outmoded ones are given more prominence than their successors

Recent Advances in Anæsthesia and Analgesia (8th ed London J & A Churchill 1957 Pp 295 40*s*)—Dr J Alfred Lee has joined Dr C Langton Hewer in producing the new edition The subject matter has been completely revised and, without doubt the book now represents the most up to date and useful work of reference to the latest developments in anæsthesia

Venoms (Washington, D C American Association for the Advancement of Science London agents Bailey Bros & Swinfen 1956 Pp 467 86*s*)—The papers given at the first international conference on this subject which was held in 1954 at the annual meeting of the American Association for the Advancement of Science have been published under the editorship of *Eleanor E Buckley* and *Nandor Porges*

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THE LANCET

LONDON SATURDAY, JUNE 8, 1957

Walls of Jericho

BEFORE mental illness we have been comparatively helpless, and the public attitude towards it has reflected the fear and suspicion which helplessness often breeds. The law, in an honest endeavour to protect both community and patient, has by its complexity and caution often increased public prejudice and unnecessarily restricted the liberty of the individual. But in the last decade or two, new methods of treating mental disorder have altered the picture. Our mental institutions are becoming, in fact as well as in name, hospitals instead of asylums, and with success in the treatment of acute illness fresh efforts are being made to restore health to patients who have been ill for a long time. Despite overcrowding, shortage of staff, and old-fashioned buildings and equipment, the emphasis is changing from custodial care to therapy; and more and more patients are enabled to return to their homes or to lead more normal lives in the hospital. These changes have had their effect on the public, which is beginning to accept mental illness as a disability comparable to physical illness. In this new climate of opinion it became apparent that the law relating to mental disorder must be reconsidered, and in 1954 a Royal Commission was appointed under the chairmanship of Lord PERCY OF NEWCASTLE. The commission's recommendations (summarised on p. 1187) are based on the principle that the mental patient should have access to the health and welfare services as freely and with as little formality as any other patient. Many of the so called safeguards of the present law not only are unnecessary but are a barrier between the patient and the help he can be given.

Today, of course, most patients are admitted to hospital with their own consent; yet every year some 20,000 are certified—often only because they are unable, because of their illness, to fill in the necessary form. The commission believe that, unless a patient refuses to go to hospital, we should assume that he agrees to treatment. The law should regard this as the usual procedure, and the use of compulsion, though sometimes necessary in the patient's interests, should be exceptional. Even for these cases, "certification" should be discontinued in favour of a medical recommendation authorising a hospital to accept the patient for treatment; and if the hospital finds itself unable to provide suitable treatment it should be allowed to refuse to accept the patient. The emphasis would thus be on the clinical needs of the patient and not on his segregation. The recommendation for his admission would ordinarily be signed by a psychiatrist and the family doctor. The present procedure of calling in a justice of the peace is not only ineffective as a safeguard but inappropriate; and such intervention by the law is one of the reasons why relatives find certification so distressing. This prejudice may be unreasoning and unreasonable, but it is deep seated; and the commission speak of the common belief that certification implies illness so grave that a patient is "really mental" and will never completely recover. From the hospital's standpoint, too, admissions are needlessly complicated by protocol. Thus a "designated" hospital cannot accept a patient unless the legal niceties are observed; and as an escape from the complexity of the system, some hospitals have had to create (with good intent if barbarous language) "dedesignated" villas and beds. For the past few years hospitals for mental defectives have been encouraged to accept some children without certification, and the commission would like to see this practice extended, without waiting for further legislation. Many parents are understandably reluctant to part with their child if they feel that they are formally resigning their rights over it.

The commission have recognised how untrue it is to say that "names will never hurt you." To patients and relatives much of the blunt terminology of the Mental Health Acts is unnecessarily wounding. "Idiot" and "imbecile" are offensive to many; "moral defective" is often misunderstood. A new name is often said to attract the odium of the old; but at this time, when the public attitude to mental disease is changing, the commission feel that it would be worth introducing a fresh terminology that will not only be free of unhappy associations but also be readily understood. The three new groupings which they suggest for patients—mentally ill, psychopathic, and severely subnormal—are for broad administrative purposes and, they insist, not "labels for life." Their use of the word "psychopathic" for patients with a personality disorder is wider than is customary, and it is, as they admit, not altogether happy. To those familiar with popular "psychiatrese" it has criminal associations; for the less sophisticated it will be a difficult and unfamiliar word.

In Parliament, the courts, and the press attention has lately been drawn to patients who are said to have been improperly detained in hospital or under licence. The commission, not unexpectedly, had some evidence of this kind submitted to them, which they found useful as an indication of public fears, against which the present Acts, for all their complexity and however justly administered, do not offer sufficient safeguards. To allay public doubt on this score they propose that regional mental-health review tribunals should be set up to which patients and their relatives should have ready access. This shift of control from the centre to the periphery should also, the commission suggest, apply to the scrutiny of documents. These changes, and the sharp reduction in the use of powers of compulsion, would end the work of the Board of Control, already greatly reduced since 1948 when the Ministry of Health took over the general supervision of mental-health services. The board in its evidence to the commission committed administrative hara-kiri, for it supported the very changes which, when they become law, will end its own life.

The findings of the commission recognise another shift of emphasis, this time from the hospital to the community.[1] They suggest that the local health authorities should assume full responsibility for the preventive and aftercare work of the mental-health service The commission look forward to a time when the hospitals will look after only those patients who need specialist treatment or training or continuous nursing The local authorities will then provide not only social services, to help and support patients who return to their families, but also residential homes and hostels for young subnormal and psychopathic patients and for the elderly who are mentally infirm This change would succeed only by joint endeavour by the hospital and the local authority Nottingham has already shown that this can be achieved even within the present more rigid administrative framework [2]

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[1] See *Lancet*, 1956, ii, 1087.

The return of the patient to the community, either to his home or to some small hostel, will depend not only on administration It will depend also on his acceptance by the community and on their willingness to welcome him with as much sympathy as they do the physically handicapped The recommendations of the commission, when given their legislative due, will speed the day when this change in public attitude will allow the mental-health service to fall into its proper place in the pattern of the health services of the country At present the law, like the over-heavy fortifications of an enclosed city, cuts it off from the outside world After a careful survey of the obsolete ramparts the commission have called for their demolition They have sounded their trumpet loudly, and it is up to doctors, patients, and public to join in the fanfare that will make these walls at last come tumbling down

Medical Education the New Freedom

THE profession in this country is sometimes charged with producing wise words and reports on medical education, while stopping short of actual reform, so it is perhaps worth stating that our medical schools have made substantial progress in the past decade Following the direction given by the Goodenough report in 1944, the smaller schools have been enlarged, full-time university units in clinical subjects have grown and multiplied, and introductory courses of various patterns have been devised to link preclinical with clinical teaching Responsibility for vocational training has been partly transferred from the undergraduate course to the preregistration year The standard of clinical care displayed before the students has risen immeasurably through the growth of medical teams, in which the oracular pronouncements of the consultant to his houseman are largely replaced by informal discussion in a group—a group in which the awesome gap between senior physician and new boy is filled by lecturers and registrars, not all of whom are the "angry young men" of popular report The vital contributions of the laboratory technician, the radiographer, the pharmacist, the social worker—all the members of the Greater Medical Profession—are now so much a part of medical care that the student need no longer be cajoled into noticing them And all these things have been done in medical schools built for fewer students, and in hospitals at least twenty years old

This evolution in medical education has been paid the compliment of criticism of many kinds, the expected balance between the cries of "Too fast" and "Too slow" is somewhat upset by dissonant voices claiming that we are moving in the wrong direction entirely Though Babel cannot be summarised, perhaps we can discern behind it all a conflict of principle between those who emphasise practical and vocational training, and those who favour a liberal scientific education When it comes to method, the trainers pin their faith largely to didactic instruction, including substantial lecture courses and a rigid examination system, while the educators are experimenting with discussion groups, seminars, modified tutorial arrangements, and interdepartmental classes But trainers and educators alike believe that the student should spend more time with patients, both in the wards and under conditions approaching those of general practice, and they also unite in deploring any further adventitious addition to the curriculum While the main hindrance to reform has no doubt been the conservatism of medical faculties and the jealous guarding of departmental prestige, the would-be reformers have also been hampered by the excessive precision of many of the *Recommendations* on the medical curriculum issued by the General Medical Council in 1947 They will be all the more disposed to welcome the new *Recommendations*, approved last week, which are shortly to be circulated to medical schools Both this document itself, and the introductory statement which accompanies it, are informed by a new spirit of freedom most grateful to those who, like ourselves, hold that a doctor must not be a certified technician but an educated man capable of assessing and applying new knowledge and of helping his patients by his personality as well as by his technical skills

Instead of taking its decennial opportunity to add to the tasks of student and teacher, the council has generously accepted the criticism that its 1947 *Recommendations* "were too detailed and precise, and left insufficient scope for the exercise of initiative and experiment on the part of Licensing Bodies and of Schools" (A good deal of the credit for making this widely felt criticism both manifest and powerful must go to the Royal College of Physicians of London, which has presented its views to the council [1] and has also helped to prepare for the future by convening the conference on medical education held last November) The welcome change in outlook is well seen in a paragraph which says that the new *Recommendations* "indicate the minimum length of the whole period of professional study, but refrain from specifying the period of time to be allotted to particular subjects and the sequence in which they should be taught Specialties and subdivisions of the principal subjects are no longer specified, and no attempt has been made to indicate precisely the scope of the instruction which should be given in particular branches" Though the council has examined carefully the possibility of reducing the length of the curriculum, it has (in our view correctly) decided against doing so at present On this its main argument is that the primary need is to reduce congestion —"to instruct less and to educate more"—and if the curriculum were simultaneously to be shortened "the principal object of the proposed reform would be thwarted"

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[2] Macmillan, D *Ibid* p 1091

[1] *Lancet* 1955 ii 132 *Ibid*, 1956 i, 437

Under Sir **David Campbell**'s leadership, the council has thus taken a notable step away from restrictive practices But, having obeyed the classical injunction *Primum non nocere*, it must now look to the individual medical schools for the fruition of the new opportunities A statutory nation-wide council can create the conditions for reform, but cannot itself take positive and specific action towards it The council is making its experience available to medical schools in the form of "notes ' added to the different *Recommendations*, and it hints that medical schools may in future be "visited ' more frequently and less formally, by small groups—a practice which, though it originates in the need to safeguard the public, could develop into something also very useful to the schools themselves Responsibility for improvement has now been definitely thrown back, however, to the universities, which are encouraged to consider as soon as possible what use they can make of it To expect that all will want to experiment would be unreasonable, and the merit of the new arrangements is that they allow different ways of teaching to be used simultaneously in different schools But we shall be much surprised and disappointed if three, four, or half a dozen do not rise to the new challenge to show that they can do better, or at least have the spirit to try We trust that the individual schools in London will not be denied this chance

Macewen's Eternal Triangle

Nowhere is the influence of antibiotics on surgical techniques better seen than in the treatment of cerebral abscess Until the advent of efficient antiseptics compatible with living tissues, methods of dealing with intracranial infection were designed to prevent a fatal spreading meningitis[1] The methods were extremely varied, and their relative merits were hotly contested Simple aspiration followed later by excision vied with tube drainage and even with marsupialisation Reports published within the past ten years show, by contrast, a remarkable unanimity of approach The aim is to aspirate the abscess at the earliest possible moment through a clean field and to insert a wide-range antibiotic or a combination such as penicillin and streptomycin, together with about 1 ml of 'Thorotrast' This completes the first operation As soon as an organism has been grown and its sensitivity has been established—which takes about forty-eight hours—the specific antibiotic cover is introduced The abscess is aspirated every two days or at longer intervals, according to progress, until the pus is sterile and the thorotrast shadow no longer enlarges again after aspiration As it is observed over the subsequent weeks it should shrink progressively until it represents only a small crenated scar If the contents do not become sterile or if the abscess does not collapse excision is undertaken[2]

This regime is also applied with modifications in subdural and epidural collections of pus Provided the correct antibiotic is found in time and administered in adequate dosage, the results are excellent—though a subdural collection alongside the falx may cause diagnostic difficulties, best resolved perhaps by the maxim Pus somewhere, pus nowhere, pus alongside the falx (It is of help to remember that subdural pus tends to spread under the influence of gravity) The therapeutic miracle of yesterday has today become the commonplace, and even intraventricular rupture of an abscess is no longer invariably fatal, if specific therapy is instituted immediately at first by intraventricular instillation But deaths still occur from these disasters, from spreading encephalitis (usually due to pneumococcus or streptococcus), and from multiple abscesses It should be remembered that hæmatogenous abscesses are not necessarily multiple, but that a high proportion of them, associated with a cardiac abnormality, are ' paradoxical '[3]

The signs of intracranial lesion together with those of an infective illness suggest the diagnosis, which may be confirmed by finding an increased number of cells or increased protein in the cerebrospinal fluid or a raised erythrocyte-sedimentation rate Electroencephalography is of help in differentiating an intracranial abscess from a more widespread lesion, and ventriculography or angiography may be necessary Management of the very acute stage of encephalitis remains debatable Sucking out the infected area[4] has not been regarded with sustained enthusiasm, and the stoutest friend of the surgeon here is undoubtedly the correct antibiotic In some centres the abscess is later excised routinely, unless it lies in an unsuitable site—for instance, near a speech area It is still doubtful whether excision of a completely sterilised abscess scar reduces the likelihood of subsequent epilepsy

Gurdjian and **Webster**[5] conclude from their series that the incidence of cases due to ear infection is decreasing in the U S A and from this series it might be inferred that the intracranial sepsis secondary to ear infection is largely preventable In this country, on the other hand, **Pennybacker**[6] did not find that otogenic cases were diminishing, they represented in his series over 40% of all brain abscesses **Pennybacker** plead strongly for an investigatory approach to intracranial sepsis through a clean field Anyone with any experience of this problem admits that the intracranial abscess is occasionally unpredictable A negative exploration " of a septic cavity in which the flora is unknown frequently leads to spreading infection, which is all the more tragic because it is due to the treatment rather than the disease **Crabtree**[7] says In earlier days brain abscesses were explored through the infected mastoid wound We never dream of doing this now, any intracranial exploration being through an independent clean field It would be another step forward if we could limit ourselves in the treatment of lateral sinus thrombosis to a meticulous clearance of extradural disease, except perhaps for excision of a rare intra-sinus abscess " To the mastoidectomist the dura represents a Halt sign which he crosses at his patient's peril On the other hand, an otogenic abscess should be treated by an adequate mastoidectomy as soon as the patient's condition permits—usually within four or five days Only by intelligent cooperation between the neurosurgeon and the otologist can the best results be obtained in the treatment of cerebral sepsis

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[1] Webster J E Gurdjian E S *Surg Gynec Obstet int Abstr Surg* 1950 90 209
[2] Ballantine H T jun White J C *New Engl J Med* 1953 248 14
[3] Newton E J *Quart J Med* 1956 25 201
[4] Le Beau J *J Neurosurg* 1946, 3 359
[5] Gurdjian E S Webster, J E *Surg Gynec Obstet* 1957 104 205
[6] Pennybacker J *Ann R Coll Surg Engl* 1950 7 105
[7] Crabtree N *Proc R Soc Med* 1955, 48 394

Annotations

THE HARVEY TERCENTENARY

Last Monday was the tercentenary of the death of William Harvey In London there was a commemoration service at St Paul's Cathedral arranged by the Royal College of Physicians, the congress organised by the Harveian Society of London opened at the Royal College of Surgeons, and throughout the week the occasion has been celebrated in various ways by a re examination of ideas old and new about the circulation

The congress has been discussing some of the latest physiological and clinical developments in the study and treatment of circulatory disease, and we hope to record some of the proceedings in our next issue At the week end the scene will change to Folkestone, where Harvey was born in 1578, and where the congress will hear accounts of Harvey's life and work in its different stages

The Royal College of Physicians has sponsored an excellent new translation by Prof K J Franklin, of *De Motu Cordis* (to which we refer on p 1176), and a new edition of the colour film about Harvey and the circulation has been on view at the college

In the film Sir Henry Dale explains that this is a remake of the earlier black and white silent film which he made in 1928 with the late Sir Thomas Lewis While Sir Henry is tracing the dates and events of Harvey's life, the camera occupies itself with old prints and drawings, many of which were on view at an exhibition in the college library During readings from *De Motu Cordis*, the film demonstrates, from animal experiments and clinical observations, the facts on which Harvey based his deduction His delightful descriptions are beautifully illustrated The colour photography is of the high quality customary from the Wellcome Film Unit, who produced the film [1]

Among the other activities of a busy week in London was an exhibition illustrating Harvey's life and ideas, which has opened at the Wellcome Historical Medical Museum, and on Thursday the British Cardiac Society held a special meeting at the Royal College of Surgeons

THE COST OF AMERICAN MEDICINE

The cost of medical care continues to exercise the minds of the American people, and the situation is discussed in an article in the *New York Times* [2]

Although some two thirds of the population of the United States have some form of medical insurance (often included as fringe benefits in a trade union contract) this does not by any means always pay the whole cost of a serious accident or illness Indeed, it meets only about 25% of the big bills, for comparatively few schemes afford full cover Some pay bills up to a certain sum, others bills beyond a certain sum, but in either case the patient pays the rest For mental disease and tuberculosis, which many policies exclude, free treatment is commonly provided by individual States, but other long term illnesses are sometimes not covered, and benefit often ceases at the age of 65 American opinion is divided on whether a comprehensive health system would cost more than what medicine is costing now—which is estimated at some 4–5% of the total national income Meanwhile hospital charges continue to rise, and the need is particularly felt for insurance that can be paid for during the healthy middle working years and that will provide for old age, as well as for the children of the insured

According to the *New York Times* writer, many physicians are wary of change and pessimistic about the future, and relations between physicians in various medical specialties, and between other workers in health fields, are more strained than they were "there appears to be less concern about putting up a solid front for the public and more real competition for patients and insurance fees" Many practising doctors hold that it is not their responsibility to plan health services, and they do not like to "get into politics", but "the prevailing widespread opinion is that physicians—and not many others in health fields—are lagging in planning the future of the health services system in the nation" It seems clear that in the near future public opinion is going to demand more readily available medical care

POLIOMYELITIS VACCINATION

Last year was a comparatively mild one for poliomyelitis and that is one of the reasons why it has been hard to assess as fully as was expected the degree of protection conferred by the British vaccine which was given to 210,000 children in May and June, 1956 Moreover, supplies of vaccine were not as ample as had been hoped for and there was little time—only six weeks—in which to give it before vaccination was stopped at the end of June Vaccination was restricted to children born in the years 1947–54 Nearly 400,000 injections were given and there was no evidence that they had been accompanied by any mishap The number who completed the course of two injections was 148,684 In this group the protection was of the apparent order of 80%—very similar to that observed in the 1954 trial in the United States Discussing the results at a meeting of the section of epidemiology and preventive medicine at the Royal Society of Medicine on May 31, Dr John Knowelden, secretary of the Medical Research Council's poliomyelitis vaccines committee gave these figures for all forms of *paralytic* disease, the onset of which fell between July 1, 1956, and Jan 31, 1957

	1947–50 births			*1951–54 births*		
	No of children	*No of cases*	*Attack rate per 100,000*	*No of children*	*No of cases*	*Attack rate per 100 000*
Vaccinated	74 660	1	1 3	74 024	3	4 1
Unvaccinated	1 116 159	91	8 2	446 857	90	20 1

The attack rate of those illnesses reported as non paralytic poliomyelitis did not seem to be affected by vaccination The findings are set out in detail in the report [1] of the poliomyelitis vaccines committee

In 1955 the M R C's committee on safety tests of poliomyelitis vaccine advised against the inclusion of the virulent type I Mahoney strain in the British vaccine, and the less virulent Brunenders strain was used as the type I representative in the vaccine prepared by Glaxo Laboratories Despite the small number of observations, it seems clear that the Brunenders strain is able to protect against the kind of type I infections that were prevalent in Britain last year, and that the vaccine also protects the younger children

That this and other vital information has been obtained so quickly, despite the enormous difficulties and the vast amount of work involved, is a striking achievement The vaccine protects the most important of the questions still unanswered is for how long it protects

PENICILLIN MODE OF ACTION AND CHEMICAL SYNTHESIS

Earlier indications that the mode of action of penicillin on gram positive organisms is specifically on the cell wall have been confirmed [2] Penicillin inhibited cells were found to accumulate uridine nucleotides in the cytoplasm,[3] and elucidation of the structure of these compounds has shown the principal one to be uridine 5' pyrophosphate linked through a hitherto unknown sugar (3 O carboxyethyl hexosamine) to a pentapeptide of D glutamic acid L lysine and DL alanine

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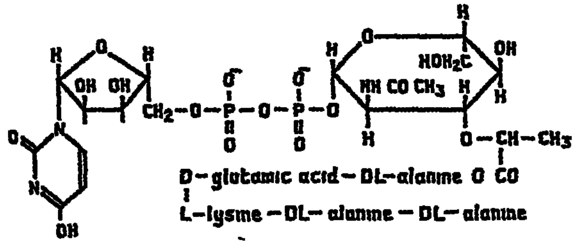
[1] Further information about the film (16 mm sound colour 25 min) may be obtained from the Royal College of Physicians Pall Mall East London S W 1

[2] Plumb P K New York Times Jan 7 1957

[1] Brit med J June 1 1957 p 1271

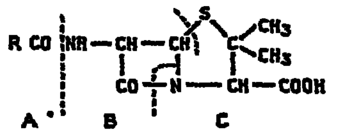
[2] Park J T Strominger J L Science 1957 125 99

[3] Park J T Johnson M J J biol Chem 1949 179, 585

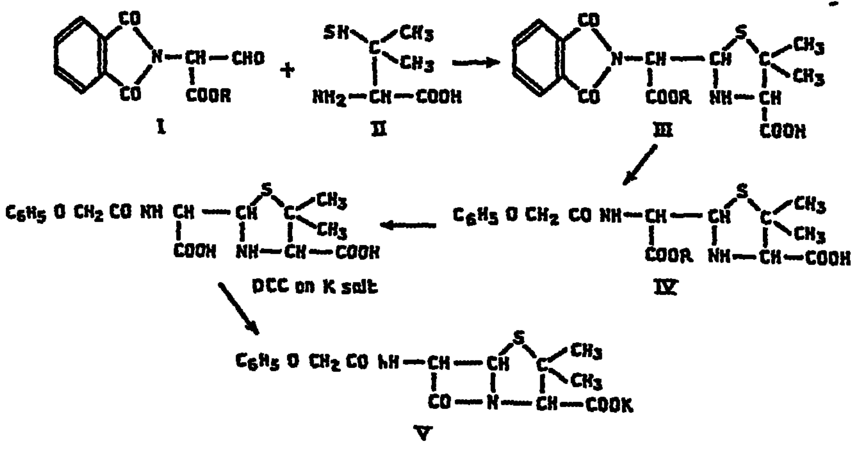

D-glutamic acid – DL-alanine O CO
L-lysine – DL-alanine – DL-alanine

As the peptide hexosamine fragment is almost certainly identical with an important part of the structure of the bacterial cell wall,[4] penicillin probably acts by interfering with the transfer of this fragment from the uridine pyrophosphate to the acceptor site on the cell wall The use of this uridine nucleotide in transferring units of monosaccharides in polysaccharide synthesis, and of units of glycerides for lecithin synthesis, has been well established

Reaction mixtures containing minute traces of penicillin activity were prepared in 1944, both in England and in the United States, and painstaking isolation procedures showed that the active moiety in such mixtures was indeed penicillin[5] But such a synthesis, interesting though it was, had no value in the production of new "unnatural" penicillins, nor for proof of structure of this sensitive molecule Professor Sheehan and his colleagues[6] at the Massachusetts Institute of Technology have just crowned ten years' work with an elegant synthesis of penicillin V This follows suggested biosynthetic pathways which envisaged the molecule as derived from an acid residue (A) linked through α-formylglycine (also known as amino-malonsemialdehyde) (B) to penicillamine (C)



The protected amino-malonic ester semi-aldehyde (I) condensed with D penicillamine (II) to give the thiazolidine (III) The amino group was uncovered and condensed with the appropriate acid residue to give (IV) The ester group was removed without further rupture of the molecule, and water was then eliminated by reaction with dicyclohexylcarbodiimide (DCC) to complete the 4 membered lactam ring in (V), which product was shown to be identical with natural penicillin V The reactions devised were all carried out at or below room-temperature to avoid breakdown of the unstable ring structure



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[4] For references to the original literature see Park and Strominger (ref 1)

[5] du Vigneaud V, Carpenter F H Holley R W, Livermore A H Rachele J R *Science* 1946 104 431

[6] Sheehan J C Henery-Logan, K R. *J Amer chem Soc* 1957 79 1262

TUBERCULIN TREATMENT IN PULMONARY TUBERCULOSIS

SINCE 1890, when Koch first suggested its use in therapy, tuberculin has been widely if inconsistently used in treating various forms of tuberculous disease Success has been claimed from time to time with lesions of the eye and skin, and tuberculin still enjoys a vogue on the Continent, particularly in France, but clinical impressions do not seem to be supported by controlled statistical studies In this country tuberculin has had its most striking success as an adjunct to chemotherapy in the treatment of tuberculous meningitis At Oxford, Smith and Vollum[1] administered the purified protein derivative (P.P.D.) intrathecally to three patients with tuberculous meningitis in whom the prognosis seemed hopeless, in all three an unprecedented improvement followed, and two recovered permanently and completely, the third patient died, but at necropsy it was found that the exudate surrounding the mid-brain had resolved These findings have been confirmed,[2] but P.P.D therapy is not held to be necessary or desirable in all cases of tuberculous meningitis, for when the disease is detected early patients make excellent recoveries with chemotherapy alone

In pulmonary tuberculosis there was no convincing evidence before the introduction of chemotherapy that tuberculin was effective, but in 1955 Madigan and Young commented favourably on its clinical effects, and Howells and Swithinbank[3] have described a pilot statistical trial done to determine whether tuberculin in association with streptomycin and *p* aminosalicylate (P.A.S.) had any therapeutic value The investigation, carried out in Bantu patients at Durban, suggested that those treated with chemotherapy plus tuberculin had a limited advantage over those treated by chemotherapy alone The advantage held only up to the 30th week of treatment and was most manifest in the worst cases, where it was statistically valid Howells and Swithinbank attribute the improvement to hyperæmic reactions (caused by the tuberculin) in the tuberculous lesions, allowing the antimicrobial drugs increased access After the 30th week these reactions, which were of course accompanied by symptoms and fever, tended to become fewer and less pronounced, and the fact that after this time no improvement in results, compared with the controls, was evident, suggests that the thesis is at least partly correct But improvement under tuberculin therapy has also been ascribed specifically to its desensitising property, and according to this view tuberculin negativity should be maintained indefinitely The Durban study does not seem to support this hypothesis

Tuberculin treatment is apparently free from serious danger, but it entails a certain amount of discomfort for the patient from the reactions it produces, and (especially if continued over years as outpatient therapy) it involves time off work for the patient and a considerable organisational effort by the chest clinic There seems to be no strong case for using tuberculin as a routine It may yet be shown to be useful where the lesions are recalcitrant to ordinary methods—for instance, those with organisms becoming resistant to chemotherapy But it has not yet been proved to give a satisfactory response in the chronic, fibro caseous type of lesion which commonly produces resistant organisms, and for the early acute lesion the administration of cortisone in association with chemotherapy seems preferable

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[1] Smith H V Vollum R L *Lancet* 1950 ii 275

[2] Smith H V Vollum, R L Taylor I M Taylor K B *Tubercle*, 1956 37 301

[3] Howells G H L Swithinbank J *Ibid* 1957 38 7

APARTHEID IN NURSING

THE Amending Bill[1] to the Nursing Act, which the South African government has introduced during its present parliamentary session, fits logically with the Bantu Education Act and the Separate University Bill into the pattern of apartheid There are to be separate registers for white, coloured, and native nurses, special examinations may be arranged for each group, and different uniforms may be worn There is no room for doubt in this case that the non-European nurses are to have an inferior status, for the Bill specifically lays down that the South African Nursing Council shall have white members only, and only white nurses may vote for the elected posts on the council Advisory boards are to be established for coloured and native nurses but with limited functions All nurses are bound by statute to join the South African Nursing Association, but under the Amending Bill meetings of white, coloured, and native members of the association will take place separately The Bill lays down that "a decision of the majority of the members of the Association present at any meeting held under this Act, by members who are white persons, shall constitute a decision of the Association," while decisions taken at meetings of non-white members are considered as recommendations only The controlling board of the association is to consist of white members only and the electorate for board members are all to be white Non whites may elect advisory committees, again with limited advisory functions

A later clause of this Amending Bill is aimed at the non European doctor and his relationship with nursing staff "Any person who causes or permits any white person who is registered or enrolled to be employed under the control or supervision of any person who is not a white person, in any hospital or similar institution or in any training school, shall be guilty of an offence and liable on conviction to a fine not exceeding two hundred pounds"

A recent letter to the *South African Medical Journal*[2] shows that non European nurses are fully alive to the implications of the Bill and fear for their status, and indeed for the standard of nursing, which they feel is at stake, in the non European hospitals It is also clear that these nurses, although legally compelled to be members of the Nursing Association, have no official voice, and were not enabled to give evidence to the Select Committee which drafted the present amendment What does seem surprising is that both the South African Nursing Council and the South African Nursing Association, in their evidence to the Select Committee, favoured racial discrimination, and are not at present voicing any dissent to the Bill The South African Nursing Association is affiliated to the International Council of Nurses, and to avoid prejudicing this international tie, its board proposed[3] not separate associations for the different races but a single (white) association, in control of a standing committee representing non-white nurses Though it had taken only a limited canvass of association members, the board gave evidence to the Select Committee in favour of discrimination The matter had not even been referred to in their official organ, the *South African Nursing Journal*, when the South African nurses were thus committed to apartheid At the last biennial conference of the association, a motion that the organisation should ask for equal pay for equal work for its members (African nurses earn just over half the salaries of white nurses) was voted down by a majority of white nurses Apparently, the South African Nursing Association does not recognise fully its duty to its non white members, and its present actions do not seem to be in line with the International *Code of Nursing Ethics*

The South African Nursing Council also gave evidence to the Select Committee,[4] recommending discrimination "You cannot have one standard for a highly developed race and the same for a lower developed race" The council asked that non European nurses should not be eligible for election to the Nursing Council, "a body which exercises disciplinary powers over thousands of women in this country (because) if such a nurse is able to sit in judgment on a European nurse who has transgressed you would wreck the nursing service in South Africa" To this, outsiders might reply that uniform standards would protect the status of white and black, and that there is no intrinsic reason why a white nurse should sit in judgment on a black but not vice versa

The effects of the Bill may be far-reaching for South Africa At present, the non European hospitals depend on non-European nurses With the limited professional opportunities offered them, many well educated and well principled young African women have been glad to train as nurses, welcoming the opportunity to serve their people and to gain status in their community The Amending Bill must reduce the standard and number of recruits, since non-Europeans in South Africa are naturally very sensitive to discrimination As it is, good nurses have been difficult enough to train within the present framework of the hospitals and the new Bill can only increase the difficulty The African nurse is an especially important link where most doctors (who are white) do not speak the language or share the cultural background of most patients (who are black) No reasonable standard of medical practice will be possible in the non-European hospitals without good nurses Indirectly, then, this Bill is a further and serious blow to the medical profession and its standards Doctors are resisting the imposition of double standards of training within their own ranks The case of the nurses seems to require the same response

INFLUENZA THREATENS

EPIDEMIC influenza is on the march again The epidemic in the Far East apparently started among refugees in Hong Kong in the middle of April Within a few weeks it has spread widely to other countries in Asia[5] and has now reached India, Japan, and Siam A laboratory report suggests that the virus is a new epidemic variant of influenza A, very different from previous epidemic varieties of this virus This finding has two implications first, it is unlikely that any population will have specific immunity to the new virus, secondly, vaccine made from virus of the previous epidemic variety will probably not give much protection against the new variant This country is unlikely to escape attack by this virus, but, since winter epidemics are the rule here, we may have a few months of respite If so, there should be an opportunity to prepare limited amounts of influenza vaccine with the new virus So far the death rate has been low, young children and old people seem to have been the hardest hit There is at present no reason to fear that the epidemic will increase in virulence, but a careful watch will undoubtedly be kept for deaths among young adults

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DR G F BUCHAN, medical officer of health for Willesden from 1912 to 1946 died on June 3 at the age of 78

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[1] Bill to Consolidate and Amend the Law relating to the Exercise of the Calling of a Nurse or Midwife and Other Incidental Matters A B 59 of 1957

[2] *S Afr med J* May 4 1957 p 439

[3] Evidence given to the Parliamentary Select Committee by the South African Nursing Association

[4] Evidence given to the Parliamentary Select Committee by the South African Nursing Council

[5] *Lancet* June 1, 1957 p 1139

Special Articles

MEDICAL CARE OF HUNGARIAN REFUGEES

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ON Saturday, Nov. 17, 1956, the first 50 Hungarian refugees arrived in this country and were taken to hostels in London. Twenty-six days later, when the Dakota *Sierra Whiskey* came through the low cloud and touched down at Blackbushe Airport, its passengers raised the total number of those that had been carried by air alone to 7524. It had been the biggest airlift ever to be organised from purely civilian sources; and its success made it necessary to open, at short notice, several reception and transit camps in the Aldershot area. On Nov. 23 Beaumont Barracks received 300 refugees; on Nov. 26 Talavera Barracks started to take in 1000; and, on the following day, Haig Lines Camp in Crookham received the first of 1200. More than 4000 refugees passed through these camps between mid-November and mid-February, when the last of the three, Haig Lines Camp, was closed. During these three months we were members of a team of general practitioners and officers of the Royal Army Medical Corps who were responsible for medical cover and, after the first rush, medical care. Medical centres were established in all camps, and sick-bays were equipped by the Cambridge Military Hospital and the British Red Cross Society at Talavera Barracks and Haig Lines Camp. Not counting those who came to us with mild headache, toothache, air sickness, cuts, bruises, broken spectacles and other minor complaints (and excluding routine medical examinations required for emigration and special employments) we saw 800 patients, more than two thirds of them during the first four weeks.

Emergencies on Arrival

Most of the refugees had already been through Austria—and almost all had passed through casualty-clearing stations on the Austro-Hungarian frontier—but some had only spent a few hours there before their onward flight to this country; and a few needed emergency treatment on landing.

A factory worker of 21 was in a crowd of demonstrators attacked with hand grenades on Oct. 24 in Gyor. Wounded in his left arm, chest, and face, he was taken to a local hospital where he received a blood transfusion and first-aid dressing. Because of the shortage of staff and equipment, no further treatment was possible. Ten days later, with 8 of his fellow patients, he set out for the Austrian frontier. The journey involved a walk of 15 miles through a forest and over ploughed fields, and six hours were spent in a rowing boat on Lake Ferto. (One of this group, a man of sixty, died in Austria from exposure; another, a child of 6, had to have bilateral below-knee amputations for frostbite.[1]) The patient, however, declared himself fit; and he was allowed to proceed direct to Linz and board a plane to this country. Eight hours later he reported at the medical centre in Aldershot, complaining of stabbing pain in his chest.

The left side of his chest was extensively scarred (with some superficial discharging wounds), wasted, and almost immobile. His left arm was also wasted and scarred; and shoulder movements were painful and restricted. He had several scars on his face and his left eye was inflamed. On questioning he admitted that his vision had become increasingly hazy in the left eye over the past six days and that he had a dull aching pain at the back of his eye. Radiographs at the Cambridge Hospital in Aldershot showed multiple metallic foreign bodies in the left chest wall and lung fields (but no fluid in the pleural space), and many in the left shoulder region. In the left eye there was a large shining pointed foreign body, with several splinters, and considerable retinal disturbance. This demanded priority treatment, and as soon as he had recovered from general exhaustion and his wounds were cleaned he was transferred to the Moorfields Eye Hospital in London. There, on Dec. 3, two foreign bodies were removed with the magnet. Though vitreous hæmorrhage obscured the view of the fundus, escape of subretinal fluid suggested a local retinal detachment; and at the follow-up visit four weeks later early retinitis proliferans was diagnosed. Back in the transit camp he received daily atropine and hydrocortisone drops in the medical centre. His vision in the left eye is at present exceedingly poor (counting fingers at 0·5 metre) and unlikely to improve. He gets an occasional sharp jab in his left chest on bending down; and he suffers from attacks of moderately severe, aching pain in his left shoulder after lifting.

Despite his disabilities, this patient was fortunate in many respects. Not only was he among the first arrivals, thus receiving the first wave of public sympathy, but he also escaped, through his illness, the inevitably demoralising effect of transit camps. However miserable he may have been at times in hospital—and one frequently found him in tears—nurses and fellow patients (mostly young soldiers evacuated from the Middle East) took turns teaching him English, shared with him presents from home, and made him part of their community. During his brief stay in the transit camp in February the difference between his outlook and that of many of his able-bodied fellow refugees, who had spent the preceding weeks (and the Christmas festivities) in the camp, was striking. He was anxious to start work, and employment was soon found for him as a nursing orderly in one of the London teaching hospitals. There, by all accounts, he is acquitting himself well.

Though minor degrees of frostbite were common, only 1 patient—a nun of 65—had to be referred for this to hospital. (She eventually had to have several gangrenous toes amputated.) Others who had to be sent straight to hospital included an exsanguinated woman with incomplete abortion, which had started during her wanderings on the Austro-Hungarian frontier; a young woman in status asthmaticus; 2 children with diarrhœa; an elderly bronchitic man with incipient heart failure; a case of active pulmonary tuberculosis who had had a second-stage thoracoplasty six weeks previously; and a mentally defective girl of 6 who had been so heavily sedated in Austria that she arrived in what appeared to be deep coma.

She was brought back to the camp two days later by her father, who a week earlier, had carried her across the frontier. She is a primary ament who had been treated unsuccessfully with large doses of glutamic acid for four years in Hungary. She cannot sit, stand, speak, or feed herself; she does not understand the Hungarian language; she has no control over her sphincters; and it is doubtful whether she recognises her parents. With her brother and sister she fell ill with whooping cough a few days later; and the whole family was isolated for ten days in a side ward of sick-bay. A fortnight later the family was presented with a cottage in an industrial town by newly won friends where the mother looks after the children. The father, a qualified engineer, earns a living as a factory worker.

Despite material shortages and difficulties (most of which were later overcome) the first few weeks saw such an extraordinary surge of human kindness that—hard as it is to recall its immediate effect even from the distance of a few months—they could not but leave a happy and exhilarating memory. Waiting for the first refugees to arrive, our first patient was in fact an R.A.M.C. corporal who had given up his long-planned holiday to help the Red Cross, and who, having worked to get the medical centre ready for the past thirty-six hours almost without a break, injured his hand chopping firewood for sick-bay. Gifts of expensive drugs, baby-food, and medical equipment had already begun to arrive from drug-houses, local pharmacists, hospitals, and anonymous donors; and voluntary workers soon came from all parts of the country to offer not only physical and material help but also a spirit of welcome.

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[1] Walter, B. Personal communication (1957) of material to be published.

The Language Barrier

There can be few aspects of refugee work where lack of a common language creates greater difficulties than medical care. Confronted, for several days and nights running, with coach-loads of exhausted, bewildered, pale, and often vomiting people of all ages and both sexes, most of whom complained of what sounded like (but one could not be sure that it was) nausea and abdominal pain, those of us who understood no Hungarian could not help feeling very uneasy labelling them, after a cursory glance, victims of air sickness. Mass relief always imposes a strain on doctors; and, unnoticed by themselves, they tend to concentrate more and more (in a hectic but profitless frenzy) on inessential trivialities. With the added language difficulty we were fortunate in missing only one major and obvious surgical emergency—a case of leaking ectopic pregnancy. She was diagnosed a few hours after admission to sick bay when an unexpected and distinguished non-medical visitor, who had asked to be conducted round, commented on her pallor.

There was, throughout the three months, a constant shortage of trained interpreters; and for this reason we had to refuse many offers of help from local practitioners. (It is unfortunate that—unlike food, clothing, or drugs—this most serious of all shortages, conceals itself. It is the probable explanation of explosive trouble reported from some camps in this and Continental countries where the camp authorities genuinely believed that all was well.) Untrained, incompetent, or merely tired and overworked interpreters can become a serious nuisance in medical work. Not only does this demand from them a high degree of accuracy and discretion, but medical topics also have an irresistible fascination to many lay minds. Most interpreters assigned to us were admirable in more than one way; but there were one or two who could not refrain from embellishing doctor's instructions with homely advice (painfully obvious from the length of time they took to translate a brief sentence) or from commenting on the merits (or otherwise) of all treatment prescribed; and, with a growing number of "difficult" patients, some—usually those least able to afford such extravagance—could not resist giving them, without our authority, "a piece of their mind". Occasional interpreters, much as one appreciated their intentions, often did a great deal of harm. In response to a nation-wide broadcast appeal more than 50 came during the first weekend to supplement the usual 3–4; and, wandering about the camps and comforting the refugees, but without any specific task, many succumbed to a Father Christmas attitude of vague promises and hopeful but inaccurate information. Dictionaries were exceedingly scarce; and most of the early improvised lists of "useful words and phrases" were a source of light entertainment rather than of enlightenment. Hungarian is quite unlike any other European language; and, though one soon realised that many *nems* and *semmis* in the medical history were a favourable prognostic sign, it was usually simpler to try to look comprehending than to try to comprehend.

On the other side of the language barrier hospital patients suffered much misery. Enfeebled by physical illness, lying in bed unoccupied in complete linguistic isolation, they could not guess what was about to befall them, nor could they be kept informed about their families and fellow refugees. Unfounded but appalling rumours which had already caused much nervous tension in the camps sparked off fits of hysteria when they reached the hospitals; and many patients discharged themselves against medical advice.

One night in December a three day post-appendicectomy patient was found by the driver of an Army truck, wandering about in her dressing gown two miles from hospital. She had misunderstood a piece of information given by a visitor to another patient, and had formed the impression that the camp, where she had left her young children in our charge, was to be moved to Scotland next morning. She was eventually pursuaded to return to hospital but discharged herself again three days later.

Hungarians, like most Continental people, take—by upbringing and by temperament—a far more active part in their illness than the average English patient. Detailed hospital reports which they carried around with them, and which gave diagnosis, the results of investigations, and often a far from favourable prognosis, showed how freely they had discussed their ailments with their doctors; and they held decided views about their own treatment. Lack of information thus imposed great mental strain on them, and delay in starting investigations and treatment for lack of interpreters (especially with gynæcological patients) prolonged their anguish. Despite the familiar difficulties of treating patients with even minor illnesses in barracks, steadfast refusal of parents to part with their children often made this an unwelcome necessity; and in two cases of infectious fevers one of the parents had to be admitted to the isolation hospital with their sick child. Relatives and visitors from the camps were otherwise taken on daily "milk rounds" of the local hospitals by special bus; and progress reports about Hungarian inpatients were received at the camp medical centres every morning and passed on to relatives who called later in the day.

The Seriously Ill

The standard of physical fitness amongst the refugees was generally high; but it was equally remarkable how many seriously ill patients had embarked on the journey. A whole group of young men and women with advanced rheumatic heart disease had escaped because they had felt—rightly perhaps—that conditions in Hungary did not allow adequate treatment of their illness, and because they had read (or heard on the radio) that it could be cured by surgical means in this country and in America. Most of them had mitral incompetence in addition to mitral stenosis; one had an acute relapse in the camp, with joint swelling and pericardial effusion, and had to be sent to hospital; and all the others were put on prophylactic sulphonamides.

Liver disease was another illness which was surprisingly common and often difficult to manage under camp conditions.

Lying in a wet ditch for several hours on the Austro-Hungarian frontier, a woman of 32 caught a chill. On arrival in Aldershot she complained of general malaise, shivering, nausea, constipation, and a dragging sensation rather than pain in her abdomen. She gave a history of acute hepatitis in 1951 for which she had had two weeks in hospital; but, though she had been on a waiting list for two years she had not received any inpatient treatment since then. She was persuaded with some difficulty to go to hospital, where investigations showed gross impairment of liver function. Anxious to return to her fiancé in the camp she was discharged at her own insistence after ten days. In the transit camp a special diet was arranged for her; and in the medical centre she received extra fruit, biscuits, and compound vitamin tablets. She remained well except for amenorrhœa and occasional abdominal discomfort. Both she and her fiancé had left Hungary hoping to emigrate to Canada where a job is waiting for him. They are now expecting to be called for a medical examination to be certified fit for emigration.

Most other chronic illnesses were represented among the refugees—duodenal ulcer, pulmonary tuberculosis, bronchiectasis, ulcerative colitis, thyrotoxicosis, and diabetes mellitus. We looked after several cases of gunshot wounds, a 40-year-old man with abdominal carcinomatosis, a 30 year-old gipsy woman with advanced Cushing's syndrome, and a woman of 26 who—after an attack of mumps encephalitis at the age of 10—started to put on weight and now weighed 23 st. Our most unusual cases were a married couple with diabetes insipidus.

The husband was the last in a queue of new arrivals, most of whom had come to the medical centre for tablets against headache, toothache, constipation, sore throat, dysmenorrhœa, or air sickness. He came to ask for a fresh supply of posterior pituitary extract. He had run out of tablets in Hungary ten days before, and since then he had been drinking over 14 litres of fluids daily and passing a corresponding amount of urine. He had no other complaints. He was 35, his home had been on the Hungarian-Rumanian frontier, and he professed to be an "importer and exporter of various goods." In June, 1956, he had escaped capture by frontier guards by falling into a well, and on his way home next morning had noticed unusual thirst and the need to pass urine frequently. A week later his doctor diagnosed "pituitary insufficiency due to shock", and on tablets of posterior pituitary extract his fluid intake fell to about 2½ litres daily. Four months later the outbreak of the Hungarian revolution caught him ill with gastritis in Budapest, and he volunteered the information that during three days spent vomiting and in semi-starvation in an air raid shelter his symptoms improved spontaneously.[2]

He drank 3 litres of fruit juice during our first interview and later he passed 3½ litres of clear urine. Next morning we provided him with posterior pituitary snuff and an insufflator which was an unqualified success. The organic nature of his symptoms was later confirmed in hospital by urine concentration tests and the intravenous hypertonic-saline test[3]—and diabetes mellitus and renal disease were excluded—but the underlying lesion was not easy to determine. There was no positive family history, his past history revealed no illness which could be incriminated, and clinical examination, and serological and radiological investigations were negative. It thus seemed reasonable to ascribe his illness to the traumatic episode eight months previously, despite several atypical features.[4–6]

He remained well-controlled on posterior pituitary snuff, which he preferred to intramuscular vasopressin tannate, but he was worried about his wife who had left Hungary a few days after him and who had had a nervous breakdown in Austria. After a somewhat laborious process of tracing her we learned from her Austrian doctors that she had already recovered from her anxiety symptoms but that she was now being investigated for severe diabetes insipidus. A further exchange of telegrams followed and she finally arrived, her polydypsia perfectly controlled on unlabelled phenobarbitone gr ½ three times daily.

Mental Illness

Diagnosis and treatment of psychiatric disorders depends, more than that of any other type of illness, on the spoken word, and they are perhaps least suitable for management in transit camps where a great deal of undesirable publicity can never be avoided. Chronic psychotics are probably few among the refugees (we only saw one recently treated case of schizophrenia, though several others were seen at a specialist hospital in London[7]), but minor psychiatric disorders may yet prove a bigger and more formidable problem than physical illness. The emotionally unstable, the perpetual drifters, the chronic failures—in whose catastrophic lives revolution and escape were but passing episodes—often reacted violently to the growing stresses of refugee life. Friends of nobody and their own worst enemies, it was not only hard to visualise them settling down to normal life, but, unable to make themselves understood, they ran a very real danger of being misdiagnosed as cases of major psychosis certified, and taken to mental hospitals. (Cut off from all contact with doctors, nurses, and fellow patients, even a brief sojourn there could only have a disastrous effect on them.) Hardly less gloomy appeared the future of the dull and the high-grade mental defectives. Most of those have been able to lead a normal, if limited, existence in their own milieu, but, despite popular good will and full employment, it was already becoming clear that many will be incapable of coping with their accustomed work in addition to the burden of learning a foreign language and adapting themselves to a foreign way of life. The future of young children was often our most immediate concern.

The younger of two usually quiet and well behaved brothers, a boy of 10, caused great stir amongst the other children when he collapsed and had a grossly histrionic fit. From the parents we gathered that both boys had been "difficult" for some months past: the younger had already had fits of naughtiness, whereas the older had become excessively shy and had recently started to wet his bed. The father appeared nervous, secretive, and mistrustful: the mother, who had already undergone neuro psychiatric treatment in Hungary, roused all other inhabitants of her barracks two nights later when she had a fainting and screaming fit herself. This was followed by excruciating headache and transient blindness. We referred the whole family to the Maudsley Hospital in London for psychiatric interview by a Hungarian speaking doctor. He reported that "both boys appeared intelligent and their symptoms are reactive to maternal mishandling. The mother has had considerable difficulties in her personal relationships and the marriage had been under stress for many years. . . . The tragic events of the last few months, their present unsettled circumstances, and uncertain prospects are further endangering her already precarious adjustment. She now shows a tendency to translate her difficulties into somatic terms. I couldn't find anything wrong with the father . . . but he says that he is heading for a nervous breakdown if his wife continues to behave as she has done in recent months."

The family was eventually, and not without difficulty from both parents, transferred to a London hostel so that the mother and children should be able to attend for psychiatric outpatient treatment. There they soon got into further trouble. The father—a morose and unpopular man—was said by some of his more vocal fellow refugees to have been in the secret police in Hungary and even now to be travelling to and from Hungary regularly to report on refugees in England. (This was a not uncommon, often genuinely held, but usually quite ill founded accusation. In this case, we could easily have disproved it, since he had spent the days of his alleged journeys to Hungary in the camp near Aldershot.) The mother drifted into loose company, refused for several weeks to see the psychiatrist, and aroused the bitter resentment of the more sober group of refugees. The father then abruptly returned to Hungary, leaving his wife and two sons—who are still causing grave anxiety to the hostel authorities—to fend for themselves.

Most hysterical manifestations in the camp—rare at first, but gradually becoming commoner—were of this crudely transparent type, conforming more to the picture of the disease familiar from popular fiction (and to Charcot's classical case-histories) than to the more subtle and complicated forms seen in medical practice in Western countries today.

Welfare

Individual and communal welfare—as also the day-to-day administration of the camp—was in the very capable hands of the Hampshire branch of the British Red Cross. The 54 pregnant women whom we saw and registered at the medical centre received extra food, vitamins, and clothing, and most of them were examined in the antenatal clinic of the Louise Margaret Hospital in Aldershot. (The first refugee child was born there on Dec. 14, 1956.) Great efforts were also made by the camp authorities to find for expectant mothers some more suitable accommodation than Army barracks, where they could receive continuous antenatal and postnatal care This unfortunately proved difficult although cubicles were provided, and there were communal heating and washing facilities, privacy for individual families was inadequate in most camps and hostels

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[2] Peters, J. P. *J. Amer. med. Ass.* 1944, 126, 1027.
[3] Carter, A. C., Robbins, J. *J. clin. Endocrin.* 1947, 7, 753.
[4] Rowntree, L. G. *J. Amer. med. Ass.* 1924, 83, 399.
[5] Jones, G. M. *Arch. intern. Med.* 1914, 14, 706.
[6] Porter, P. J., Miller, R. A. *J. Neurol. Psychiat.* 1948, 11, 258.
[7] Mezey, A. Personal communication (1957).

Like expectant mothers, babies were supervised at the medical centre Most mothers looked after them extremely well—if in a different manner from English parents—and neglect and cruelty were unknown Older children, however, reflected with uncanny fidelity—usually by how they behaved rather than by what they said—the prevailing moods, preoccupations, and tensions in the camp For a week or two in January, when a rumour circulated that the whole camp would be shipped to Northern Ireland, there was an "epidemic" of children going off their food, and mother after mother came to the medical centre, exasperated (both persuasion and chastisement having failed) and insisting that their children would simply fade away We reassured them as best we could, and we gave the children tonics and vitamin tablets "to keep them going" but real improvement only came when the Red Cross and school authorities arranged for all children to attend the local schools regularly They were collected and taken there by special bus every day, and almost all seemed greatly to enjoy the experience

Perhaps the most difficult, if least medical, aspect of welfare—the moral welfare of young people—could hardly be tackled properly in a transit camp The rootless and the restless not only formed a comparatively large proportion of the camp population (especially as more and more of the others found work outside), but in the camp atmosphere of enforced idleness, uncertainty, and lack of all personal responsibility they also influenced many young waverers The generally agreed policy was one of minimal interference with the private lives and living arrangements of the camp population, but one could not escape a feeling of profound misgiving when girls of 15 and 16, some of whom had left behind a stable and happy family background, came to the medical centre "to have something done" about their unwanted early pregnancies (Birth control was practically unknown among the refugees and, by all accounts, abortion had been semi legalised in Hungary during the past few years)

Problem Patients

One of us, who speaks Hungarian, had to deal with a growing number of "problem" patients, many of whom were brought to us from other parts of the country by their hosts or employers

A farmer motored up from Devon with a young Hungarian—one of four whom he had taken away from the camp soon after their arrival and to whom he had given a cottage and work on his farm The patient had apparently been quite happy during the first week in his new job, but since then he had been complaining of a variety of digestive symptoms These were ascribed by his doctor—who, according to his letter, could neither make sense of what the patient told him, nor convey to him his own instructions—to peptic ulcer, gastritis, or a grumbling appendix The patient's main complaint was ill localised abdominal pain which gave him no respite and which was unaffected by food, the doctor's medicine, or posture He also complained of much nausea but no vomiting, his bowels were regular, and his appetite was fair He mentioned giddy spells on bending down, and a 'feverish' feeling at night, but he slept well, and he had lost no weight Clinical examination was negative, except for diffuse abdominal tenderness and a spastic sigmoid colon

The patient was emphatic about liking his new work and his employers and he seemed distressed at the thought that he might be taken for the Hungarian equivalent of a 'skiver" On closer questioning, however, he was resentful on several counts First, he received £2 less in weekly wages than the English farm workers (This, because of the language difficulty, he considered not unreasonable, but "why was he not told before?") Second, his wife (to whom he was not legally married) had been asked to do housework without extra pay Third, he felt that he ought to have been investigated in hospital from the onset of his troubles In a more general vein, he was critical of most features of English life, including the weather

In Hungary, he had been a miner for the past six months, but, at 29, he had already travelled in four continents At 17 he ran away from home, joined the Hungarian army, and was taken prisoner by the Russians After several unsuccessful attempts he escaped from a P O W camp to China, only to be handed back to the Russians six months later by the Chinese Communist army From another P O W camp in the Ukraine, however, he eventually made his way back to Hungary, just in time to attach himself to the German army in its retreat to Austria In 1945, from a displaced persons' camp in the French zone, he enlisted into the French Foreign Legion, and he fought in Madagascar and Indo China for six years In 1952, he was shipped back to Germany, deserted, and, by way of Italy and Yugoslavia, returned to Hungary There he married his first wife, by whom he had a child, and he held a succession of jobs interrupted by several prison sentences and a brief spell as an army officer Although he took no active part in the revolution, he now "just couldn't stick the regime" any longer

Even in ordinary practice such cases are troublesome and medically unrewarding, but here there were additional difficulties Normally when advising patients against expensive and time consuming hospital investigations, one does so with the comforting thought at the back of one's mind that they are left with an almost unlimited choice of alternative doctors whose counsel they can seek This patient, on the other hand, would not get another chance for a long time even to voice his discontent Similarly, even the slight benefit of superficial psychotherapy would be denied to him as soon as he had left our consulting-room One also feared that discussion with his employer of his grievances—some of which may not have been entirely unjustified—might cause ill feeling and one was far more aware than many of the refugees themselves how much their future welfare depended on public good will Finally, one's loyalty to the individual patient was strongly assailed by the knowledge that there were many other young men in the camp who, hard working and dependable, would have been anxious to take on his job and would have done far better in his place However, we reassured the patient about his symptoms, we had a frank talk with his employer (who proved far more understanding than we had expected), and we wrote a detailed case history to the doctor

We saw the patient again three days later when he came for a routine medical check with a group of young men who had volunteered for the mines He looked cheerful and ("thanks to your tablets, doctor") he felt perfectly fit, and there was, of course, no medical reason against his returning to his old occupation Later, however, we got in touch with his previous employer who told us that not only had the patient left him at a most awkward time and without giving notice, but that he had also persuaded three of his fellow refugees to do the same, that his doctor had already gone to a great deal of trouble in arranging hospital investigations for him, and that in no circumstances would he or any of his friends employ Hungarians again

Not so much the patient as his employer's reaction was in many ways typical it reflected a dishearteningly widespread misconception of the refugee problem Events in Hungary had stirred most people's imagination in this country, but during their impressive display of human solidarity towards the victims few faced the fact that the migration of more than 150,000 people had been a tragic side effect, not part, of the political drama Thousands of families were not driven out of Hungary either by famine, fear, or force of arms, nor, of course, did they simply try to escape physical discomfort The forces which uprooted them were probably as irrational and abnormal by ordinary peace time standards as the forces which, in war, drive gentle and law abiding citizens into action Few soldiers in battle think in ideological or even national terms and it is doubtful if more than a handful of refugees did so before setting out on their flight The outbreak of the revolution caused not only a sudden and complete upheaval of their country's social and political order, it also upset all conventions of behaviour and the open Western frontier, sealed for so long, was certainly a powerful force of attraction even to the least adventurous

Most refugees arrived in the West still in this unsettled state of mind, and only there, and only gradually, were they to realise that they had exchanged the hardships and insecurities of a political regime for the equally crippling, if more transient, hardships and insecurities of life in a foreign country Many had left young children and sick parents behind without, it seems, pausing to consider that the parting may be for good and in the intoxicating atmosphere of the revolution many must have felt that political frontiers would soon be reduced in importance to derelict level-crossings

After their escape other unfavourable psychological influences were bound to make themselves felt In a heterogenous, ill organised, and often disillusioned crowd, comradeship, leadership, and respect for those left behind —the familiar foundations for front-line morale—were lacking; and, on the other hand, the equally familiar and most potent cause of its decline, a feeling of "not being kept in the picture," was present from the start (This was only partly imposed by the language barrier Too often, especially when urgent group movements were necessary, grossly inaccurate information was used as a short cut to gaining the cooperation of the refugees Even force is preferable to such a policy which only creates a vicious circle of disappointment, mistrust, passive resistance, and even more glamorous and unsound promises) Many refugees became acutely aware—and some were almost obsessed by the thought—that in the eyes of their hosts any refugee must appear "pretty much like the next one" but it was usually the highly sensitive ones—those who protested their individuality most—who found it least easy, when the time came, to abandon the security afforded by being part of a crowd It is hardly surprising that many refugees—even those emotionally most stable and intellectually sometimes brilliant—passed through a phase which no more reflected their normal selves than it fitted into the normal life of the country which gave them refuge

It cannot be too strongly emphasised that this is not a political problem and it is doubtful whether physical measures alone, modelled on disaster relief at home, can solve it They may be needed, but to be effective they must be applied with a clarity of judgment which can only come from a thorough understanding of the underlying psychological conflicts and difficulties Individual charity too has an immensely useful part to play, but it must guard against drawing too sharp a distinction between the "deserving" and the "undeserving poor," and it must be given not only with sympathy and patience but also with some degree of detachment However generous, it can never be a short cut to the resettlement of many thousands of homeless people of varying intelligence, background, and physical fitness This is a task which requires highly trained teams of social, psychiatric, educational, and medical workers There is no doubt that the trouble and expense of recruiting such teams, however great, would prove a sound investment both materially and in terms of human happiness

Only to a few of those who have helped us—sisters nurses, interpreters civilian and R A M C voluntary workers, and both English and Hungarian medical colleagues—can we express our thanks by name and for the work done by staff and members of the British Red Cross Society we can but record our admiration We should like, however, to thank especially Miss E Balfour O B E, the Red Cross Camp commandant, and Miss E Pilkington, deputy commandant for their unfailing coöperation, and to Colonel A. N Odbert, O B E, A D M S Aldershot District, we should like to express our gratitude for his guidance and interest both in our work and in the preparation of this article We were greatly helped by the patience and ingenuity in overcoming the language difficulty of the medical, nursing, and administrative staff of the Cambridge Military and Louise Margaret Military Families' Hospital in Aldershot, and the Aldershot General, Northfield Isolation, and Farnham Hospitals We also wish to thank Colonel H C Benson, commandant, R.A M C Depot and Training Establishment, Crookham, and his staff, for manifold assistance, Capt B Pritchard, R A D C, for looking after our dental patients, Dr J Craig Lindsay, medical officer of health for Aldershot, for valuable support, and Dr A Mezey, senior registrar at the Maudsley Hospital, London, for devoting so much thought and time to some of our most difficult cases

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MENTAL ILLNESS AND THE LAW

Recommendations of the Royal Commission

TIMES change, and the law must change to keep in tune with them This is the burden of the Royal Commission's unanimous report[1] The objects of the law are to give the patient the best care, to protect the public, and to prevent the abuse of compulsory powers, but "advances in medical knowledge, new methods of treatment and the development of new organs of government and new social services have naturally demanded changes in the medical and administrative methods by which these objects are pursued" The present laws were passed at a time when it was assumed that all mentally disordered patients must remain in custody during treatment, and it will now be necessary to repeal the Lunacy and Mental Treatment Acts and the Mental Deficiency Acts A new Act will be needed to take their place, and certain other statutes will have to be amended—e g, those concerning marriage, divorce, and property of mentally disordered persons and sexual offences against them, Broadmoor Institution, and liability to National Service The Board of Control will be abolished

The new recommendations of the commission are summarised below

The Patients

For legal and administrative purposes, three main groups of patients should be recognised

(1) Mentally ill patients, including the aged with mental infirmity The term 'person of unsound mind" would no longer be used

(2) Psychopathic patients The commission use the term "psychopathic personality" in a wide sense to include any type of aggressive or inadequate personality which is recognised medically as a pathological condition but do not render the patient incapable of leading an independent life The term includes all such patients now classified as feeble minded or moral defectives needing care

(3) Patients of severely subnormal personality—i e, those incapable of leading an independent life The term would include all those now classed as idiots and imbeciles, and some now classed as feeble minded The terms "idiot," 'imbecile," and "defective" would no longer be used

'The administrative distinction between mental illness and mental deficiency has a sound practical basis, but the rigidity with which it has been enforced through two separate legal codes has had some unfortunate results The grouping of all types of defectives together has led to the supposition that they must be a more homogenous group of patients than they really are"

Accordingly, there should be no rigid legal designation of a hospital catering for only one of these groups, the extent of specialisation would be a matter for medical and administrative arrangement Most of the mentally ill do not need to be admitted to hospital as inpatients, but for those requiring inpatient care new arrangements are proposed A single Act would define the procedure of admission to hospital of mentally disordered patients of all three groups

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[1] Royal Commission on the Law Relating to Mental Illness and Mental Deficiency 1954–57 Report Cmd 169 Pp 324 H M Stationery Office 10s 6d

Admission for Care

At present a patient can be admitted to a mental hospital only (1) as a voluntary patient (i e, he must be well enough to sign an application form), or (2) on certification, which may carry a certain social or moral stigma, because many people wrongly think that "certification" implies that the patient is permanently deranged or dangerous The term should be dropped Instead, "all forms of hospital and community care should be available in future to patients who are content to receive them" The voluntary-admission procedure should be abandoned Admissions should be arranged in the same way as admissions to general hospitals, with no statutory fixed notice of intention to leave, patients should be assumed to be content to be admitted unless they positively object This should apply to patients in all groups

> "Every effort should be made to persuade patients and their relatives to agree to care without compulsion But if such efforts fail, doctors and others should not be too hesitant to use the compulsory powers which the law provides, when this seems the only way of giving a patient treatment or training which he badly needs or when such powers are necessary for the protection of others"

Many of these will need admission to hospital, but some are better placed under the guardianship of the community, and to them the same principles apply Local health authorities should have a duty to act as guardians where necessary

The special position of psychopathic patients is considered They are distinguished from normal citizens not by their loss of reason or lack of intelligence but by their behaviour, and the special wide powers of compulsion allowed by the present law is not now justifiable, though there are grounds for providing compulsory training for the young, and for compelling psychopathic patients of any age to enter hospital for only short periods Unless, then, he has broken the criminal law, a psychopathic patient should be liable to compulsory admission (where necessary) if under the age of 21 at the time of admission, but must be discharged by the age of 25 (unless he has become liable to compulsion for other reasons) At any age psychopathic patients (as well as mentally ill and severely subnormal patients) should be liable to compulsory admission, for observation for periods not exceeding twenty eight days, or for care after criminal conviction when the court thinks it necessary and the hospital is willing to provide it Criteria for distinguishing psychopathic and severely subnormal patients are outlined in the report, but detailed definitions should not be written into the law The authorities should not be reluctant to bring a criminal charge against a psychopathic patient, for he is responsible in the eyes of the law, and a conviction may be the only way to ensure that he is treated

No formal designation is necessary by the Minister of Health of hospitals to which "compulsory powers" apply, it should be for the hospital boards and committees to decide which hospitals have powers of detention No hospital should be obliged to admit a patient for whom it cannot provide suitable care Patients compulsorily admitted should have the same status as others No letter written by any patient should be censored except at the request of the addressee, but hospital authorities should be empowered to withhold from the patient any incoming letter which it might harm him to receive There should be no statutory notification of a patient's discharge, but the relatives and general practitioner should be notified informally, as well as the local health authority if it is to provide aftercare

In sum, the main procedures for admitting a patient to compulsory care are

(1) Except in emergency, there should be two medical recommendations—preferably one by a doctor experienced in mental disorders (usually on the staff of the admitting hospital) and one by a doctor who already knows the patient In emergency, one recommendation would suffice, but the second must be added within seventy-two hours (twenty-eight days in the case of guardianship) (The present reference to a justice of the peace—often merely a formality—should cease, for it links treatment of mental disorder with the authorities responsible for the punishment of crime)

After twenty-eight days, a patient compulsorily admitted to hospital as an emergency would have to agree to continue in care (if this was necessary), otherwise a fresh application would have to be made with medical recommendations and a more precise diagnosis (Psychopathic patients over the age of 21 could not thus be detained unless this was authorised by a court after criminal proceedings)

An application for compulsory admission to hospital or guardianship, with two supporting medical recommendations, would authorise detention for up to a year Before the end of this year, if the patient was still detained, the medical superintendent or medical officer of health should review his case, and (if compulsory care was still thought necessary) sign a recommendation of further detention, with reasons, this would be reviewed by the hospital management committee or local health authority Similar recommendations would be made at increasing intervals where necessary

(2) The recommendations for admission must contain either a diagnosis of mental illness, of psychopathic personality, or of severely subnormal personality, and a recommendation for hospital or community care, or a diagnosis of mental disorder and a recommendation for up to twenty-eight days' observation in hospital In the first case, full explanation must be given of the need for hospital care or guardianship and of the necessity for compulsion

(3) Application by a relative or mental welfare officer, supported by medical recommendation, should authorise the detention, without reference to a magistrate

(4) Powers of discharge would be held by the patient's nearest relative (unless a certificate barred this because the patient was dangerous), a responsible doctor, any three members of the governing authority, and on special occasions, mental health review tribunals The tribunals would be appointed on a regional basis, by the Lord Chancellor, and include medical and legal members patients or relatives would be able to appeal to them against detention in certain circumstances

(5) Where an appeal is made against the decision of the tribunal, the Minister of Health (represented by a staff of part-time medical and non-medical officers) should scrutinise the documents in the case, and if necessary make further inquiries, with the power to discharge patients against the tribunal's decision This staff must be ready to visit any patient who asks to be visited

(6) Admission and renewal documents should be scrutinised by the hospital or local health authority staff—not centrally as at present Members of hospital management committees should visit patients regularly, and patients should be allowed private interviews

Other procedures would apply when it was necessary to override the wishes of the patient's nearest relative

(7) The local health authority should have a duty to provide special training for children for whom an ordinary school is inappropriate Hospital or community care would be appropriate in some cases under the Children and Young Persons Act

(8) In other cases where the nearest relative unreasonably opposes the provision of care an application (with

medical evidence) should be made to a magistrate's court for some other person to be granted the relative's power to apply for admission and discharge. The relative would have the right of appeal to quarter sessions and would retain the right to apply for discharge and to ask for a review by a mental-health tribunal.

(9) In emergencies, if another relative or the mental-welfare officer was so convinced that the nearest relative was acting unreasonably that he was prepared to apply to a magistrate's court for his wishes to be set aside, the main emergency procedure (as in (1) above) could be used, with a statement that the nearest relative was acting unreasonably.

Special considerations apply to court cases and transfers from prisons or approved schools.

(10) Where persons brought before a court were said to be mentally disordered, a medical report should be given by two doctors of standing similar to those who recommend compulsory admission. If the report agreed that the person was mentally disordered it should include advice as to the best way of dealing with him, and (if care was recommended) a statement of acceptance by the doctor who would be responsible for treatment or training. For some patients penal methods would be more suitable than medical. If the court was satisfied that penal measures alone were insufficient, and that care was necessary, care should be provided with the knowledge of the court but without its order.

(11) If a court of quarter sessions or assize was satisfied that immediate release of a patient would lead to further offences, it should direct that the patient should not be set at large without the Home Secretary's consent, and if the hospital or local authority wished to discharge the patient before the Home Secretary wished him to be released, other arrangements for his detention should be made.

(12) When admission followed court proceedings, the nearest relative should have power to apply for discharge but not to order it. In the case of an adult psychopathic patient, the need for compulsion should be reviewed annually by the authority caring for him.

(13) The Home Secretary should be able to authorise the transfer to care of persons, in prisons or approved schools, who are found to be mentally disorderd. The mechanism would be similar to that for court cases.

Private hospitals and nursing-homes, whether run for charity or for profit, receive special consideration.

(14) No member of the staff should be able to make application for compulsory admission, and both medical recommendations should be from outside doctors. Powers of visit and discharge should be held by members of the registering authority, and they must be allowed to inspect documents authorising detention.

Provision is also made for private persons (rather than local authorities) to become guardians, if authorised by a local authority or court, or after court proceedings.

Hospital and Local Authority

A new definition is made of the functions of the hospitals and local authorities.

> "There is increasing medical emphasis on forms of treatment and training and social services which can be given without bringing patients into hospital as inpatients or which make it possible to discharge them from hospital sooner than was usual in the past. It is not now generally considered to be in the best interests of patients who are fit to live in the general community that they should be in large or remote institutions such as the present mental and mental deficiency hospitals. Nor is it a proper function of the hospital authorities to provide residential accommodation for patients who do not require hospital or specialist services nor to provide other care for patients who have left hospital apart from necessary medical follow up or outpatient services. The division of functions between the hospitals, local authorities and other official bodies should be broadly the same in relation to mentally disordered patients as in relation to others."

The hospitals should provide inpatient and outpatient services for those needing specialist medical treatment or continuous nursing, including the subnormal who cannot be nursed at home, and inpatient training for subnormal and psychopathic patients where this necessitates psychiatric supervision. The local authorities should be responsible for preventive services and for all types of community care for those who do not, or who no longer, need inpatient care, including day or residential training-centres, residential accommodation in private homes or hostels, especially for the old, and general social help and advice. They should provide aftercare as long as it is necessary, without needing compulsory powers.

The local health-authority services should thus be much expanded, and should continue to include the provision of special training centres, though local education authorities should be allowed to cater for more children in the lower ranges of ability where possible. Some buildings now used by mental deficiency institutions might suitably be transferred to local authorities for these purposes; for the rest, Exchequer help is recommended.

Diagnostic clinics should be set up, on the lines of child-guidance clinics and perhaps based on them, but dealing with adults. They would be particularly useful for the diagnosis and assessment of psychopathic and severely subnormal patients, for clinical conferences between hospital and local-authority staffs on the best course in individual cases, and for advising the courts in cases where there is a possibility of mental disorder.

The provision of some community services by the local authority is at present a duty only for defectives and the aged infirm: it should be a duty for all mentally disordered patients.

Administration

The central supervision of all health and welfare services is now a function of the Minister of Health, and, in line with the integration in them of the mental-health services, the Board of Control would cease to exist, for it would have no function. This was suggested by the board itself. The functions of visitors appointed by justices would be taken over by the mental health tribunals and the local authorities.

The Minister should have powers of control over the standards of residential homes provided by the local authorities, while the local authorities should take responsibility for registering private institutions for mentally disordered patients, and for the oversight of patients in private houses: this would need new legislation.

The Minister of Health should consider whether the three State institutions should be brought within the administrative system of the National Health Service, or be managed by one or more special committees. In either case the committee(s) should include members who could often visit the hospitals as in any other mental hospital. The Minister should also review the arrangements for central collection of statistics.

Perhaps the kernel of the report is contained in these sentences:

> We consider it essential that the mental health services should continue to be an integral part of the present national health and welfare services. There is no longer any need for special mental health legislation to provide authority for the provision of public hospital or community services or the registration or approval of private establishments.

The report includes a tribute to the work of the Board of Control since 1913, and ends with an expression of thanks to Miss H. M. Hedley, the commission's secretary.

The members of the commission were:

Lord PERCY OF NEWCASTLE (chairman), Sir CECIL OAKES, Sir RUSSELL BRAIN, P.R.C.P., Dr T. P. REES, Lady ADRIAN, Mr C. BARTLETT, Mrs E. M. BRADDOCK, M.P., Sir HARRY HYLTON-FOSTER, Mr R. M. JACKSON, Dr D. H. H. THOMAS, and Dr J. GREENWOOD WILSON. Mr J. E. S. SIMON, Q.C., M.P., replaced Sir Harry Hylton Foster on his resignation.

GENERAL MEDICAL COUNCIL

SESSION MAY 28–29

NEW *Recommendations as to the Medical Curriculum*, designed to give greater discretion to licensing bodies and medical schools, were approved by the council last week. The number of subjects on which students must be examined has been reduced from 15 to 10, but the length of the curriculum is not altered. "A lighter and more flexible curriculum is the first essential," states the introduction to the *Recommendations*. "If a reduction in duration is to follow, a second operation will be required."

REPORT OF CURRICULUM COMMITTEE

The committee's introduction said that the most important criticism of the *Recommendations* of 1947 was that they left insufficient scope for initiative and experiment on the part of the licensing bodies and schools.

Until recently it was possible to proceed to independent practice immediately after qualification, and the council's *Recommendations*—and indeed medical education in general—had therefore emphasised vocational training and experience. This emphasis, together with the advance of knowledge and increase in specialisation, had caused the curriculum to become congested, and students had tended to concentrate unduly on memorising factual data. "The council feel no doubt that an effort should be made to reduce the congestion," the report continued, "and this has been their primary purpose in modifying the form and content of their *Recommendations*." In contrast to those of ten years ago, the present *Recommendations* indicated the minimum length of the whole period of professional study but refrained from saying how long should be allotted to particular subjects or the sequence in which they should be taught.

Corresponding changes had been made in the *Recommendations as to Professional Examinations*. While the council specified 10 subjects in which candidates should be examined they did not specify subjects in which separate examinations should be held.

Some licensing bodies and schools had suggested that the duration of the medical curriculum should be reduced. But the council felt that the primary task at the present time was to find means of reducing the congestion in the curriculum—to instruct less and to educate more. If it were simultaneously to be shortened, the principal object of the proposed reform would be thwarted. The council could say to licensing bodies and schools: "We are lightening the *Recommendations*, and we hope that in future your courses need no longer be overloaded"; but they could not reasonably say at the same time: "We ask you also to shorten your courses."

In professional education it was desirable that "inter-departmental teaching should be encouraged throughout the whole period of professional study. The memorising and reproduction of factual data should not be allowed to interfere with the primary need for fostering the critical study of principles and the development of independent thought." To ensure that students are fit to continue the work which they have undertaken, "there should be an adequate test or examination in normal structure and function not more than two academic years after the student has entered on the period of professional education."

Instruction in medicine and surgery should include clinical clerkships in medicine, surgery, and pædiatrics for not less than fifteen months in the aggregate. "It is desirable that for a part of the time of clinical clerkship the student should reside in hospital or conveniently nearby"; and "the student should be given opportunities to learn something of the work of the general practitioner." Instruction in psychological medicine should be carried out mainly in a psychiatric department, where neuroses and psychoneuroses could be studied. Not less than two months of the time devoted to clinical instruction in midwifery should be spent by the student in residence either in a maternity hospital or in a hostel attached to a maternity hospital or in the maternity wards of a general hospital, during which period the student should personally conduct an adequate number of cases of labour. Instruction in pathology and bacteriology should be given in association with clinical studies.

Candidates should be examined in anatomy, physiology, biochemistry, medicine, surgery, midwifery and gynæcology, pathology, bacteriology, and pharmacology. Examinations in the subjects included under medicine (child health and pædiatrics, social and preventive medicine, and psychological medicine), and in the various specialties in medicine and surgery, may be separate examinations or may form part of examinations in medicine and surgery. The final or qualifying examination is to be in medicine, surgery, and midwifery and gynæcology. "Examiners should be empowered to take into account the duly attested records of the candidate throughout his course of study."

DISCUSSION

In introducing the report Sir **DAVID CAMPBELL** spoke of a spirit of adventure now abroad in medical education—a desire to experiment. As regards training in the basic sciences, he rejected the suggestion that these are not cultural subjects. He thought it desirable that such training should take place in university or medical schools, "but unfortunately we have got to face the situation that a great many receive the training in schools."

Prof. H. R. **DEAN** (Cambridge) said he had been struck by the immense time taken in schools in reaching the standard in these subjects—two or three years compared with the single year spent on them in a medical school. This had unfortunate results in that it shortened the period of general education.

Turning to professional education, Sir **DAVID** pointed out that "adequate experience of dissection" was now laid down, as compared with the 1947 recommendation that the whole of the human body should be dissected. "We leave it to the medical schools," he said, "to interpret the word 'adequate' in this connection." In regard to midwifery it was impossible to lay down a definite number of cases of labour to be conducted. In view of the claims made for drugs, and the visits received by practitioners from "those itinerant professors of therapeutics, the representatives of pharmaceutical firms," he thought it highly desirable that the student should have adequate instruction in pharmacology, *including* the principles governing the design and interpretation of clinical trials.

Prof. J. H. F. **BROTHERSTON** (Edinburgh) welcomed the form of the *Recommendations*, which he described as "an enabling statute which gives freedom to experiment." He wondered whether it was still necessary to specify the period to be spent in residence during clinical instruction in midwifery. Edinburgh University also saw with some regret the dropping of specific reference to therapeutics. They felt that therapeutics had played an important part in the training of students and there was a place for it, perhaps alongside pharmacology.

Dr. J. G. **MCCRIE** (Sheffield) also appreciated the freedom of the *Recommendations*, but he agreed with Dr. Brotherston about the midwifery period. Similarly he thought that there was perhaps no reason to specify a particular period of time—fifteen months—for the clinical clerkships in medicine, surgery, and pædiatrics.

Mr. **VICTOR LACK** (Royal College of Obstetricians and Gynæcologists) said that they had fought for a long time to get a decent period of residence, so that students could see the work of the department of obstetrics, which after all took place mostly at night. If the council made a loophole, the standards in that branch of the student's education would be endangered

Professor DEAN emphasised the value of a close correlation between anatomy, physiology, and pathology Often it was not until the student saw changes in a diseased kidney or lung that he realised he did not know what the normal appearance was a course in the abnormal was something which stimulated a desire to know about the normal, and for that reason Professor Dean would have been happier if pathology and bacteriology had come with human anatomy, physiology, and biochemistry, before medicine

Prof P J MOIR (Leeds) was disappointed that there was no mention of the preregistration year the way that year was used must have a considerable influence In his school they felt that it did away with the need for long clerkships in medicine and surgery It would be possible so to arrange the course as to give some of the more practical parts less influence and use the time in teaching more fundamental matters Some consideration should be given to the function of the preregistration year vis à-vis the undergraduate stage Prof G A CLARK (Crown member) thought that the preregistration year was the responsibility of the licensing bodies but not of the council

Prof T N A JEFFCOATE (Liverpool), replying for the curriculum committee, said he was opposed to mentioning periods if this could be avoided, but the committee thought it important that the old system of apprenticeship should be retained He was a little in sympathy with what had been said about the two-month period for midwifery, but the fact had to be recognised that any practitioner was entitled to practise midwifery It was impossible to teach even very simple matters of safety unless the student was resident for a reasonable period Dr D J A KERR (Royal College of Physicians of Edinburgh) said that the professor of midwifery in Edinburgh would like the specific period of two months deleted and some such words as "a sufficient period" substituted Mr R A STONEY (Royal College of Surgeons in Ireland) thought it useless to make a student resident for less than two months A great deal of his time was taken up in getting used to the routine of hospitals

Professor BROTHERSTON formally moved and Dr KERR seconded, that "sufficient time" should be substituted for "two months" in the period of residence recommended for midwifery Sir HAROLD BOLDERO opposed The stipulation of the number of cases had been removed and he thought they should wait some years

Sir DAVID CAMPBELL said that the committee thought that at least fifteen months in clinical clerkships was desirable and that by keeping the two months while dropping the number of labours they could ensure that students were adequately trained in midwifery He asked the council to reject the amendment It did so, six members voting for the amendment

Replying to other points raised in the discussion Sir David said that the therapeutic uses of drugs were included in pharmacology As to the correlation of pathology and bacteriology with anatomy and physiology, it was recommended that "interdepartmental teaching should be encouraged throughout the whole period of professional study" There was nothing to prevent Professor Dean's school teaching the elements of bacteriology as indicated The preregistration year was not—perhaps unfortunately—the concern of the council It was for the licensing bodies to see that their students received adequate instruction in the preregistration year

On the recommendations as to professional examinations, Sir David mentioned that the curriculum committee would have liked to say that examiners should be compelled to take into account the duly attested records of students, but this recommendation was not possible in the case of bodies which were purely examining bodies

REVIEW OF EXISTING CURRICULA

The revised recommendations, together with the introduction, will be published by the council and circulated to licensing bodies and medical schools No date of operation has been specified, but the council hopes that licensing bodies and medical schools will review their curricula in the light of the new recommendations as soon as they conveniently can

THE PHARMACOPŒIA

Dr GUY DAIN, chairman of the Pharmacopœia Committee, announced the committee's decision that colour should be allowed to be attached to tablets in cases where the preparations were the monopoly of one firm and could not be made by anyone else—and only in those cases This would cover nine items only, and possibly a tenth At present no colour is allowed for any tablet

MEMBERSHIP OF THE COUNCIL

Dr J M O'CONNOR has been appointed representative of the National University of Ireland for three years, and Professor CLARK has been reappointed for five years

Medical Disciplinary Committee

The committee met on May 29, with the President in the chair

APPLICATIONS FOR RESTORATION

Charles Kingsley Colwill, who was not present but was represented by Mr E B McLellan, counsel, instructed by Messrs Le Brasseur and Oakley as solicitors to the Medical Protection Society, applied successfully for the restoration of his name to the Register

An application from *William Arthur Nason*, whose name was erased in 1954, was rejected

POSTPONED JUDGMENTS

To give *William Frank Cruickshank*, registered as c/o Milne, Broxy Cottage Westmuir Brechin, Angus, M.B Glasg (1935), a further opportunity of rehabilitating himself, the committee had postponed judgment a year ago Dr Cruickshank asked for postponement for a further year so that he might obtain suitable references This was agreed

The Registrar was not directed to erase the name of *John Millar Matthew*, registered as of 176, Farley Road, Selsdon, Surrey, M B Camb (1932) Judgment had been postponed for a year

The committee noted with satisfaction the letters sent to the council concerning *James Watson Richmond* registered as of Rosskeen, Kelty, Fife, M B Glasg (1929), in whose case judgment will be given in May, 1958

Andrew Francis Amerherst Gallen, registered as of 20, Orchard Drive, Giffnock M B Glasg (1932), had had judgment postponed for a year In view of satisfactory information as to his conduct the committee decided that his name should not be removed from the Register

James McKenzie, registered as of 255, Rochdale Road, Middleton Manchester, M B Aberd (1944), appeared for judgment, postponed from last May He was represented by Mr N Leigh Taylor, of Messrs Hempsons as solicitors to the Medical and Dental Defence Union of Scotland In view of information as to his conduct, which had been received, his name was not erased

Joseph John McMenemy registered as of Burnside, Bargeddie, Glasgow, L.A H Dubl (1947), had had judgment postponed until the present session He was not present and Mr Taylor, who had had no instructions, explained that he was abroad Judgment was further postponed

In another case in which judgment had been postponed, the committee, for the first time, varied a decision which it had announced

The practitioner concerned was *Robert Lindsay*, registered as of 8, St Ninian Drive, Inverness, M B Glasg (1945), who had been convicted, in 1951, 1952, 1954 and 1955, of committing breaches of the peace and of being found drunk A decision had originally been postponed for a year in May, 1955, in order to give Dr Lindsay an opportunity of reconsidering his habits, and last year the chairman announced that the committee had decided to postpone their judgment for a further period of a year, until May, 1957 "This decision is taken in your own interests," he added

Dr Lindsay was present and was not represented He said he was sorry for everything and hoped things would be better in the future In answer to the chairman, he said that for about ten months he had not been in practice He did not want to say in public what he was doing, for he did not want it bandied all over Scotland

Mr G J K Widgery, solicitor to the council, said there were a number of testimonials The Chairman I do not want them read

The committee deliberated in camera and then the chairman announced that, in Dr Lindsay's own interests, the committee had determined to postpone judgment for a further period of one year He would be asked to furnish the names of professional colleagues and other persons of standing to whom the council would be able to apply for information, to be given confidentially, as to their knowledge of his habits and conduct in the interval

Dr Lindsay Being on probation should not be a hardship There is one difficulty about it If you were in a job it would not be so bad I find it difficult to approach people

The chairman then asked if this was why he was doing his present work

Dr Lindsay I thought it would be a good thing to do work in the open air

The Chairman I wish you had called our attention to that before Do you mean you have difficulty in getting employment because you are on probation ?

Dr Lindsay That is my attitude When I was drinking I had no difficulty It is only since this publicity

Dr Lindsay added that it had cost him £25 coming to the meetings of the committee

The Chairman Would the committee like to consider this in the light of the statement which has now been made by Mr Lindsay and which we had not before us when we discussed this matter ?

Strangers were ordered to withdraw When they were readmitted the chairman announced

"In the light of the statement you made to us just now and after further consideration of this case the committee have now determined that the registrar shall not be directed to erase your name by reason of the convictions That concludes the case May I express the personal hope that you will see to it that you do not appear again ?

Dr Lindsay I thank you very much indeed

CONVICTION FOR SHOOTING

Robert Philip Strang, registered as c/o Hempsons, 33, Henrietta Street, London, W C 2, M R C P (1946) had had judgment postponed for two years in May, 1955, following his conviction, at the Central Criminal Court in 1954, upon indictment of shooting at Edward Anning with intent to do him grievous bodily harm, for which he had been ordered to be imprisoned for 18 months Dr Strang was not present, but was represented by Mr Taylor in his private capacity

Mr Widgery said that there were three testimonials

Mr Taylor read a statutory declaration from Dr Strang which stated that he left England last January with the object of practising medicine overseas He had now succeeded in making a new start and begged the committee to allow him a chance to rehabilitate himself

In view of the information concerning Dr Strang's conduct the committee determined not to erase his name

ADULTERY WITH A PATIENT

Kenneth Leopold George Nobbs, G M, registered as of 3, Cotman Gardens, Edgware, Middlesex, M B Lond (1930), was charged with committing adultery with a woman patient and having been found guilty of adultery with this woman by a decree of the Divorce Court

Mr Widgery, solicitor to the council, alleged that the woman was still on Dr Nobbs's list on Aug 27, 1956, when the adultery took place, which was found proved in the Divorce Court, but in a letter to the council Dr Nobbs said she left his list on Aug 23 He had known the lady and her husband socially, they were on Christian name terms

In evidence Dr Nobbs said that when they knew they were in love he wanted her name transferred from his list—not that they had any intention of adultery, it was purely that he was not treating her properly because he could not treat her objectively

MR WIDGERY I put it to you that the real reason was that you were then planning adultery ?—That was quite untrue It could not be less true Our one idea was to prevent any such occurrence

Mr Taylor of Messrs Hempsons, solicitors for the Medical Defence Union submitted that what occurred arose in no way out of the professional relationship but out of the social relationship, which was, the evidence showed, unusually close in this case It was not wrong for a doctor and patient to develop a very high degree of friendship In the nature of things that friendship sometimes would go too far If that happened between a doctor and his patient the doctor would have sinned, but would he have sinned professionally, any more than if he were a solicitor, an architect, or a candlestick maker ? What was the professional sin in those circumstances ? In this case there was not one jot of evidence that Dr Nobbs had over abused the professional relationship in its narrower sense

In his final address Mr Widgery said

"This lady came to Dr Nobbs as a patient She later became his mistress The best that can be said is that there may have been a gap of four days when she was technically not his patient at any rate for the purpose of the National Health Service regulations before the proved adultery took place on Aug 27 I submit that cannot be any answer to a charge of this nature and also you have the evidence of Mr Hills that Dr Nobbs gave Mrs Hills medical treatment if only first aid, on a date in September'

The committee found the facts proved and that Dr Nobbs was guilty of infamous conduct in a professional respect The Registrar was directed to erase his name This is subject to the entering of an appeal to the Privy Council

CONVICTIONS FOR DRUNKENNESS

Patrick Francis MacDonald, registered as c/o A MacDonald, solicitor, Main Street, Granard, co Longford, M B N U I (1941), admitted being convicted on various occasions since 1950 of charges arising from the influence of drink

The chairman announced that, in the opinion of the committee, the convictions indicated habits which were not only discreditable to Dr MacDonald and to his profession but might be dangerous to his patients To give him an opportunity to overcome his tendency to drink to excess, the committee determined to postpone judgment for one year

CANVASSING CHARGES NOT PROVED

Nancy Winifred Holloway, registered as of Curridge, Newbury, Berks, M R C S (1923), appeared on six charges of *canvassing for the purpose* of obtaining patients, between October, 1954, and March, 1956, but Mr Taylor, of Messrs Hempsons, as solicitors for the Medical Defence Union, who appeared on behalf of the complainant, Dr J A Richards, withdrew three of the charges Dr Holloway was represented by Mr E B McLellan, instructed by Messrs Le Brasseur and Oakley, as solicitors to the Medical Protection Society She denied that she canvassed the persons named in the charge or any other person or persons for the purpose of obtaining patients She had a considerable practice and in any event was proposing to retire

The committee determined that the facts alleged were not proved to their satisfaction and accordingly found Dr Holloway not guilty of infamous conduct in a professional respect

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Medicine and the Law

Agranulocytosis and a Tranquilliser

A WOMAN of 43 died of agranulocytosis after treatment in a mental hospital with a tranquillising drug, 'Pacatal' At the inquest[1] the coroner remarked that this drug, which could damage the bone marrow, had until recently been freely obtainable at chemists The drug, he added, should be given only to people who were psychotic and then only when all other forms of treatment appeared to be ineffective Because so little was known about the drug, doctors should not use it in general practice

In evidence, a pathologist said that blood counts made during this form of treatment could give a false sense of security because the effects on the marrow could appear suddenly But many people, he continued, could be given the drug without suffering any harm, and he thought it was a recognised treatment in mental hospitals, but it should not have much place in general practice The dose given in this case was not excessive A registrar at the mental hospital told the coroner that the patient could have been treated with phenobarbitone but the calming effect would have been less sure and rapid A verdict of 'death by misadventure" was recorded

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[1] *Wolverhampton Express and Star*, May 22 1957

Conferences

ANGLO-FRENCH SURGICAL MEETING

British and French surgeons met in London last week at an international conference with a difference. At the invitation of the president and council of the Royal College of Surgeons, the Académie de Chirurgie de Paris were the visitors and members of their party gave all the formal papers. The British contribution was a series of demonstration operations which were televised in colour and were seen by the delegates at the college while they were actually in progress at St Bartholomew's Hospital. The facilities for this were provided by Messrs Smith, Kline, and French Laboratories Ltd.—a service already familiar to North American surgeons.*

The technical quality of the picture was little better than that at a similar demonstration in Chicago in 1949. There is still a curious bluish green over all the images; the skin appears quite corpse like and the shadows opaque, and depth is difficult to judge. The truly stereoscopic effect which is so valuable in colour photography has not yet been achieved. The sound reproduction was often quite indistinct. The production, on the other hand, was excellent. Operations were chosen for their visual interest, and the team of surgeons were acknowledged masters of their special subjects. Each session was under comment by a moderator and a two man panel, and these three, themselves distinguished in the subject under demonstration, kept up an interesting series of questions which the surgeon had to deal with as he went along. The audience, too, could pass up their own queries for answering, so the demonstrators faced quite an inquisition. They were more than equal to it, however, and the defects of the picture were forgotten in the valuable discussion which accompanied it.

The papers were generally most stimulating and impressive—some in French and others in English. There was no translation service, but the quality of the material and slides lessened the need for one. Difficult subjects were included—for example, J. L. **LORTAT-JACOB** on his eleven years' experience of over 700 cases of carcinoma of the œsophagus. His experience has resembled that of most British surgeons who have written on this condition. The number of five year cures is small, but the resectability-rate is high, perhaps because all the operations were through the left chest, and even fixed growths were often removed.

MERLE D'AUBIGNÉ showed a fine colour film of his remarkable operation for reconstructing the knee after local resection of malignant tumours of the lower end of the femur. Replacement is by an ingenious combination of homograft, sliding autograft, and pedicled patella, while an intramedullary nail holds the whole thing together. Patients are able to walk in two to three months. Sarcoma is not a promising tumour for this kind of management, but a special indication may be found in the dangerous type of recurrent osteoclastoma after curettage and radiotherapy.

P. **PORCHER**, whose cineradiographs of the abnormal œsophagus were found so enlightening in this country last year, threw further light on the problem of *ulcères peptiques*, which in French has the narrower meaning of anastomotic ulcers. In his films recognition of the elusive crater in the stomal loop is eased by the curious fixity of the surrounding mucosa, whilst all else is incessantly mobile.

R. **SOUPAULT** showed how the deeper mysteries of the lower end of the common bile-duct may be solved in some cases by a combination of those techniques associated in Britain with the name of Professor Mallet-Guy—per-operative cholangiography and measurement of biliary pressures. Whether or not a stone is present this kind of investigation is yielding important information which may lead to a better understanding of the region.

Anterior approaches to the cervicodorsal spine have been worked out by **JEAN CAUCHOIX** and **JEAN-PAUL BINET**, and the former presented an interesting short paper showing the value of these operations in cases of paraplegia, often after laminectomy has failed. He raised the question of how many intercostal arteries could safely be divided in freeing the aorta; there is still no final answer to this in man.

In pelvic peritoneal reconstruction after Wertheim or other pelvic clearance operations, H. **BOMPART** has found that a long flap or sheet of the lower anterior abdominal peritoneum can be taken back and sewn to the pelvic brim just above the iliac arteries and the rectum. The whole of the pelvic cellular and lymphatic tissue can be removed below this level. A small plastic tube with mechanical suction soon obliterates the space, and the patients recover their abdominal functions correspondingly quickly.

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[*] As Dr Brian Stanford pointed out last week (p. 1149) this is not, as we had asserted, the first such demonstration in this country. Operations were televised in colour, using British equipment, at the International Congress of Ophthalmology in London in 1950.

Parliament

QUESTION TIME

Royal Commission's Report

Dr **DONALD JOHNSON** asked the Minister of Health if he would make a statement of his policy in regard to the implementation of the recommendations of the report of the Royal Commission on the Laws Relating to Mental Illness and Mental Deficiency.—Mr **DENNIS VOSPER** replied: I welcome this valuable and comprehensive report, and I am at present studying the many recommendations made in it. I must have time to consider them before making any further statement. But I am glad to have this opportunity of expressing the Government's gratitude to the chairman and members of the Royal Commission for undertaking this important inquiry.

Dr **JOHNSON**: Will the Minister take some action, prior to legislation—which we realise must take time—on those recommendations which do not require legislation, particularly the review of patients at present in hospital?—Mr **VOSPER**: Most certainly I shall consider what can be done by administrative means in advance of any legislation.

Mr **KENNETH ROBINSON**: Will the Minister agree that, as a result of the recommendations of the Royal Commission, the present procedures will now give rise to increased anxieties and frustrations on the part of parents, psychiatrists, and patients? Is not that an added reason for early action on the recommendations?—Mr **VOSPER**: That is certainly true, but any legislation will be of a very complicated and prolonged nature and must receive adequate consideration before it is introduced.

Certification

Mr N. E. **DODDS** asked the Minister if he was aware that, of recent years, a much greater use has been made of the one doctor process of certification than of the two doctor process for which the law also provides; and whether, pending the introduction of amending legislation, he would use the resources of his department to give publicity to the existence of the two doctor process of certification.—Mr **VOSPER**: Two medical certificates are required in all cases of certification of mental defectives. In mental illness, relatives or friends of the patient can initiate the procedure involving two medical certificates, and the one certificate procedure can be used only where the duly authorised officer is satisfied that there are no relatives or friends able and willing to initiate action or that the patient is not under proper care and control.

Mr **DODDS**: Does the Minister appreciate that every week now 400 people are certified under the one doctor procedure and the doctor does not need to have any special knowledge of mental illness? As the relatives do not know about these things until long after the deed has been done, can he not see the dangers of this system ?—Mr VOSPER The hon Member said that the relatives do not know, but it may be that they would prefer to use the one certificate procedure In any case, the medical superintendent also examines the patient In considering whether any action should be taken on the administrative side of the proposals made by the Royal Commission, I will look at this point

Private Patients

Mr JOHN HALL asked the Minister if he would now amend the National Health Service Act, 1946, so as to allow private patients to utilise the other facilities provided by the Act, and so as to allow the provision to all private patients free of charge, other than the prescription charge, a selected list of preventive and life saving drugs and drugs designed for the alleviation and treatment of lethal diseases —Mr VOSPER replied The private patients of general practitioners have full access to all the facilities of the National Health Service, other than the supply of drugs as part of general medical services The provision of a selected list of drugs for private patients would raise many problems of great difficulty My predecessor invited the British Medical Association to discuss this matter with the department, and those discussions are about to take place

Cost of Prescriptions

Mr R W SORENSEN asked the Minister if he had now reviewed the effects of increased prescription charges, and what information he had in respect of the decrease in the number of prescriptions and their cost —Mr VOSPER replied Examination of a sample of prescriptions dispensed in December has shown that the increase in average cost of about *5d* was probably due almost entirely to doctors prescribing larger quantities The trend of costs since December suggests that this has continued The number of prescriptions has also been much lower than a year ago, but this must be due partly to the low incidence of sickness Mr SORENSEN Could the Minister indicate to what extent the anticipation of these increases has been fulfilled financially ?—Mr VOSPER So far as I can gather at present, the anticipated saving and the actual saving will be about the same Mr ARTHUR BLENKINSOP Does not the Minister recognise the very real danger of waste involved in prescribing larger quantities, which he himself is encouraging ?—Mr VOSPER I cannot accept that, which suggests that the general practitioner is not competent to exercise discretion The ordering of larger quantities is not wasteful if there is a continuing need It does help people with chronic or continuing illness That, I believe, is what is happening at the moment Dr SUMMERSKILL Would the Minister say it is an overstatement to say that most people have in their bathroom cupboards unused tablets, lotions and ointments which have cost the country a great amount of money ?—Mr VOSPER I have seen allegations to that effect, but I have no evidence that it is true

Radiostrontium in Bone

Mr D HOWELL asked the Prime Minister what advice he had received from his medical and scientific advisers about the fact contained in the report of the Atomic Energy Research Survey that the bones of a stillborn child in Carlisle contained about seven times as much radiostrontium as that found in older people examined at about the same time

Mr MACMILLAN replied that the heavier concentration of radiostrontium in the bones of children compared with adults was fully considered in the M R C report It was for this and other cognate reasons that the maximum permissible level of radiostrontium in the human skeleton accepted by the International Commission on Radiological Protection was regarded as being too high for the general population The Medical Research Council considered that the maximum concentration of radiostrontium in the bones of the general population with its proportion of young children, should not be greater than a tenth of the maximum permissible level for adults in special occupations

Mr HOWELL asked whether it was not disturbing to find such quantities of strontium in a baby that has neither breathed nor fed ? Because the M R C report showed that babies up to one year of age already had 1 2 units of strontium, and because of the growing medical and scientific perturbation about this, would not the Prime Minister refer this matter specifically to his advisers

Mr MACMILLAN pointed out that, in the case mentioned the figure was 0 47 unit That was still a hundred times less than the average allowable level of the amount of radiostrontium in the bones of both children and adults

Expenditure on Social Services

Mr G P STEVENS asked the Chancellor of the Exchequer how the increase in expenditure on the social services by the central government the National Insurance Fund, and the local authorities between 1951–52 and 1956–57 compared with the rise in retail prices during the same period —Mr J ENOCH POWELL, the financial secretary to the Treasury, replied Between 1951–52 and 1956–57 expenditure on the social services increased by 38% and retail prices by about 23% Mr STEVENS I ask my hon Friend whether he agrees that despite economic difficulties in the past few years, there has been a very substantial advance in the provision of real social services for the people ?—Mr POWELL Yes, Sir Mr ARTHUR BLENKINSOP Does not the hon Gentleman also recognise that a very large part of any increased expenditure is in fact due to rises in prices, and that the real increases in the value of the services are extremely limited ?—Mr POWELL That does not detract from the fact that there has been a substantial increase in real terms over the period—about 12½%

Mental Illness outside the Hospital

In England and Wales the attendances at psychiatric outpatient clinics were 523,000 in 1950 and 714,000 in 1955 The number of domiciliary psychiatric visits in 1950 was 5600 and in 1955 11,200

Some Hospital Figures

In England and Wales, altogether 474,000 patients were on waiting lists in 1954, and 455,000 in 1955 The provisional figure for 1956 is 430,000 Though there has been an improvement in the E N T section, that and general surgery still have the longest waiting lists

The annual number of patients per allocated bed in hospitals other than mental hospitals, for 1954 was 13 1, for 1955, 13 2 for 1956, 13 4

Public Health

Influenza in the Far East

IN addition to the countries which we mentioned last week,[1] outbreaks of influenza have now been reported from India (Madras and Bombay), Cambodia, Indonesia, *Sarawak, and North Borneo* Epidemics continue to be widespread, but the disease itself has remained mild In a ship recently arrived in Rotterdam from the Far East 30 % of those aboard had had influenza By the time the ship reached Rotterdam the outbreak appeared to have died out So far there is no news of outbreaks in the Northern hemisphere, where epidemic influenza usually breaks out in the winter months

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[1] *Lancet*, June 1, 1957 p 1139

Infectious Diseases in England and Wales

Disease	Week ended May			
	4	11	18	25*
Diphtheria	1	3	4	3
Dysentery	574	669	[illegible]	773
Encephalitis				
Infective	2	5	1	9
Post infectious	1	8	[illegible]	6
Food poisoning	161	150	226	163
Measles excluding rubella	23 191	18 270	16 704	19 [illegible]
Meningococcal infection	25	23	[illegible]	22
Ophthalmia neonatorum	11	19	31	11
Paratyphoid fever	1	1	1	2
Pneumonia primary or influenzal	147	392	374	340
Poliomyelitis				
Paralytic	35	39	48	30
Non paralytic	[illegible]	10	18	[illegible]
Puerperal pyrexia	211	207	[illegible]	210
Scarlet fever	180	497	664	618
Smallpox				
Tuberculosis				
Respiratory	613	617	[illegible]	602
Meninges and C N S	[illegible]	12	13	9
Other	[illegible]	47	80	76
Typhoid fever	2	1	2	4
Whooping cough	2109	[illegible]	2261	[illegible]

* Not including late returns

In England Now

A Running Commentary by Peripatetic Correspondents

ON arriving at Euston, I had ten minutes to get to the Royal College of Physicians When I asked the taxi-driver to take me there he said "Is that the one in Lincoln's Inn Fields or is it the one where the gentleman who discovered the circulation of the blood is over the entrance ?" He said that he was sorry that he had forgotten the name of this doctor and I informed him that it was Harvey, but I was not sure enough of my facts to tell him that it was Linacre who stood over the door and that Harvey was in a niche on his left In 1957, 300 years after his death it is pleasant to think that the man in the street looks up to the discoverer of hæmodynamics

* * *

A meeting of the British Society of Deviation Medicine was held on April 1, at the National Deviation Hospital, with Sir CYRIL OBLIQUE (London) the president in the chair His presidential address, entitled Fifty Years of Deviation Medicine, embodied a succinct and inspiring account of the principles underlying this concept of medicine Sir Cyril, however, pinpointed the main problem facing the modern deviationist if the object of the practitioner was to treat all organs but that affected, how should he tackle such generalised conditions as polyserositis and subacute lassitude ?

Dr A ZIGZAG (Isle of Dogs) said that treatment of the whole man was a heresy into which deviatric and adeviatric doctors were equally likely to fall he went on to enlarge on the distinctions between deviatrics and deviatology

Dr I L FLYOFF (Novokhruschevograd), spoke as official observer from UNDO He thought psychodeviatrics was the answer to many such problems In his clinic, the attempt to limit therapy to unaffected organs was considered an insufficient safeguard psychosomatic parallelism demanded that the mind should be the sole recipient of treatment in bodily disease, and vis-à-vis

Mr STEER CLEAR (Land's End) gave a clinical demonstration of the results of deviatric surgery His thesis—that classical eccentric therapy may leave much to be desired—was amply borne out by a case-demonstration of a gangrenous foot from which the patient had been enucleated

Dr O CIRCUIT-JONES (Ysptty Chwith) then gave a paper on deviapædiatrics Prophylactic treatment, he said, should be begun in utero The danger of contaminating pathological tissues was being met in Wales by the use of isotope-containing polypharmaceuticals Mr G RICH QUICK (Mayfair) said that gynæcology offered a particularly promising field for the indirect approach and Dr ASHTON (Ashton-under-Lyne) underlined what had been said

* * *

A mild form of blackmail, which seems to be on the increase, is to send with a begging letter a stamped addressed envelope. When this envelope is of the "business reply" type, with the two vertical black lines on its right-hand side, the appeal to one's generosity is weak, but when the envelope bears an unfranked 2½*d* postage stamp, something prevents you from depositing it in the W P B As a result it lies for several days on top of your desk, a perpetual challenge, until you are finally forced to a decision You think here is a poor charity that has actually expended 2½*d* in hard cash and therefore you are in duty bound to use the envelope, so you send a donation

This can become chronic but there is a cure To achieve it you have to tear the 2½*d* stamp off the envelope and place it in your stamp-drawer for later soaking-off when you have run out of stock This first removal of a stamp produces immune bodies, and thereafter no effort of will, or appeasement of conscience, is needed to remove the stamps from subsequent envelopes As there is no appropriate heading in your income-tax form to record the annual profit so derived, it is not subject to tax—as yet

* * *

Things are not what they seem in our prem unit Outwardly, all the babes are neatly labelled with the names of their mothers choosing, with a card at the head of cot or incubator enabling the correct infant to be pointed out to proud father or grandma But underneath the surface, things are different Sister has her own labelling system For instance there is no mention of Keith Maldwyn P on many pages of the ward record-books Sister doesn't much care for either Keith or Maldwyn as forenames (as the G P O would now call them), and she just doesn't use them Instead, she likes Oscar and Michael ("Because he's small, so it suits him") All this means that Michael is liable to appear perplexingly in a list of Wts and Temps with no surname at all, and when there's *no baby of that name in the unit* If this system is carried to its logical (or illogical) conclusion we shall need a new ward book with tables showing both Sister's and parents' versions of every baby's name

Even the waste-bins have been affected by this cryptographic disease Whereas the right-hand bin labelled "LINEN" actually contains linen-waste, the left hand bin is also labelled "LINEN," but is really intended for paper-waste Somewhere, I suppose, there must be a pair of PAPER bins of equally mixed contents

It's all very confusing

* * *

Peripatetic correspondents should help each other, and I hope that Bill's father and Pam's doctor (see this column last week) will get together, with Bill in the chair It would not take Bill very long to advise Pam's doctor (with Bill's father as interpreter), and I suspect that Pam's doctor would scribble "Cortisone" on the back of an envelope and dash back to his evening surgery with his mind at rest

* * *

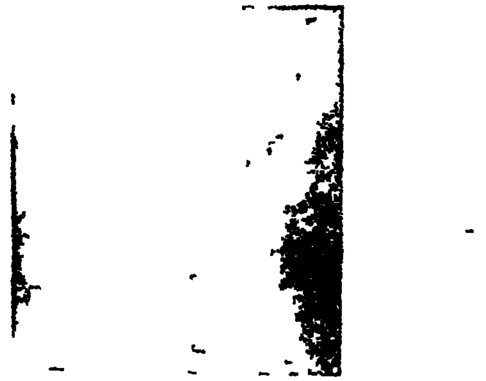
The bronchoscopist was also an enthusiastic yachtsman As he demonstrated to us the opening of the upper-lobe bronchus he remarked, "You will usually find it half an inch past the carina on the starboard wall of the main bronchus A somewhat scholarly physician took the wind from his sails when the patient's X ray was inspected a few minutes later The lung markings on the sinister side are more prominent than those on the dexter" he said

* * *

He is a diabetic, a pleasant fellow long accustomed to the courtesies of the profession He does not give his physicians at all times their full titles "Dr So-and-So" but calls each simply "Doctor" Recently he has had to have a lung resection What more natural, then, that he should address me and a fellow surgeon each simply as "Mister" ?

* * *

John Edward Page
Was a hippophage
I mean of course
That he swallowed a horse
But can that be true
At the age of two ?
Indeed tis so
Just see below



Letters to the Editor

STEATORRHŒA AND HYPOPARATHYROIDISM

SIR,—I am very glad to note that Dr Jackson (May 25) has drawn further attention to the occasional finding of biochemical signs suggestive of hypoparathyroidism in cases of steatorrhœa, and I entirely agree that we should all look out for more cases of this kind, and for opportunities to investigate them further However, I write to add to his letter that not only should one carefully consider plasma levels of calcium and phosphorus in such cases, but also the skeletal X rays in some detail For this latter purpose Dr C J Hodson and I have for some time standardised the procedure of taking X rays of the ' abbreviated skeleton " as we call it this comprises lateral skull, chest postero-anterior view (for ribs and scapulæ), both hands and wrists, straight picture of abdomen and renal tract (for kidneys), lateral lumbar spine, pelvis and hips, both knees antero posterior Such a routine procedure covers most of the best sites where signs of osteomalacia and/or hyperparathyroidism are likely to be detectable It is important to preserve X rays that are apparently negative at the time since comparison with subsequent X rays after suitable treatment of the patient will sometimes show that signs of metabolic bone disease were originally present, though not then diagnosable

My special reason for suggesting this is that we are now studying two patients who have shown simultaneously and over a period of at least some months biochemical signs of hypoparathyroidism (low calcium, high phosphorus) and radiological signs considered specific for hyperparathyroidism (subperiosteal erosions, &c) as well as a high plasma alkaline phosphatase In one of these cases marked steatorrhœa was present and the patient was obviously a survivor of cœliac disease from childhood In the other patient no steatorrhœa, renal failure, or any other disease could be discovered In both cases, vitamin D cured simultaneously the signs of hypo- and of hyper parathyroidism

This situation seems even more curious than that raised by Dr Jackson, and will presumably have to be explained only by destroying one of our present concepts Perhaps our diagnostic criteria for hypo or hyper parathyroidism are wrong , perhaps there is more than one parathyroid hormone and sometimes one can be increased and the other decreased Whatever the explanation, we should like to draw people's attention to this possibility We shall not publish our cases until the follow-up has lasted a bit longer

For this particular disease I can only suggest the name " *hypo-hyperparathyroidism* with and without steatorrhœa "—the precedent for rather unusual nomenclature in this field having been firmly set at Boston, Mass

University College Hospital Medical School
London W C 1

C E DENT

FATAL CARDIAC ARREST WITH FLUOTHANE

SIR,—Dr Foster has done a great service by his letter of June 1, if only by drawing attention to errors in the use of ' Fluothane ' (halothane)

All the literature to date points out that concentrations of up to 2% or, in the very robust, 3% are adequate to produce the optimum effects I hesitate to think what concentration was obtained by putting it in the ether container of a Boyle's type II circle absorber, and putting the lever to the sixth notch. I have heard of a fatal case during a similar operation where a similar technique was used with ether

I have used fluothane in a closed circuit, vaporising it in a Rowbotham attachment With the lever " full on " this gives 3 8% concentration, which is rarely necessary Warning has also already been given about attempting to produce full abdominal relaxation with fluothane, the use of succinylcholine chloride being advised. The same paper [1] also warns against using gallamine or tubocurarine with fluothane

It will be a pity if this apparently useful addition to the anæsthetist's armamentarium were to be condemned on insufficient grounds

Worthing

F R GUSTERSON

SIR,—It was with the deepest regret that I read the first account of a fatal cardiac arrest under ' Fluothane ' (halothane) anæsthesia I agree that it is impossible, in the absence of an electrocardiographic tracing of the collapse, to determine the cause of the fatal outcome Vagal arrest is a strong possibility, however, as the patient was suffering from a condition associated with increased vagal activity

The anæsthetic technique described by Dr Foster is remarkably similar to one which I have used to induce vagal inhibition and arrest of the human heart with cyclopropane, ether, and trichlorethylene—positive pressure insufflation of these vapours into the lungs of non atropinised patients [2,3] I am quite certain that fluothane in man is equally if not more effective in producing cardiac arrest in this way This type of arrest is completely preventable by adequate atropinisation and it is most unwise to assume that it is due to a toxic effect on the heart Scopolamine is not a suitable substitute for atropine [4] and there is no evidence to indicate that gallamine would be a suitable alternative

Dr Foster has been wise in drawing attention to the hazards of using fluothane in uncalibrated vaporisers incorporated in closed circuits, since unnecessarily high vapour concentrations must inevitably be attained, particularly when the gases are warmed by soda lime The importance of restricting the vapour concentration to 2% or less has already been stressed The hypotension sometimes associated with fluothane anæsthesia has been no more difficult to control than that associated with spinal analgesia , if considered necessary it can be prevented by a suitable vasopressor, even during deep fluothane anæsthesia

I should have thought that Dr Foster would have been convinced by recent experimental and clinical reports that fluothane has little if any pharmacological resemblance to chloroform or any other volatile anæsthetic agent My case of non fatal syncope, to which he refers, was described in order to illustrate the dangers of simultaneously using drugs pharmacologically incompatible with fluothane and was essentially an example of the mismanagement of a patient under fluothane anæsthesia , it did not reflect in any way on the efficiency of fluothane as an anæsthetic agent

I should like to assure Dr Foster that, far from being " onerous," the patients, surgeons, nursing staff, colleagues, other " sponsors " and I have found fluothane to be a delightful anæsthetic agent in many respects I admit that we have encountered some mildly unpleasant reactions but, in each instance, they have been related to errors of technique rather than to any inherent pharmacological defect in the drug

Department of Anæsthetics
Royal Infirmary Manchester

MICHAEL JOHNSTONE

ASTHMATIC WHEEZING

SIR,—While the explanation of asthmatic wheezing given by Dr Dekker and Dr Groen in their article of May 25 may be partly correct (which indeed is all they claim), it cannot be the complete answer

Otherwise it is difficult to account for the wheezing still to be heard occasionally during anæsthesia of a

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1 Bryce Smith R O Brien H D *Brit med J* 1956, ii 969
2 Johnstone M *Brit J Anæsth* 1955 27 566
3 Robertson J D Swan A A B *Anæsthesia* 1957, 12 182
4 Brennan H J *Proc R Soc Med* 1957 50 196

susceptible patient, who has been both so well curarised as to be incapable of producing the intrathoracic pressure postulated, and has the lumen of his trachea preserved by the presence of a wide-bore endotracheal tube

Royal Infirmary,
Preston.

A J GRAY

SMOKING AND LUNG CANCER

SIR,—New evidence about the link between excessive smoking and lung cancer is likely to be published soon

One thing is certain · the enormous increase in lung cancer is closely allied to the increase in the smoking of Virginian cigarettes It is striking that cigar smokers do not show a similar increase in lung cancer Nor do we hear of the growth of lung cancer in countries where they smoke just as much as in this country but non-Virginian tobacco

Virginian tobacco is different from any other, not only in its mass production and harvesting, but also in the way it is cured Statistics show that the arsenical content of various brands of American cigarettes has increased threefold in the past twenty years This rise is attributed to the use of arsenical pesticides widely used on American tobacco plantations Sales and production records show that cigarette smoking has also increased in the same proportion during the same period And at the end of 1954 statistics illustrate that the death-rates from lung cancer in the United States had risen by 200% in women and 600% in men[1] Similar figures are available in countries where smoking of Virginian tobacco became fashionable only after the wars when it was introduced by the American and British armies of occupation

These facts surely suggest that the relationship between lung cancer and smoking incriminates Virginian tobacco rather than tobacco in general

London W 1

ALBERT W BAUER

CLICKING PNEUMOTHORAX

SIR,—The case described by Dr Bourne in his paper of June 1 reminds me of a personal experience in 1950 The sharp pain was situated behind the left shoulder and in the left side of the chest It was only moderately severe I was persuaded to have a chest film taken after a colleague had confirmed the clicking noise which I could hear when sitting back in a chair The ordinary postero-anterior film in full inspiration did not show the pneumothorax, which was visible when a second film was taken in full expiration

I believe that clicking is unusual in left- or right-sided artificial pneumothorax, and in small right-sided spontaneous pneumothorax This suggests that the volume of air on the left side is the deciding factor The very small effusion of fluid or blood which goes with it may make the pleural surfaces sticky In the leaning-back position the air pocket will move forwards as the lung sinks back into the posterior costodiaphragmatic trough The movement of the heart then causes the clicking sound If this is the right explanation there is no need to postulate mediastinal emphysema, in which condition air rises into the neck behind the deep cervical fascia This together with severe precordial pain and loud crunching noises constitute Hamman's syndrome of mediastinal emphysema[2]

The sites of reference of the pleuritic pain in Dr Bourne's patient suggest that the air had in fact passed up over the lung to the apex and laterally Perhaps a film taken in full expiration, when the apex of the lung would be at its lowest point under a pneumothorax in the absence of gross adhesions, might have demonstrated the presence of air

Maelor General Hospital
Wrexham

C F HINGSTON

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[1] Satterlee H S New Engl J Med 1956, 254 1149 1191
[2] Hamman L Bull Johns Hopk Hosp 1939, 64 1

X RAYS AND LEUKÆMIA

SIR,—I was interested in the report by Dr. Stewart and her colleagues[1] and in the following discussion, in view of our survey since 1950 of many diagnostic radiological installations in the metropolitan area of New York City and North Jersey, and of the practices of the operators of these units, and of a study now in press (with Dr Robert Berman) detailing intravaginal measurements of the dose of radiation delivered to a group of patients during X-ray pelvimetry and hysterosalpingography.

Discussion of the varied problems concerning human somatic and genetic effects of ionising radiation is often maintained on a rather high emotional level Definitive answers are eagerly sought, but unfortunately there are none at present We are, however, treated too often to a plethora of publicised views and counter-views by more or less assured "experts," who have slight hesitation in asserting their non-disprovable opinions, particularly about the effects of fallout. There are serious limitations to our knowledge, which is admittedly missing or fragmentary in many areas, and until more secure information is at hand there must be a continuing and enhanced educational campaign urging (perhaps ultimately demanding) increasingly higher standards of care and usage by those employing any type of radiation-emitting equipment or material in industry, government, and public health Valuable information about radiological protection has long been available, but its dissemination and resultant impact has clearly not been as extensive as necessary

Care in writing and speaking about radiation and man is very important today because of a heightened interest among a public which cannot know whether opinions spread via mass communication media, have firm or insubstantial grounds Dr Reid[2] refers to the fear-engendering publicity in England following the report of the Stewart group in which information was presented suggesting that an "apparently harmless examination [X-ray pelvimetry] may occasionally cause leukæmia or cancer in the unborn child" manifest in the first decade of childhood The press reaction was to be expected, as with any dramatic announcement, but we may wonder just what was gained by the publication of this "preliminary analysis" of the approximate initial third of the prospective data of a potentially valuable epidemiological survey The data were few, and detailed supporting information was scarce My misgivings over the treatment of this initial material will still exist, even if the final report of Dr Stewart and her group convincingly implicates radiological pelvimetry as having a significant rôle in the development of childhood malignancy It is difficult to have to admonish the admonishers when one has frequently been linked with them

The paucity of supporting information in the interim report led to requests in succeeding issues of *The Lancet* for additional data There have been requests for information about the time in pregnancy when the examinations were made, about the number of mothers who received sulphonamides or antibiotics during the relevant pregnancies, and whether the children of the case and control groups were matched for birth rank Subsequently[3] (but not in the original report) we were told that the children "were deliberately *not* matched for birth rank," and further that "the exact dates and estimates of ionising radiation have still to be determined But since most of the photographing was done for twins, breeches, disproportion, and placenta prævia most of the films were taken after the 30th week" Because of the possibility of critical periods in fœtal radiosensitivity, more precise information would be welcome (From two to five radiographs may be taken in a pelvimetric study, not all portions of a late term fœtus are equally exposed in every film, and the dose delivered to the fœtus can vary by factors of two or more) May I request additional information ? *It is insufficient to note that approximately* equal numbers of children in the case and control groups had received postnatal diagnostic exposures We should ask when they were exposed, what was the type of examination were single or multiple films used, how many children received more than one diagnostic study, and what were the dosages involved in these examinations Such data will be difficult to secure, or may be unobtainable in many instances, but without them we cannot consider this variable (i e , postnatal radiographic examination) as *having a lesser role than* diagnostic pelvimetry, or no rôle, in the ætiology of malignant disease in childhood Without complete information, should we accept the statement that " although they are alike in other respects, there is one important difference between the children who died and their controls the number of mothers who had an X ray of their abdomen during the relevant pregnancy was 85 for the cases and only 45 for the controls " ?[1] Equal numbers on two sides of a ledger do not necessarily connote likeness of treatment or exposure *We should also like to have information* as complete as possible on the history and kind of infectious processes in all the survey children

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[1] Stewart A. Webb J Giles D Hewitt, D *Lancet* 1956, ii, 447
[2] Reid F *Ibid* Feb 23, 1957 p 428
[3] Stewart A. *Ibid* 1956 ii 573

The future may vindicate the wisdom of Dr Stewart and her colleagues, but on the basis of what was initially presented, as well as what was lacking, the conclusion regarding X-ray pelvimetry is hardly firm

A genetic component in the onset and development of leukæmia[4 5] (and other pathological conditions) cannot be *overlooked, and the Stewart group has noted this possibility* The fact that a genetic factor or factors may have more or less ætiological significance warrants consideration in the selection of appropriate controls If feasible, it would have been valuable in the present instance to secure data about the sisters (and their progeny) of the mothers of the dead children Parents with a common genetic background would thus be used in the quest for an environmental agent or agents important in the initiation of childhood malignancy In other studies concerned with the effects of progeny on parental exposure[6 7] to radiation, more significant information could have been obtained had siblings of like sex been used as control parents

I regret having to present this criticism of a well-motivated group of investigators engaged in a difficult and potentially important study The tempo of discussion regarding somatic and genetic risk from ionising radiation derived from different sources has quickened in the past year or two, and perhaps criticism at this time is as necessary as continued research In the United States we have too many voices making quantitative prognostications with respect to radiation effects in man at a time when quantitation is hardly in order A " popular " subject is attractive and quantitation lends an air of authority

Newark College of Arts and
Sciences Rutgers University,
Newark 2 New Jersey U S A B P SONNENBLICK

MALARIA IN RUMANIA

SIR,—*Your account* (May 25) of the medical congress in Rumania last month mentioned that malaria has been virtually eradicated The following figures show the result of the campaign against this disease over the past nine years

	No of cases		*No of cases*
1948	338 198	1953	3114
1949	233 962	1954	916
1950	95 469	1955	376
1951	42 025	1956	259
1952	14 217		

The success of the campaign has been brought about by spraying the houses once a year with either dicophane (D D T) or gammabenzene hexachloride (B H C) against the adult anopheles, and also by schizontocidal treatment and chemoprophylaxis among the population It is confidently believed that during the next two or three years malaria in the whole of Rumania will be eradicated It may be interesting to record that Professor Sergheev, of the Soviet Union, said that there were 4,800,000 cases of malaria in the Russian fighting services during the late war Unlike the British and American troops who were engaged in campaigns in highly malarious tropical countries, the Russians were confined to Europe—which shows, not for the first time in history, how serious malaria in Eastern Europe can be in a military campaign

Malaria Reference Laboratory
Horton Hospital,
Epsom, Surrey P G SHUTE

WORLD HEALTH ASSEMBLY

SIR,—Your note of June 1 about W H O is rather misleading in its second paragraph The proposal for the ban on atomic bomb tests was put forward by one of the member States

The World Federation for Mental Health, which is mentioned in the preceding sentence, has had nothing to do with this We have drawn the attention of W H O and various other agencies to the need for the study of mental health problems in connection with the *peaceful uses* of atomic energy This, it would seem, is not made quite clear in your note

World Federation for Mental Health,
London, W 1 J R REES

MEDICAL STAFFS OF MENTAL HOSPITALS

SIR,—With great pleasure, but unhappily with small hope, I support the plea re stated by Dr Strauss and others (May 4) for a substantial increase in the medical staffs of mental and mental deficiency hospitals, although, despite the truth of what they write about inadequate buildings, I wish they had kept to the essential defect *in the psychiatric services of today—the painfully* made quate number of available trained staff I have had plenty of experience in large mental hospitals and write with that in mind, but my points can best be illustrated by reference to the small 67-bedded psychiatric hospital in which I work

Since 1946 the hospital has enjoyed almost all the aims of a progressive mental hospital, in terms of appearance, situation, lack of sex discrimination, complete absence of legal orders, 100% parole, and almost unlimited visiting (made possible by the absorbent benevolence of Holloway Sanatorium, Virginia Water, as an invisible support, even though its services are rarely required)

Over recent years the psychiatric staff has been increased from 2 to 4 During the same time the number of admissions and the number of new *outpatients* has increased very little, only the outpatient attendances have increased significantly (roughly about four times) About a third of the admissions come from a distance, but this letter is concerned with the other two thirds who are local, most of whom have been deteriorating for some time despite monthly or so psychiatric interviews elsewhere, the *maximum* attention which can possibly be given by the number of local psychiatrists available Many are ill for long periods only because of the delay in providing proper treatment, but *as a rule* such patients improve rapidly with three interviews a week and could leave hospital in a *few weeks*, but here comes the rub *If* improvement is *to go on*, interviews must *continue* at least twice weekly, and if the patient is discharged from hospital there is a waiting-list from which another admission can be chosen for the same process to be repeated The factual results are (1) the *hospital* always has an average of about *17* empty *beds*, (2) quite a number of *resident* patients could easily leave at any time if staff were available to deal with new admissions (I would estimate that the bed space is used at about a third of its capacity), and (3) the morale of ancillary staff is reduced because of the *obvious lack*

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4 Anderson R C *Amer J Dis Child* 1951 81, 313
5 Johnson M J F Peters C H *J Amer med Ass* 1957, 163 20
6 Macht, S H , Lawrence P S *Amer J Roentgenol* 1955, 73 442
7 Crow, J F *Ibid*, p 467

of urgency and the repetitive nature of so much of the work I am informed that the "official" view is that since there are empty beds there is clearly no need of further staff! The hospital has no psychologist keeps its one psychiatric social worker post filled with difficulty, and is short of nurses, so much so that treatment obviously indicated, such as prolonged narcosis &c, has often to be put off

The situation cries out for some authority, in practice completely lacking which can integrate the hospital into a wider scheme of mental health service The money being spent on schemes now afoot for increasing the bed accommodation could be used to gauge the effect of adequate staff for an experimental period of several years

St Ann's Hospital,
Canford Cliffs Dorset

D N. PARFITT

SURGERY OF CHRONIC PANCREATITIS

SIR,—In your account (May 18) of a recent meeting at the Royal Society of Medicine, at which chronic relapsing pancreatitis was discussed the term "caudal pancreaticojejunostomy" is applied to the operation of removal of the left part of the gland and the implantation of the cut end into a Roux loop of jejunum

When Dr J. Buckwalter and I described this operation, in order to distinguish it from the pancreaticojejunostomy previously described by Dr R B Cattell we selected the title "retrograde pancreaticojejunostomy" as the least imperfect of several imperfect alternatives

The term "caudal pancreaticojejunostomy" implies that the tip of the tail of the gland is amputated and the cut end implanted into the jejunum The tail of the pancreas is really very short It is that narrow part of the gland which lies between the two layers of the lieno-renal ligament in contact with the inferior part of the gastric surface of the spleen In none of the cases in which we have done this operation has it been convenient to implant the tail of the gland into the jejunum The gland has always been transected through the body or, preferably through the neck, and it is the body or neck that has been implanted into the jejunum The operation of pancreaticolithotomy has sometimes to be done as a preliminary to pancreaticojejunostomy and it is not possible to scoop our stones from the head of the gland by way of an incision across the tail if the term 'tail' is restricted, as the anatomists restrict it to the part of the pancreas which lies between the layers of the lieno renal ligament In order to avoid a rather difficult distinction between "caudal pancreaticojejunostomy" and corporal" or "cervical pancreaticojejunostomy I would plead that the title 'retrograde pancreaticojejunostomy" be retained

Postgraduate Medical School of London
London W 12

IAN AIRD

CIRCUMCISION WITH BONE-CUTTERS

"SIR,—The method of circumcision performed with the aid of bone-cutters has very much to be said in its favour but many house-surgeons are loth to use it on account of the fear of accidentally removing the terminal part of the glans Moreover, through this not unfounded fear they may be over cautious when using this method only to find that insufficient foreskin has been removed. This is due to the fact that when the bone cutters are applied, it is difficult to feel the glans on account of the rounded blades of the bone cutters precluding the fingers

I have found that if the bone-cutters are applied initially in reverse (i e, with the flat surface proximal), the glans can be palpated easily during the application and there is no hazard of it being involved After one minute the cutters are removed and reapplied on the crushed foreskin with the flat part of the blade now distal. After a further two minutes the surplus skin is excised in the usual manner

St Bartholomew's Hospital
London E C 1

DAVID B L SKEGGS.

PROPHYLACTIC VALUE OF TYPHOID VACCINE

SIR,—The World Health Organisation's reports of field trials of typhoid vaccine in Yugoslavia[1] prompt me to write on our Indian experience with T.A.B inoculation The data which follow are taken from the reports of the health of the army, which are particularly informative because (a) the T.A.B inoculation-state of the army is always at least 80%; (b) the means of laboratory diagnosis is about as good as one could hope for in any controlled field trials; and (c) this community represents a comprehensive cross-section of the population in India

In the war years 1940–45, sanitary facilities were often inadequate for the rapidly expanding Forces Large numbers of recruits from all parts of India were camped in jungle areas where often the only source of water was shallow wells or ponds The incidence of the dysentery and diarrhœa group of diseases steadily increased the rate amongst Indian troops (418 per 10 000) being more than double that before 1940. But in the same period only 5 Indian soldiers in every 10,000 had enteric fever—a remarkable tribute to the value of preventive inoculation with T.A.B vaccine. Hardly thirty years ago, typhoid was one of the principal diseases among soldiers

In 1947 only 2 soldiers out of every 10 000 had enteric fever, though in those days of partition there were unprecedented movements of population in Northern India involving millions of refugees, among whom epidemics were rife and our troops were concentrated in the affected areas under very unhygienic conditions In the same year 355 soldiers out of every 10,000 had an illness of the dysentery and diarrhœa group, for which no prophylactic vaccine exists

The report on the health of the army for 1950–52 gives the incidence of enteric fevers as 1 3, 1 6, and 1 8 per 10,000 for the years 1950, 1951, and 1952 respectively During the same years the incidence of dysentery was 65 6, 55 4, and 47 6 per 10 000, and of diarrhœa from other causes, including enteritis, 83 1, 95 6, and 63 0 per 10,000

British experience in India is equally impressive In 1930–34 admissions of British troops to hospital for enteric fever were of the order of 30 in 10,000; in 1935–39 the figure was 13 in 1940–44 it was 11, and in 1945 it was down to 7 During the same periods the incidence of the dysentery and diarrhœa group of diseases was 406, 435 987, and 1229 per 10,000 per annum respectively

T A B vaccine used for the protection of Indian troops is a heat killed phenolised vaccine prepared by the Central Research Institute, Kasauli, from locally isolated smooth strains which are renewed at intervals The present evidence justifies the faith of the army authorities in phenolised T A B vaccine In this connection it is interesting to record the following statement of the Director of Medical Services in India in 1945[2]

> Following the sharp rise in the incidence of the enteric fevers among British troops in 1942, a rise which was not shared by the Indian troops it was decided that every British soldier as soon as possible after his arrival in India, should be given a boosting dose of 0 5 c c of the Kasauli vaccine, irrespective of when he had last been inoculated with the Home T.A.B vaccine That this policy was sound is not contradicted by the incidence of enteric fevers in 1943 During 1943 typhoid had decreased from 16 per 10,000 in the previous year to 7 per 10 000

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[1] Chron Wld Hlth Org 1956 10, 153

[2] Annual Report Health of the Army in India, 1943, 6 Pt. 1, p 16

Alcoholised T A B vaccine was never adopted for the Armed Forces in India

The decline in the incidence of typhoid fevers following prophylactic immunisation is considered one of the greatest achievements of preventive medicine today Better sanitation and improved environmental hygiene do not entirely account for the low incidence of typhoid fevers under conditions which show a striking increase in other bowel diseases

India House, London M L AHUJA

TO COMFORT ALWAYS

SIR,—It appears that that doughty crusader, Dr Learoyd (June 1), misunderstood what Sir Frederick Armer meant to convey in his recent address (May 18, p 1031)—namely, that the *proportion* of patients voluntarily seeking aid at our mental hospitals has gone up by leaps and bounds these past ten years, surely a welcome fact It is sad to think that a colleague who means and writes so well must express himself so unfortunately, all along, when it comes to psychiatry

But for correspondence in your columns, Sir, few of us would be able to quote (more or less aptly) the grand *guérir quelquefois, soulager souvent, consoler toujours,* which, as pointed out by your correspondents,[1] goes back to Hippocrates It is meant to comfort the physician, the tone being on guérir

Isleworth Middlesex H PULLAR STRECKER

DUODENAL ULCER TREATED BY GASTRO-ENTEROSTOMY WITH VAGOTOMY

SIR,—It is not for me to comment on the surgical aspect of Mr Hindmarsh's paper last week, but attention must be drawn to the reasons advanced in justification of the method of gastro enterostomy with vagotomy, because the deductions drawn from the results of experimental ulcer are not applicable to the spontaneous chronic ulcer as seen in man and are, therefore, inadmissible and misleading

Mr Hindmarsh says that "there is much evidence that the main factor in the causation of duodenal ulcer is the presence of unbuffered gastric acid combined with the free pepsin produced by psychic or nervous stimulation" and that "the flow of gastric juice under nervous stimulation may in itself produce the ulcer" I am unaware of any evidence in support of this assertion

The experimental evidence to which he refers shows clearly that the ulcers which are produced by the action of hydrochloric acid are exclusively formed in the alkaline milieu and have no relation whatsoever to the ulcer of the first part of the duodenum which has an acid milieu It is imperative to make this fundamental distinction in the location of the ulcer because for the ulcers which occur in the *alkaline* milieu—namely, the anastomotic, œsophageal, and Meckel's diverticulum ulcers—the action of hydrochloric acid by itself is sufficient to produce the lesion and its complications, whereas in contradistinction to the ulcers of the "ulcer-bearing area" which occur in an *acid* milieu, the action of hydrochloric acid by itself is not sufficient to produce the lesion A priori, it is not conceivable that any cell secretes a substance which by its own action may ultimately lead to its own destruction

An analogous situation may be observed in respect of bile, which performs its physiological function while it remains in its own milieu, the small intestine, but is violently destructive when it invades the stomach

Detailed evidence in support of this point of view will be found in a recently published monograph[2]

London W 1 J JACQUES SPIRA

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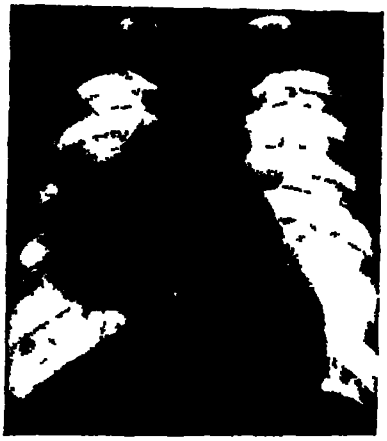
[1] Asholt O Michaelides G I *Lancet* 1957 i 576
[2] Spira J J Gastro Duodenal Ulcer London 1956

DERMOID OF THE CHEST

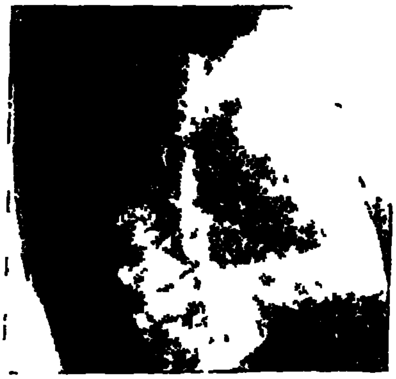
SIR,—Willis[1] defines a teratoma as "a true tumour or neoplasm composed of multiple tissues foreign to the part in which it arises" In the mediastinum a teratoma is almost always a benign cystic tumour of the anterior portion "Dermoid cyst" is a synonym for benign cystic teratoma Of 146 dermoid cysts seen in 1930-52 at the Lahey Clinic, only 2 were in the chest[2]

All teratomas are probably congenital, but, because of their situation and small size at birth, mediastinal teratomas are rarely discovered much before the end of the second decade of life, and sometimes not until after the third decade They grow slowly and accumulate hair, skin, bone, cartilage, teeth, and sebaceous material A mediastinal dermoid rarely gives rise to symptoms unless it ruptures,[3] and it is often an incidental finding in chest films taken for unrelated symptoms, or during a routine survey It was in this way that the following case came to light



A man, aged 27, was radiographed in Germany on March 26, 1956, with all the other people at the hostel where he was living An opaque mass was found in the right side of the chest, and I saw him in England on April 9

He had no symptoms Nothing abnormal had been seen in chest radiographs in 1948, 1949, and 1953 By courtesy of Dr W D R Thompson, medical director of the mass radiography unit, Pine Street, London, E C 1, I was able to see the one taken in October, 1953 Dr J McLaren, of St Thomas's Hospital, also saw this and considered it normal



The patient was admitted to St Thomas's Hospital on April 24, 1956 He had no physical signs The X ray appearances were those of a dermoid cyst in the anterior mediastinum The outline of the cyst was lobulated There was no evidence of calcification or teeth Tomography showed three areas of bone or calcification in one of the smaller lobules lying medially at the bottom There was also some peripheral diminution in density which could represent fat or sebaceous material, or possibly some necrosis breaking down Two male toad tests were negative and so were Wassermann and Kahn reactions Full blood count, erythrocyte sedimentation rate, and electrocardiogram were all normal

On April 30 he was operated upon by Mr N R Barrett The dermoid was larger than had been expected and was very firmly adherent to all structures with which it came in contact, particularly the upper and middle lobes of the lung, the peri cardium, and the great veins The cyst extended from the apex of the chest to the diaphragm, and passed across the midline beyond the aortic arch

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[1] Willis, R A Teratomas In Atlas of Tumour Pathology Armed Forces Institute of Pathology 1951 Section III F 9 p 7
[2] Colcock, B P Sass P F Staudinger L New Engl J Med 1955 252 371
[3] Hanten, S J Keyes T F Meyer P P *Radiology*, 1955 64 348

The vascular pedicle came from the vicinity of the left innominate vein, and the veins in the pedicle were almost as large as a man's little finger The tumour was lobulated, soft, and thin walled, and contained some solid nodules about the size of chestnuts from which long fair hairs were sprouting The cyst contained sebaceous material which was not infected Histologically it was a benign cystic teratoma

Convalescence was uninterrupted, and on discharge on May 18 he was well and radiographs of his chest were very satisfactory The patient is now very well and is playing tennis and swimming

The interesting feature of this case is the rapid growth of a presumably congenital tumour during two and a half years of adult life

R F GUYMER

London E C 3 Chief Medical Officer, Lloyds Bank

ANTIDIURETIC HORMONE AND SERUM OSMOLARITY IN LIVER CIRRHOSIS

SIR,—According to present knowledge, the liver is the most important site of inactivation of the antidiuretic hormone (A D H)[1] It has been assumed, therefore, that the oliguria and water-retention of advanced liver cirrhosis are partly due to impaired A D H inactivation in the diseased liver Many investigators have found abnormally large amounts of antidiuretic substances in the urine in liver cirrhosis with ascites, but others deny that there is such an increase Stein et al [2] could find no increase in antidiuretic activity in the plasma in liver cirrhosis The A D H bio assays in rats have not been sufficiently accurate, sensitive, or specific,[3] so that the importance of A D H in the pathogenesis of the ascites in liver cirrhosis has not been clarified

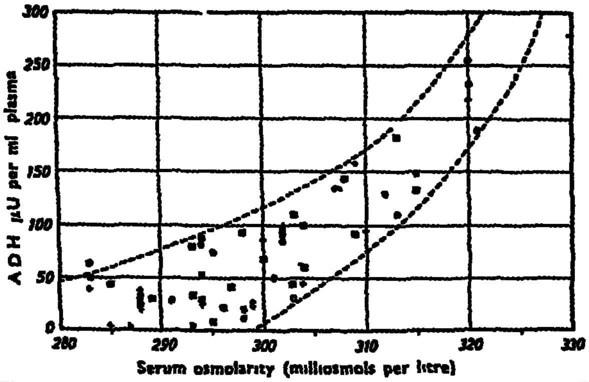

Fig 1—Plasma-A D H level and serum osmolarity in liver cirrhosis (■) and heart failure (●), and in normal adults (+)

Verney [4] demonstrated a relationship between serum osmolarity and diuresis, and it is assumed that hypo thalamic osmoreceptors control A D H secretion from the posterior pituitary We have therefore studied the relationship between serum osmolarity, cryoscopically measured, and antidiuretic plasma activity by a highly sensitive and specific bio assay of A D H on the toad *Bufo vulgaris* [5] This method is sensitive to 10–1000 µU per ml of plasma

There is a highly significant correlation ($P<0.001$) between plasma-A D H level and serum osmolarity (fig 1), which is independent of the nature of the disease, there is no difference between the findings in normal adults, patients with liver cirrhosis with and without ascites, and patients with heart-disease with and without water-retention No correlation was found with the degree of ascites or œdema formation

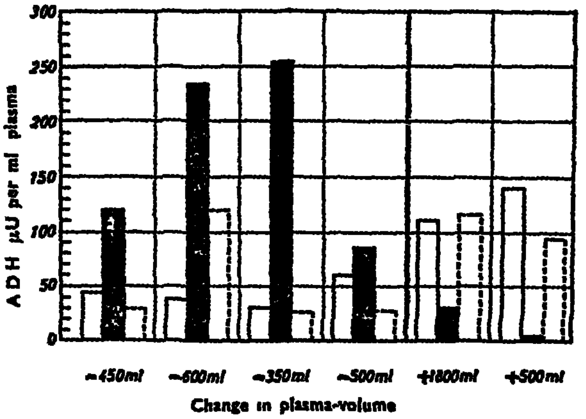

Fig 2—Plasma-A D H level and plasma-volume changes before and after paracentesis in 6 cases of liver cirrhosis, and levels expected from serum osmolarity ☐ Before paracentesis ■ After paracentesis ⌐ Change expected from serum osmolarity

Thus in liver cirrhosis and in congestive heart-failure, it seems that the discharge of A D H from the posterior pituitary is determined by the serum osmolarity and not by factors specific for the disease Delayed A D H inactivation by the diseased liver is also unlikely, since the balance between A D H release from the posterior pituitary and A D H inactivation in this disease is normal Thus in our opinion excessive liberation or persistence of A D H is not an important cause of water retention in diseases with ascites or œdema

There is, however, an exception to this correlation, in long-lasting plasma volume changes after paracentesis for ascites If the plasma volume is decreasing, the plasma A D H level increases considerably above that expected from the serum osmolarity In contrast, an increase in plasma volume causes a decrease of plasma A D H below the level expected from the serum osmolarity (fig 2) Under these circumstances the A D H secretion is, therefore, regulated not only by the serum osmolarity but also by the plasma volume [6–8] The inhibition of diuresis provides a quick replacement of plasma-volume Otherwise, in normal adults, in liver cirrhosis, and in congestive heart failure, water retention follows A D H production, which is stimulated by sodium retention

This work, which was supported by a grant from Deutsche Forschungsgemeinschaft, was published at length in *Klinische Wochenschrift* [9]

Medical Clinic I of the University
Munich E BUCHBORN

TREATMENT OF A DIABETIC DOG

SIR,—Memories of an unhappy Christmas Day vainly spent in trying to rescue my fox-terrier bitch from hypoglycæmic coma prompt me to warn Dr Howick Smith (May 18) that his canine patient may yet prove as fickle as some human ones

Judy, aged 10, developed severe diabetes with ketosis in the late summer of 1955 I started insulin therapy cautiously towards the end of October, and by December she was sugar free on a daily dose of insulin zinc suspension (lente) of 80 units and *no dietary restriction* Her weight rose from 19 lb to $24^1/_2$ lb and she enjoyed long rambles in the Surrey woods

Unlike Dr Howick Smith's dog, she was used to only one meal a day and this was in the evening This was her undoing because though she invariably ate her meal after the injection, she did not do so on Christmas Eve I made the mistake of leaving her unattended, confident that instinct would provide the necessary stimulus to eat her meal

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[1] Heller H Urban F F *J Physiol* 1935 85 502
[2] Stein M, Schwartz R Mirsky I A *J clin Invest* 1954, 33 77
[3] Van Dyke H B Adamsons K, Engel, S L *Recent Progr Hormone Res* 1955, 11 1
[4] Verney E B *Proc roy Soc* B 1947 135 25
[5] Buchborn, E *Z ges exp Med* 1955, 125 614
[6] Leaf, A, Mamby, A R *J clin Invest* 1952 31, 54
[7] Leaf, A, Mamby A R *Ibid*, p 60
[8] Henry, J P, Gauer, O H, Reeves, J *Circulation Res* 1956, 4 85
[9] *Klin Wschr* 1956, 34 953

Post mortem examination revealed no macroscopic evidence of disease The pancreas was small and islets were small and scattered but histological findings were unreliable because of post mortem changes

Buckhurst Hill Essex J T WRIGHT

COSTING IN THE CHEMOTHERAPY OF PULMONARY TUBERCULOSIS

SIR,—More patients are now encountered with tubercle bacilli which are resistant to one or more of the commonly used antituberculous drugs—that is, streptomycin *p* aminosalicylic acid (P A S), and isoniazid The following figures are based on a random sample of the patients now under treatment at this hospital

	No of patients
Total	177
Negative cultures since admission	73
Awaiting culture or sensitivity	31
Sputum positive	73
Showing partially or totally resistant strains to one or more drugs (streptomycin, P A S , isoniazid)	37
Percentage of *sputum positive* showing resistance	51

These are patients who for the most part have had chemotherapy before admission In your leading article of April 20, you drew attention to the observation that of 974 positive sputa obtained from newly diagnosed and untreated patients 5 1% showed resistance to one or more of the above mentioned drugs

Considering the price of "resistance" in terms of *£ s d* , the accompanying table shows the relative costs of treating patients with the various agents in use at this hospital, and is based on prices to hospitals, which are lower than those charged when the drugs are prescribed on form E C 10 It is evident that the drugs which we are now sometimes forced to use are very much more costly than the régimes in force hitherto It may be calculated that the cost of maintaining 1 patient for three months on a combination of viomycin and oxytetracycline is some £152 10*s* greater than the cost of streptomycin and P A S Thus in a hospital with a yearly average of, say, 10 patients on this régime the annual difference in cost would be £6100

Drug	Daily dose	Daily cost per patient
Streptomycin	1 g	1*s* 6½*d*
Isoniazid	300 mg	1*d*
P A S (mixture)	20 g	7*d*
P A S (cachets)	19 5 g	11*d*
P A S +isoniazid (combined in cachet)	18 g +300 mg	1*s* 3*d*
Viomycin	2 g twice weekly	7*s*
Oxytetracycline	5 g	28*s* 7*d*
Pyrazinamide	2 5 g	5*s*

These figures show that in addition to creating a major problem in treatment, the resistant bacillus may also be responsible for a progressive increase in the hospital's drug bill

Pharmaceutical Department
Sully Hospital
Penarth Glamorgan
G LENNOX

TELEVISION AND MEDICINE

LAST week Dr G B Stanford corrected our statement of May 25 that "the first colour television demonstrations of surgery in Great Britain will take place this summer" Messrs Pye Limited, of Cambridge now point out that in 1950 they installed equipment at St Thomas's Hospital for a five week series of operations televised in full colour to audiences which included an international convention of ophthalmic surgeons "This successful demonstration of the value of colour television excited considerable interest and was, in fact, the first time that colour television had been put to such a use in this country

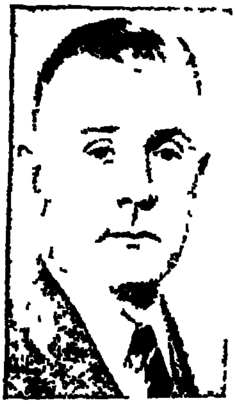
Obituary

ARTHUR GRIFFITH MAITLAND-JONES

O B E , M C , M D Lond , F R C P

Arthur Maitland-Jones will be remembered at the London Hospital as the first director of the children's department, which, especially in its early years, owed much to his clinical wisdom and unfailing kindness

He was born in 1890, the son of the late Rev Joseph Maitland-Jones, and he was educated at Taunton School and the London Hospital Having qualified in 1913, he held house-appointments there before he joined the R A M C on the outbreak of war in 1914 For his services he was twice mentioned in despatches, awarded the Croix de Guerre and the Military Cross, and appointed O B E



On demobilisation he returned to the London Hospital to work as an assistant in the medical unit, and he was associated with Panton and Riddoch in their work on the relation of hæmolytic disorders to pernicious anæmia During these years he took the qualifications for which there had been no time during his war service In 1921 he graduated M B with honours, and in the following year he became M D and M R C P Soon afterwards he was awarded a research fellowship at the Johns Hopkins Hospital in Baltimore, where he worked with Prof John Howland and had opportunity to develop his growing interest in pædiatrics On his return to this country he rejoined the staff of the London Hospital, and in 1924 he became physician in charge of the new children's department He was also appointed to the staff of the Infants Hospital, Westminster, and he was consulting physician to Dr Barnardo's Homes, the Royal Merchant Navy School, and the National Adoption Society He was a valued member of the expert committee of the League of Nations on infant and child nutrition

During the late war Maitland-Jones was hospital sector officer under the Emergency Medical Services and he was also senior hospital officer to Southern Command of the Army These were strenuous years of heavy responsibility, and after his retirement in 1945 he moved to the West Country where he had a farm A year ago he went north to Breconshire But even after he left London he continued to take a benevolent interest in his specialty He had served the British Pædiatric Association as secretary from 1934 to 1943, and in 1949 he was elected president Of his work for the association A A M writes

Arthur Maitland Jones did much to consolidate the pattern and standard of "Windermere" which Donald Paterson had set up Although he was out of sympathy with the change during the war years from what was called a friendly club to the association's concern for 'Medical Politics" (his capitals in a letter to the secretary) he continued to be a regular attender at the annual meetings and was happy in his year of presidency He was always courteous and particularly kind and welcoming to the younger generation who felt confidence in his realistic advice even if they did not always follow it Many will have a lasting memory of his boyishness his friendly smile and eager interest Maitland Jones also did much for the D C H examination to get it started and to see that a satisfactory standard was established He and Leonard Parsons were the first pair of examiners and successors learnt from them and passed on the knowledge of what was intended by this diploma Just after the end of the war he took charge of beds at Great Ormond Street for a period and he admitted in a charming letter at the end of his time there that he too had fallen under the spell of The Hospital for Sick Children which outsiders often regard as a form of arrogance It was typical of him to make this generous confession

Dr Maitland-Jones married in 1928 Miriam, only child of Dr John Ritchey of Oil City, Pennsylvania and she survives him with a son and daughter

EDWIN THOMAS HARRIES DAVIES

M D , M S Lond , F R C S

Mr E T H Davies surgeon to Tredegar Hospital died on May 14 He was a native of Carmarthen and was educated at the local grammar school, the University of Wales, and St Mary's Hospital, London As a student he won many scholarships and prizes at his hospital After qualifying in 1906 he held resident appointments there, and later he became surgical registrar to the London Temperance Hospital In 1908 he took the M.D and in 1910 the M S and F R C S He was the only successful candidate in the M S examination that year

In 1911 he began his work at Tredegar Besides his main hospital appointment he was medical superintendent of the Tredegar Medical Aid Society, medical officer of health for the urban district, and medical superintendent of the infectious-diseases hospital When he retired from his hospital appointment in 1949 a ward was named after him For some years he continued to hold a part-time surgical appointment under the Welsh Regional Hospital Board

I D. writes.

Tredegar was fortunate to secure Edwin Davies s services as surgeon to the former Tredegar Iron and Coal Company and he remained there throughout the whole of his professional life of nearly forty years He was skilled in all branches of surgery, including ophthalmic surgery I met him occasionally in consultation, for I was the visiting physician to his hospital It was soon evident that this densely populated industrial area had received the services of a first class surgeon and he maintained a high hospital standard throughout his working life He was also available for consultations by his colleagues in the town and district His enthusiasm and skill never diminished, and this large community will remember his devoted service and surgical skill.

Mr Davies leaves a widow and a daughter, Dr Caryl St John Davies

Dr HAROLD TRIMBLE

G S T writes

I would regard Harold Trimble as an international figure not only for his work on diseases of the chest but also for the way in which he fostered friendship between the medical profession of America and England He travelled widely all over the world his one idea to gain knowledge from others and cement friendship between the medical professions of the countries visited A man with a striking personality to meet him was at once to like him, and this soon grew to affection

He was always searching after new knowledge in his chosen subject of chest disease and even with his busy clinical life found time to be a member of many prominent committees, both on the administrative side of chest organisation and on the research side

Appointments

CALDWELL A S M B Glasg D.P H senior assistant M O Perth and Kinross

COTTON L T B M Oxfd F R C.S consultant surgeon King's College Hospital London and surgical tutor to the medical school

LAING NORA M L R.C P I assistant school M O Scunthorpe area of Lindsey

MERSKEY HAROLD B.M Oxfd assistant psychiatrist (S H.M O) Cherry Knowle Hospital Ryhope Sunderland

ROSS H S M B St And deputy physician superintendent (psychiatrist) State Mental Hospital and State Institution for Mental Defectives Carstairs Lanarkshire

Manchester Regional Hospital Board

DAWSON D W M.B Edin M R.C P E consultant pathologist north Manchester group of hospitals

MACAULAY DUNCAN M D Glasg M R C.P D C H consultant pædiatrician south Manchester group of hospitals

MARSDEN H B M.B Manc D C H D PATH consultant pathologist Royal Manchester Children s Hospital Pendlebury

MURRAY D B L.R.C P I D.A assistant anæsthetist (S H.M O), Blackburn and district hospitals

PANIKKAR SANKAR, M B Manc. F R.C.S D.L.O consultant E N T surgeon Blackburn and district hospital centre

RYAN D J M B N U I D A assistant anæsthetist (S H.M O) Wigan Leigh and Wrightington hospital centres

Notes and News

WORLD HEALTH ORGANISATION

AT the close of the World Health Assembly on May 24, the president, Dr S H Al-Wahbi of Iraq said he thought there was general agreement that the World Health Organisation was going in the right direction by devoting increasing efforts to the coördination of research in the control or eradication of disease This did not mean that W.H O was withholding assistance to projects for the control of disease in the field , for example, malaria had been eradicated in 10 countries or territories eradication was under way in 15, and had been initiated or planned in 38 The total population of these 63 countries, the president remarked, was 1211 million—almost half the population of the world

The Darling Foundation medal and prize for outstanding achievements in the control of malaria was awarded to Dr Paul F Russell, of the Rockefeller Foundation For his work in social medicine, Dr Marcin Kacprzak, of Poland, was awarded the Leon Bernard Foundation prize

On May 28 the executive board of W H O concluded a two day meeting under the chairmanship of Sir John Charles, chief medical officer of the Ministry of Health Among the technical reports whose publication was authorised were the fifth report of the expert committee on mental health, the third report of the I L O -W H O expert committee on occupational health and the first report of the expert committee on yellow-fever vaccine

APPROVED NAMES FOR DRUGS

THE British Pharmacopœia Commission has issued the following new supplementary list of approved names for drugs

Approved name	*Other names*
Amisometradine	6 Amino 1 methallyl 3 methylpyrimidine 2 4-dione Rolicton
Florantyrone	γ-Fluoranthen 8 yl-γ-oxobutyric acid Zanchol
Halothane	2 Bromo 2-chloro-1 1 1 trifluoroethane Fluothane
Norethandrolone	17α Ethyl 17-hydroxy 19 norandrost 4-en 3-one Nilevar
Pentacynium	4-(2-[N-(5-Cyano-5 5 diphenylpentyl)-N-methylamino]ethyl) morpholine dimetho chloride Presidal
Prochlorperazine	1-[3-(2-Chloro 10 phenothiazinyl)propyl] 4-methylpiperazine Compazine , Stemetil
Tolpronine	1 (1 2 3 6 Tetrahydropyridino) 3 *o* tolyloxypropan 2-ol Proponesin is the hydrochloride

A COURAGEOUS MATRON

Miss MacManus of Guy's has become a legend One of the most eminent nurses of her time, she played a big part in nursing affairs, travelled widely, and contributed much to the shaping of her profession She has written her memoirs,[1] an unusual and welcome action in a profession traditionally reticent about its personal life

She was the daughter of an Irish doctor in Battersea and niece of the Guy s superintendent s wife, Lady Perry, with whom she spent much of her girlhood It was natural, therefore, that she should exchange the Superintendent's House for the Nurses Home, where she qualified in 1912 In the 1914–18 war she was an Army sister serving mainly in France, and the account of her exciting and strenuous experience is the best part of the book After a short spell as matron of the Bristol Royal Infirmary she returned to Guy's and spent the rest of her career as its matron

The book will delight her many friends and admirers In it they may find themselves and certainly many they have known Miss MacManus s memory is capacious and retentive (or else she has very full diaries) and there is much detail In her memories of two wars, however, enjoyment of adventure and hardship has winnowed the chaff, and here the kind resourceful, and courageous woman shows herself in all her quality

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University College of the West Indies

Students at this college work for the M B , B.S degrees of the University of London At the examinations for these degrees held in Jamaica in April the following were successful

A St J P Jones S E H Brooks G S McLeod

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[1] Matron of Guy s By EMILY E P MACMANUS, C B E London Andrew Melrose 1956 Pp 228 25s

University of London

The title of reader in histochemistry has been conferred on Dr A G E Pearse in respect of his post at the Postgraduate Medical School of London

Medical Women's Federation

The first Christine Murrell fellowship has been awarded to Dr Ann Mullins for her research on disability resulting from obesity

Royal Medico-Psychological Association

Child Psychiatry Section —A meeting of this section will be held at 10 A M on Friday, July 5, at the Warneford Hospital, Oxford, when there will be a symposium on the longitudinal study of physique and personality in a group of children at 7 and 11 years The speakers will include Dr R G McInnes and Dr R W Parnell

Institute of Social Psychiatry

A course on the social approach to mental and emotional difficulties will be held from July 26 to 28 at Moor Park College, Farnham, Surrey Lectures will be given by Dr Joshua Bierer, Dr W Schindler, Dr E K Ledermann, Dr Kraupl Taylor, and Dr Paul Senft Further particulars may be had from the Institute, 9, Fellows Road, London, N W 3

Social Security Agreement with Sweden

The reciprocal agreement on social security between the United Kingdom and Sweden came into force on June 1

Under this agreement, British families will qualify for Swedish family allowances as soon as they become civilly registered in Sweden, and British tourists will be entitled to use the Swedish health services while they are in Sweden The agreement covers also the cash benefits provided by the two countries for unemployment sickness, maternity, old age, widowhood, orphanhood, and industrial injury

Index Ophthalmologicus

A new edition of the *Index*, containing a list of ophthalmologists in all parts of the world, will be issued for the 18th International Congress of Ophthalmology, to be held in Brussels in 1958 Any ophthalmologist who is not a member of the Faculty of Ophthalmologists or the Ophthalmological Society of the United Kingdom, and who wishes to have his name included in the list, is asked to write to the hon secretary of the society, 45, Lincoln's Inn Fields, London, W C 2, before July 31, 1957

Psycho-Endocrine Association

This association was formally constituted on May 21 at a meeting of the Psycho-Endocrine Research Group Its objects are to promote the study of the interrelationship between the endocrine system and mental functions, normal and disordered, to apply the knowledge of these principles to psychological medicine, and to provide a forum for the discussion of psycho endocrinological and related knowledge Anyone, at home or abroad, who wishes to apply for membership should write to the hon secretary of the association, St Ebba's Hospital, Epsom, Surrey The annual subscription has been provisionally fixed at 10s

Neurotics Nomine

The first public meeting of this organisation was held in London on April 29 Dr Joshua Bierer, who presided, said that the future of mental health depended more on public opinion than on what takes place in the consulting-room Mr Christopher Mayhew, M P, said that mental illness was the worst kind of illness and in terms of human suffering was Britain's biggest problem today The aims of the N N (Neurotics Nomine) group are

1 To help patients and ex patients to make contact with each other and with people living normal lives

2 To assist the patient to take the first steps towards more social living and readjustment

3 To support each other by meeting at home or talking over the telephone in an emergency

4 To provide a panel available to discuss or answer questions to an audience of general practitioners or members of social services who have contact with psychiatric patients

5 Generally to help remove the stigma and fear that still surrounds mental illness

6 To help the members themselves in their own integration by providing, through these activities opportunities for useful work, social contacts, and self expression

The hon secretary may be addressed at 9, Fellows Road, London, N W 3

British Medical Association

Dain Fund —During 1956-57 the fund has spent £1460 in helping sixteen cases, including three new ones All the children whom the trustees have been helping for some years are making good progress at their schools and universities

Royal College of Nursing

Miss Catherine Hall, S R N, has become general secretary of the college in succession to Miss Frances Goodall, O B E, S R N, who has retired

Institute of Dermatology, London

A semipermanent exhibition, by Dr R H Meara, on the xanthomatoses, will be available at the institute, Lisle Street, W C 2, till June 29

A course is to be held from Sept 16 to 20 for general practitioners, especially those working in dermatological clinics Applications should be sent by July 8 to the dean of the institute

Hospitals' Symphony Orchestra

This orchestra is holding a concert on June 26 in the library of St Mary's Hospital School, London, W 2 Tickets (7*s* 6*d*, 5*s*, and 3*s* 6*d*) can be had from Miss M A Whipp, A M I A, the Secretary, South Western Hospital, Landor Road, Stockwell, S W 9

Medical Golfing Society

At the summer meeting of this society at Sunningdale the winners were

Lancet Cup (Scratch)—Dr F B Briggs (3) 74
Henry Morris Cup—Dr A A M Reckie (9) 1 up

Diary of the Week

JUNE 9 TO 15

Tuesday, 11th

INSTITUTE OF CHILD HEALTH The Hospital for Sick Children, Great Ormond Street W C 1
5 P M Prof T P Magill (New York) The Recurrence of Epidemic Disease

INSTITUTE OF DERMATOLOGY, Lisle Street, W C 2
5 30 P M Dr R H Meara Less Common Skin Diseases of Infancy and Children

Wednesday, 12th

UNIVERSITY OF LONDON
5 P M (Westminster Medical School, Horseferry Road S W 1) Dr Andre Cournand (New York) The Syndrome of Alveolar Hypoventilation

ROYAL SOCIETY OF MEDICINE 1, Wimpole Street, W 1
4 30 P M *Physical Medicine* Dr A C Dornhorst Dr J L Livingstone, Dr D A Brewerton Breathing Exercises—Are they of Value ?

INSTITUTE OF DISEASES OF THE CHEST, Brompton, S W 3
5 P M Dr W D W Brooks Prevention of Pulmonary Tuberculosis

INSTITUTE OF DERMATOLOGY
5 30 P M Dr Henry Haber Histopathology of some Rare Skin Conditions

UNIVERSITY OF OXFORD
5 P M (Radcliffe Infirmary) Prof H de Watteville Nutritional Deficiencies During Pregnancy and their Influence on Fœtal Development (Litchfield lecture)

Thursday, 13th

ROYAL SOCIETY OF MEDICINE
5 P M *Ophthalmology* Dr John Gloster, Mr E S Perkins Dr C R S Jackson Tonometry

INSTITUTE OF DERMATOLOGY
5 30 P M Dr C D Calnan Hæmangiomata—Classification and Treatment

HONYMAN GILLESPIE LECTURE
5 P M (University New Buildings, Teviot Place Edinburgh) Dr J G Macleod Unsuspected Thrombosis

Friday, 14th

POSTGRADUATE MEDICAL SCHOOL OF LONDON Ducane Road W 12
10 A M Prof D M Douglas Dr K G Lowe Patent Ductus Arteriosus
4 P M Dr J D N Nabarro Modern Methods of Assessing Adrenal Cortical Function

ST MARY'S HOSPITAL MEDICAL SCHOOL W 2
5 P M Mr Aleck Bourne Physiology of Menstruation

INSTITUTE OF OBSTETRICS AND GYNÆCOLOGY
3 P M (Hammersmith Hospital, Ducane Road, W 12) Dr Elizabeth Tylden Psychiatric Problems in Pregnancy

MIDLAND CENTRE FOR NEUROSURGERY, Holly Lane Smethwick Birmingham
8 P M Prof K J Zülch (Cologne) The Clinical Value of the Morphological Classification of Cerebral Tumours

Saturday, 15th

INSTITUTE OF OBSTETRICS AND GYNÆCOLOGY
11 15 A M (Chelsea Hospital for Women, Dovehouse Street, S W 3) Mr K V Bailey Utero vaginal Prolapse

MECHANICAL FACTORS IN ATHEROSCLEROSIS

J B DUGUID
M.D. Aberd.
PROFESSOR OF PATHOLOGY

W. B ROBERTSON
B Sc, M.B St And
DEMONSTRATOR IN PATHOLOGY

UNIVERSITY OF DURHAM

THE question of diet in atherosclerosis has occupied so much attention in recent years that the mechanical factors recognised by the older writers seem almost to have been forgotten

More than thirty years ago one of us (Duguid 1926) wrote emphasising the importance of taking functional activity into account in interpreting arterial lesions, and suggesting that atheroma (as it was then called) represented a form of mechanical injury brought about by the discordant movements which followed loss of elasticity of the intima Of late we have been concerned with the thrombogenic hypothesis in relation to atherosclerosis, but we have seen nothing to make us wish to modify the mechanical one put forward in 1926 On the contrary, we have found evidence to support it, and are more than ever convinced that there can be no clear understanding of atherosclerosis until the mechanical factors concerned in arterial function are taken into account The mechanical hypothesis and the thrombogenic are complementary and should be considered in conjunction

Functional Activity of Arteries

The mechanical hypothesis is based on the assumption that the aorta and larger arteries dilate and recoil with each pulse beat This, we must admit, has been called in question It has been stated that the arteries, except the aorta, are kept at an even calibre by contraction of their medial muscle Though we do not believe that this view is widely held, we feel that it has to be considered, if only to bring out certain points which have a bearing on the distribution of the lesions

When a volume of blood is expelled from the left ventricle at systole, the aorta must dilate to accommodate it, and so to some extent must its larger branches It is true that as the pulse wave travels towards the periphery it is gradually smoothed out and dissipated by the elastic yielding of the arterial walls, hence in the smaller vessels the stream becomes practically an even flow, but that is one of the points on which the mechanical hypothesis is based It is not in the smaller vessels that atherosclerosis tends to develop but in the aorta and the coronary and other medium-sized arteries which receive most of the impact of ventricular systole The lesions develop mainly at bifurcations, branchings, and flexures where the stream strikes directly against the vessel walls, they are most prominent in arteries which, being loosely supported, are less restricted in movement (e g, the extramural coronaries and the cerebral arteries), they are prevalent in such conditions as hypertension where the pulse pressure is high, and in short they abound wherever and in whatever conditions pulse movements are accentuated

If, as is generally acknowledged, the conversion of the blood-flow from an intermittent to a continuous one depends on the elastic yielding of the arterial walls, then there must be movements of the walls How great these movements are, or how far they are carried towards the periphery, is uncertain, but in so far as they are known to occur they must be regarded as potential sources of strain

Arterial Structure

To understand the possible effects of pulse movements it is necessary to consider certain peculiarities of arterial structure The arteries are elastic tubes composed of at least three different tissues—muscle, elastic tissue, and fibrous tissue Since these differ in their elastic properties, the efficiency of the structures as a whole depends to a great extent on the special arrangement and freedom of interaction of these elements It should be understood that, although muscle predominates in many of the arteries, there is no question of a muscular contraction and relaxation at each pulse beat Muscular contraction is concerned with the tone of the arteries, which determines their mean diameter relative to the blood-pressure, but muscle is also elastic and can therefore be stretched and will recoil again to its original length when the stretching force is removed This is the property which enables the arteries to dilate and recoil with the pulse beats

It is sometimes thought that the elasticity of arteries depends essentially on the so-called elastic tissues they contain, but, judging by the appearance of the elastic laminæ in histological sections, the elasticity of these is not of a very high order In this connection there is a fundamentally important point which is commonly overlooked MacWilliam and Mackie (1908) showed that arteries contract after death, and that the degree of contraction is indicated by the wavyness of their elastic laminæ and the wrinkling of their intimal surfaces This is important in two respects (1) it means that most arteries examined are in a state of post-mortem contraction, a fact which should always be taken into account in interpreting pathological appearances; and (2) it shows that the elastic laminæ cannot shorten to the same extent as the muscle and so have to adjust themselves by folding or wrinkling The same applies to the fibrous tissue of the intima, which is usually finely wrinkled in sections

Since it is obvious that all these tissues have to stretch to the same point when the artery is dilated, it follows that the muscle, which is responsible for the contraction, has a greater range of recoil than either of the other elements—in other words, a greater degree of elasticity This may seem trivial but it is important, not so much as a measure of the elasticity of the various elements as in the fact that it illustrates how the elements adjust themselves to movements beyond their contractile range From it we see that for complete functional efficiency there must be looseness and flexibility of the tissues

Mechanical Hypothesis

The suggestion put forward in 1926 was that impairment of the elasticity or flexibility of the intima of an artery must lead to just that kind of structural disorganisation which is seen in atherosclerosis In that condition there are dense fibrous thickenings which obviously stiffen the intima, and their disruptive effects are brought into prominence by post mortem contraction In the atherosclerotic aorta, for example, the thickened intimal plaques, being too stiff to conform in the normal way to the contraction, become coarsely crumpled, with the result that in parts they bulge into the lumen and are torn away from the media (fig 1) Post mortem contraction, it was suggested, is merely an exaggerated recoil, and the pulse movements in life, although more limited, must have similar effects Accordingly atheroma

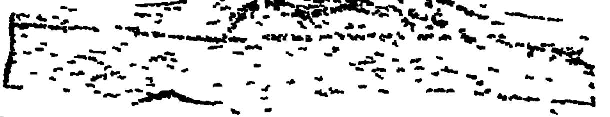

Fig 1—Atherosclerotic plaque in aorta (frozen section) post-mortem contraction has caused the stiffened intima to buckle inwards and become loosened from the media. It is suggested that the same effect is produced by pulse movements in life, and that the spaces so formed becoming filled with fatty debris, constitute atheromatous foci (Hæmalum × 10)

was viewed as the tearing and destruction of tissues which resulted from thickening and loss of elasticity of the intima

This conception was but a slight modification of a view which had long been current, Virchow having regarded atheroma as a loosening of the tissues of the intima Later Aschoff, in Germany, and Sir Clifford Allbutt, in this country, described it as an effect of shearing between the layers, and though all these authorities recognised pulse movements as the damaging forces they ascribed the damage to overdistension of the arteries rather than to the elastic recoil, and imagined a sliding of one coat over another rather than a tearing apart of the layers

The new hypothesis had little appeal since it was based on a post mortem appearance which had no ascertainable relationship to conditions in life Even on the assumption that the arteries moved with pulsation, it could not be claimed that any pulse movement would be comparable with the contraction occurring in an artery when it is emptied of blood, and there seemed to be no way of showing that the elastic recoil in life could ever be forceful enough or extensive enough to injure the tissues in the way suggested The apparent bulging of the intima in atherosclerosis had always been taken for a swelling or proliferation of the tissues together with an accumulation of fat, and in view of this apparently straightforward explanation the crumpling idea seemed a little fanciful Moreover it did not adequately explain the two most important processes in atherosclerosis—fatty change and fibrous thickening Ever since Anitschkow showed that a cholesterol rich diet produced lipoid deposits in the arteries of rabbits, it had been taken for granted that fatty change was the primary and essential one, and no theory which did not explain it was likely to be acceptable

Nevertheless the new hypothesis was of value in that it provided a fresh way of looking at arterial diseases, and one by which many of the old-established notions would not bear scrutiny There was, for example, one important feature of atherosclerosis which was commonly interpreted in a way that could not easily be reconciled with the mechanical point of view—namely, narrowing

It had always been taken for granted that the narrowing of arteries was due to overgrowths of the intimal fibrous tissue encroaching on the lumina, but, when functional activity was taken into account, this seemed very unlikely Arteries are elastic tubes, dilating and recoiling with each pulse beat, and, whereas the dilatation is a movement imposed on them by the pulse pressure, the recoil is a function of their own elasticity, and anything like a fibrous overgrowth which reduces this must interfere with their ability to recoil They will thus be left in the more or less dilated position and, deprived of their elasticity, will be likely to stretch progressively under the influence of the blood-pressure

To those accustomed to the orthodox view this may seem an awkward line of reasoning, but it is largely borne out by the vast majority of atherosclerotic lesions In them the arteries are for the most part wider than normal, and it is only occasionally and in some parts that they are narrowed, but the narrowing, when it occurs, tends to dominate the picture, with the result that it has come to be regarded almost as an essential part of atherosclerosis

Thrombogenic Hypothesis

It was, as we have stated, difficult to see how an overgrowth of the intima could narrow an artery, but the fact remained that the arteries were in some instances narrowed, and it seemed that some explanation other than an overgrowth was to be found One could imagine various ways in which the lumen of an elastic tube could be reduced, the simplest being by partially occluding it by solid matter, which was exactly what happened when a mural thrombus formed in an artery, but in the early part of this century arterial thrombosis, apart from total occlusion, was not regarded as very common, and it did not therefore suggest itself as a likely solution to this problem Nevertheless a search was made in cases of coronary and aortic atherosclerosis for evidence of mural thrombosis, and the results were surprising (Duguid 1946, 1948) Thrombi of all kinds were found with astonishing frequency, ranging from large masses of red clot, almost occluding the lumina of the arteries, down to thin mural deposits of fibrin, so small as to be hardly detectable Some were freshly formed and others partly organised, and from a comparison of the various examples it soon became evident that thrombosis, instead of being an occasional complication of atherosclerosis, was an important factor in its pathogenesis

When a mural thrombus forms in an artery it becomes covered with endothelium and is incorporated in the vessel wall, with the result that, on subsequently being organised, it forms a fibrous thickening of the intima The endothelium is in fact an adjustable membrane (Duguid 1952) capable of rearranging itself so as always to interpose a cellular lining between solid matter and the blood-stream, and by this mechanism tissues which form part of a vessel wall may actually have originated as hæmatogenous deposits in the lumen Mural thrombi, especially if they are of the red type, commonly undergo fatty change and thus assume the characters of atherosclerotic plaques, and there is good reason to believe that a considerable proportion of the lesions classified as atherosclerosis are altered thrombi

The thrombogenic hypothesis has been confirmed by a number of observers, including Harrison (1948), Geiringer (1951), Heard (1952), Crawford and Levene (1952), Morgan (1956), and others, and thus, out of the application of the mechanical hypothesis, the long forgotten teaching of Rokitansky was revived and a new principle in arterial pathology established in the light of which much of arterial pathology needs to be reconsidered

It is therefore easy to see how narrowing of the arteries is brought about, and it may seem surprising, in view of the frequency of mural thrombosis, that narrowing is not more constant But there is, as we shall show, a compensating mechanism whereby that danger is usually averted

Effects of Mural Thrombosis

There can be no doubt that the incorporation of a mural thrombus into the intima of an artery reduces both the elasticity and the flexibility of that coat Mural thrombi, when newly formed, may be relatively soft and plastic, but under the influence of the pulse pressure they are soon beaten into compact layers of hyaline substance, and when they are converted into fibrous masses they affect the vessels in various ways according to their relative size In the first place, quite apart from their occluding effects, they may, if large and firm, practically immobilise the particular segments of the vessel walls to which they are attached, and, when they do so, the walls are fixed nearly always in the dilated position

To understand this fundamental point it is necessary to remember that the thrombi, if they leave enough room for an effective blood stream to pass, immediately come under the influence of the blood-pressure and have to conform to such movements as it imposes They have to accommodate themselves to the shape of the vessel wall at the height of the pulse wave, and, being more plastic than resilient, they become moulded to that shape, so that when they are subsequently converted into fibrous tissue they may, if firm, virtually clamp the vessel wall in the dilated position Thus mural thrombi, although they at first reduce the lumina of the arteries, tend to increase their mean diameter, thus cancelling out the initial narrowing, if it is not too great When this effect is coupled with the progressive dilatation which follows loss of elasticity, the compensation may be more than adequate. Consequently atherosclerotic arteries, even when greatly thickened, are often wider than normal—the "senile ectasis" of Aschoff (1937)—and it is only when relatively large thrombi form in small vessels that there is absolute and permanent narrowing.

Smaller thrombi, on the other hand, have a more localised effect; and this, we believe, is what constitutes the atherosclerotic process. A thrombus may be too small to interfere with the resilience of the vessel wall, but if it cannot move in unison with the rest of the structures it is bound to create local discord, and, if movements continue in spite of it, something has to give way. In the contracted artery post mortem we have seen what may happen, but it remains to be shown that the same happens in the living artery, and it is in this connection that intimal hæmorrhage is significant.

Fig. 2—Atherosclerotic plaques in aorta, showing thickened intima coarsely crumpled and in parts loosened from media. Dark patches at angles of separation represent hæmorrhages. (Direct photograph × 10.)

Intimal Hæmorrhage

The transformation of mural thrombi into fibrous thickenings has been adequately described elsewhere, but there is one feature to which we must draw special attention because it concerns the evidence we present. Where large thrombi are concerned, a full-scale process of organisation is established, such as is seen in a fibrinous exudate. Capillaries enter from the lumen of the vessel and from the vasa vasorum (Geiringer 1951, McLetchie 1952) and invade the mass, vascularising the intima. Since many of these new vessels remain after the organisation is completed, they become a feature of advanced atherosclerosis. Such vessels may be a source of hæmorrhage, and it is in this we find the evidence of mechanical effects.

Intimal hæmorrhage has long been recognised as a feature of atherosclerosis, but special attention has been paid to it in recent years, chiefly as a result of the detailed studies by Winternitz et al. (1938), Paterson (1938), and Wartman (1938). It is perhaps unfortunate that some of the most conspicuous examples are seen in cases of fatal coronary thrombosis, and that more attention has been paid to these, and their possible relationship to coronary occlusion, than to the small and inconspicuous extravasations of blood which are far commoner and in our opinion no less significant.

These small extravasations are usually seen in the deeper layers of the intima and quite unconnected with the surface, so there is no reason to suppose that they play any part in fatal occlusion. They often consist of no more than a few erythrocytes lying free in the tissues, and where there is much fatty change they are easily overlooked. Winternitz et al. noted that they were often situated at the margins of the atheromatous foci, but they related this to the fact that vascularisation was plentiful in these areas, and, beyond remarking that mechanical factors might play a part in their production, they did not connect them with injury. Nevertheless these extravasations occur just at the points where the layers of the intima are apparently being torn apart, and their presence seems fairly clear proof that the tearing has occurred in life.

Our attention was first drawn to this in a common iliac artery excised surgically because it was occluded. The intima in this vessel was greatly thickened by several layers of fibrous tissue, one of which was fractured. The fracture might have passed as an artefact, caused by rough handling, had there not been signs of old hæmorrhage around it, showing that it had taken place some time before the vessel was excised.

This observation led us to look for other evidence of the same kind, and one of the first coronary arteries to be examined with this in mind provided it. In this vessel there was a patch of thickened intima canted upwards and thrust into the lumen, so that it was almost severed from the neighbouring part, and again there was antemortem hæmorrhage at the point of tearing.

Of 50 cases of severe coronary atherosclerosis, not all with fatal occlusion, we found hæmorrhages in 33. These hæmorrhages were typical examples of a condition with which we had long been familiar, but it was not till we came to study their exact situation that their significance became apparent. In 16 of them they were almost all at the margins of the atheromatous foci, just at the points where the layers of the intima were being torn apart, and even in the other 17, where the extravasations were more widespread, there were usually some points of leakage in these same situations.

This feature is most easily demonstrated in the aorta. For example, fig. 2 shows a patch of thickened intima coarsely crumpled and partially torn away from the media in several places, the dark patches at the angles of separation are hæmorrhages. This finding, which is by no means uncommon, seems to provide the strongest support for the mechanical hypothesis, for it indicates, as clearly as any histological sign could, that the same forces as tear the layers of the intima apart in post-mortem contraction are also in operation in life and are a source of injury to living tissues.

Hæmorrhage and Atheromatous Degeneration

One of the deficiencies of the mechanical hypothesis as put forward earlier in this paper was the fact that it did not explain the fatty changes in atherosclerosis. It was subsequently noted incidentally that mural thrombi themselves undergo fatty changes, but it was not suggested that all the fatty debris which accumulates in atherosclerosis is derived from thrombi. The debris is altogether too plentiful, and the accumulations occur in the deeper layers of the intima, beneath the thrombi, rather than in them, so obviously there must be some other sources of the fat. The view we now wish to bring forward was prompted mainly by a demonstration by Dr A. D. Morgan to the Pathological Society of Great Britain and Ireland in January, 1956.

Morgan recalled that Winternitz et al. in 1938 had suggested that atheromatous material was derived from intimal hæmorrhage, but it was his own demonstration that convinced us of the truth of this and showed how the thrombogenic hypothesis could be linked with the mechanical one. In his monograph on *The Pathogenesis of Coronary Occlusion*, Morgan (1956) concludes that the cholesterol and other fatty debris in atherosclerosis are products of blood destruction and can be accounted for by small hæmorrhages recurring over long periods. Our own findings confirm this. The hæmorrhages almost always communicate with the atheromatous foci, and disintegrating corpuscles are usually so intimately mixed with lipoid droplets, cholesterol crystals, hæmosiderin, ceroid pigments, and other debris that it is hard to avoid the conclusion that the larger atheromatous accumulations are the products of recurring hæmorrhages.

It would hardly seem prudent at this stage to suggest that all the fatty changes in atherosclerosis could be products of hæmorrhages or thrombi, since neither hæmorrhages nor thrombi are detectable in most of the early lesions. Yet Paterson et al. (1956) have reported that iron pigment is demonstrable even in the very early fatty lesions, and we have been able to confirm this. Since blood is the most likely source of such pigment, we are forced to conclude that intimal hæmorrhage must be commoner than is generally supposed. It is perhaps difficult to accept the idea of hæmorrhage where there is no vascularisation of the intima, but it should be recognised that, in the arterial walls, there are peculiar physical conditions making the introduction of blood into the intima possible without vascularisation, especially when there is no great thickening.

Many writers have discussed the question of tissue pressure in relation to permeation of the arterial walls by fluids and hæmorrhage (Drury 1954), but few have taken into account how pressure may be affected by pathological processes. In the normal artery the intimal tissues are constantly under a positive pressure which varies with pulsation, but the same conditions do not necessarily obtain in the atherosclerotic artery. When, during recoil, the thickened intima is crumpled and loosened from the media, there must be phases of reduced pressure at the points of loosening, with the result that fluids are drawn in to fill the spaces thus formed. The most readily available fluids are blood and plasma, and the fact that fats are found need not be surprising in view of the fact that these fluids may be rich in lipids. It seems hardly necessary, therefore, to postulate disturbances of the lipid metabolism, or specific affinities on the part of the arterial tissues for lipids, to explain the presence of these substances in the arterial walls.

Experimental Evidence of Mechanical Factors

In 1933 Harrison recorded some experiments which seem never to have received due attention. He produced cholesterol lesions in rabbits previously treated with large doses of calciferol to produce medial calcification of their aortas. Whole segments of their aortic walls were rigidly calcified; and, when the affected rabbits were later given the standard cholesterol treatment, only the parts of their aortas which still remained mobile developed cholesterol deposits, while the rigid parts remained free. The only exceptions were one or two instances where the rigid layers had fractured and presumably injured the overlying intima, which was heavily infiltrated with cholesterol at these points. In most of the cases, however, the greatest depositions were immediately around the margins of the calcified areas, where local discord was likely to have been most acute.

If there is anything to be learned from experiments on animals regarding the cause of atherosclerosis, surely it is that movement is the crucial factor. Cholesterol experiments have repeatedly been cited as evidence that fats are the prime factors in atherosclerosis, but Harrison's experiments *show that cholesterol is merely a very* effective "marker" of structural damage which is otherwise obscure. Aschoff (1924) stated that: "The lipoid concentration of the food does not cause atheroma, but essentially influences the characters of the atheromatous patches by determining the presence or absence of fatty change," and Harrison's experiments seem to bear this out.

We have also seen this borne out in the recent case of a coloured Jamaican who died of carcinoma of the liver. He was so emaciated that even the atheromatous fats in the aorta and coronary arteries were replaced by a gelatinous substance. The arteries were in no way improved by this, however, for there was still the same structural disorganisation. There was, in fact, still the same degree of atherosclerosis, but the character of the atheromatous patches was influenced by a shortage of fats.

The Genesis of Atherosclerosis

It has been shown how mural thrombosis leads to atherosclerosis, but little has been said about the cause of the thrombosis itself. The factor commonly cited is damage to the vessel walls, and the findings in atherosclerosis bear it out, since most of the recognisable thrombi in that condition are associated with lesions of the underlying intima. Atherosclerosis is itself a form of damage and tends to promote further thrombosis; so the typical plaque is often built up of successive fibrin deposits, one on top of another in a laminated formation; but how the process begins in the first place is a more difficult problem.

There are many conceivable ways in which the internal lining of an artery may be damaged, and to cite any one as the primary lesion in atherosclerosis can only be speculative. Atherosclerosis begins in childhood (Geringer 1948), and in the arteries in children it is often difficult to distinguish normal changes from pathological ones. In man there is a progressive fibrous thickening of the intima of the larger arteries almost from birth, and so universal is this that it can be taken as a natural growth process. One might therefore hesitate to compare it with atherosclerotic thickening, yet Levene (1955) has found that, even in the aorta of young children, the subendothelial layers contain fibres which in their electron microscopic pattern resemble fibrin. If his findings are confirmed, we may have to conclude that in normal development, as well as in atherosclerosis, the intima is increased by the incorporation of solid matter from the blood stream.

We are accustomed to thinking of normal growth processes as beneficial, and we assume that, so long as these natural thickenings of the intima are even and uniform, harmony would be maintained; but in point of fact they seldom are uniform. Even in young children the intima of the aorta around the openings of the intercostal arteries is usually thicker than elsewhere, and it is perhaps significant that these are the sites of the earliest fatty streaking in young people as well as of some of the severest lesions in adults. It seems likely that even the slightest local overloading of the intima with fibrous tissue may interfere with coordination of the structures, and, although in ordinary circumstances a slight stiffening may be tolerable, it must nevertheless reduce the ability of the tissues to adapt themselves to any increased vascular activity that may arise. Thus even in our natural growth processes there may be the potentialities of disease.

Dangers of Atherosclerosis

We are therefore forced back to the position of the older writers who regarded atheroma as part of the wear and tear of life, and this, in view of the increasing incidence of deaths from coronary disease, may seem alarming. It need not unduly disturb us, however, for coronary disease is not quite the same as atherosclerosis. "Coronary disease" is a clinical term implying narrowing or occlusion of the coronary arteries, and narrowing is not an essential part of atherosclerosis. There can be severe atherosclerosis of the coronary arteries, for instance, without any narrowing, just as there can be fatal narrowing without much atherosclerosis. Hence the death-rate from coronary disease in a community is no reliable gauge of the prevalence of atherosclerosis.

This may seem paradoxical in view of our contention that atherosclerosis and arterial narrowing are both products of thrombosis, but it must be appreciated that thrombosis is a double-edged process. It may on the one hand be part of a natural protective or reparative mechanism, or it may on the other be a dangerous pathological process; and the thrombi which are responsible for atherosclerosis may be quite different in their nature from those which cause occlusion. Atherosclerosis is universal in adults, and all adults have thrombosis in their coronary arteries from time to time, but so long as the thrombi are small no great harm is done There are factors in the blood or in the tissues which control thrombosis and keep it within safe limits, and it is when such factors fail that the process gets out of control and becomes a danger That state of affairs is a complication of atherosclerosis rather than an essential part of it

It is beyond our present scope to discuss the factors which govern thrombosis Astrup (1956) has referred to the multiplicity of agents, activating and inhibiting, which maintain the equilibrium between the formation and removal of fibrin in the living body, and in summarising them has made a strong case for regarding fibrinolysins as the critical factors Mole (1948) has made similar suggestions and it seems clear that fibrinolysins are among the first problems to be tackled in the campaign against coronary disease

Uncomplicated, or simple atherosclerosis (if we may use the term), is a very different problem Although thrombosis plays a part in its development, it is a relatively benign part, and if we are to treat the condition as an evil whose cause must be eliminated we have far fields to explore in seeking the cause In the past thirty years medical thought has tended to veer away from the idea of wear and tear and to ignore mechanical factors, perhaps because these factors have been rather vaguely represented, but it is doubtful if any worker in this field would entirely rule them out For our part, we have repeatedly asked ourselves what must happen when a layer of relatively inelastic material is fixed to the inner surface of a pulsating elastic tube, and the answer has always been something which in its general configuration would reproduce very closely what is found in atherosclerosis

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PROGNOSTIC FACTORS IN MYOCARDIAL INFARCTION

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From the Radcliffe Infirmary Oxford

(*concluded from p 1161*)

LONG-TERM PROGNOSIS

WE have already shown that, of 543 patients with myocardial infarction admitted to the Radcliffe Infirmary in 1940–54 195 died within eight weeks—a period arbitrarily selected as covering the acute attack Thus there were 348 survivors of the acute attack We review here the prognostic factors influencing the course of these survivors

TABLE XXX—NUMBER OF DEATHS IN REMAINDER OF THE FIRST YEAR IN DIFFERENT TREATMENT-PERIODS

Period	No surviving acute attack	Deaths in remainder of first year	
		No	%
I (1940–47)	66	10	15 2
II (1948–51)	105	14	13 3
III (1952–54)	177	25	14 1
Total	348	49	14 1

TABLE XXXI—DEATHS AMONG SURVIVORS OF THE ACUTE ATTACK IN REMAINDER OF THE FIRST YEAR

Sex	Good risk			Bad-risk		
	No of patients	Deaths		No of patients	Deaths	
		No	%		No	%
Male	127	7	5 5	110	26	23 6
Female	50	3	6 0	61	13	21 3
Total	177	10	5 6	171	39	22 8

Findings

Prognosis during the Remainder of the First Year

The chance of dying during the remaining ten months of the first year was still considerable. 49 patients (1 in every 7) died in this period The majority of these 49 deaths were in the earlier months after the acute attack—33 in the first four months In other words, about 10% of the survivors of the acute attack died during the succeeding four months During the period covered by our study (1940–54), there has been no improvement in this respect (table XXX)

Some individual factors are of considerable importance in determining prognosis during this first year We have confined ourselves to clinical factors which can be recognised early in the course of the acute attack From our own data the important factors associated with a bad prognosis in patients who survive the acute attack are

TABLE XXXII—DEATHS AMONG TWO MAIN AGE GROUPS IN REMAINDER OF FIRST YEAR

Age (yr)	Good risk			Bad risk		
	No of patients	Deaths		No of patients	Deaths	
		No	%		No	%
Under 60	100	5	5 0	63	12	19 0
Over 60	77	5	6 5	108	27	25 0

(*a*) Evidence of cardiac distress in the early days of the acute attack (1) cardiac failure, either left ventricular or congestive, and not necessarily severe, (2) cardiac arrhythmia (auricular fibrillation or flutter, or multiple extrasystoles), or (3) gross cardiomegaly

(*b*) A history of a previous attack of myocardial infarction, though this is less important than the factors covered in (*a*)

Factors which seemed to have little bearing on prognosis in this stage included known hypertension, diabetes mellitus, and previous angina of effort We can therefore divide the survivors of the acute attack into good risk and bad risk cases, the bad-risk ones being those with cardiac distress early in the acute attack or whose recent infarction was not their first During the remainder of the first year the bad-risk patients are four times as likely to die as the good-risk patients (table XXXI) As in the acute attack, sex did not influence the prognosis

Age has negligible importance in prognosis compared with whether the patient is a good or bad risk as already defined As individual age groups are small, we have fused them into two main age groups (table xxxii, fig 11)

Among the good-risk patients the development of another myocardial infarct was the major cause of death Among the bad-risk patients, death from recurrence was commoner than among the good-risk patients, but death from cardiac failure unassociated with a fresh infarct was the outstanding cause of the difference between the two groups (table xxxiii)

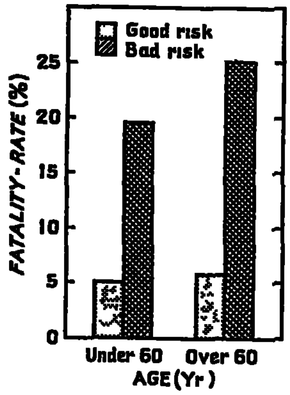

Fig 11—Fatality rates two to twelve months after myocardial infarction in good risk and bad-risk patients aged under 60 and over 60

Prognosis over Several Years

The fatality-rate in the second year after an infarct was lower than in the first year but still considerable, 1 in every 10 patients died in this period Thereafter, the fatality-rate ran at a lower level Allowing for random fluctuations, about 5% of the survivors of the original acute attack died each year after the second year (table xxxiv, fig 12) It will be recalled that, though all but 1 of the patients were followed up to January, 1956, the length of follow-up varied, and therefore the number of patients shown as followed up dwindles progressively over the years We have included a cumulative fatality rate because this gives a good overall picture of the subsequent fate of the survivors of the acute attack Of every 5 survivors of the acute attack 2 died within five years, and by ten years the proportion had risen to 2 out of every 3 The population at risk contained many old people, however, and a considerable number of deaths would be expected in any event The Registrar-General (1956) has given the survivorship ratio for each age group of men and women over the course of five years, 1946–50—a period which falls conveniently in the middle of the time covered by the present study We have taken these figures to estimate expected fatality-rates for the survivors of the acute attack Over five years the fatality rate among the survivors of the acute attack of myocardial infarction was 39 3%, the corresponding figure for a sample of the same age and sex composition, but taken from the general population, was 16 1%—i e, the chance of dying within the next five years was $2^1/_2$ times as great for survivors of myocardial infarction as for persons of the same age and sex in the general population

TABLE XXXIII—CAUSES OF DEATH IN REMAINDER OF FIRST YEAR

Cause of death	Good risk (177 patients)	Bad risk (171 patients)
Recurrent infarction	7 (*4 0*%)	13 (*7 6*%)
Cardiac failure unassociated with recurrent infarction	3 (*1 7*%)	19 (*11 1*%)
Other known causes	0	3 (*1 7*%)
Uncertain	0	4 (*2 3*%)*

* In some of these patients there was presumptive evidence of cardiac failure

TABLE XXXIV—PROGNOSIS OF SURVIVORS OF ACUTE ATTACK

Period of follow up	No of patients followed	Deaths in corresponding period		Cumulative fatality rate (%)
		No	%	
Remainder of 1st year	348	49	14 1	14 1
2nd year	292	29	9 9	24 0
3rd year	236	15	6 4	30 4
4th year	179	8	4 5	34 9
5th year	137	6	4 4	39 3
6th year	105	8	7 6	46 9
7th year	87	11	12 6	59 5
8th year	66	2	3 0	62 5
9th year	56	3	5 4	67 9
10th year	48	0	0 0	67 9

Long-term Prognosis of Good risk and Bad-risk Patients

We have already defined the factors influencing death in the first year, and it is interesting to see for how long these factors operate The bad-risk patients were four times as liable to die in the first year as the good risk patients and twice as liable to die during the second year, but thereafter the two groups had a similar risk of dying (table xxxv) After five years, three-quarters of the good risk patients and half the bad risk patients were alive Another way of looking at the same information is to compare the expectation of living five years for the good-risk and bad risk patients with that of samples of the general population of the same age and sex A good risk patient had less than twice an "average man's" chance of dying, while a bad-risk patient had more than three times this chance (table xxxvi, fig 13)

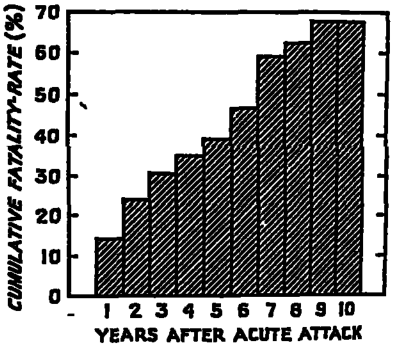

Fig 12—Cumulative fatality rate among survivors of acute attack

Prognosis in the five years after the acute attack depended on the age of the patient as well as on whether he was a good or bad risk Good-risk patients did better than bad risk patients in both age groups (table xxxvii), but the good-risk patients over the age of 60 years fared better than the corresponding patients under the age of 60 (fig 14) The chance of death in the patients over 60 in the good-risk group was about the same as that of the general population In the under 60s, the survivors of a myocardial infarction had more than three times the normal expectation of dying within the next five years Fatality-rates in the bad-risk patients were greatly above the "expected" levels in both younger and older patients, but the outlook in the younger age groups (though better in absolute figures than that in the older age groups) was worse when considered in relation to normal expectation

TABLE XXXV—SURVIVORS OF ACUTE ATTACK SEPARATELY FOR GOOD RISK AND BAD RISK CASES

Length of follow up (yr)	Good risk				Bad risk			
	No of patients	Deaths		Cumulative death rate (%)	No of patients	Deaths		Cumulative death rate (%)
		No	%			No	%	
1	173	10	5 8	5 8	175	39	22 3	22 3
2	146	9	6 2	12 0	146	20	13 7	36 0
3	117	7	6 0	18 0	119	8	6 7	42 7
4	83	4	4 8	22 8	96	4	4 2	46 9
5	61	3	4 9	27 7	76	3	3 9	50 8

In view of these findings, it is of great interest to know the causes of death in the various groups In most of the patients who died, we know fairly precisely the course of events, though there is a minority for whom the information is inadequate Our main concern was

TABLE XXXVI—PERCENTAGE FATALITY-RATE OVER FIVE YEARS IN GOOD-RISK AND BAD-RISK GROUPS COMPARED WITH EXPECTED RATE IN GENERAL POPULATION OF SAME AGE AND SEX

—	Good-risk group	Bad-risk group
Survivors of myocardial infarction	27·7	50·8
General population	15·3	15·2

to see whether death followed a recurrent infarction or whether it was due to cardiac failure without clinical evidence of fresh infarction.

The relatively bad prognosis in the good-risk patients under 60 years was almost entirely due to recurrent infarction (table XXXVIII). Among the bad-risk patients, the chance of dying from recurrent infarction was about the same as for the *good-risk* patients under 60, but in addition there were many deaths from cardiac failure not due to a fresh infarction, and it was the combination of these two risks which made their outlook poor. The small number of deaths following recurrent infarction in the older good-risk patients seems the chief reason for their favourable prognosis.

Long-term Prognosis from Time of Admission to Hospital

We can now see the total prognosis of patients admitted to this hospital in the past fifteen years (table XXXIX, fig. 15). In simple terms, 1 patient in every 7 admitted died in the first forty-eight hours, and a third were dead by the end of the eighth week (which we have taken as concluding the acute attack). By the end of two years from admission, half the original patients were dead. Thereafter, the risk of dying diminished, but another 10% died in the next three years, and by the end of five years 3 out of every 5 patients admitted were dead. The fatality was therefore formidable. But the risk of death was not evenly distributed, and the correct recognition of good and bad prognostic features makes it possible to select patients who, provided they survive the acute attack, have an expectation of life similar to that of persons of a corresponding age in the general population.

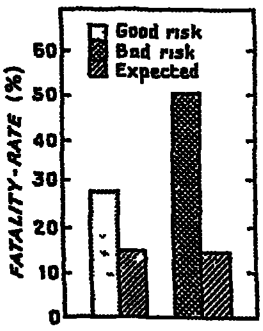

Fig. 13—Fatality-rate over five years in good-risk and bad-risk cases compared with expected rate in general population of like sex and age composition.

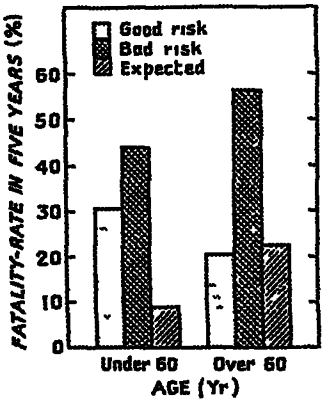

Fig. 14—Proportion of survivors of acute attack who die in next five years, compared with expected figures.

Discussion

Various studies have been made in the past twenty years of the long-term prognosis of myocardial infarction. Before that time, though it was realised that some patients could survive for many years, these were regarded as exceptional.

TABLE XXXVIII—MODE OF DEATH IN THE FIVE YEARS AFTER MYOCARDIAL INFARCTION IN VARIOUS GROUPS

—	Good-risk		Bad risk	
	Under 60	Over 60	Under 60	Over 60
Mode of death				
Recurrent infarction	15	5	11	17
Cardiac failure	2	4	7	23
Other known causes	1	0	3	3
Uncertain	4	2	2	8
No. of patient/years of follow-up	346	254	222	370
Rate of recurrent infarction taking good risk <60 as 100	100	45	114	106

In 1934, a meeting of the Royal Society of Medicine concluded that there was insufficient evidence for any assessment of the long-term prognosis (Hay 1934).

Palmer (1937) analysed the records of patients known to have survived a coronary thrombosis and found almost 75% alive at the end of five years; unfortunately 45% of the patients could not be traced, so this estimate was subject to gross error.

Bland and White (1941) found that 31% of those who survived the acute attack were alive ten years later, but their study is open to the grave criticism that they included patients in whom coronary occlusion had been diagnosed retrospectively; naturally, such patients would bias the results in a favourable direction.

Katz et al. (1949) made a better study with a 97% follow-up lasting one to five years. Their results bear some resemblance to our own, except that their patients showed a generally worse prognosis. In their study, there was a very heavy incidence of recurrent infarction.

The present study has the advantage of being virtually 100% complete. There is the limitation that the period of follow-up varies from one to sixteen years, but we have been encouraged to treat the group as homogeneous because the proportion of patients dying in the first year

TABLE XXXVII—PROGNOSIS IN GOOD-RISK AND BAD-RISK PATIENTS

—	Good risk								Bad risk								Totals	
	Under 60				Over 60				Under 60				Over 60					
	Followed	Deaths			Followed	Deaths			Followed	Deaths			Followed	Deaths			Followed	Deaths
		No.	Rate (%)	Cumulative rate (%)		No.	Rate (%)	Cumulative rate (%)		No.	Rate (%)	Cumulative rate (%)		No.	Rate (%)	Cumulative rate (%)		
Period of follow-up																		
1st year	100	5	5·0	5·0	77	5	6·5	6·5	63	12	19·0	19·0	108	27	25·0	25·0	348	49
2nd	87	8	9·2	14·2	63	1	1·6	8·1	54	5	9·3	28·3	88	15	17·0	42·0	292	29
3rd	69	4	5·8	20·0	52	3	5·8	13·9	43	3	7·0	35·3	72	5	6·9	48·9	236	15
4th	50	3	6·0	26·0	37	1	2·7	16·6	35	2	5·7	41·0	57	2	3·5	52·4	179	8
5th	40	2	5·0	31·0	25	1	4·0	20·6	27	1	3·7	44·7	45	2	4·4	56·8	137	6
Expected 5-year fatality-rate (%)				9·7				22·4				8·3				22·1		

TABLE XXXIX—PROGNOSIS FROM TIME OF ADMISSION TO HOSPITAL UP TO TEN YEARS LATER

Period of follow up	No of patients followed	Deaths in corresponding period		Cumulative fatality rate (%)	Survivors (%)
		No	%		
0–2 days	543	75	13 8	13 8	86 2
2 days	543	120	22 1	35 9	64 1
Remainder of 1st year	543	49	9 0	44 9	55 1
2nd year	464	29	6 3	51 2	48 8
3rd ,,	376	15	4 0	55 2	44 8
4th ,,	290	8	2 8	58 0	42 0
5th ,,	229	6	2 6	60 6	39 4
6th ,,	177	8	4 5	65 1	34 9
7th ,,	144	11	7 6	72 7	27 3
8th ,,	111	2	1 8	74 5	25 5
9th ,,	94	3	3 2	77 7	22 3
10th ,,	79	0	0 0	77 7	22 3

of follow up has been remarkably constant throughout the total period covered by the study This being so, simple actuarial procedures allow us to make use of the whole series to estimate survival-rates Long-term anticoagulant therapy was used in so few patients that it can be ignored, and the present results therefore represent the survival of patients in an era before long term anticoagulant therapy was in vogue

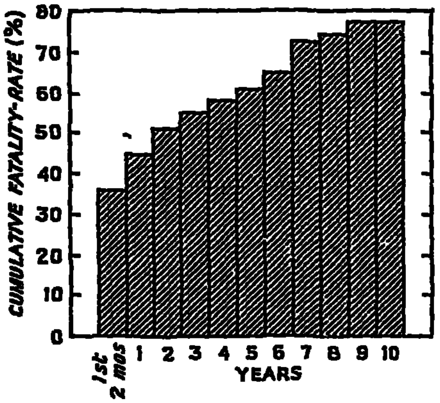

Fig 15—Prognosis from time of admission to hospital to ten years later

With respect to the individual factors which make for a good or a bad long-term prognosis, our results are definite The importance of recurrent infarction emerges from this as from other studies The only subgroup which is relatively free from this hazard is that composed of good-risk patients over the age of 60 years These patients have the same chance of living five years after the acute attack as individuals of the same age and sex in the general population From the point of view of future preventive treatment, the high rate of recurrence among good-risk patients under 60 is especially important It is this risk alone that causes them to have a much greater chance of dying than other people of the same age in the general population (table XXXVIII, fig 14) This finding emphasises the possible importance of long-term anticoagulant therapy in reducing this risk We expressed scepticism of the value of anticoagulant therapy in the acute attack except in so far as it reduces the risk of fatal pulmonary embolism to a negligible level But to say that anticoagulants have little effect on the course of an established myocardial infarct per se is not to imply that they are valueless in preventing one Various studies suggest that long term anticoagulant therapy improves long term prognosis (Keyes et al 1953, Owren 1954, Tulloch and Wright 1954, Suzman et al 1955) But none of these have fulfilled the criteria of a fully controlled trial, and, in view of the great practical importance of the subject, it is to be hoped that such a study will be made

Summary

Among 543 patients admitted to hospital for acute myocardial infarction in 1940–54, there were 348 survivors of the acute attack, which is defined as lasting two months from admission These were all followed up until early 1956, except for 1 man who was lost after three years of follow-up

Of the survivors of the acute attack, 1 in about 7 died in the remaining ten months of the first year, and this rate was constant throughout the whole period covered by the study In the second year a further 10% died Thereafter, about 5% died each year

Bad prognostic factors, which can be recognised early in the acute attack, were evidence of cardiac failure (either left ventricular or congestive and not necessarily severe), cardiac arrhythmia including multiple extrasystoles, gross cardiac enlargement, and (though less important than the foregoing) a previous attack of myocardial infarction

Patients who displayed one or more of these features constituted a bad risk group They had four times the chance of dying in the remainder of the first year as did the patients with none of them Over the course of five years, their chance of dying was double that of the good-risk group

Age was of negligible consequence in the long-term prognosis compared with whether the patient fell into the good-risk or the bad-risk group

Among the good risk group, the main cause of death within five years of the acute attack was recurrent infarction The incidence of this was high among the patients under 60 and was the sole cause for their expectation of life being much worse than that of a sample of the same age and sex of the general population By contrast, the patients of the good-risk group over 60 years had a low rate of recurrent infarction Their expectation of life was the same as that of other people of their age and sex

Among the bad risk group, recurrent infarction was common in both main age groups In addition, cardiac failure not associated with another infarction was a potent cause of death

We are grateful to the physicians of the Radcliffe Infirmary for permission to make this study and to Dr A H T Robb Smith for permission to use the post mortem records, to Miss P Coombs, the records officer, and to Miss Betty Merry of her staff for assembling the case notes, to Miss M C McLarty for preparing the figures, and to Mrs E M Hower and Mrs B Humphreys, who in succession were responsible for the heavy clerical work

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SOME POSTPRANDIAL EFFECTS OF EATING VARIOUS PHOSPHOLIPIDS AND TRIGLYCERIDES

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DIETS containing a high proportion of fat are thought to be related to atherosclerosis and coronary thrombosis, possibly through the hypercoagulability of the blood which sometimes follows a fatty meal.

O'Brien (1956a) has shown that single meals of 50 g. of butter, margarine, and cooking-fat all produce a similar increase in the clotting-time accelerated with Russell's viper venom ('Stypven' time). The ingestion of two eggs, which contain only 10 g. of triglyceride but 3 g. of phospholipid, produced a similar or even greater effect. The stypven time of platelet-poor plasma is very sensitive to the artificial introduction into the plasma of minute quantities of phosphatidyl-ethanolamine (P.E.), a substance that can be used instead of platelets in many clotting-tests (O'Brien 1956b). It appears, therefore, that the activity of the meal of eggs might be due, at least partly, to its content of P.E., some of which might enter the blood-stream relatively unchanged.

I report here a study and comparison of the effects of ingestion of eggs and of two kinds of phospholipid.

Bronte-Stewart et al. (1956) and other workers have shown that a diet of moderately saturated fats raises the fasting levels of serum-cholesterol and serum β lipoprotein, and that these raised levels are restored to normal if some unsaturated fats are substituted in the diet. I have tried to find out whether the difference in saturation of ingested fats influenced the changes in postprandial clotting times. Chemical analyses were made to identify the substance responsible for the observed changes in clotting-time.

Previous Work

Maclagan and Billimoria (1956) report that the ingestion of butter, but not that of margarine, shortened the postprandial stypven time. This latter observation contradicts O'Brien's (1956a) findings; but the composition of the margarine, which can vary widely, is not stated.

Keys et al. (1957) studied the effect of fatty meals on the whole-blood clotting time in siliconed tubes. The fats used were sardine oil (iodine value 185), corn oil (I.V. 120), butterfat (I.V. 38), and hydrogenated coconut oil ('Hydrol') (I.V. 2·5). These workers found that the silicone clotting time of whole blood was significantly shorter after all fatty meals, irrespective of the degree of saturation, but not after the control carbohydrate meal. Merskey (1956) and Merskey and Nossel (1957) found no change in the ordinary clotting tests four hours after large meals of unsaturated vegetable oil and of more saturated animal fats, including bacon, eggs, and butter. The only test that showed a significant shortening was the stypven time; and this shortening was observed irrespective of the type of fat eaten.

Methods

The subjects of the present experiments were eight apparently healthy men and women, aged 20–40, all of whom initially showed a well-marked and approximately similar degree of change in the coagulability of their blood after a fatty meal. One of them took part in all the experiments. For each comparison the same subjects were studied; but not all the subjects ate all the different meals.

The volunteers fasted from 8 P.M. on the preceding evening. At 9 A.M. 20 ml. of blood, called the fasting sample, was collected by venepuncture. A breakfast of toast, marmalade, tea, and a little milk was then taken with 50 g. of the prescribed fat. At $2^1/_2$ and $3^3/_4$ hours after the meal further 20-ml. samples of blood were taken.

The 20 ml. samples of blood from each venepuncture were mixed with 2·0 ml. of 3·8% sodium citrate in siliconed tubes and immediately centrifuged at 3500 r.p.m. for 20 minutes, and the plasma was separated. 1·0 ml. of this platelet-poor plasma was then diluted with 4 ml. of saline solution. To 0·1 ml. of dilute plasma in a water-bath at 37°C was added 0·1 ml. of Russell's viper venom (stypven) 1 : 100,000, and a minute later 0·1 ml. of M/40 $CaCl_2$. The time taken for clotting was recorded as the stypven time. The results shown in the accompanying tables are the averages of at least two determinations.

The rest of the postprandial plasma sample that had the shorter stypven time, subsequently called the lipæmic sample, and the fasting plasma were then taken for biochemical analyses. The total ether extractable fatty acid was estimated by a modification of the method of Van de Kamer et al. (1949), which in our hands had an error of about ± 15%. For the estimation of free and total cholesterol the method of MacIntyre and Ralston (1954) was used; this had an error of ± 5%. The lipid phosphorus was estimated in duplicate by the method described by Varley (1954); this also had an error of ± 5%.

The fats given were chosen to give as wide variation as possible.

The cod-liver oil (I.V. 165) was "non-cold filtered and deodorised" and contained 25% of the highly unsaturated arachidonic acid and 9% clupanodonic acid. The hardened cod-liver oil (I.V. 68, melting-point 36/38°C), a solid at room-temperature, was the same oil but hardened and possessed rather less than half the number of double bonds. The vegetable oil—soybean oil (I.V. 130)—contained different triglycerides, including 52% of linoleic acid, which is not present in cod-liver oil. The coconut oil (I.V. 8·5) was solid and, as well as being almost fully saturated, contained a large proportion of short-chain fatty acids, including 48% lauric acid and 17% myristic acid. These natural fats are mixtures of triglycerides but contain virtually no phospholipid. However, "pure" trilaurin and triolein containing no phospholipid were obtained in small quantities and were given as "meals."

The phospholipid that was freely available was a commercial extract from soybeans called 'Asolectin.' This contains less than 5% of triglyceride and about 30% of lecithin, 30% of P.E., and 35% of 'lipositol,' which is a mixture of inositol-containing phospholipids.

The egg lecithin was prepared specially for this experiment and contained less than 1% of P.E. Added artificially and in optimal concentration to platelet-poor plasma, it had no effect on the stypven time. 20 g. was isolated from five dozen eggs.

Results

The levels of free and of combined cholesterol in all the fasting and lipæmic plasmas from all the meals were estimated, and no significant changes were recorded.

Table I gives the results arranged in order of the iodine value of the fat eaten, and includes for comparison the average figures from previous experiments with meals containing 50 g. of butter, margarine, and cooking-fat.

TABLE I—AVERAGE % CHANGE FOLLOWING FATTY MEALS OF DIFFERENT IODINE VALUE

Fat eaten	Iodine value	Weight eaten (g.)	No. of meals	No. of volunteers	Stypven time	Total fat	Lipid phosphorus
Nil			2	2	−6	2	−1
Cod-liver oil	165	50	2	2	48	56	22
Soybean oil	130	50	6	3	39	22	8
Hardened cod-liver oil	68	50	5	3	40	27	2
Average of above fats		50	13	3	40	29	8
Average of butter, &c.*	30	50	32	8	27		
Coconut oil	8·5	50	5	3	−14	6	1
Coconut oil	8·5	100	2	2	−15	20	5

* These figures are abstracted from a previous study (O'Brien 1956a).

TABLE II—AVERAGE % CHANGE FOLLOWING FATS OF DIFFERENT CHAIN LENGTH

Fat	Chain length	Weight eaten (g)	No of meals	No of volunteers	Stypven time	Total fat	Lipid phosphorus
Trilaurin	12	10	1	1	0		
Coconut oil (48 % lauric acid)	12–20*	50	5	3	–14	6	1
Soybean oil	18*	50	6	3	39	22	8
Cod liver oil	16–20*	50	2	2	48	56	22
Triolein	18	50	1	1	23	7	3

* Chain length of major components

(O'Brien 1956a) The "average % change" for each type of estimation is obtained by taking an average of all the fasting figures and subtracting from this value the average postprandial figure This difference is expressed as a percentage of the fasting figure The chemical estimations usually showed a postprandial increase, a decrease is indicated by a negative sign The postprandial stypven times usually were the shorter When they were longer, the average per cent change is preceded by a negative sign

Table I shows that cod-liver oil produced a considerably greater postprandial increase in the total fat and in the lipid phosphorus, but only two volunteers drank this oil, and, with the considerable variation in individual responses, these changes are not significantly greater than those following the ingestion of other fats However, it will be seen that, apart from coconut oil, all the other oils of widely differing degrees of saturation gave similar results—i e, the stypven clotting-time was shortened and the total fatty acid was increased, and there was a small variable increase in lipid phosphorus

Coconut oil gave quite different results The stypven clotting time was not shortened but (on average) lengthened The increase in total fatty acid after the five meals of 50 g was significantly less than after the ingestion of the other fats Only after 100 g had been given did the fatty acids increase to a figure commensurate with those obtained after giving 50 g of the *other fats* It will be seen that, even with this larger meal the changes in clotting-time remained completely different from those after the other fats

TABLE III—AVERAGE % CHANGE FOLLOWING MEALS OF EGGS AND FATS

Fat eaten	Weight eaten (g)	No of meals	No of volunteers	Stypven time	Total fat	Lipid phosphorus
Nil		2	2	–1	–3	–3
5 eggs	25	2	2	40	38	
All fats*	50	13	3	40	29	8
3 eggs	15	4	4	29	17	17
Soybean oil	15†	4	4	12	9	0

* From table I all fats excluding coconut oil
† One volunteer ate 50 g of soybean oil

In table II the various meals are arranged in order of the chain length of the fatty acids in the triglycerides eaten It will be seen that the "meal" of trilaurin with twelve carbon atoms in the fatty acid was followed by no change in the stypven time, whereas triolein, with eighteen carbon atoms, shortened it considerably The results obtained with the mixed natural oils transcribed from table I are included It will be seen that coconut oil, with its preponderance of short-chain fatty acids, gave results similar to those obtained with pure trilaurin, whereas the other natural fats gave results similar to those obtained with triolein

In table III are reported two experiments designed to investigate the suggestion (O'Brien 1956a) that eggs are more active than might be expected from their fat content alone In the first experiment each of two volunteers ate five eggs containing 25 g of triglyceride The effects on the stypven time and plasma fat are compared with the effects in these same volunteers and one other volunteer of eating meals containing 50 g of fat (see table I) It will be seen that the changes in clotting time and the increase in total fatty acids are of the same order, although five eggs contained only half as much triglyceride, but the eggs contain about 7 5 g of phospholipid, whereas the natural fats contain almost none

In the second experiment each of four volunteers ate three eggs, containing 15 g of fat, for one meal, and 15 g of soybean oil for another meal It will be seen that 15 g of oil produced changes, in the clotting times and in the amount of total fatty acids, which are hardly significant in view of the small numbers involved The three eggs produced changes of almost double the magnitude and a considerable rise of the plasma lipid phosphorus level

TABLE IV—AVERAGE % CHANGE FOLLOWING INGESTION OF PHOSPHOLIPIDS

Lipid eaten	Weight eaten (g)	No of meals	No of volunteers	Stypven time	Total fat	Lipid phosphorus
Asolectin	20	3	3	35	12	9
	10	1	1	23	8	0
Asolectin Soybean oil	10 15	2	2	23	4	3
Asolectin	5	2	2	17		
Asolectin	2½	1	1	30		
Lecithin	10	1	1	20	27	–3
	7½	1	1	–11		
	2½	1	1	20		

Table IV summarises the results of various "meals" of phospholipids It will be seen that 20 g of asolectin considerably shortened the postprandial stypven time, slightly increased the total fatty acids (much less than did 50 g of triglyceride), and raised the level of the lipid phosphorus as much as did three eggs or 50 g of triglyceride A combination of asolectin and triglyceride did not obviously have a greater effect Small quantities of asolectin (1 0–2 5 g), that must have produced no chemical changes detectable in the blood by our methods, still produced definite changes in the clotting time The effect of various quantities of asolectin was not further investigated, because it was desired primarily to establish that the ingestion of *phospholipid* in *the* absence of triglyceride could change the clotting time

The 20 g of pure lecithin available was given in different quantities to three different volunteers It can be concluded that ingestion of this phospholipid can produce postprandial changes in the clotting time even when given in small quantities

It is obvious that the phospholipids are considerably more active weight for weight than the triglycerides

TABLE V—THE DEVELOPMENT OF "TOLERANCE" TO FATTY MEALS SHOWN BY ONE VOLUNTEER

Date	Fat eaten	Stypven time (sec)			Total fatty acid in plasma (mg per 100 ml)		
		Fasting	Lipæmic	Difference*	Fasting	Lipæmic	Difference*
June 24 1956	A	53	35	18	327	474	147
26 ,	B	48	34	14	305	476	171
29,	C	53	24	29	432	551	119
July 17 ,,	A	57	33	24	437	514	77
18, ,,	C	51	46	5	416	159	43
Aug 10 ,,	A	56	52	4	410	446	36

* The difference in seconds or milligrammes between the fasting and the lipæmic samples
A soybean oil
B, cod liver oil
C, hardened cod liver oil

in shortening the stypven time after a meal, 10–20 g. produces about the same effect as does 50 g. of fat. A detectable change in the stypven time is produced by 2·5–5·0 of asolectin and by 15 g. of fat. It therefore seems that asolectin may be about five times as "active" on a weight basis as triglyceride. Clearly, in view of the small numbers of experiments and the variability of response, this is only a very rough approximation.

Table v shows the results in one of the volunteers. It will be seen from table i that the three fats eaten normally produced about the same changes. However, the magnitude of this volunteer's response both in the clotting-time and in the total fatty acid level, to the meals decreased significantly. During the months of these experiments his health and diet did not alter. The only unusual feature was the eating of nine meals containing 50 g. or, in one case 100 g. of fat. Only one other volunteer had as many fatty meals, and he showed little or no evidence of tolerance.

Discussion

The cause of the postprandial shortening of the stypven time remains uncertain. Poole (1955) and Robinson et al. (1955) suggested that a postprandial increase of unesterified acid might, at least partly, be responsible. They also suggest (Robinson and Poole 1956) that a postprandial rise in the level of plasma-P.E. may be responsible for the changes in clotting-time. Gordon and Cherkes (1955) have shown that there is an increase of unesterified fatty acid after a fatty meal, and a smaller but definite increase after a period of starvation. The ingestion of phospholipid, some of which may be absorbed comparatively unchanged (see below), has a considerably greater effect on the stypven time than has ingestion of a similar weight of triglyceride, and there is no evidence that the level of free fatty acid in the plasma is higher after eating phospholipids than after eating triglycerides. Thus it is possible that the stypven time under these conditions is largely measuring the level of available active phospholipid in the plasma.

With two exceptions the triglycerides, irrespective of wide variation in the degree of saturation of their fatty acids, all considerably shortened the postprandial stypven time. The exceptions were coconut oil and trilaurin, which slightly lengthened the stypven time. This suggests that the degree of saturation of the ingested fat is irrelevant to the postprandial changes observed in clotting time. The short-chain length of the fatty acids in coconut oil and trilaurin may have been responsible for their different effect. If this is so, it suggests that, in man, the short-chain fatty acids are metabolised differently from the longer-chain fatty acids.

Bloom et al. (1951) have shown that, in rats, the long-chain fatty acids down to myristic acid (C14) are transported almost exclusively in the lymph after absorption. Considerably less lauric acid (C12) and only a minor part of the absorbed decanoic acid (C10) were recovered from the lymph, and the results of other experiments (Kiyasu et al. 1952) suggest that the short-chain fatty acids are transported mainly via the portal pathway. These findings are supported by the Lund group of workers (Blomstrand 1955a and b, Borgström 1955) who showed also that the degree of saturation of the fatty acids had no influence on the way they were transported.

It is confirmed that eggs shorten the stypven time more than can be explained by their content of neutral fat; this discrepancy is almost certainly due to their high content of phospholipids, since it has also been shown that ingested phospholipid in the absence of triglycerides is about five times as active in shortening the stypven time as is the same weight of triglyceride.

Bloom et al. (1954) and Blomstrand (1955b), who produced radioactive phospholipids by biosynthesis and fed them to rats with lymph fistulæ, reported that about 20% of the activity absorbed was recovered in the lymph as phospholipid and the remaining 80% as triglyceride. After the ingestion of triglycerides only about 2% of absorbed activity was recovered in the lymph as phospholipid, in contrast to the 20% recovered after the ingestion of phospholipid. This is about a tenfold increase. If the stypven time really measures free phospholipids, these changes observed in man (weight for weight, phospholipid was about five times as active as triglyceride) are of the same order as the chemical estimations in the lymph of rats.

Egg lecithin has been shown to shorten the postprandial stypven time when eaten, yet when added artificially to starving plasma it has no effect. This discrepancy may be due to the breakdown of the lecithin during absorption and to the synthesis of other phospholipids active in this clotting-system. Blomstrand (1955b) has shown that, during the absorption of lipids, some of the molecules are broken down, and that there is randomisation during resynthesis of the phospholipids and triglycerides that appear in the lymph.

Keys et al. (1957) report that 120 g. of hydrogenated coconut oil shortens the silicone clotting-time to the same extent as do other triglycerides. This observation is hard to reconcile with the present experiments, in which the ingestion of 50 g. or of 100 g. of untreated coconut oil lengthened the stypven time. It is, however, possible that under these conditions the silicone clotting-time measures a phenomenon which does not affect the stypven time. Indeed I have found that shortening of the stypven time is not always accompanied by shortening of the clotting-time.

It has been shown that, when one man ate nine meals of 50 g. or of 100 g. of fat during three months, the postprandial changes in clotting-time decreased considerably. Swank (1954) reported that his dogs also rapidly became able to absorb large quantities of fat without appreciable alteration of their plasma-lipids. In the present study three types of response to repeated fatty meals have been noted:

(1) *An absence of effect*: one person rejected from the present series showed no change in clotting-time for five hours after eating fatty meals.

(2) *The maintenance of a well-marked change*: the volunteer who ate most meals gave as good a response at the end as at the beginning.

(3) *The development of "tolerance"* (see table v).

These three types of response are not clear-cut, and many intermediate types were seen.

The biosynthesis of plasma lipids which are presumably involved in lipid transport, can be changed by altering the type of fat in the diet, as Bronte Stewart et al. (1956) and many others have shown. It is not known whether this change or some other factor alters the response to a single fatty meal. Nor is it known if these different types of response are of any clinical significance, but clearly they might be.

The clinical importance of these results is difficult to assess. Intact platelets are inactive in the stypven test (O'Brien 1956a) and the phospholipid in them becomes available for this test only when the platelets are broken up or otherwise "activated." Presumably, therefore, the phospholipid in platelets becomes available for other in-vitro coagulation tests only after the platelets have been "activated" during the initial stages of coagulation. If lipæmic plasma contains free phospholipid, this would be immediately available for blood coagulation and would short-circuit some of the initial stages. Such blood might be more coagulable. But Merskey and Nossel (1957) found, after a fatty meal, no changes in in-vitro coagulation tests other than a shortening of the stypven time. The connection, considered more fully elsewhere (O'Brien 1957), between these highly artificial in-vitro coagulation systems and the formation of a thrombus in the coronary artery is remote indeed

Summary and Conclusions

The maximal changes in the Russell-viper-venom-accelerated clotting-time (the 'Stypven' time) of platelet-poor plasma, the total ether extractable fatty acid, the cholesterol (free and combined), and the lipid phosphorus were measured after meals containing various lipids There was no correlation between the changes in clotting-time and in the amount of total fatty acids, and only poor evidence that considerable changes in clotting time were associated with an increase in total phospholipids The cholesterol levels did not alter postprandially

Four fats of widely different degrees of saturation all shortened the postprandial stypven time by the same amount It is concluded that probably the degree of saturation of ingested fats is immaterial to the postprandial changes in clotting time Trilaurin and coconut oil either did not change or lengthened the stypven time It is concluded that fats containing short chain fatty acids may have a different effect from those with long chain fatty acids These conclusions are in agreement with other workers' results, obtained in rats and cats, which show that the degree of saturation of ingested fats does not affect the method of their transport after absorption, whereas chain length does

A "meal" of phospholipids, compared weight for weight with a meal of triglycerides, shortened the stypven time much more, suggesting that some phospholipid is absorbed relatively unchanged This result is independent of the activity or the inactivity of the phospholipid when added artificially to a test system of fasting plasma and Russell's viper venom These results may be explained by the conclusions of other workers that, during the absorption of ingested phospholipid in rats, there is extensive hydrolysis, and that randomisation occurs during the resynthesis

In one man the magnitude of the response to these fatty meals decreased during a period of three months The development of this "tolerance" is discussed

It is suggested that under these conditions the stypven time is primarily measuring the level of some phospholipids in the plasma

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THE STATE OF DEVELOPMENT OF NEWBORN AFRICAN CHILDREN

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IN the course of work intended to define the psychological changes accompanying kwashiorkor it became necessary to obtain information about the psychomotor development of African children who were healthy and well nourished The development was assessed by Gesell tests, as used in Paris (Roudinesco and Guiton 1950) It was found that, up to the age of about 3 years, the development was usually in advance of European standards, and that the degree of advance was greatest in the youngest children The tests, which are normally considered to be applicable only to children more than 1 month old, were extended to younger children, and it was established that, at the age of 2 or 3 weeks, the development was equal to that of European children twice or three times that age The results were not altogether unexpected, because clinical observation of African children in the first year of life had already shown that the accepted "milestones" of development—raising the head, sitting, standing, walking, and so on—were passed at an earlier age than in European children Some of the results have already been published (Geber 1956) The present communication describes a recent extension of the work—the study of the African child at birth

Material and Method

The technique used was that of André Thomas and his collaborators (Thomas and Saint Anne Dargassies 1952, Saint Anne Dargassies 1954, Koupernik 1954) Of 107 babies, 101 were seen in the maternity department of Mulago Hospital, Kampala, where they had been born, the others had been born at home and were seen there They were all born in July or August, 1956 At birth none weighed less than 2 5 kg, and only 1 (who weighed 4 8 kg) more than 4 1 kg All the babies and their mothers were without any known disease, and delivery had not been assisted with instruments or by operation About 60 children were of the Ganda tribe, which is indigenous to the region round Kampala and belongs to the Bantu-speaking groups, and the rest were of other tribes, some of them Bantu, but others Nilotic or Hamitic No difference associated with tribe could be distinguished There was no selection of cases The nurses were asked to bring for examination any children that were available in the maternity wards Twins and children delivered either by cæsarean section or by forceps were brought with the others and were examined but were excluded from the present series For the examinations a bench or a table with a hard top was used, covered with a thick white cloth

The children numbered 107 Their ages at the time of examination were as follows less than 24 hours, 37, 25–48 hours, 45, 49–72 hours, 14, 73–96 hours, 6, 6 days, 1, 7 and 8 days, 2 of each There were 52 boys and 55 girls

Technique

Since the technique of detailed examination of newborn children is not practised widely in Britain, an account of some of the more important points may be helpful It has been drawn largely from Koupernik (1954) and Thomas et al (1955)

At birth the European child usually adopts an attitude that is a continuation of the intra uterine position the arms and legs are held tightly in flexion and the fingers clenched over the thumb; lying on his back, he has his head to one side, and the positions of his arms and legs are asymmetrical, flexion and asymmetry being characteristic of the earliest age.

The tone of the arm muscles can be judged by the resistance to extension and by pulling the hand across the thorax and over the opposite shoulder. The position is like that reached when a scarf is thrown over the shoulder, and "the scarf movement" is an appropriate name. The legs are not only flexed but also externally rotated. Their hypertonicity causes the angle at which the knees can be bent to be limited to 90°, and the angle between the legs in abduction to be only 60° (a child whose legs are continuously in extension, or whose hands are permanently open, is deemed to be pathologically hypotonic). If the child is placed on his belly he turns his head to the side, with his cheek laid flat. The head cannot be turned from this position, nor, if the chin is put to the table, can the head be raised to free it. The rest of the body is bunched up, with the arms bent and the elbows in to the sides and the thighs flexed so that the buttocks are raised. Sometimes, in this position, the child makes a kind of creeping movement (reptation). If the child is put into the sitting position, his trunk tends to collapse, with a kyphosis extending from the neck to the sacrum. The head falls forwards, and falls back if the trunk is made to lean backwards. The falling back, or rather the "head lag" is seen best when the child is drawn up by his hands into a sitting position.

Many details of reflex activity have been described. The most spectacular and one of the most consistent in European children, is the Moro reflex. It is best seen when the child is on his back and can be elicited in many ways, including knocking sharply on the table on which the child is lying, and by almost any sudden movement of the limbs or trunk —for instance, by raising the body by pulling on the arms until the head is just clear of the table and letting go. The arms are thrown out in full extension (one name for the reflex is "the arms of the cross"), the back is extended or arched, the head is drawn back, the fingers are fanned out, and the legs are extended. After the extension there is a characteristic return of the arms across the trunk.

The grasping reflex is well known and is also very constant. It should be equal in left and right hands and has two components, one the closing of the hand when the palm is pressed, and the other the maintenance of tension in the flexors, which makes it possible to raise the whole child by a stick grasped in the two hands.

Two other important reflexes can be shown when the child is held standing with his feet on the table: one, which can be called the "straightening reflex," is a tendency of the whole body to be straightened from its usual flexion; the other is the "automatic march" which is a walking step made with the knee flexed and the toes raised, the heel being the first part of the foot to touch the ground.

Tendon-reflexes are usually easy to find but vary with the tone of the part of the body.

Of the cutaneous reflexes the easiest to examine is the plantar reflex. It can be elicited over a large area of the outer side of the legs, as far up as the thighs, but is complicated by the grasping reflex of the toes, which is much like that of the fingers.

Among many other reflexes may be mentioned the ciliary and the photomotor (the tight closing of the eyes when the eyelashes are stroked or a light is shone into them), the "doll's eye" (the movement of the eyes in the opposite direction to passive movement of the head), the auricular (the turning of the head away when the lobe of the ear is rubbed), and the masseteric (the raising of the jaw when the chin is tapped).

Most of the hypertonicity disappears in the normal European child after 6–8 weeks, and the general attitude of flexion is lost. The ability to control the head so that it no longer flops forwards or back, and to straighten the back in the sitting position is not acquired until 8–12 weeks. The Moro reflex, the automatic march, and the straightening reflex do not persist after 6–8 weeks.

Children at about 2 weeks follow with their eyes near moving objects and at 3 or 4 weeks start to move the head to help the pursuit.

Results

It was immediately obvious that the distribution of muscle tone in the African child differed from that in the European. When the African child was lying quietly at rest, his flexion was much less accentuated (fig. 1). Often the knees were only slightly flexed, and only one of the arms was flexed, with its hand half-open; the other arm might be fully extended, with its hand open completely.

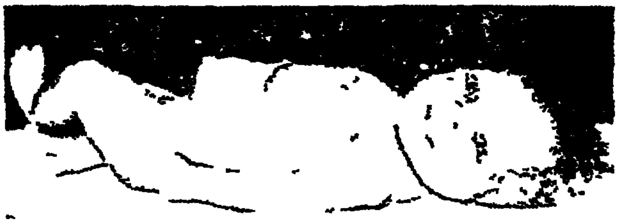

Fig 1—Aged 48 hours lying with limbs extended: cheek is slightly raised, and liveliness of eyes is remarkable.

When the child was put down on his back his head was usually on one side but could be turned from side to side and held in the median position. The eyes were wide open, and had a lively look. In many children, even in the first days moving objects could be followed with the eyes, and rotation of the head accompanied the pursuit. There was plenty of spontaneous activity, and it was not unusual for the child to turn half on his side. The activity of the arms and legs was bilateral and symmetrical but greater in the legs than in the arms. The legs were chiefly flexed and extended but were also crossed and uncrossed. The feet were usually rotated so that the soles faced each other. The arm movements were not so brisk as those of the legs. The flexion of one arm and extension of the other have already been mentioned; when the child had his head to one side, the arm of that side would often be abducted and lying beside the face. The hands, which were usually open, were moved in all directions and were carried frequently to the face, particularly to the mouth. One child, a day old, who had received at birth a slight scalp wound in the occipital region, continually fingered the bandage over the wound. The thumb was less active than the other fingers but was often in extension. The fingers were spread from time to time.

When he was placed on his belly the child immediately turned his head to one side or (even more remarkable) raised his head, propping himself on his forearms (fig. 2). Sometimes the head was only raised momentarily in the median position and was then lowered, resting on the chin, but most of the children raised the head for several seconds, with the lumbar lordosis and the flexion of the legs increased, and with the arms pressed firmly on the table, the elbows against the body, and the forearms straight ahead. The hands were open, and sometimes the fingers clawed and scratched. The knees were as often flexed as partly extended, but the thighs were almost always flexed on the abdomen so that their fronts were rarely in contact with the table. The legs were less active than when the child was on his back but fairly often they made creeping movements.

By far the most remarkable feature of the prone position was the control of the head and neck; it seemed almost as though all efforts were concentrated on that

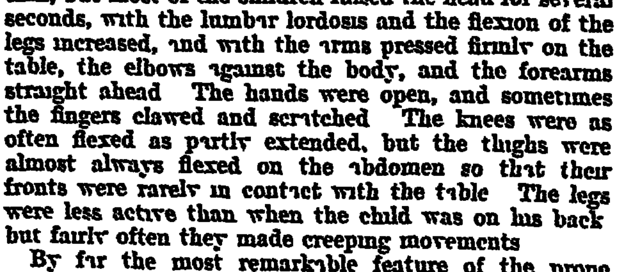

Fig 2—Same child as in fig 1, raising chin clear of table.

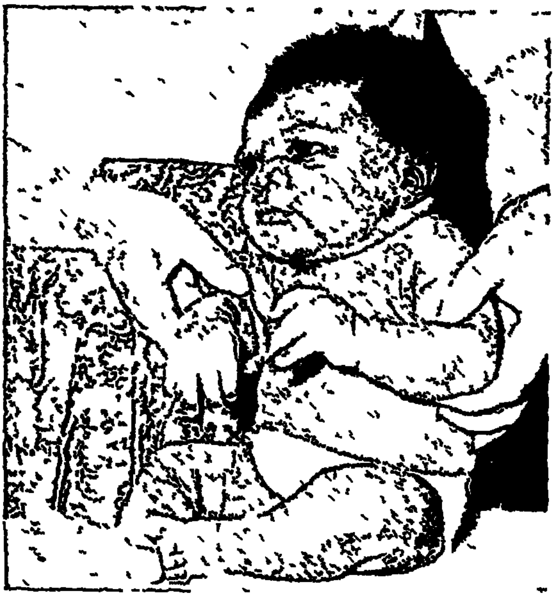

Fig 3—Aged 9 hours, able to prevent head from falling forwards

control, which was evident again when the children, lying on their backs, were drawn *up into a sitting position* (figs 3 and 4) Of the 107 children, 90 could prevent their heads from falling back In these children the trunk remained straight

When the child was sitting the head remained in the median position and was sometimes turned from side to side before finally falling forwards When it had fallen, many children could immediately raise it again The back was straight and upright, or inclined forwards, and a kyphosis was exceptional The knees were moderately flexed, and the feet were rotated internally

Some children, when being drawn into a sitting position, pressed on their heels as they were raised and straightened themselves until they were nearly standing Held upright with the feet touching the table most of the children produced a straightening reflex, some pressing hard with both feet, and some with only one A few children merely bent the legs The "automatic march" reflex was found in only a few children, all aged 1–3 days

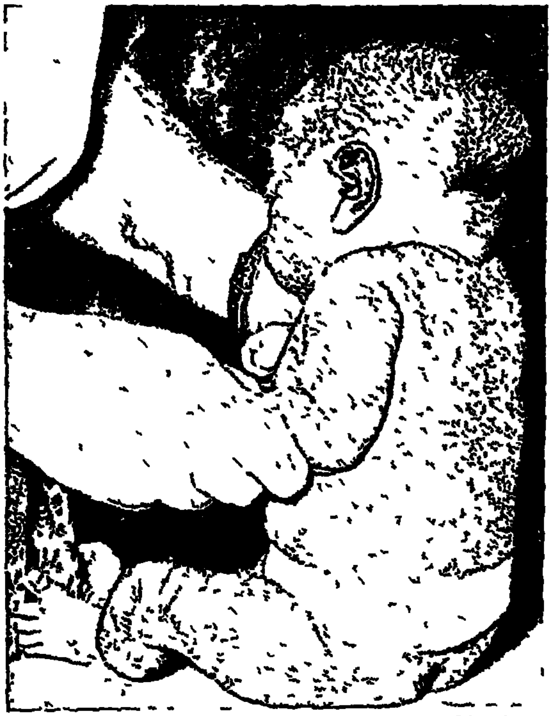

Fig 4—Aged 28 hours, held sitting, back is straight and head upright

The Moro reflex was by no means constant In some children, mostly aged 1 or 2 days, the reflex was brisk and full, with extension and abduction of the arms and the usual slow return to the position held before, but in others, whatever means were used for trying to elicit the reflex, the amplitude of the response was poor The reflex was found in no child aged more than 4 days (*Although* the present communication is limited to the description of children who weighed 2·5 kg or more, it is relevant that some smaller children, who might have been premature, produced a thoroughgoing reflex) The grasping reflex was also inconstant, and if the child closed his hand on the object pressed into his palm he rarely continued to hold it firmly but soon relaxed his fingers and allowed the hand to resume its former attitude

Further examination of tone showed that the extensibility of the flexors, in arms as well as legs, was much greater in African children than in European The flexion was less hypertonic, it was easy to extend the forearms, and they did not return immediately into flexion but usually remained outstretched On the contrary, the angle of flexion of the wrist was greater than 90° (fig 5) The scarf movement, the test of adduction of the arm, could be made easily Abduction and the carrying of the forearm behind the shoulder also met with little resistance Similarly, in the legs the popliteal angle was more than 90° and the angle between the straightened abducted legs more than 60°

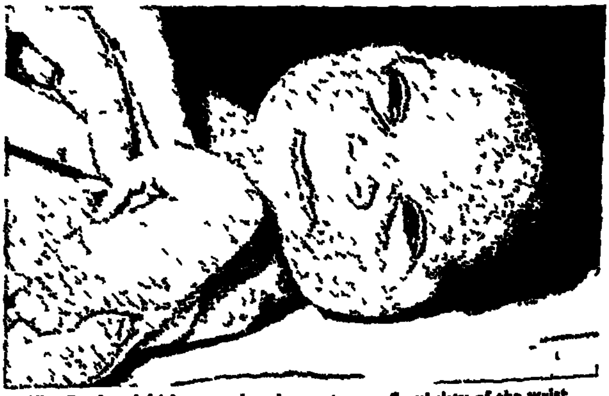

Fig 5—Aged 14 hours showing extreme flexibility of the wrist

On the whole, then, the tone of the flexors in the African children was less in the limbs but more in the head and neck Other reflex activity—ciliary, photomotor, masseteric, the sucking reflex, and the turning of the head on stimulation of the corners of the mouth—was present On the other hand, the "doll's eye" and auricular reflexes could not be elicited Of the tendon reflexes the patellar was very easy to elicit and the radials were almost as easy Curiously, despite the relatively light tone of the arm flexors, the olecranon reflex could not be obtained The cutaneous plantar reflex was nearly always extensor, and the grasping reflex of the toes was more constant than that of the fingers

When the child was held horizontally face downwards on the open hand of the examiner, the back was straight, the head was kept from falling forwards, and the legs were usually extended in the line of the trunk (fig 6) Held similarly, but face upwards, the child let the head fall back, and his back arched

So far as could be determined in this series the results did not vary with the sex of the child, its birth-weight, or the parity of the mother Unfortunately it was impossible to discover the length of the period of gestation, because the dates of the last menstruation were not accurately known

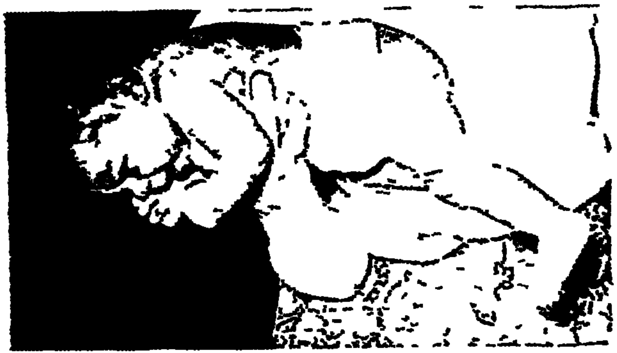

Fig 6—Aged 43 hours: back is straight, head controlled, and left leg extended

Discussion

There seemed to be no doubt that these African children had been born at a more advanced stage of development, judged by the method used, than the normal European child The results of the examination were so consistent, and the degree of advance was so great that there was little room for uncertainty Much of the activity corresponded to an age of 4–6 weeks Some was even more precocious for example, the raising of the chin and the scratching of the fingers on the table, when the children were placed on their bellies might be expected at 6–8 weeks, and so might the maintenance of the head in the mid-position when they were on their backs

We do not intend at this stage, to advance theories or facts in attempted explanation, but it is clear to us that the state at birth is consistent with some clinical observations that the African child sucks vigorously at the breast almost from the first hour, and that he passes the milestones of development at a very early age It is consistent also with the findings of psychomotor precocity in the earliest years to which we have already alluded As we have said elsewhere (Geber 1956) an extensive investigation of all facets of the development of the African child is imperative A more detailed study of the newborn child is planned, and will include twins, children born by cæsarean section, others whose birth has been associated with trauma, and others born before term The last named should be especially interesting, it is well recognised that African children whose weight at birth would by ordinary standards cause them to be classed as "premature," are often sturdy and active and can be reared without the special care that has to be lavished on European children of the same weight

It is conceivable even if it is in our opinion unlikely, that some of our findings could be explained by the existence of local conditions obtaining at Kampala, which is almost on the equator, and about 3500 ft above sea-level We are prepared to consider a number of possibilities but we have one piece of evidence that may be helpful in making a judgment At the same time as the African children a group of 15 European children—all that were available in the European Hospital, Kampala—and another group of 60 Indian children in the Asian Hospital were studied by the same method The European children gave exactly the results that have been found in Europe and the Indian children gave almost similar results Neither group showed any great degree of overlap with the African children The work on the European and Indian children will be reported when it has been extended to greater numbers at the moment it may perhaps be admitted as a confirmation, in part of the validity of the findings in the Africans

Summary

The technique of neurological examination evolved by Andre Thomas in European children is described

107 newborn African children who were considered to be normal at birth were examined by this method

They proved to be at a more advanced state of development than newborn European children

The advance was shown chiefly by a lesser degree of flexion, by a remarkable control of the head, and by the frequent absence of primitive reflex activity.

The results were consistent with clinical observations and Gesell tests made on young African children

We are very grateful to Prof Coralie Rendle-Short, the head of the obstetrical and gynæcological departments at Mulago African Hospital and the European and Asian Hospitals, Kampala, for allowing us to visit the maternity wards and to examine the children there, and to the nurses, who accepted most willingly our disruption of their routine We have also to thank Dr Saint-Anne Dargassies for her assistance in the use of technique of examination, and Dr. Andre Thomas for his criticism of our findings The expenses of the investigation were paid from grants made by the International Children's Centre, Paris, and the mental health section of the World Health Organisation. and we thank especially Dr Maurice Gaud, in charge of the African affairs of the Centre, and Dr Ronald Hargreaves, formerly chief of the section.

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GASTRIC ULCER AND THE ABO BLOOD-GROUPS

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PATIENTS with carcinoma of the stomach are more likely to belong to blood-group A and those with duodenal ulcers to group O than are controls; and patients with gastric ulcers come somewhere in between (Aird et al 1953, 1954, Clarke et al. 1955, Koster et al 1955) Koster et al suggested as an explanation that blood-group A was associated with a tendency for the mucosa of the body of the stomach to atrophy, and that the atrophic mucosa and consequent hypochlorhydria produced a lessened liability to duodenal ulcers and an increased liability to carcinoma

Scepticism about the association between hypochlorhydria and the origin of gastric carcinoma led us to test this hypothesis by seeing whether blood group A was in fact associated with carcinoma of the body rather than with carcinoma of the antrum We could do this because in a series of cases of relatively early carcinoma we had already determined the probable site of origin

Contrary to what the hypothesis demanded, there was an excess of group O in the carcinomas of the body, and of group A in carcinomas of the antrum (Jennings et al 1956) These results being only on the borderline of statistical significance they were not reported until further study showed that simple gastric ulcers behaved in a similar way—i e , simple ulcers of the antrum tended to be associated with blood group A, whereas the common gastric ulcer just above the angulus was associated with blood-group O.

Publication of our results was deferred because of criticism of our previous paper by Haddock and McConnell (1956), which led us to restudy our original material together with additional cases seen in 1954–56 Meanwhile Billington (1956a and b) published results which agree closely with ours It seems possible or probable that the results of Haddock and McConnell differ owing to the difficulty of deciding the site of origin of a gastric carcinoma unless the decision is made at operation by comparing the clinical history and X ray films with the fresh specimen In the fixed specimen uninvolved parts of the stomach shrink more than the growth, and consequently lesions of the body often seem to arise only a short distance in front of the pylorus In other cases, where there has been delay in making a diagnosis, a prepyloric carcinoma may extend upwards to involve much of the body of the stomach

Material and Methods

Up to July, 1956, 216 partial gastrectomies for gastric ulcer (uncomplicated by a duodenal ulcer or a scar) were indexed in the combined medical and surgical peptic-ulcer clinic, most of them since 1950 The decision whether an ulcer near the sphincter was prepyloric or duodenal was made at the time of operation by the surgeon , or, if he was doubtful, the pathological department was asked to report on the nature of the mucosa above and below the lesion All ulcers across the sphincter —i e , with gastric mucosa above and duodenal below—were classified as duodenal

In 5 of the 216 cases there is no record that the blood group was determined , 6 patients belonged to groups B and AB , and 13 other cases are omitted because the operation was an emergency one, there had been no previous barium meal, and the site of the ulcer relative to the angulus was uncertain

The remaining 192 cases were classified into three groups by inspection of X-ray films taken in the erect position The difficulty of deciding whether an apparent prepyloric ulcer was really a sphincteric or a duodenal one did not arise, because the method of selection ensured that all the ulcers were gastric Ulcers associated with a “ hanging bag ” deformity—i e , ulcers starting at the angulus but eventually drawn towards the pylorus by scarring and contracture of the prepyloric lesser curve—were classified as antral Other ulcers at the angulus or on the vertical part of the lesser curve were classified as “ mid gastric ulcers ” The third group of “ high ” gastric ulcer consisted of those on the sloping part of the lesser curve below the cardia No attempt was made to estimate the distance from the cardia in centimetres

Results and Discussion

In the accompanying table the gastric ulcer patients are compared with our previously published carcinoma series At each site in the stomach the relative proportion of blood groups A and O is similar in simple ulcer and carcinoma, group A being more frequent in antral lesions (A/A + O = 0 7), and group O in lesions of the body (A/A + O = 0 45) In both sexes group A predominates in antral lesions, but the excess of group O in lesions of the body is only found in males This difference between the sexes in lesions of the body is unexplained and needs confirmation The few high gastric ulcers and carcinomas of the cardia resemble the antral lesions in showing an excess of group A These results are similar to those reported by Billington (1956a and b), who did not, however, distinguish between the sexes

Hitherto it has been thought that gastric carcinoma was associated with group A and peptic ulcer with group O Our results support Billington's (1956a) suggestion that the important association is between the *site* of the lesion and the blood group, and that the *nature* of the lesion, whether simple ulcer or carcinoma, is irrelevant The overall association of carcinoma of the stomach with group A, and of gastric ulcer with group O, results from the fact that most carcinomas occur in the antrum (in lesions of which group A predominates) and most ulcers in the body (in lesions of which group O predominates) The effect of comparing all carcinomas with all ulcers has been to confound a real association between blood-group and the part of the stomach affected, and to produce a spurious association between blood group and the type of lesion, whether carcinoma or ulcer

192 GASTRIC ULCERS AND 119 CARCINOMAS OF THE STOMACH CLASSIFIED BY SITE, SEX, AND BLOOD GROUP

Lesion	Males					Females		
	A		O		Ratio A/A+O	A	O	Ratio A/A+O
Prepyloric ulcer	25	55(43 3)	17	32(43 6)	0 60	4	3	*
Carcinoma of pylorus and antrum	30		15		0 67	12	5	0 70
Midgastric ulcer	37	46(60 6)	57	76(61 3)	0 40	20	11	0 64
Carcinoma of body	9		19		0 32	9	4	0 70
High gastric ulcer	8	16(13 0)†	5	10(13 0)	0 62	2	3	*
Carcinoma of cardia	8		5		0 62	2	1	*
All ulcers	70		79		0 47	26	17	0 60
All carcinoma	47		39		0 55	23	10	0 70
	117		118			49	27	

* Insufficient for calculation

†Expected figures (in parentheses) based on the hypothesis that there is no relation between site and blood group

χ^2 for men alone = 13 3 (2 degrees of freedom) p< 0 0025

χ^2 for both sexes = 7 5 („ „ „ „) p< 0 025

Summary

In 192 patients with gastric ulcer, and 119 patients with carcinoma of the stomach, blood group A predominated when the lesion was in the pyloric antrum and blood group O when it was in the body of the stomach

The association between gastric carcinoma and blood group A on the one hand, and that between gastric ulcer and blood group O on the other, may be attributable to the fact that most carcinomas are in the antrum, whereas most gastric ulcers are in the body of the stomach

We wish to thank Dr H B May, director of the clinical laboratories, for providing the results of the blood group determinations

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“ Because the problem of nutrition is largely a cultural one, the approach to its solution must be principally through cultural means But what is the problem of nutrition which we are concerned to solve ? It is, surely, how one can get human beings to eat foods which at every stage of their growth and development are those most likely to contribute to their optimum health No matter how complete our knowledge of the biochemistry, the physiology, and the nutritional value of food may be, unless we attend to the sociopsychologic or cultural factors first we are not likely to succeed in our endeavors ”—M F ASHLEY MONTAGU, PH D , *Amer J clin Nutr* 1957, 5, 237

MYASTHENIC CRISIS

THERAPEUTIC USE OF *d*-TUBOCURARINE

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IN the past few years progress has been made in determining the mechanism of the neuromuscular failure in myasthenia gravis. The former concept that a "circulating curare-like substance" was responsible for the neuromuscular block has now been virtually abandoned in favour of an alteration in the response of the motor end-plate to acetylcholine or one of its breakdown products (Churchill-Davidson and Richardson 1953). Recently the work of Grob et al. (1955) has indicated that an abnormal response of the motor end-plate to choline (a derivative of acetylcholine) may be the primary factor.

Since 1934, when Mary Walker introduced the use of physostigmine for the purpose, the treatment of myasthenia has centred on various anticholinesterase drugs. Some patients respond more readily than others, and Rowland et al. (1955) have shown that occasionally these drugs, instead of improving the patient's muscle weakness, bring about a rapid deterioration. We describe here a case of this kind and report a new therapy for such patients which is consistent with the present concept of myasthenia.

Case-report

Our patient was a housewife, aged 56, weight 12 st. 3 lb. She was admitted to hospital for investigation.

APRIL, 1954

She had had a drooping right eyelid for three months, slurring speech for two months, and weakness of the jaw for six weeks. These signs were all made worse when she became excited and at the end of the day. The jaw weakness was such that she had to hold her chin up when talking or eating. She could take only semi-solid foods.

Investigations.—No radiological evidence of a mediastinal mass. Serum-creatinine level 0·98 mg. per 100 ml.; serum-creatine 0·35 mg.; serum-cholesterol 118 mg. Hb 84%. Intramuscular neostigmine 2·5 mg. produced dramatic improvement in the muscle weakness. Intravenous decamethonium 2·5 mg. produced peripheral and facial muscle weakness with severe dysphagia and dysphonia. The action potential of the hypothenar muscles (after supramaximal stimulation of the ulnar nerve at the wrist 10 times a second) showed a 10% reduction of the control value. Subsequently, intravenous 'Tensilon' 10 mg. led to a dramatic improvement in the muscle weakness for about two to four minutes.

The reactions are typical of generalised myasthenia gravis in the second or "dual" phase (Churchill-Davidson 1950).

Treatment with pyridostigmine ('Mestinon') 60 mg. four times a day produced good results. After consultation, thymectomy was considered advisable.

MAY, 1954, TO NOVEMBER, 1955

Thymectomy.—The thymus gland was removed in May, 1955, by Mr. N. R. Barrett. It weighed 33·5 g. Microscopy showed "evidence of hyperplasia and atrophy in the mass, but the predominant change was hyperplasia of the large thymus cells. The process appeared to be analogous to nodular hyperplasia in other organs affected by hormones—for example, chronic mastitis. There was no evidence of neoplasm."

Progress.—The patient made an uneventful recovery. Three weeks later she left hospital considerably improved but taking twice the amount of pyridostigmine that she took before the operation—i.e., 60 mg. two-hourly. She was seen regularly at the follow-up clinic every two months, but during the next fourteen months her condition gradually began to deteriorate despite temporary improvement obtained by increasing the dose of pyridostigmine.

DECEMBER, 1955, TO MARCH, 1956

Readmitted in December, under the care of Dr. H. J. Anderson, she felt "terribly tired" and had a myasthenic facies with considerable drooping of both eyelids.

Treatment.—Neostigmine, 22·5 mg. two-hourly for seven doses daily, led to a temporary improvement lasting three days, but she had to be roused regularly during the night; otherwise she was too weak even to swallow in the morning. Pyridostigmine 120 mg. was again tried as the last dose at night in the hope of getting a more prolonged response, but there was only slight improvement. Then neostigmine 30 mg. two-hourly for eight doses daily was tried, again with temporary improvement.

As increasing doses of neostigmine were not producing any general improvement in muscle strength, and the patient was too ill to undergo thoracotomy, she was given another anticholinesterase drug—WIN 8077 (Schwab et al. 1955)—two-hourly in a dosage which gradually increased from 10 mg. initially to 30 mg. two-hourly on the third day. Muscle strength greatly improved on this dosage but was maintained for only about an hour of the two-hour interval between doses; hence, by the time the next dose was due the patient had again become very weak.

Cholinergic Crisis.—On the fourth day after the start of treatment with WIN 8077 the patient suddenly collapsed while on a bedpan. Respirations ceased, and the pulse became feeble. Artificial respiration was begun, and the house-surgeon gave intramuscular neostigmine 2·5 mg. This dose was repeated thirty minutes later, when there was still no sign of spontaneous respiration. The patient was then intubated and maintained on manually controlled respiration with a nitrous-oxide/oxygen mixture. Intravenous tensilon 10 mg. produced no response, and it was then concluded that the patient was probably having a "cholinergic crisis"—i.e., an overdose of anticholinesterase drugs (mainly WIN 8077).

Weak respiratory activity returned three hours later, but could be temporarily abolished by intravenous tensilon 10 mg.

No further drugs were given that day. Five hours later the patient breathed spontaneously and appeared to improve after the intravenous injection of tensilon 10 mg.; so neostigmine 2·5 mg. was given intramuscularly. During the next twenty-four hours the patient twice stopped breathing, on each occasion soon after taking neostigmine 22·5 mg. by mouth.

At this point it was decided to withhold anti-cholinesterase drugs for some days and to maintain adequate artificial ventilation.

Tracheotomy was performed under thiopentone/nitrous-oxide/oxygen anæsthesia, and a cuffed tube was inserted. Ventilation was then maintained with air (supplemented by two litres of oxygen per minute) on a Beaver mark II respirator. Adequate nourishment and fluids were given through a stomach-tube. Sedation was achieved with amylobarbitone sodium and chlorpromazine.

At the end of ten days on this routine the patient was again given neostigmine 22·5 mg. two-hourly. The response was dramatic. Next day all signs of the ptosis had gone, and she could swallow and talk. She dispensed with the respirator during the day but was not sufficiently confident to do so at night.

Progress.—A week later her morale was high, and the improvement in the myasthenic symptoms was striking; but thrombosis of both deep femoral veins necessitated anticoagulant therapy. Four weeks later she was able to get out of bed, and for the first time for many months, could see clearly to read the papers; she was able to knit, and write. The tracheotomy tube was withdrawn, and the wound allowed to close.

Seven weeks later she was discharged convalescent, taking neostigmine 22·5 mg. two-hourly for eight doses daily.

MARCH TO JULY, 1956

Nine weeks later her myasthenic symptoms started to return; she became very tired, and her left eyelid was drooping again.

She was readmitted to hospital, and gradually over the next few weeks her weakness increased, swallowing became extremely difficult, and her voice was hardly audible. She had to be roused at night to receive tablets because she was otherwise too weak in the early morning. Pyridostigmine was again tried as a substitute for neostigmine as the last dose at night, but again this only led to some temporary improvement

Her general condition became so poor owing to continuous salivation and inability to swallow sputum, poor respiratory excursion, and grossly inadequate diet, that it was decided to reinsert the tracheotomy tube and to maintain nourishment through a nasal stomach tube

Second Tracheotomy—Thiopentone 0 15 g and succinylcholine 40 mg were given, and respiratory activity was paralysed for four and a half minutes, during and after which respiration was controlled with a nitrous oxide oxygen mixture through an endotracheal tube up to the time that the tracheotomy tube was inserted

Progress—All neostigmine therapy was stopped On recovering consciousness half an hour later the patient breathed unaided, but four hours later she became cyanosed and very distressed, with poor chest movements The Beaver respirator was again used Her jaw became so weak that it had to be permanently supported by a bandage For the next fourteen days respiration was controlled automatically and adequate nourishment was given through a nasal stomach-tube Light suction of the trachea and bronchi was performed half hourly, or whenever necessary

After a fortnight's treatment the patient was again put back on neostigmine 22 5 mg two hourly for seven doses followed by pyridostigmine 120 mg two hours later The effect was again impressive Gradually over the next few days she could do more and more until she was strong enough to get out of bed for a short time, swallow liquids, knit, write, and read the paper The improvement was maintained for about two weeks and then gradually began to wear off until she again became pitifully weak, being unable to swallow liquids or to breathe adequately without assistance

The pattern of events became remarkably cyclic a period of improvement in muscle power with neostigmine was followed by a gradual deterioration, and then, after a complete rest from drug therapy, a return of the response to neostigmine It was assumed that the dose of neostigmine used after the initial improvement was repeatedly poisoning her, and it was decided to give her another fourteen days of complete rest from all drug therapy but then to try much smaller doses of neostigmine

At the end of the fortnight's complete rest, using the Beaver respirator, the patient was given neostigmine 22 5 mg t d s Again there was an initial improvement in muscle power, enabling her to close her jaw and swallow liquids, but it lasted only for short periods after swallowing the neostigmine After a fortnight the initial improvement began to subside The morale of both patient and attendants was beginning to fall, and desperate measures were now considered necessary

Thyroid Treatment—The first was to try to make her thyrotoxic to see if the myasthenic symptoms would improve After eight days on thyroid extract gr 10 t d s her personality had greatly changed she was irritable, weepy, and unable to be pleased Three days later she became completely unmanageable, so the thyroid treatment was abandoned During this period there was no sign of any improvement in the myasthenic state

At this point the patient's morale was very low, and she could only talk feebly while supporting her jaw with her hand Her diet was entirely fluid because she could not chew or swallow solids, and she seemed completely unable to move her tongue She could neither knit, write, nor read Repeated doses of chlorpromazine 50 mg p o and morphine gr $^{1}/_{8}$ were given with heavy barbiturate sedation at night

AUGUST TO OCTOBER, 1956

(Curare Therapy)

Repeated attempts to "rest" the motor end plate by withholding neostigmine had led to temporary but clear improvement on three separate occasions It was decided, therefore, to go one stage further and to attempt complete "rest" of the motor end-plates for a week by screening them from activity by using repeated doses of *d* tubocurarine

On Aug 27 thiopentone 0 3 g was given, followed by *d* tubocurarine 15 mg Amylobarbitone sodium gr $3^{3}/_{4}$ and chlorpromazine 50 mg were given eight hourly as general sedation. Respiration was maintained on Beaver respirator (mark II) with an expiratory volume of 450–550 c cm per breath at a rate of 12 per min Muscle paralysis was measured both by the visible signs of movement and by stimulation of the ulnar nerve at the wrist at a twitch rate (i e, 10 per sec) and observing the absence of a visible response in the hypothenar muscles Any sign of returning muscle activity was taken as an indication for a further dose of curare The degree of consciousness was measured daily with an electroencephalograph and the appearance of alpha rhythm was taken as a guide for increased sedation In the early stages more frequent electroencephalographic measurements are advisable Electrolyte balance, prothrombin time, urine output, pH, and plasma-bicarbonate level were measured daily

The intake of fluids averaged 3240 ml in twenty four hours A diet of 1500 calories contained per each 12 oz

Protein	105 0 g	Vitamin B_1	3 9 mg
Fat	55 0 g	Riboflavine	3 7 mg
Carbohydrate	150 0 g	Nicotinic acid	25 0 mg
Calcium	2 8 g	Pantothenic acid	10 0 mg
Phosphorus	2 7 g	Choline	250 0 mg
Sodium	1 8 g	Pyridoxine	1 4 mg
Chloride	2 5 g	Vitamin B_{12}	7 0 µg
Potassium	3 7 g	Vitamin C	34 0 mg
Iron	37 0 mg	Vitamin D	750 0 units
Vitamin A	3750 0 units	Vitamin E (acetate)	18 0 mg
		Vitamin K	3 7 mg

The dosage of curare was as follows

1st day (7 0 P M –midnight)	65 mg	6th day	90 mg
2nd day	155 mg	7th day	115 mg
3rd day	140 mg	8th day	60 mg
4th day	140 mg	9th day	Nil—respirator continued
5th day	110 mg		
Total dose of curare			875 mg in eight days

8th day The last dose of *d* tubocurarine was given at 11 20 A M By 5 0 P M right thumb and wrist were seen moving By 7 0 P M lower lip and both eyelids were showing weak but vigorous movement Able to answer questions by squeezing hands Attempts being made to speak

9th day after quiet night now sitting up with eyes wide open Jaw muscles regaining good tone and able to eat light breakfast Off respirator for a few hours at a time Still no neostigmine given

10th day remarkable improvement Able to eat full breakfast, and steak for lunch for first time since admission to hospital Able to get out of bed unaided but still unsteady on legs Now off respirator altogether

11th–20th days continuous, steady, daily improvement Without any neostigmine patient now eating better than at any time for two years Jaw muscles feel firm and eyes are widely open Knitting, reading, and writing well Able to walk length of ward slowly but unaided

21st day left eyelid notice drooping towards end of day

22nd–25th days steady return of myasthenic symptoms, including drooping of eyelids, husky voice, dysphagia, jaw weakness, and general tiredness

Neostigmine therapy on a reduced scale was started again in the dosage of 22 5 mg t d s effect was again dramatic all signs of the myasthenia vanished and the patient could once more eat, see clearly, talk, and walk During the next week the patient was gradually restored to full confidence As there were slight myasthenic signs in the late evening, the dose of neostigmine was increased to four times a day

Four weeks after the end of the curare treatment the patient left for a weekend in the country after having been nearly a year in hospital After a further week's observation in hospital, during which time her tracheotomy tube was removed, she was finally discharged to her home on Oct 12

Condition on Discharge—She was still on the same dosage of neostigmine, both eyes were widely open at all times and she was eating well, reading, knitting, and talking strongly There was no apparent weakness of the facial muscles and she smiled freely Despite her weight of nearly 13 st she walked well and climbed stairs unaided

Final Illness—Unfortunately her only relatives lived in a remote part of Scotland, but in view of what she had already endured, and fully realising the possible consequences, we allowed her to return home We followed her condition by constant correspondence, from which it appears that her improvement was maintained for a further six weeks, making a total of about three months After this, first the left eyelid started to droop, and then the jaw muscles became weak again, despite a constant dosage of neostigmine The general weakness became worse The patient died quite unexpectedly during the night some three weeks later, from what appeared to be an acute onset of respiratory failure

DISCUSSION

The main trouble in myasthenia gravis appears to be an alteration in response of the motor end-plates to acetylcholine or one of its breakdown products (Churchill-

Davidson and Richardson 1953) This supposition is supported by the finding of Grob et al (1955) that choline (a breakdown product of acetylcholine) produces a non depolarisation block in myasthenic patients—i e, instead of producing a simple depolarisation of the muscle fibre as in the normal subject it may produce a prolonged neuromuscular block similar to that produced by *d*-tubocurarine There is no evidence that the choline of myasthenic patients differs in any way from that in normal subjects, on the contrary, experience with decamethonium suggests that this explanation is very unlikely, because it is not the drug that has changed but the response of the motor end-plate

The action of neostigmine at the motor end-plate has not been fully established There is no doubt that its major action is to depress the activity of both the plasma and the true cholinesterase, with the result that the concentration of acetylcholine at the motor end-plate increases Apart from this, it has an action similar to that of acetylcholine on the motor end-plate and possibly on the muscle fibre

The therapeutic value of neostigmine in myasthenia is generally attributed largely to its anti cholinesterase properties, but this may not be the sole reason for it Rowland et al (1955) have shown that, whereas one patient tolerated as much as 2500 mg a day by mouth, another became extremely weak after receiving 16 mg intravenously in ninety minutes This variability in response to neostigmine, not only in different patients but also in the same patient at different times, is characteristic of the disease The altered response of the motor end-plates might be explained by an alteration in the ratio of acetylcholine molecules to those of choline, the former producing depolarisation during their fleeting life-span, and the latter persisting indefinitely and producing a non-depolarisation block like that of *d* tubocurarine

This may help to explain why myasthenic muscle which ceases to respond to neostigmine can be made to respond again if the neostigmine is withheld for a while The present case illustrates this point well, for the anti-cholinesterase drugs apparently induced a "cholinergic crisis" or respiratory failure Then, after a suitable rest, neostigmine produced a striking response in muscle-power, but gradually over the next few weeks this response deteriorated Again, on two separate occasions a rest produced a dramatic improvement, only to be lost a few weeks later It seems almost certain that it was the neostigmine itself that was gradually producing this deterioration The gap between the improvement in muscle strength and the period of deterioration due to possible poisoning became narrower and narrower as the therapy continued, only to widen again after a suitable rest, yet a small concentration of neostigmine was essential to normal respiration and fundamental activity

The fact that the periods of rest were always followed by improvement in the response to anti-cholinesterase therapy led to the next logical step—an even more efficient method of resting the motor end plates Conscious patients, even when on a breathing machine, use their muscles to a limited extent We assumed that if such a patient were sedated and completely paralysed, then only a small amount of acetylcholine would be produced at the nerve terminal The presence of a high concentration of a muscle relaxant—e g *d* tubocurarine—would so raise the excitation threshold of the motor end plate that the concentration of acetylcholine ions would be insufficient to cause stimulation Thus the motor end-plate would enjoy a period of complete rest In such circumstances any substance, whether anti cholinesterase or choline, that has accumulated at the motor end plate would be removed This rather slender hypothesis was the basis for trying what might otherwise be described as *dangerous* treatment—namely, to give large doses of *d*-tubocurarine to a myasthenic patient The results justified the attempt

Six hours after the last dose of *d* tubocurarine, and without any neostigmine at all, the patient was moving both arms and legs, and within eighteen hours some of the previously myasthenic muscles were showing even more muscle power than they had ever done before on full neostigmine therapy This was best exemplified by the patient's being able to eat a full breakfast, and even to chew meat, which she had not been able to do since entering hospital Both eyelids remained widely open, and the absence of any myasthenic symptoms persisted for about ten days, after which they began to return gradually At this stage a reduced dosage of neostigmine produced a dramatic response, with the abolition of all myasthenic symptoms This was maintained far longer, and in a fuller degree, than on any of the three previous occasions, where rest alone had been used

Those who witnessed the effects of the curare therapy had no doubt of its benefit These were not maintained indefinitely, but in some patients it should not be impossible to repeat this form of therapy at intervals Nevertheless, treatment of this kind is dangerous and demands constant medical and nursing attention, it should be undertaken only in units experienced in dealing with long-term respiratory paralysis

Griffin et al (1956) reported the successful treatment of a severe case of myasthenia by thymectomy in the presence of respiratory insufficiency

Before the operation the patient was treated by artificial ventilation on an intermittent positive pressure breathing-machine This was continued for thirty five days without any apparent improvement in muscle power despite varying doses of neostigmine To make comparison with the present case easier we emphasise that the ventilating machine was so balanced that the patient made the initial *respiratory* effort himself and the machine then ensured that it was of sufficient volume—i.e, the patient did some of the work At the end of this time he underwent thymectomy, but after the operation, so that he would be spared postoperative distress, respiration was maintained automatically for four days On the sixth postoperative day the patient could breathe easily, and after the ninth day the respirator was not needed again

So striking are some of the resemblances between the case reported by Griffin et al (1956) and the present case that it is impossible not to ask how much of the effects are due to thymectomy and how much to complete rest If complete rest alone can bring about a striking improvement, is this why thymectomy sometimes does so ?

Another remarkable feature of this case is the absence of evidence of "curare sensitivity" even in a patient with extremely severe myasthenia The degree of sensitivity described by various workers varies from 10- to 100 fold, but, as this is probably the first published case in which massive doses have been deliberately administered, the absence of any obvious sensitivity reaction is important Previous tests with both decamethonium and *d*-tubocurarine have shown that it is important, when talking about myasthenic muscle, to differentiate between that which shows clinical weakness and that which does not Those muscles which are already partially paralysed by the myasthenic process naturally become the first to show increased weakness after the injection of *d* tubocurarine On the other hand, it appears that the "apparently unaffected" muscles require a normal dosage level to bring about complete paralysis

These remarks are based on a single case, but the onset of a "myasthenic crisis" is rare and not easily foretold If the circumstances warrant it, there seems to be a reasonable theoretical and practical basis for resting the motor end plates in the manner described. The treatment is hazardous but in ideal conditions is feasible If more such cases were so treated and successful results obtained, the whole value of thymectomy would need to be carefully reviewed.

Summary

A patient with myasthenia gravis who had undergone thymectomy gradually responded less and less to neostigmine Various anticholinesterases were tried, but the patient finally collapsed apparently from excessive drug therapy

Complete withdrawal of all neostigmine like drugs for seven days led, on resumption of therapy, to much improvement This, however, was maintained for only a few days *before* severe myasthenia again became evident

Large doses of *d*-tubocurarine, which provided complete rest for the motor end-plates, led to a dramatic improvement, which was sustained with the aid of reduced neostigmine therapy for nearly three months

The implications underlying this form of treatment are discussed

We want to record our sincere appreciation of the advice and encouragement we received from Mr N R Barrett, under whose care the patient was admitted, and also from Dr H J Anderson and Dr R Kelly We emphasise our admiration for the nursing care by Sister R Stephenson and her staff We are indebted to Dr R S Schwab for the supplies of WIN 8077 This work was carried out with the help of a grant from the endowment fund of St Thomas's Hospital

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Preliminary Communication

A pH-ENDORADIOSONDE

As a means of obtaining information from the digestive tract, the use of a small radio transmitter, which the patient can swallow, has two advantages (1) that its presence is not noticed by the patient, and (2) that it provides information that cannot be got in any other way We have recently described a unit which simultaneously transmits pressure and temperature data during its passage through the alimentary canal[1]

In designing a unit that would similarly transmit information about hydrogen-ion concentration, we found that the high impedance of glass electrodes is a disadvantage in connection with the low input impedance of most transistor circuits With the transistors available in this country, we have not been able to construct a small enough endoradiosonde for telemetering pH with a glass electrode

It seems necessary to employ at least two transistors and some sort of high input impedance feedback circuit (e g, the input transistor common collector coupled and another as a radio frequency oscillator) Such endoradiosondes can eventually be constructed, since the active elements in present transistors constitute only a small fraction of their total physical volume The advantages of a glass electrode pH unit are rapid response and high accuracy

The endoradiosonde described here embodies a mechano chemical transducer that changes its dimensions with pH Certain polymers have the property of expansion and contraction with pH changes[2] A copolymer of 20% polyacrylic acid and 80% polyvinyl alcohol gives a reversible change in physical dimensions of 60% for a shift of pH from 3 to 8 After formation by vulcanisation under tension at 80°C for thirty minutes it is insoluble in body-fluids A foil having a dry thickness of 0 05 cm gives an 80% response in twenty minutes, thinner films being faster This copolymer has good mechanical strength, unlike some others having larger expansion and contraction properties Polymethacrylic acid gels, for example, are less suitable as transducers, because they are weak

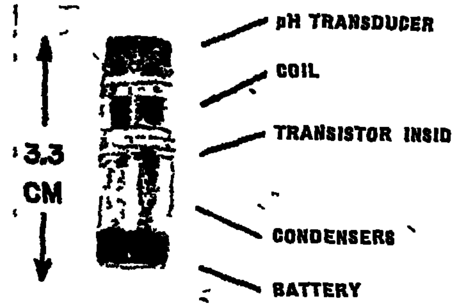

Fig 1—Radiosonde to be swallowed to transmit pH readings during its passage through the gastro intestinal tract. (Actual size) The battery drives the unit continuously for fourteen days

In principle, an osmotic method using the motion of the interface between two opposing dialysing bags would be more sensitive in specified pH ranges and possibly faster But in an experiment in which one bag contained a cellulose derivative soluble in acid, and the other bag contained one soluble in basic solution, the results were less satisfactory than with the copolymer transducer, because of sensitivity to electrolyte concentration

The change of mechanical dimension of the pH sensitive element is transferred to an iron core moving inside a coil constituting the inductance of a transistor oscillator The circuit and construction of this oscillator are similar to that of the unit for measuring pressure and temperature[1] (Since simultaneous temperature measurement was not considered of interest in these preliminary experiments, the mode of operation of the 400 kilocycle oscillator was such as to give non-quenched *oscillation* This was achieved by making the turns ratio of the 500-turn coil 1 10) The change of position of the iron core causes the frequency of the oscillator to shift Thus the pH is telemetered as a frequency modulated signal A limp second diaphragm over another opening in the capsule can render the unit insensitive to pressure changes in the abdomen

The radio signal is picked up by a small loop antenna connected to a standard radio receiver The tuning of the receiver thus gives information of the pH value in the gastro intestinal tract One can track the endoradiosonde through the body with the antenna or, for more accuracy, by X-ray observation

With this unit we have been able to observe the shift in pH from acid in reaction in the stomach towards alkaline in the intestine The slow response time of the copolymer seems not to obviate its use since the speed of pH changes is usually of less importance than the actual final values The accuracy of the unit has not yet been thoroughly investigated in conditions where the electrolyte concentration is much different from that in the calibration liquids

The mechano chemical transducer unit has a length of 0 5 cm and the endoradiosonde with this attached has a total length of 3 3 cm The diameter is 0 9 cm, like that of the unit for pressure and temperature

We are indebted to Dr Birger Blombäck and Dr Victor Mutt for valuable suggestions This work was performed while one of us (R S M) was on leave from the University of California Medical Center as a Guggenheim fellow

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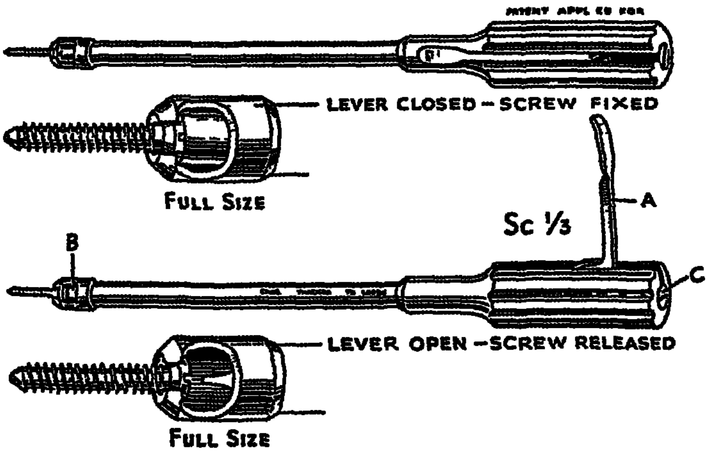
New Inventions

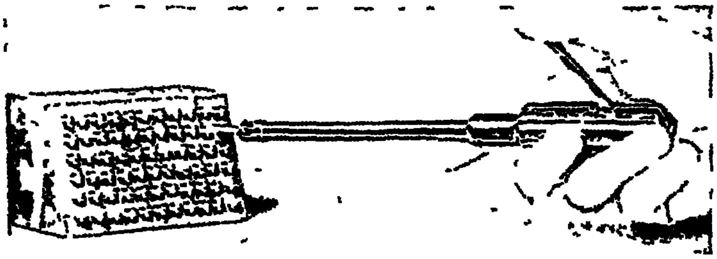
AN IMPROVED SCREWDRIVER

All the self-holding screwdrivers now in use have the disadvantage that they need three hands to load them With the instruments here described, screws can be loaded single-handed and with far greater speed These instruments have been in constant use by myself and other surgeons over the past four years and have proved extremely satisfactory

The screwdriver is an adaption of the Burns pattern, in which the screw-fixing device at the base of the handle has been replaced by a quick-action lever recessed into the handle.

All the usual standard screws, such as Sherman's or Lane's pattern, can be used with this instrument (up to $^{5}/_{32}$ in external diameter of thread with head diameter of $^{5}/_{16}$ in), for the shaped tubular shaft at the distal end has been made to suit a wide variation of shapes of screw head





After the screw has been inserted to the required depth and the screwdriver removed from the screw head, it is possible to drive the screw fully home with the same instrument by merely closing the lever, the end of the tubular shaft is concave externally to accommodate the top of the screw head A special feature is an adjusting screw in the base of the handle This permits the lever to be set to give a firm fixation of the screw head, and once set, it is not necessary to alter it unless a screw with a larger or smaller head is required

All parts of the instruments are made of stainless steel except the handle, which is anodised aluminium The illustration shows the screwdriver being loaded for use

To avoid the difficulties associated with holding the screws in forceps to load them into the screwdriver, it has been found useful to mount them on a solid block of duralumin drilled to receive six screws of each size, ranging from $^{3}/_{8}$ in to 2 in, with the heads protruding When this "screw bank" is loaded, the whole can be easily sterilised by boiling

My thanks are due to Mr A B Hallam of Messrs Thackray, who was responsible for the technical details involved in the construction of these instruments

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AN ADAPTABLE WARD BED

A STANDARD WARD BED ADAPTABLE FOR THE UNCONSCIOUS, DISTURBED, OR CHRONIC SICK

This bed was developed at Napsbury Hospital for patients having Sakel's insulin-coma therapy, and has been in use for over a year It is an attempt to meet the ward situation where permanent "cot-beds" are undesirable yet additional facilities may help in nursing the unconscious or restless patient

Insulin treatment involves the patient in a daily period of coma and recovery There are particular risks in precarious metabolism, physical restlessness, and a confused (and often disturbed) mental state Besides appropriate nursing, management entails nasal feeding, intravenous injections, and, at times, electroconvulsive therapy The medical team is often numerically small, and is simultaneously seeking to provide an understanding and careful relationship where purely restrictive physical handling is minimal These specific problems are seen in the insulin unit, but they arise in differing contexts throughout general and mental hospital practice

Fig 1 shows the bed for use as a standard ward bed and the means of fitting the end-pieces to the frame Unlocking and removing the foot-bow and head-piece converts the bed to a trolley, permitting easy access to the patient, particularly from the head—e g, during nasal feeding and electroconvulsive therapy The sliding tray under the head provides a surface for instruments, &c It draws out on either side with stops to prevent over-extension The bed is fitted with a standard wheeling device at the foot, and with individually locking wheels at the head.

Fig 2 shows both padded ends and one padded side in position After removal of the arm-rest, fitting the second padded side completes the cot The padded ends fit and lock in the same way as the foot-bow and head-piece The padded sides run in gutters at either side of the end-pieces The sides and ends are interchangeable between beds, making it possible to use one set of padded ends and sides in conjunction with a number of bed-frames

The cot provides a relatively draught-free space where the necessity for protective handling (which provokes restlessness) is considerably reduced The top of the padded side is 3 ft 8 in above the floor and allows a nurse of somewhat under average height to give nursing attention (other than lifting the patient) without removing the sides With adjacent sides removed, two cots can be fitted together by means of the staples shown, making a protective pen about 6 ft square

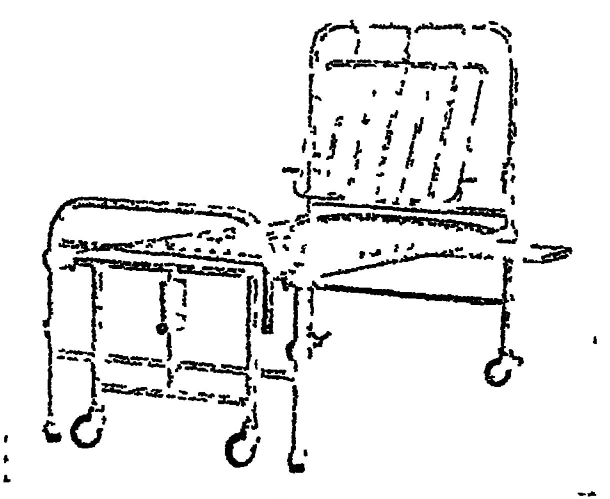

Fig 1

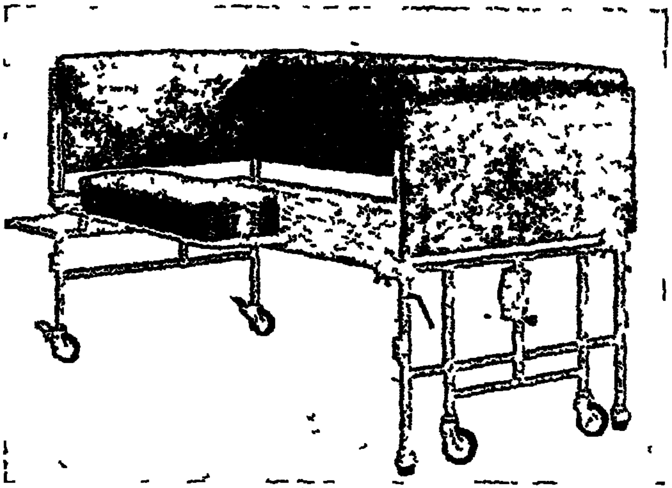

Fig 2

The arm-rest fits by means of pegs into either side of the bed-frame It is padded level with the mattress At the head end there is provision for fitting an aneroid sphygmomanometer, and at the foot a space for a kidney-dish The bed can be tilted by means of a standard tilting frame

I should like to thank the Medical Superintendent and staff at Napsbury Hospital for their help and interest, and acknowledge the proficiency of Messrs S B Whitfield in converting the prototype to a " production model "

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Reviews of Books

Practical Forensic Medicine

FRANCIS E CAMPS, M D, *reader in forensic medicine* London Hospital Medical College, W BENTLEY PURCHASE, O B E, M C, M B, barrister at law, coroner for the Royal Household and the county of London London Hutchinson's Medical Publications 1956 Pp 541 75s

IN a preface the authors say that they write " to give medical practitioners and others a fair idea of what the subject comprises " They have not been as comprehensive as this suggests, and that may be fortunate since the subject is, as they remark, already well documented What the book has done is to make a novel and partly successful assault on the established format It starts with A for abortion, accidents, and alcoholic intoxication, and proceeds through the alphabet to W for wounds It then embarks on toxicology, but discards the alphabetical order for a collectanea

There is much that is practical and useful, and the authors' enthusiasm for their subject is apparent Because of this enthusiasm perhaps some sections are handled brilliantly and illustrated well, leaving others either inadequately treated or frankly neglected Thus, identification receives nearly 50 pages of sound and absorbing interest, but perplexing deaths in infancy—an everyday problem—are given a bare 10 and the medicolegal necropsy gets only 2 Barbiturates are generously treated, but there is nothing about the current menace of tranquillisers, and the danger of potentiation by alcohol is summarily dismissed The text is uneven, so that thoughtful and practical passages are followed by material less skilfully handled The English is forthright if not always elegant though most readers will know what is meant by the " time taken for a body to be skeletonised," " any law of local force," or " she was inflated with oxygen "

Nevertheless, this is a refreshingly new approach, which reflects the authors' wide knowledge of legal medicine in a way that the occasional forensic pathologist will find most helpful An index would have avoided the frustration of searching for the information that the book undoubtedly contains, but that is the only really unpractical feature of this attractive work

Physiologic Principles of Surgery

Editors L M ZIMMERMAN, M D, professor and chairman of the department of surgery, Chicago Medical School, R LEVINE, M D, chairman, department of medicine, and director, department of metabolic and endocrine research, Medical Research Institute, Michael Reese Hospital Philadelphia and London W B Saunders 1957 Pp 988 *105s*

ALTHOUGH its main roots remain in anatomy and pathology, modern surgical thought and practice is increasingly concerned with disturbances of function, as seen both in disease processes and as a result of surgical procedures themselves Consideration of such problems must be based on a clear appreciation of the physiology of the systems involved, and this book is intended as an " authoritative statement of the current status of the various physiologic problems in surgery " In this intention it largely succeeds

Separate sections, each written by an expert, deal with the various basic, general problems, such as hæmorrhage, tissue transplantation, and pain, and all the more specialised problems arising in each and every branch of surgery The extent to which purely clinical considerations are emphasised varies from section to section, but each is essentially a study in applied physiology The book contains a vast amount of valuable detailed information not to be found in any other single volume, and deals fully with the great range of subjects now covered by modern surgical research Each section contains full references to the subject concerned

Focusing attention on fundamental physiological processes, this volume is a valuable addition to surgical literature It is of particular interest to postgraduate students and those engaged in surgical research work, but practising surgeons should find here much of interest and value to them

Family and Kinship in East London

A Survey by the Institute of Community Studies MICHAEL YOUNG and PETER WILLMOTT London Routledge & Kegan Paul 1957 Pp 232 25s

THE first of a series of reports to be issued by the Institute of Community Studies, this survey deals with the effect on family life of the new housing estates which have been built in their hundreds since the war The first part of the book studies the close kinship, the intimate family and living conditions in Bethnal Green, with Mum always close at hand The second part discusses the effects of moving to a new housing-estate, Greenleigh, a few miles away, where the young family is very much on its own and where the common complaint is that other residents are unfriendly and snobbish

The authors conclude that most residents in Bethnal Green, tied to the district by time and by a lasting attachment to their families, wish to continue to live in the East End They believe that the authorities should do more than they are at present doing to enable them to continue to do so, rather than insisting that more thousands should migrate beyond the city, and that if the authorities regard community spirit as an asset worth preserving, they should build new houses around the social groups to which the people already belong

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Treves' Surgical Applied Anatomy (13th ed London Cassell 1957 Pp 591 30*s*) —The first edition of this book appeared in 1883, so it is the oldest textbook of surgical anatomy in English still in current use It is a tribute to the practical wisdom and literary skill of the original author and of subsequent editors that it should also be one of the best Prof Lambert Rogers is responsible for the latest edition It is more than a safe guide through the finals with its wealth of clinical information, it fulfils the wish, expressed in the preface to the first edition that " it should make the dry bones live " This edition is unlikely to be the last

THE LANCET

LONDON SATURDAY, JUNE 15, 1957

Polyarteritis Nodosa

CORTISONE and corticotrophin were the first agents reported to have a convincing effect on polyarteritis nodosa.[1 2] But the important question whether cortisone prolongs survival remained unanswered, and a panel of the Medical Research Council has sought to resolve this by a controlled therapeutic trial. The task presented serious difficulties and the outcome has been somewhat disappointing. The panel rightly decided that it would be ethically wrong to adopt the procedure (used in therapeutic trials in less lethal diseases) in which selected patients are allocated at random to treated and control groups. The only alternative was to treat all patients fulfilling the criteria for diagnosis, and to compare their fates with those of patients selected retrospectively on the same criteria. The scarcity of cases made it necessary to collate observations made by a large number of physicians in many hospitals. Complete suppression of the disease was the goal, and the dosage of cortisone was limited only by the need to avoid intolerable side-effects. The analysis of the results of the first year of the trial[3] is based on 17 cases in which the diagnosis was made and treatment started in 1950. The untreated control series consisted of 19 patients, from the same hospitals, in whom the disease had started between 1941 and 1950. The two groups were similar in all major respects, with the important exception that hypertension was very much more common in the untreated group (42% at the time of diagnostic biopsy) than in the treated group (6%). The prognosis is much worse in hypertensive patients, and it is not surprising that only 7 of the 19 untreated patients were still alive a year after diagnosis; of the 17 treated patients, 14 were still alive. Thus the untreated group failed to provide a satisfactory control for the treated group, and no firm conclusion could be reached about the efficacy of cortisone in prolonging life. It was concluded that "assessment of therapeutic activity by the use of retrospective controls is an inherently fallacious method and no substitute for the strictly controlled clinical trial."

In patients severely ill with polyarteritis nodosa the initial effects of cortisone were always definite and often dramatic. Within two or three days fever abated, appetite and well-being improved, and pains in joints and muscles decreased. But complete clinical remission and maintenance of a normal erythrocyte-sedimentation rate were rarely achieved—for example, in only 3 of the 15 survivors during the seventh and eighth months of treatment. But the dosage used varied, and truly suppressive doses (which may be as high as 300–500 mg. daily) were not always given. At such high doses, gross features of Cushing's syndrome appeared, and in one patient a gastric ulcer perforated; in a second patient, taking 300 mg. of cortisone daily, a duodenal ulcer developed, but healed without any change in the dosage. During treatment, the blood-pressure rose in the sole hypertensive patient, and 5 other patients became hypertensive —1 died with malignant hypertension. It was impossible to decide whether the increase in pressure in these patients was due to specific renal lesions (for which there was evidence in 4) or to cortisone.

The collection of untreated control cases for the M.R.C. panel was undertaken by Dr. G. A. ROSE, and this part of the investigation yielded some important data on the natural history of polyarteritis nodosa, gleaned from 104 case-records. In their analysis ROSE and SPENCER[4] distinguished a group of cases with involvement of the lungs and other special features. Indeed, the presence or absence of lung lesions seemed to be a more useful basis for classification than the size of vessels involved or the separate types of vasculitis distinguished by ZEEK.[5] The features common to the 14 patients with pulmonary polyarteritis (and much less common in the remainder) included a respiratory illness initiating the disease, the presence in various viscera of unusual necrotising and granulomatous lesions, and mucosal ulceration of the alimentary tract and trachea. In a further 18 cases, pulmonary arteritis was not seen (necropsy material was inadequate in some), but the presence of the remaining special features justified their inclusion in the same "lung-involvement" group. The granulomatous lesions in these cases were found in sites remote from arteries. High eosinophil-counts in the blood (1500 or more cells per c.mm.) and polyarterial lesions containing giant cells or many eosinophils were commoner in this group, and nasal and middle-ear granulomas were never seen when the lungs were not involved. The initial respiratory illness was classed as bronchitic, pneumonic, or asthmatic. Even at this early stage it was often clear that the illness was not a straightforward one. Patients with a bronchitic illness often lost weight steadily and general weakness became prominent. Pneumonic cases ran a rather chronic course, with productive cough, pleuritic pain, and hæmoptysis; antibiotics were ineffective. Asthmatic attacks were frequent and severe, usually with eosinophilia in the peripheral blood. In two-thirds of these cases, over a year elapsed before systemic polyarteritis nodosa became manifest. The onset of the respiratory phase was often insidious, but in the systemic phase deterioration was rapid and the course shorter than it was when there was no initial involvement of the lungs. This rapid progression of the systemic phase may explain why patients with lung involvement are less prone to hypertension than those with more slowly progressive disease without respiratory features, though an apparently identical glomerulitis was seen in both groups.

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[1] Ross B Parr J A P Pump K K, Stanford R L *Canad med Ass J* 1950 62 6

[2] Shick R M, Baggenstoss A H, Fuller B F Polley H F *Minn Med* 1951, 34 842

[3] Report to the Medical Research Council by the Collagen Diseases and Hypersensitivity Panel *Brit med J* March 16 1957, p 608

[4] Rose G A, Spencer H *Quart J Med* 1957, 26 43

[5] Zeek, P M *Amer J clin Path* 1952, 22 777

Small series of polyarteritis nodosa with lesions in the lungs have been reported in the past, but the other distinctive features of such cases have not always been appreciated **CHURG** and **STRAUSS** [6] described fully the non-arterial granulomas present in 13 out of 14 cases with asthma, eosinophilia, and polyarteritis, and they gave the name "allergic granulomatosis and angiitis" to what they considered to be a syndrome distinct from polyarteritis nodosa It seems clear, however, that granulomatous lesions, though restricted to cases with involvement of the lungs, are not necessarily associated with asthma **ZEEK** and her colleagues [5 7] distinguished "*hypersensitivity angiitis*" from classical polyarteritis nodosa, but **ROSE** and **SPENCER** found no cases in their series which fulfilled the criteria for this syndrome

ROSE and **SPENCER** extracted from their case-records information which might form the basis of a future specific inquiry into the ætiology of polyarteritis nodosa Attempts have been made in the past to implicate various drugs, but the symptoms which prompt the giving of a drug may be those of early polyarteritis, or of an infection which is the true cause of the ensuing vascular disease Perhaps the most suggestive evidence was that which linked polyarteritis nodosa with *respiratory infections* (especially those due to β-hæmolytic streptococci) and their treatment with sulphonamides In nearly all the reported cases in which an association between a sulphonamide drug and polyarteritis has been suspected, the drug has been given for a respiratory infection The sputum had been cultured in 22 cases, and in 5 of these β hæmolytic streptococci were isolated—a finding which would be unexpected in uncomplicated bronchitis Moreover, 12 5% of the patients had active rheumatic fever or a history of an attack—a link with the streptococcus which others have noticed [8 9] Evidence against a drug was clearest in the case of thiouracil and other antithyroid drugs, but it seemed that thiouracil polyarteritis might differ from ordinary polyarteritis nodosa **ROSE** and **SPENCER** make a plea for including in the investigation of cases of polyarteritis nodosa an accurate account of any recent drug administration and an early search for cultural or serological evidence of recent β-hæmolytic streptococcal infection As in patients with recurrent rheumatic fever, prompt treatment of any acute throat infection may well be important in polyarteritis nodosa

ROSE and **SPENCER** believe that the hypertension is a sequel of renal polyarteritis or glomerulitis, but that the arterial pressure rises only during the healing stages of these lesions More than half the patients with adequate records of arterial pressure had normal readings throughout their illness and at necropsy tended to have glomerular lesions of recent origin Patients who were hypertensive throughout, or became hypertensive, usually had chronic glomerulitis or healed renal polyarteritis Rises in arterial pressure were found only after proteinuria or hæmaturia had developed **ROSE** and **SPENCER** conclude that the hypertension is nearly always a result of the polyarteritis nodosa and not a precursor

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[6] Churg J Strauss L *Amer J Path* 1951, 27 277

[7] Knowles H C Zeek, P M Blankenhorn M A *Arch intern Med* 1953, 92 789

[8] Ophuls, W *Ibid*, 1923, 32, 870

[9] Friedberg, C K, Gross, L *Ibid* 1934 54, 170

The Endocrine Complex

WITH some reason the anterior pituitary has been allotted a prominent position in the hierarchy of endocrine glands Thus, it is believed to form at least six hormones—thyrotrophic (T S H), adrenocorticotrophic (A C T H , corticotrophin), follicle-stimulating (F S H), luteotropic (L H), mammotrophic (prolactin), and growth (G H) Five of these substances are known to be directly concerned in regulating other endocrine glands, and the sixth (G H) appears to be important for the growth and maintenance of all tissues The parathyroids and thymus seem to be *independent* of the anterior pituitary, though their actions are obviously modified by its absence, owing to a general disturbance of all functions Intensive research has partly elucidated the functions of the endocrines and, because of this and the availability of hormones such as cortisone, it has become feasible to remove, for therapeutic purposes, apparently normal pituitary glands This operation has underlined the urgent need for yet more information about endocrine functions and interconnections, partly in order to determine when the operation will be beneficial, and partly to obviate the need for this heroic and blunderbuss method—hypophysectomy offers only temporary respite from the progress of cancer of the breast and is useless against cancer at many other sites More information is needed, too, in order to help patients with so-called simple endocrine disorders

The rationale of hypophysectomy for breast cancer lies in the endocrine control of mammary growth, about which *there is now agreement on general* principles [1–4] Observations on animals after removal of one or more of the anterior pituitary, adrenals, and ovaries has shown that moderate doses of œstrogens induce growth of the mammary ducts, and that œstrogen plus progesterone given in a ratio of about 1 30 induces lobular-alveolar growth, but that œstrogen and progesterone are ineffective in the absence of the anterior pituitary In unoperated animals a combination of œstrogen and prolactin leads to lobular-alveolar growth since prolactin is itself luteotrophic, and therefore promotes the production of progesterone If to an otherwise normal animal enough œstrogen is given to cause pseudo pregnancy, again mammary development is seen because the œstrogen stimulates the anterior pituitary which releases prolactin, and this stimulates the release of progesterone, so that once more these three substances are present Thus, œstrogen and progesterone from the ovary and prolactin from the anterior pituitary are necessary for the development of the mammary glands The prolactin has a dual rôle in stimulating the production of progesterone from the corpus luteum of the ovary, and in exerting some other and more directly growth-promoting function, since œstrogen and progesterone together are inadequate It is not known whether in its non-luteotrophic activity prolactin directly stimulates the mammary glands or influences metabolic processes in a general way, the former is a possibility since in an animal

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[1] Folley S J *In* Ciba Foundation Colloquia on Endocrinology London, 1952 vol 4 p 381

[2] Folley S J The Physiology and Biochemistry of Lactation Edinburgh 1956

[3] Lyons, W R *Proc Soc exp Biol*, N Y 1942, 51 308

[4] Nelson, W O *In* Ciba Foundation Colloquia on Endocrinology *London* 1952, vol 4, p 402

previously treated with œstrogen and progesterone prolactin injected into one milk duct has a well-localised action[3] Mammary growth can be induced even in the absence of adrenal cortical tissue, but, not surprisingly, growth is more nearly normal if the tissues receive their proper quota of both adrenal steroids and G H In the absence of the ovaries the adrenal cortex produces ovarian hormones, so ovariectomy alone will not deprive a malignant breast growth of its needed hormones for more than a short time The exact part played by G H is still little understood[5] All these observations point to the importance of the anterior pituitary Some recent work[6] suggests that the posterior lobe, too, may have to be drawn in, since there is evidence that one of its hormones—oxytocin—causes the release of prolactin In addition, the thyroid has to be considered owing to the observation that patients with hypothyroidism are more prone than patients with hyperthyroidism to cancer of the breast and genital organs This may be compared with the observation of TRENTIN et al[7] that in rats after thyroidectomy the mammary glands are particularly sensitive to the effects of œstrogen and progesterone From all this it is clear that the actions of a hormone cannot be considered in isolation, but only in the context of other hormones

In the hitherto vain attempt to establish which patients will benefit from hypophysectomy, several interesting facts have come to light—for instance, that the excretion of œstrogens continues after ovariectomy and is not necessarily abolished by subsequent adrenalectomy and even, in some cases, hypophysectomy[8] This means either that the so-called hormone-independent growths are perhaps not really independent, or that in some people there is accessory anterior pituitary tissue which is active throughout life or becomes so after removal of the anterior lobe Anatomical evidence of accessory tissue was described by BOYD,[9] who examined the region of the roof of the nasopharynx, from which the anterior lobe develops embryologically, and found groups of cells resembling differentiated anterior-lobe cells Another point of interest is the rate of atrophy of those endocrines which depend largely on anterior-lobe hormones for their activity thus, vaginal smears suggest that the ovaries atrophy in about 4 weeks, urinary excretion of gonadotrophin ceases in 2 weeks to 3 months, and clinical myxœdema appears in 1 to 6 months[10] This is roughly what might have been expected from observations in other species

The object of hypophysectomy in the treatment of cancer is to reduce the output of G H, corticotrophin, and gonadotrophins RUSSELL[11] suggested that this object might be achieved no less certainly by low-stalk section, which is much simpler than total removal of the gland The arterial supply of the anterior lobe of the pituitary is interesting in that all the capillaries are second-group capillaries arising from vessels which are derived from a mass of first-group capillaries lying either in the hypothalamus or in the tissue of nervous origin low down in the pituitary stalk[12] A mid-stalk section results in reduction of anterior-lobe volume by as much as 68–83%,[13] but this leaves more than enough pituitary tissue to maintain other glands in working condition[14] In two of the three clinical cases considered by RUSSELL, low-stalk section led to complete necrosis of the anterior lobe, presumably because even the most ventral supply vessels had been divided Experience alone can show whether this simpler operation is adequate

Besides the interactions of the endocrine system already considered, some others are well recognised, such as the control of T S H and corticotrophin release by the activity induced in the target organs, thus, the amount of circulating adrenal steroids and thyroxine is directly related to the amount of corticotrophin and T S H liberated Other less well-known relationships are now being found It has been noted clinically and histologically[15] that absence of adrenal cortical steroids may be accompanied by thyroid hypertrophy Recently it has been shown that there is sometimes an inverse relationship between corticotrophin and T S H release[16] Certain types of stress, surgical trauma, or hæmorrhage, which are known to cause the release of corticotrophin, inhibit the rate of release of ^{131}I from the thyroid—i e, less thyroid hormone is liberated This inhibition occurs even when the thyroid gland is denervated and also after adrenalectomy, and must, therefore, depend on central nervous system influences, and the likeliest route by which these can affect the thyroid is by alterations in secretion of T S H from the anterior pituitary[16] A similar inhibition occurs on administration of fairly large doses of corticotrophin and cortisone On the other hand, in Addison's disease and in adrenalectomised animals small doses of cortisone may increase thyroid activity[17] Though its mechanism is unknown, this reversed action is understandable since in the patient with Addison's disease thyroid function is below par owing to the absence of a substance necessary for normal cell activity, whereas the situation is quite different when the concentration of adrenal steroids is raised above normal in a healthy animal

Events in the central nervous system profoundly affect endocrine activity—usually by means of hormones liberated from the anterior pituitary, and rarely by direct nerve stimuli as in the adrenal medulla It is generally believed that the anterior lobe has no secreto-motor supply and must therefore be influenced by hormones Some of these, such as adrenal steroids and thyroxine, come from the peripheral organs, but what, if anything,[18] is released from the central nervous system to affect anterior-lobe activity is unknown A vascular path for such a substance exists in the double capillary system already mentioned, the first part of which lies in nervous tissue and leads via the so called portal vessels to the second part in the substance of the anterior lobe It is clear that the proper continuity of this vascular link is important for some aspects of pituitary activity For example, if this path is cut or the anterior lobe transplanted to another site, eosinopenia still follows stimuli which can be classed as systemic, but not those which can be called neurotropic[19] Also, in animals the weights of the ovaries are directly correlated with the presence of the vascular connections between the hypothalamus and the anterior lobe[19] With regard to the thyroid

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[5] Smith, R. W jun Gaebler O H Long, C N H The Hypophyseal Growth Hormones, Nature and Actions New York 1955

[6] Benson G K Folley S J *J Endocrin* 1957 14 xi

[7] Trentin J J Hurst, V, Turner C W *Proc Soc exp Biol*, N Y 1948, 67 461

[8] Bulbrook R D Greenwood, F C *Brit med J* March 23 1957, pp 662, 666

[9] Boyd J D *J Endocrin* 1956, 14 66

[10] *Lancet* March 9 1957 p 515

[11] Russell D S *Ibid* 1956 i, 466

[12] Xuereb G P, Prichard M M L, Daniel P M *Quart J exp Physiol* 1954, 39, 199, 219

[13] Campbell H J, Harris, G W *J Physiol* 1957, 136 333

[14] Ganong W F Hume D M *Endocrinology* 1954, 55, 474

[15] Kracht, J *Acta endocr, Copenhagen* 1954, 15 355

[16] Brown Grant, K, Harris, G W, Reichlin, S *J Physiol* 1957, 136, 364

[17] Hill S R, Reiss, R S Forsham, P H, Thorn, G W *J clin Endocrin* 1950, 10, 1375

[18] Thomson, A P D, Zuckerman, S *Nature, Lond* 1953, 171 970

> "it may be concluded that the pituitary divorced from anatomical connection with the hypothalamus retains a residuum of autonomous activity with regard to the secretion of the thyrotrophic hormone and that this activity can be inhibited in an apparently normal way by a raised blood level of thyroid hormone and by the stress of physical trauma The function of the hypothalamus in relation to T S H secretion seems to be to *maintain* the normal rate of secretion and to *modify* this rate of release in response to stimuli acting through the central nervous system "[16]

That is to say, the activity of the anterior lobe is modified by both the central nervous system and the blood concentration of thyroid hormone Whatever view is held of the mode of control of the anterior pituitary, it is clear that even a successful graft does not function as satisfactorily as the gland in its proper position in relation to the hypothalamus

The last aspect of the problem is the one about which we know the least, but on which much work is now being done—that is, the action of the various hormones on the nervous system[20] That hormones do affect the nervous system is evident from cases of hyperthyroidism or hypothyroidism, premenstrual tension, and other disorders The possible modes of action are many, from changes in activity of one or more cellular enzyme systems and changes in intracellular and extracellular electrolytes and water concentration to alterations in ease of synaptic transmission between some types or groups of neurones whose activity specifically affects the anterior lobe That man can live without an interior lobe but with a modicum of substitution therapy shows that for all his complexity he has remarkable powers of adaptation

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[19] Fortier, C, Harris, G W, McDonald, R *J Physiol* 1957, 136, 344

[20] Hoagland, H Hormones, Brain Function, and Behaviour New York, 1957

Annotations

CIGARETTE-SMOKING AND RESPIRATORY DISEASE

Doll and Hill[1] found an association between smoking and lung cancer, Lowe[2] one between smoking and respiratory tuberculosis, and Leese[3] one between smoking and chronic bronchitis Edwards[4] now describes an analysis of the relationship between cigarette-smoking and respiratory disease, based mainly on the data compiled by these workers The association between cigarette smoking and cancer of the lung was confirmed Adenocarcinoma, however, did not seem to be commoner in smokers than in non smokers, and, although smoking seemed to increase to a comparable extent the liability of men and women to oat cell carcinoma, it seemed much less liable to provoke squamous carcinoma in women Assuming that the smoking habits of Lowe's controls represented those of the general population, Edwards calculated that 84% of cases of lung cancer in men and 34% of cases in women are related to smoking If this estimate is correct, 12,000 men and 770 women died of smoker's cancer in 1954 The death-rate from lung cancer is not so high in New Zealand as in this country despite proportionately heavier smoking there[5], but the difference may be accounted for by the greater pollution of the atmosphere in Britain, for there is evidence[6] that atmospheric pollution by itself increases the liability to lung cancer, and that the carcinogenic effects of smoking and atmospheric pollution are additive With respect to respiratory tuberculosis, Edwards estimated that at least a third, and probably more than half, of the notifications in men over 30 years of age and almost a quarter of the notifications in women over 30 years of age were attributable to smoking

According to Edwards's calculations concerning lung cancer and tuberculosis, the damage done per cigarette per day tends to decrease with the number smoked Contrary to what might be expected, therefore, it seems to be less than twice as dangerous (not more than twice as dangerous) to smoke thirty cigarettes a day than to smoke fifteen a day or, to put it in another way, there would be more lung cancer and tuberculosis in a population if all its members smoked fifteen cigarettes a day than there would be if half its members smoked thirty a day and the other half did not smoke at all

The importance of the rôle of smoking in the ætiology of chronic bronchitis was harder to estimate, but Edwards considers that, although atmospheric pollution is probably the most important single causal agent, smoking is a necessary additional factor in most cases In chronic bronchitis, the damage done per cigarette per day seemed to increase with the number smoked Edwards concluded that the total number of deaths from the three major respiratory diseases in Britain—lung cancer, tuberculosis, and chronic bronchitis—would be halved in the absence of cigarette smoking

These calculations indicate the striking improvement in the public health that might be expected if cigarette smokers were persuaded to give up this habit—and if young people were persuaded not to engage in it

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[1] Doll, R, Bradford Hill A *Brit med J* 1952, ii, 1271

[2] Lowe C R *Ibid*, 1956 ii, 1081

[3] Leese W L B *Lancet*, 1956 ii, 762

[4] Edwards, J H *Brit J prev soc Med* 1957 11, 10

[5] Eastcott, D F *Lancet* 1956 i, 37

[6] Stocks, P, Campbell, J M *Brit med J* 1955, ii, 923

SURGERY IN SPINAL TUBERCULOSIS

WHICHEVER part of the skeleton it attacks, tuberculosis places the surgeon in a quandary Instinct prompts him to deal with the lesions operatively, by principles sound for other diseases—to evacuate pus where it has formed, to remove necrotic tissue, and to obliterate the defects resulting from suppuration In the past he has been restrained, when contemplating such intervention, by two very real fears It was always possible that by operation he might *disseminate* the very infection he strove to eradicate, or a secondary infection, gaining access through his incision, might produce a worse state than the initial one Only twelve years ago, Dickson[1] justifiably warned his colleagues that even "introducing a drainage tube into a tuberculous abscess makes certain a *draining* sinus will form, which will become secondarily infected and will probably never heal It has been truly said that draining a tuberculous abscess frequently signs a patient's death warrant" At no site have these risks seemed graver than the spine. Abscesses there have nevertheless been attacked surgically Treves, in 1884, described an operation in which diseased lumbar vertebræ were exposed by a paravertebral incision, any bony sequestra found were removed, and at the same time a drainage-tube was passed through the psoas abscess, emerging some distance from the involved vertebræ But such procedures were seldom undertaken, for too often they ended in disaster

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[1] Dickson F D *In* Bancroft, F W, Murray, G R Surgical Treatment of the Musculo Skeletal System Philadelphia 1945

Today, with chemotherapy, surgery for all tuberculous lesions is permissible more often, and earlier, than has been the case hitherto Wilkinson[2] emphasises how destructive the disease can be in young children when it affects the lower thoracic vertebræ Conscious of the inhibiting effect of pus on bone repair, and of the inaccessibility of necrotic areas to circulating antibiotics, he has operated on such patients within a month or two of the disease being diagnosed Foci in the vertebral bodies are curetted out and packed with bone chips, and abscesses are evacuated With adult patients he proceeds a little more slowly, watching them for some three or four months and being prepared then to operate if bone destruction is continuing, in such cases an abscess should be suspected The complications have been relatively trivial—short-lived sinuses and, occasionally, pleural effusions, they have not included miliary spread In the United States the surgery of spinal tuberculosis has recently been carried a stage further Weinberg[3] holds that permanent healing may not follow incision and drainage alone An abscess tract may be tortuous or constricted, and may give rise to irregular diverticula which cannot be satisfactorily evacuated He has removed the abscess sac in toto by extensive paravertebral and retroperitoneal dissection, proceeding into and beyond the femoral ring if necessary In 11 cases thus treated there has been only 1 recurrence, and no death But the operation is formidable

In the management of paraplegic patients, too, surgery is coming to play a more important part Hitherto there have been strong deterrents First, exposure of the spinal cord by a posterior route may remove the only stable portion of a crumbling vertebral segment and may aggravate existing deformity and cord damage, and secondly the lesion itself may prove to be due to some condition—for instance, thrombosis—not amenable to surgical relief These deterrents, plus the fact that spontaneous recovery is not rare, have in the past dictated a very conservative approach to Pott's paraplegia

In a timely monograph Griffiths, Seddon, and Roaf[4] attack this "peculiar and quite unscientific complacency" They point out that, in the largest and most recent reported series of conservatively treated paraplegic cases, a quarter of the patients died and less than half made a worth-while recovery They lay down a list of indications for exploration, emphasising that cases of rapid onset, severe degree, or persistent character should always be operated on The causal focus is usually anterior to the theca, and it is now appreciated that laminectomy, and even costo transversectomy, will not expose a lesion so situated Griffiths et al have found the anterolateral approach of Alexander[5] and Dott[6] to be the most useful In this the front of the theca is approached from the side of the vertebra, three or four ribs at the affected level are resected at their posterior ends, and the appropriate transverse processes removed, the backs of the diseased vertebræ and the pedicles well anterior to the posterior joints can then be nibbled away, an excellent view of the theca is thus obtained, but the lateral stability of the spine is preserved Perhaps the most important point which emerges from this study of Pott's paraplegia is the susceptibility of the condition found at operation to surgical treatment The pachymeningitis and cord œdema, which loomed so large in earlier accounts, are discounted as causes of paralysis In each of 49 cases explored, Griffiths et al found and removed a mechanical cause of compression—sequestrum, bony ridge, or abscess—and in 36 cases a good recovery ensued They sound a warning note when they point out that "the operation is never easy, always dangerous, and often frightening" It is obviously not one for the occasional spinal surgeon Nevertheless we may expect to see paraplegic patients more commonly operated on and more rapidly and more commonly restored to health as a result of this encouraging report

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[2] Wilkinson M C J *Bone Jt Surg* 1955 37B 382

[3] Weinberg J A *Ibid* 1957 39A 17

[4] Griffiths D L Seddon H J Roaf R Pott's Paraplegia London 1956

[5] Alexander G L *Proc R Soc Med* 1946 39, 730

[6] Dott N M *Edinb med J* 1947 54 620

CORONARY-ARTERY DISEASE

IN November, 1955, the World Health Organisation assembled a study group on atherosclerosis and ischæmic heart disease Their report[1] is a clear statement of established knowledge, and it also outlines ways in which this knowledge can be extended and applied

The need to distinguish between ischæmic heart-disease and atherosclerosis is rightly emphasised though the processes concerned in the two conditions are usually concurrent, they may be independent Proper diagnostic criteria are important both at the bedside and in the post mortem room, and the group propose that representative pathologists should meet and suggest uniform methods for examining the coronary arteries and for recording their results Uniformity in standards for clinical diagnosis would be difficult to bring about, yet it is hard to see how confusion can be avoided unless there is uniformity in the use of diagnostic terms

The factors thought to be concerned in the genesis of both ischæmic heart disease and atherosclerosis may be divided into the constitutional and the environmental Among the constitutional factors, the group think that heredity, sex, and specific inborn metabolic disorders (e g, familial hypercholesterolæmia) need further study Diet, reduced physical activity, and the stress, strain, and mental tension of modern life are three environmental factors which the group regard as important, and they discuss alcohol and tobacco, infections, and associated arterial hypertension as possible contributory agents Their account of the principal epidemiological, laboratory, and clinical findings which implicate these factors is admirable Their recommendations for research, on the other hand, are much less explicit and helpful, and this is a pity because vague generalisations can provide an umbrella covering much waste of time and money on unsuitable investigations

An appendix addressed to the public-health services shows the need for epidemiological and statistical studies, particularly in areas where the inhabitants differ greatly in their economic status for such work to be profitable, an essential is uniformity in procedures, nomenclature, and the handling and analysis of data By way of prevention, all the public health doctor has to offer at present is the advice of moderation This can be directed at men and women who take too much food, too much alcohol, too many cigarettes, or not enough physical activity, or who "over indulge in many activities" Such advice has, of course, been given by generations of wise physicians, and neglected by generations of careless patients It is still sound, but is by no means easily put over by public-health departments, whose nurses are better at showing mothers how to raise a family than at teaching business executives how to change their manner of life In point of fact, the techniques of this kind of health education have not yet been worked out, and the study group do not help much when they say that the "health officer can determine the type and appropriate-ness of educational activities, in collaboration with practising physicians, official and voluntary health associations, and interested community agencies" With prevention as with research, they point clearly to the broad highway but give little guidance through the lanes and byways which lead up to it Appreciation of their excellent report is tempered only by regret that they were not kept together long enough to go into more detail

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[1] Study Group on Atherosclerosis and Ischæmic Heart Disease *Tech Rep Wld Hlth Org* no 117 1957 Pp 40 1s 9d Obtainable from H M Stationery Office

SULPHUR AND SEBORRHŒIC DERMATITIS

THE rate and route by which substances pass through the skin from the exterior have been studied by means of radioactive isotopes The best known of these investigations concerned the vesicant war gases Scott[1] has lately investigated the beneficial effect of sulphur applied locally in various dermatoses

There is no doubt that sulphur is absorbed through the skin, since local application can lead to sulphæmoglobinæmia It has been thought that it penetrates as a sulphide, but that its therapeutic effects follow its modification into $H_2S_5O_6$ For this reason, treatment with polythionic acids was introduced, but it does not seem to have been widely successful Sulphur is normally present in the skin as sulphydryl and disulphide groups probably representing sulphur-containing amino-acids, particularly in the proteins of enzyme systems It is also represented in the intercellular ground-substance as an ingredient of mucopolysaccharides Disturbances in local sulphur metabolism may therefore have pathological consequences A striking example is blistering from the poisoning of enzyme systems by heavy metals and its relief by offering alternative thiol groups in the form of dimercaprol (BAL)

Scott has tackled the problem using radioactive sulphur by autoradiography She applied ^{35}S to the skin of healthy subjects and took biopsy specimens at fixed intervals Having established the normal rate and route of absorption, she repeated these studies in cases of seborrhœic dermatitis, acne vulgaris, psoriasis, and a few other disorders

In normal skin, absorption began two hours after application, and the element had completely crossed the epidermis within eight hours With many substances there is preferential absorption through the pilosebaceous follicles, but this was not observed with sulphur After sixteen hours most of the sulphur was in the dermis, little remaining in the epidermal layers Within twenty-four hours it had disappeared, and since it did not recross the epidermis it must have been taken up systemically There was no microscopical evidence that the sulphur was handled by the epidermal cells, its path being apparently intercellular

In seborrhœic dermatitis, penetration began within half an hour of the application of radioactive sulphur, which accumulated in the mid epidermis during the first twenty-two hours, none going into the basal layers or beyond Thereafter the sulphur migrated outwards, and during its residence in the epidermis it was apparently attached to cells In acne there was normal penetration of the epidermis, but concentration and persistence occurred in the pilosebaceous follicles from which it did not appear to be absorbed into the dermis, but the reverse is inferred from the "corresponding dermal accumulations of sulphur adjacent to the glands" In psoriasis sulphur penetrated to the basal layer within four hours, and much greater quantities were absorbed than in normal skin Little entered the dermis and most was shed outwards through the epidermis Again, there appeared to be intracellular localisation of ^{35}S In the miscellaneous group, including contact dermatitis, there was little departure from normal apart from accelerated passage through the epidermis Lichenification, however, was associated with a generally slower rate of absorption With improvement of seborrhœic and psoriatic lesions the behaviour of sulphur reverted to normal Scott suggests that sulphur applied to the skin in these dermatoses may have some significant biological action, such as involvement in the intracellular systems involving SS and SH groups

We do not yet know whether the behaviour of sulphur in these cases is peculiar to that element Would it not be reasonable to repeat the study with some element foreign to the skin? This might dispose of the suspicion that all that the tracer is doing is to reveal the dynamics of the epidermis Two factors should be considered first, the influence of œdema, and secondly the rate of cell division and outward migration Œdema might favour absorption, and Scott herself observed that erythema produced with ultraviolet light caused sulphur to penetrate much more rapidly Cell division would influence outward transference of the element, thus in lichenification, with increased cell multiplication, there is diminished absorption Combinations of different degrees of the two factors would cause varied patterns of "absorption"

Scott's findings, if substantiated, will necessitate the recognition of seborrhœic dermatitis as a genuine entity by those who regard it as merely one manifestation of eczema, and will call for further biochemical studies of this disease

EXTERNAL PANCREATIC FISTULA AFTER GASTRECTOMY

THE pancreas has been likened to a powder keg which responds capriciously to handling The dangers of operating on the pancreas, even for biopsy, are well known, and experienced surgeons are aware of the hazard of injuring this gland during subtotal gastrectomy Millbourn[1] has shown that pancreatic damage, judged by a significant increase of urinary diastase, was present in 13 of 147 patients after gastric resection, but evidence of severe pancreatic involvement was clinically manifest in only 5, of whom 2 died Both he and Warren[2] have discussed modifications in the technique of gastric resection to avoid such catastrophes

When external pancreatic fistula follows operation on the stomach one of the major pancreatic ducts has usually been injured, either as it lay in the floor of a penetrating ulcer when the ulcer was being dissected off the pancreas or when the duodenal stump was mobilised Usually these fistulæ are incomplete and close spontaneously, since in gastric resection for duodenal ulcer the duct of Santorini, being the more vulnerable, is the most commonly injured, and only rarely, as in one of Millbourn's fatal cases, does this duct exclusively drain the larger part of the pancreas

Sinclair[3] describes an external fistula which persisted, after Polya gastrectomy for duodenal ulcer, for ten weeks, during which he studied pancreatic function The pancreas responded poorly to intravenous secretin and pancreozymin, and, though the dosage of these hormonal extracts was small, this suggests that the function of the gland may have been impaired by duct injury at operation—a suggestion supported by the radiographic evidence of a dilated duct system and by the increase in serum or urinary enzymes found in the same circumstances in other cases Moreover after the Polya gastrectomy the low acidity of the chyme deviated from the duodenum and passed directly into the upper jejunum may have modified the response of the pancreas to physiological stimulants such as food Such variable factors as these may explain conflicting reports on external pancreatic fistulæ in man

When damage of a pancreatic duct or the common bile duct is recognised at operation the duct should be

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[1] Scott, A *Brit J Derm* 1957, 69 40

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[1] Millbourn, E *Acta chir scand* 1949 98, 1
[2] Warren K W *Surgery* 1951 29 643
[3] Sinclair I S R *Brit J Surg* 1956 44 250

sutured at once to the duodenum or jejunum, opposing mucosa to mucosa (A severed duct of Santorini which can be shown to connect with the main pancreatic duct may be ligatured with safety) When injury to a duct at operation is not detected at the time, it usually declares itself on the second postoperative day by upper-abdominal pain and pyrexia associated with raised serum or urinary amylase levels If division of the duct of Wirsung is suspected the region of the head of the pancreas should be drained and repair of the duct deferred to a more propitious time Otherwise the patient is treated as if he had acute pancreatitis, with continuous aspiration of the gastric remnant and intravenous administration of fluids and electrolytes, if necessary glucose and protein hydrolysates can be given intravenously, and the use of broad-spectrum antibiotics, though these do not pass into pancreatic juice, is justified at this stage In desperate circumstances a jejunostomy to feed the patient may be life saving, though in Sinclair's patient glucose given directly into the jejunum by tube stimulated the flow of pancreatic juice

Should an external fistula follow, this will usually close spontaneously, and meanwhile conservative treatment is directed towards protecting the skin from digestion, maintaining fluid and electrolyte balance, and if necessary replacing lost pancreatic enzymes It is doubtful whether measures usually recommended to depress the external pancreatic secretion, in order to encourage the fistula to close, are of much value [4] When food is taken by mouth a bland mixed diet is probably best, since fat and protein produce less pancreatic juice than carbohydrate Ephedrine, atropine, and propantheline ('Probanthine') have all been recommended to reduce the volume of secretion Conservative measures should be persisted in for several months, but if the fistula has not closed after six months, or if closure leads to pain, vomiting, or cyst formation, then operation should be considered The Lahey operation,[5] which consists in implanting the fistulous track into the jejunum, occasionally fails because the fistulous duct, having no epithelium, closes and pancreatic cysts form In these rare circumstances some other manœuvre, such as excision of the distal part of the pancreas together with the origin of the fistula,[6 7] may be necessary A possible alternative is a retrograde or caudal pancreatico jejunostomy, as performed by DuVal [8] in cases of chronic relapsing pancreatitis

CUTANEOUS URETEROSTOMY

URINARY diversion by implanting the divided ends of the ureters into the abdominal wall has never been widely favoured, for it requires a urinary collecting apparatus On the other hand, with this method there is less risk of biochemical imbalance and ascending pyelonephritis than with ureterosigmoidostomy, and in certain cases, particularly where only one functioning kidney remains, its adoption may be advisable Standard techniques, however, commonly involve an indwelling ureteral catheter, which may predispose to the very hazard that the method is supposed to avert—namely, stenosis of the ureteral stump and retrograde sepsis McDonald and Heckel [9] now describe a plastic procedure by means of which long continued catheterisation is avoided and the incidence of stricture reduced Briefly the operation consists in splitting the end of the divided ureter and embedding each half subcutaneously into two infolded skin flaps cut from the margins of the main incision Subsequent retraction of the skin flaps during healing maintains the patency of the ureteral orifice, and indwelling catheters can then be dispensed with Satisfactory results are claimed in 13 cases out of 22 operated on during the past eighteen years Although this technique does not entirely eliminate the risks and inconveniences of cutaneous ureterostomy, because of its simplicity it has much to recommend it

CONTROLLED TRIALS NEEDED

SOME of us are concerned because the rate of the increase in true knowledge in medicine seems slow in relation to the immense amount of work done It may be that, as science progresses, more effort must be expended to achieve a commensurate advance But too often results are obtained whose worth is small—though much time, thought, and money has been used up—because they are based on too small a series of observations Thus on many topics a great mass of information has been collected which cannot be integrated because the conditions under which it was collected varied so much When a subject is being tackled for the first time, many small-scale experiments are needed to get a general idea of what is involved, but once this stage is over, large controlled experiments are often needed to test the hypotheses that have arisen We have called for a certain return to planning in our professional affairs,[1] and more planning in experimental clinical medicine would be welcome

An example is the treatment of high blood-pressure Professor Pickering [2] lately contrasted our ignorance (after twenty years' experience) of how useful is sympathectomy for hypertension, with our sure knowledge of the place of drugs in tuberculosis—for there have been few controlled trials of sympathectomy We do not certainly know whether surgery benefits hypertensives (except in very severe cases), much less which operation is most beneficial With the hypotensive drugs, which have been the subject of so much investigation, the position is likely to be little better until a big trial is made with all the major variables controlled No one group of physicians could expect to see enough cases to conduct such a trial but if a large number of workers could be persuaded to treat patients in a controlled fashion as part of a prearranged plan, we might gain reliable evidence as to which drugs are indicated for which patients, and when other treatments (e g, dietary or surgical) are needed That such cooperative schemes can be successful is obvious from many reports of the Medical Research Council, and from such joint efforts as Anglo American investigation of the treatment of rheumatic fever [3]

Professor Sanjivi [4] has proposed that patients with hypertension but no symptoms should be treated with drugs in an attempt to keep the blood pressure normal, and has given an account of some of his patients treated (without controls) with reserpine Dr Hambling [5] expressed the misgivings that many doctors will feel, especially in view of the side effects of such drugs, and in our correspondence columns this week Dr Muhammad takes the view that Professor Sanjivi's patients would have done equally well with reassurance and sedation But the simple fact is that we do not know whether or not they would have done as well, and the only way to decide the very important question of whether or not active hypotensive treatment is worth while is to begin a controlled trial, treating some patients with drugs designed to lower the blood-pressure and others with reassurance and mild sedation This would take many years, though preliminary results would be to hand sooner Treating a small number of patients with transient hypertension, without using controls, will tell us little

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[4] Hellsten H Olsson O *Acta chir scand* 1954 108 443
[5] Lahey F H Lium R *Surg Gynec Obstet* 1937 64 79
[6] Cattell R B *Surg Clin N Amer* 1949 29, 779
[7] Warren K W *Ibid*, 1951, 31 789
[8] DuVal M K *Ann Surg* 1954, 140 775
[9] McDonald, J H, Heckel N J *J Amer med Ass* 1957 163, 911

[1] *Lancet* Jan 5 1957, p 31
[2] Pickering, G W *Ibid* p 1
[3] *Brit med J* 1955 i 555
[4] Sanjivi K S *Lancet*, Feb 2 1957 p 267 *Ibid* March 16 1957 p 589
[5] Hambling J *Ibid*, Feb 16, 1957, p 372

Many other conditions call for similarly controlled study Since living organisms contain so many variables, biological science is bound to be less exact than physical science But one way in which the investigator of living creatures can approach exactitude is by observing a lot of them This is not to say that large collective studies can wholly replace individual investigations the gifted research-worker will always be needed to point the way, and the worker who studies a few patients in great detail may provide information (e g, on individual variations and on side-effects) which would be missed in a large study designed to answer specific questions

ANOMALOUS PULMONARY VENOUS DRAINAGE

IN early fœtal life the venous drainage of the lungs is through the umbilico-vitelline system which connects with the systemic pre and post cardinal veins The precardinal veins unite to form the right superior vena cava, and the postcardinal veins unite to form the inferior vena cava At the same time the sino atrial region of the primitive heart tube is forming a localised pouch which becomes the left atrium, and from this a channel extends towards the lungs and finally connects with them to become the common pulmonary vein As this is dividing into the four pulmonary veins, the more primitive umbilico vitelline system is absorbed

Total anomalous pulmonary venous drainage in post-natal life results from the retention of the early stage of development with failure of the heart to make connection with the lungs by the common pulmonary vein In the majority of patients the venous drainage from the lungs enters a persistent left superior vena cava by a common channel and thus connects with the right atrium Less commonly the pulmonary veins drain directly into the right atrium or via the coronary sinus, inferior vena cava, portal vein, or a persistent ductus venosus[1] For life to be possible there must obviously be a right-to left shunt, and this is usually through the atrial septum by means of a patent foramen ovale or an atrial septal defect Part of the mixed venous return to the right atrium will then pass into the left atrium, and part will go through the tricuspid valve into the right ventricle The pulmonary and systemic venous returns are not completely mixed in the right atrium, and the pulmonary stream entering through the superior vena cava tends to be directed through the tricuspid valve into the right ventricle, whereas systemic venous blood from the inferior vena cava tends to go through the foramen ovale into the systemic arterial circulation For this reason pulmonary arterial blood may show an oxygen saturation which is as high as or even higher than that in the systemic arterial blood[2]

The incidence of total anomalous pulmonary venous drainage is greater than was previously appreciated, it accounts for about 2% of all congenital heart lesions[3] Survival into adult life has been reported with increasing frequency,[3] [4] but the disorder is of greatest importance in infancy because 80% of those affected die before 1 year of age[5]

In adults the condition clinically resembles simple atrial septal defect, from which it may be indistinguishable except by radiography or cardiac catheterisation and dye dilution studies[3] In infants the condition may be even more difficult to diagnose Mild cyanosis is often present in later life, but it is seldom obvious in the first six months, even though the systemic arterial blood is somewhat unsaturated The heart is usually of normal size at birth, but enlarges rapidly in the first few months of life A systolic murmur is often heard at the left sternal border and is thought to be due to increased blood-flow through the pulmonary artery, occasionally over the base of the heart there is a venous hum, which probably originates from the abnormal pulmonary venous return[6] The second heart sound in the pulmonary area is split, and in about a third of cases is accentuated owing to a loud pulmonary component associated with pulmonary hypertension Radiographically the heart often shows a characteristic "figure of 8" or "cottage loaf" appearance owing to persistence of the left superior vena cava with enlargement of the right atrium and right ventricle, the pulmonary artery is increased in size and activity and the peripheral vascular markings are also increased The electrocardiogram shows evidence of right ventricular and right auricular hypertrophy

The diagnosis is made from the high oxygen saturation in blood from the superior vena cava or high right atrium and from the unusual finding that pulmonary arterial blood is as highly oxygenated as systemic arterial blood

Of 30 cases reported by Gott et al[7] the majority died in the first three months of life and only 3 were living and past infancy Of the 30, several had severe symptoms, and 4 were submitted to operation Most workers believe that, if there is not severe pulmonary hypertension with pronounced reversal of blood flow through the inter atrial communication, surgical correction should be attempted Operation with the aid of an extracorporeal circulation to by pass the pulmonary circulation, or with hypothermia, has sometimes proved successful, even when undertaken in infants The operation consists in anastomosing the common venous channel carrying the pulmonary venous return to the left atrial appendage, the atrial septal defect being left unclosed[8] In three different series 3 out of 4 patients[1] 3 out of 6,[7] and 4 out of 12[3] survived Total anomalous pulmonary venous drainage must therefore take its place beside other congenital malformations of the heart and great vessels carrying a grave prognosis in early life, which may now be amenable to surgical treatment

INTERNATIONAL FEDERATION OF SURGICAL COLLEGES

AT a meeting representative of surgical colleges in many countries, held at the Royal College of Surgeons of England, with Sir Harry Platt, the president, in the chair, it was unanimously agreed to found an international federation, and the inaugural meeting is to be held at Stockholm in July, 1958 The object of the federation will be the maintenance and improvement of the standards of surgery throughout the world The members will not be individual surgeons, but such national surgical institutions as may be elected to membership

The bodies represented at the preliminary meeting were the Royal College of Surgeons of England, American College of Surgeons, Royal College of Surgeons of Edinburgh, Royal College of Surgeons in Ireland, Royal Faculty of Physicians and Surgeons of Glasgow, Royal Australasian College of Surgeons, Royal College of Physicians and Surgeons of Canada, Académie de Chirurgie de Paris, Belgian Surgical Society, Royal College of University Surgeons of Denmark, Dutch Association of Surgeons, Italian Society of Surgery, Norwegian Surgical Society, and Swedish Surgical Association

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[1] Burroughs J T Kirklin J W *Proc Mayo Clin* 1956 31 182
[2] Swan H J C Toscano Barbosa E Wood E H *Ibid*, p 177
[3] Mustard W T *Arch Dis Childh* 1957 32 1
[4] Snellen H A Albers, F H *Circulation* 1952 6 801
[5] Burchell H B *Proc Mayo Clin* 1956 31 161
[6] Du Shane J W *Ibid*, p 167
[7] Gott V L Lester R G, Lillehei, C W, Varco R L *Circulation* 1956 13 543
[8] Mustard W T, Dolan, F G *Ann Surg* 1957 145 379

Before Our Time

HARVEY

THE OCULAR PHILOSOPHER*

Sir Russell Brain
Bt, DM, LLD, DCL, FRCP, FRCOG

Throughout this week we have been celebrating William Harvey, in the way in which, surely, he would most have wished to be commemorated, by describing the results at the present day of his discovery of the circulation of the blood And what we have heard about the new work on the circulation which has been carried out even during the last twenty-five years shows that his achievement was endowed with a generative capacity for creating fresh knowledge which three centuries have not diminished, but enhanced In making the concluding contribution to this congress, I have naturally asked myself how I could hope to say anything new upon a subject which three centuries of panegyric, including three hundred Harveian orations delivered to the Royal College of Physicians, may well have rendered threadbare But a genius presents a fresh challenge to each generation, and it is therefore appropriate that for a few minutes we should look at Harvey's thought in the light of today

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Harvey, though a man of all time was also, inevitably, a man of his own time, and it is one of the values of medical history that it enables us to see the great originators against the background of the ideas which they took for granted, and so to understand better both the greatness and the limitations of their achievements Harvey's ideas were necessarily expressed in the language of his own day, which presents us with a difficulty of interpretation His thought was sometimes so far ahead of his time that the current terminology was inadequate for it Sometimes, therefore, the words he uses mean more than they meant then, and other than they mean now

This point is well illustrated by his change of view between the *De Motu* and the *De Generatione* on the relative importance of the heart and the blood, and his final emphasis upon the blood in the *De Generatione* "I maintain," he says there, "against Aristotle, that the blood is the prime part that is engendered, and the heart the mere organ destined for its circulation It clearly appears that the blood is the generative part, the fountain of life, the first to live, the last to die, and the primary seat of the soul, the element in which, as in a fountain head, the heat first and most abounds and flourishes, from whose influxive heat all the other parts of the body are cherished, and obtain their life" In the penultimate chapter of the *De Generatione* Harvey deals with the innate "heat" Here he is striving to turn the terminology of outworn ideas into scientific concepts The heat, he says, is the spirit or spirits, and both are nothing other than the blood And according to Harvey "the blood is the first produced and the most principal part of the body, endowed with each and all of these virtues, possessed of powers of action beyond all the rest, and therefore in virtue of its pre eminence meriting the title of spirit" He then goes on to reject the suggestion that the blood must contain other spirits of an aerial or ethereal nature, on the ground that being composed of elements it could have no power of action beyond these elements or the bodies compounded of them "Nor can it be admitted that there are any other bodies or qualities of a spiritual or incorporeal nature, or any more divine kinds of heat" Harvey is careful to define the word "spirit" as he uses it It means what Hippocrates called *impetum faciens*, or moving power implying by this "whatever attempts aught by its own proper effort, and causes motion with rapidity and force, or induces action of any kind" Thus "spirit" might be in part translated "function," in part "stimulus" Here, then, if we penetrate beyond Harvey's words to his thought, we find him making, as best he could in the terminology of his day, the revolutionary statement that the blood is of supreme importance because it carries out a whole range of as yet dimly discerned vital functions (spirits) solely by means of its physical constituents (elements)

Similarly it is easy to miss the fact that even when Harvey's thought was apparently dependent upon archaic ideas he often used them in a new and more profound sense A number of writers have pointed out that he was influenced by two ideas which he derived from Aristotle—the special virtue of circular motion and the belief that the living organism, the microcosm, embodies the same principles as the universe, the macrocosm Both of these ideas are illustrated in a famous passage in the *De Motu*

> "We have as much right to call this movement of the blood circular as Aristotle had to say that the air and the rain emulate the circular movement of the heavenly bodies The moist earth, he wrote, is warmed by the sun and gives off vapours which condense as they are carried aloft and in their condensed form fall again as rain and remoisten the earth, so producing successions of fresh life from it In similar fashion the circular movement of the sun, that is to say its approach and recession, give rise to storms and atmospheric phenomena."

The same comparison reappears in the *De Generatione*, when, again with a reference to Aristotle, the rhythm of life from the egg to the fowl and back again to the egg is described as a circuit and compared to the principle active in the universe which is responsible for the rising and setting of the sun

> "And this is the round which makes the race of the common fowl eternal, now pullet, now egg, the series is continued in perpetuity, from frail and perishing individuals an immortal species is engendered" And, in a phrase with which Thomas Browne might have been pleased, "the egg, I say, is a period of this eternity"

* * *

These ideas of Harvey have been used to illustrate the importance of analogy in scientific thought To a superficial view today it may seem that there is no connection between the circular motion of the sun in the heavens, or of moisture in the atmosphere, and that of the blood in the body Harvey, it might be argued, arrived at the right idea by means of a false analogy His contemporaries, whether or not they accepted his discovery, would have found nothing unreasonable in his use of such analogies, it was a method inherent in the contemporary climate of thought And we, looking back on Harvey from the vantage-point of three centuries, may perhaps pause for a moment to wonder what our successors three centuries hence will think of some of the ideas we take for granted, and indeed justify pragmatically by their scientific results

But it would be a mistake to dismiss, as merely an analogy, Harvey's interpretation of the idea that the microcosm mirrors the macrocosm, that the organism is a model of the universe This was a much more profound conception than the similar contemporary hypotheses of alchemy We see this in a striking passage in the *De Generatione*

> ' But nature, the principle of motion and rest in all things in which it inheres, and the vegetative soul, the prime efficient cause of all generation, move by no acquired faculty which

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* Final paper read at the Harvey Tercentenary Congress on June 7, 1957

> might be designated by the title of skill and foresight, as in our undertakings, but operate in conformity with determinate laws like fate or special commandments—in the same way and manner as light things rise and heavy things descend. The vegetative faculty of parents, to wit, engenders in the same way as the spider weaves her web, as birds build nests, incubate their eggs, and cherish their young, or as bees and ants construct dwellings, and lay up stores for their wants, all of which is done naturally and from a connate genius or disposition, by no means from forecast, instruction, or reason."

Here we see the full range of Harvey's mind as a scientific philosopher. Beginning with "nature, the principle of motion and rest in all things" he links together gravitation, the fertilisation and development of the ovum, and the instinctive behaviour of insects and birds, as operations "in conformity with determinate laws like fate". Hence the organism mirrors the universe, not in virtue of some occult principle of similarity, but because the universe and its minutest parts are subject to identical laws.

When Harvey seeks to explain how these laws apply to the development of the individual from the fertilised ovum his explanation has been described as vitalistic. What puzzled him was how so complex a structure as the fully developed chick could construct itself out of the homogeneous material which composed the original egg. When Harvey contrasts metamorphosis and epigenesis as modes of development of the organism we see his scientific philosophy at its best. With no knowledge of chromosomes or genes, of chemical organisers or gradients, with nothing on which to build but the unaided observations of his own eyes, he could do no more than reach a statement of the problem, but the strength of his position lies in the fact that he rejected explanatory hypotheses for which there was no evidence. His description of the development of the chick, therefore, is one which, however inadequate it was bound to be, needs only to be filled in with subsequent scientific discoveries, as the following passage shows.

> "Now it appears clear from my history, that the generation of the chick from the egg is the result of epigenesis, rather than of metamorphosis, and that all its parts are not fashioned simultaneously, but emerge in their due succession and order, it appears, too, that its form proceeds simultaneously with its growth, and its growth with its form, also that the generation of some parts supervenes on others previously existing, from which they become distinct, lastly, that its origin, growth, and consummation are brought about by the method of nutrition, and that at length the foetus is thus produced. For the formative faculty of the chick rather acquires and prepares its own material for itself than only finds it when prepared, and the chick seems to be formed and to receive its growth from no other than itself."

Thus, having reached the limit of the knowledge which was possible to a combination of naked eye observation and reflection, Harvey had to explain what he could not understand in terms of what he called "the soul or a faculty of the soul".

It may be said that if this is vitalism, vitalism is merely another name for our ignorance, and some no doubt would maintain that that is all it ever is. But in a broader philosophical sense Harvey was a vitalist, or at any rate, an antimaterialist.

> "They who assign a material cause, and deduce the causes of things either from the elements concurring spontaneously or accidentally, or from atoms variously arranged do not attain to that which is first in the operations of nature. They do not recognise that efficient cause and divinity of nature which works at all times with consummate art, and providence, and wisdom, and ever for a certain purpose and to some good end."

I wonder what Harvey would have said if he could have been shown all that the scientist of today knows of embryology. Growth, form, and nutrition were the key words to him and they are the key-words still. How delighted he would have been at the vast array of knowledge which has come to fill those empty spaces he had no means of filling! And yet I wonder if his restless mind would have been satisfied. Would he have looked beyond the mere descriptions of events to a still elusive *anima*, a principle of form, which we still lack, perhaps because it belongs to a *scientific category yet to be discovered*?

* * *

We speak of Harvey, the observer and thinker, but there are many types of observer and many kinds of thinker. The key to Harvey's thought is surely provided by Aubrey's famous statement that he "did delight to be in the darke, and told me he could then best contemplate". Harvey was a contemplative, and a visionary, whose delight came from reflecting upon the world of Nature, and whose vision found its inexhaustible satisfaction in living things. In Thomas Browne's magnificently apt description he was "that ocular Philosopher and singular discloser of truth". It will not perhaps derogate from Harvey's uniqueness to compare him with another unique "ocular Philosopher," Sherrington, the centenary of whose birth we commemorate this year. Is it altogether inappropriate to compare *The Integrative Action* with the *De Motu*? And though Sherrington's later work *Man on his Nature*, was written with a different intention from Harvey's *De Generatione*, the same spirit shines through both—an almost mystical delight in life seen with the eye of scientific understanding. Sherrington was a poet. Harvey, as far as I know, wrote no poetry, but who that has read *De Generatione* can doubt that he had a poet's delight in words. All this is to be found in that statement of faith which is so characteristic of him, a cry from a heart, indifferent perhaps to the precise formulas of reason in such high matters, but uttering its reasons which the reason cannot know.

> "Wherefore, according to my opinion, he takes the right and pious view of the matter who derives all generation from the same eternal and omnipotent Will, on whose nod the universe itself depends. Nor do I think that we are greatly to dispute about the name by which this first agent is to be called or worshipped, whether it be God, Nature, or the Soul of the Universe,—whatever the name employed,—all still intend by it that which is the beginning and the end of all things, which exists from eternity and is almighty, which is author and creator, and, by means of changing generations, the preserver and perpetuator of the fleeting things of mortal life, which is omnipresent, not less in the single and several operations of natural things, than in the infinite universe, which, by his will or providence, his art and mind divine, engenders all things."

"Finally, I wonder if we in the public dental service are not as much to blame as any one for the present lowly position of children's dentistry in the eyes of the public. Is it possible that if we had said regular six monthly examination and advice only for such a number of children as we dental officers can treat properly in the course of a twelvemonth, we should have been able to produce at least a proportion of dentally fit school leavers? Is it possible that the butter has been spread so very, very thinly that dentally speaking we have failed in our task? Is it possible that the greatest good for the greatest number resulted in dental evil for the bulk of children? The real test of the success of a dental health service lies not in a statistical appreciation in terms of millions of conservations. Intelligent treatment planning based on a policy of a reasonable number of children per operator and on a proper understanding of the growth of the jaws and teeth supporting structures, in the light of end results, designed, not necessarily for perfection but in the light of reason, would in the long run produce a high proportion of healthy, functional mouths."—W. G. SENIOR, F.D.S. R.C.S., *Publ. Hlth*, June, 1957, p. 92.

Conferences

HARVEY TERCENTENARY

DELEGATES from both hemispheres met in London last week for a congress to mark the end of the third century since William Harvey's death. It had been organised by the Harveian Society of London and a committee representing the Royal Society, the Royal College of Physicians, the Medical Research Council, and other bodies concerned with the study of the circulation. Opening the scientific programme at the Royal College of Surgeons on June 3, Mr A. DICKSON WRIGHT, the president read a message of greeting from the Queen.

Growth of Knowledge

The PRESIDENT, introducing the first session, in which the beginnings of medical science were traced from Tudor times, said that three hundred years before, almost to the hour, the clouds had descended over the conscious life of William Harvey as on that summer day the circulation of blood faltered within the brain of its discoverer, and he passed from coma into death. The President recalled the last years of Cromwell's rule, when Harvey, still a Royalist and friend of Charles II, no doubt hoped for the Restoration. Born in the reign of Queen Elizabeth I, he lived for several years in London at the same time as William Shakespeare, who died in 1616—the year in which Harvey as Lumleian lecturer in the Royal College of Physicians first spoke of his work on the circulation.

Prof K. J. FRANKLIN, F.R.S., representing the Royal Society and Harvey's own hospital, St Bartholomew's, and himself the author of the most recent translation of *De Motu Cordis*, spoke of the origins of the great work in the earlier career of its author, and of its still earlier roots in the notable anatomical studies of his teacher Fabricius of Padua, who in his own work *de Venarum Ostiolis* in 1574 had shown that valves are a feature of all the veins of the body. It was probably in the darkened anatomy theatre at Padua, while watching a demonstration in the well-lit arena below, that the purpose of the valves began to suggest itself to Harvey. Fabricius was by then an old man, but he carried on a fine tradition, begun by Vesalius and Fallopius, of study based on factual observation rather than accepted dogma. The Galenic concept of the blood-flow was of some slow, small drift of blood from the right to the left heart, with no inkling of the true circulation or of the speed and volume which it possessed. Robert Boyle had recollected Harvey saying that the valves, everywhere placed so that they can give free passage of the blood to the heart, must imply some other way for the blood to reach the outer limits of the veins and that the arteries must be there for this purpose. It was not known exactly when Harvey returned to England, but it was in the opening years of the 17th century that he became attached to St Bartholomew's, and he lived at Ludgate near old St Paul's. He soon became a fellow of the Royal College of Physicians, then a censor, and in 1615 a Lumleian lecturer—the appointment which led to the release of his researches. Passages from the lecture of 1616 showed that the essence of the work was complete though it was not actually published until 1624.

Prof JOHN FULTON (Yale) carried on the story of the circulation to the time, years after Harvey's death, when the hitherto undetected part of the circulation—the capillaries—were studied microscopically by Malpighi, Leeuwenhoek, Hales, and others. They had, as Sherrington once put it, the capacity to put questions to Nature to which she could reply; and Malpighi, studying the lungs of frogs with the aid of a crystal and candle, might have said, with Homer, "I see with mine own eyes a work trusty and great."

Sir CHARLES DODDS, F.R.S., examined the effect of Harvey's discoveries on his fate as a practising physician. Modern scientific medicine began with Harvey, but paradoxically his own system of medicine was little affected. Things were better now, but the possible conflict between scientific idealism and the conditions of practice could still afford a problem.

Dr F. A. WILLIUS (Mayo Clinic) was unable to attend, but his paper, on historical aspects of the knowledge of congenital heart disease, was ably presented by Dr T. COTTON (McGill). Harvey himself wrote that in the embryo, while the lungs were yet at rest, the two ventricles acted as one. There were many early observations on the post-mortem findings in cases of congenital heart-disease. Full understanding of the structural implications of cyanotic heart-disease was not reached until the description by Fallot in 1888 of *la maladie bleue*, but Rokitansky had in 1875 noted that septal defects appeared to be due to failure of rotation of the developing heart.

Rôle of the Heart in the Circulation

At the next session attention swung sharply to the present. Prof G. W. PICKERING, the chairman, quoted delicately from Harvey, first on the clear body of the little shrimp, with its heart-beat visible within, and the watching of a chick embryo, like a small cloud, its heart a mere point of blood, beating and disappearing. Harvey felt that there had to be a circulation of the blood, or the veins would empty and the arteries burst. Furthermore if the volume of the ventricle, in the open and closed state, were considered, at every beat an ounce or two of blood would be passed on; in half an hour 1000 beats or more would carry forward a greater quantity of blood than is found in the whole body.

Dr L. N. KATZ (Chicago) observed that the control of the circulation was adjusted to its low thrust part, and could be considered under two headings: neurohumoral and intrinsic. The intrinsic quantitative factors were the end diastolic pressure and the after-load or work when contraction begins. He and his team had produced a special heart-lung preparation in which the right heart was replaced by a pump and the isolated coronary venous return could therefore be collected. Flow and oxygen consumption across the coronary circulation was measured and related to other variables. Only a rough correlation could be made between oxygen consumption and the aortic pressure, but a steady relation existed between coronary flow and myocardial oxygen consumption. At a fixed work level they could both be made to increase, but when the work load was changed, as in stress adaptation, the oxygen consumption actually lessened in relation to the increased coronary flow: the heart appeared to change gear, and thus to gain a second wind. Under hypoxia conditions the percentage oxygen extraction increased with the oxygen lack: the coronary flow increased. Efficiency was not the only aim of the heart mechanism: protection was no less important.

Prof K. MATTHES (Heidelberg) recalled that in the fœtus and newborn child there was not much structural or physiological difference between the two ventricles, but that soon the heavier and more variable load on the left heart resulted in changes of hypertrophy rather than actual growth in relation to the right. In the adult the left ventricle could be considered almost as a cylinder in shape and action from the disposition of its fibres, while the softer right ventricle conformed more to the spiral shape of the heart itself. Functionally, the left heart showed a greater blood flow per unit mass of muscle, and the coronary blood-flow was also greater, as was the vulnerability to hypoxia; it was less distensible than the right, having a different modulus. The job of the right ventricle was to maintain, as Gowers showed, the very constant volume of filling of the left auricle. In this it was not the servant of the peripheral circulation; it could change its action quite independently of this In general it was affected by rather slow-acting factors—even those of renal function and extracellular-fluid exchanges—but the left ventricle was attuned to more rapid influences, acting in the coronary supply, and was more sensitive because of its fibre structure and load factors Ligation produced a larger zone of infarction in the left coronary supply than the right

Dr S Weidmann (Berne) had been able, with the help of a tiny glass capillary, to insert an electrode into the actual fibres of the turtle heart and thereby to conduct direct electrocardiography in relation to other changes He showed the differing behaviour of the potentials in contracting auricle, bundle, and nodal material, and also measured the outflow of radio-potassium in the sinus venosus it tallied closely with the phases of contraction The polarisation effects of the cycle were thus confirmed in relation to the electrical and mechanical changes, the latter he whimsically described as a "nuisance," for they tended to jerk his electrodes out The effect of calcium, he showed, is an intermediate one, while it magnifies the mechanical change it does nothing to the electrical potentials

Dr Paul Wood showed a colour film mainly concerned with the jugular venous pulse He recalled Mackenzie's observations and the tracings of Sir Thomas Lewis's polygraph The film showed the pattern of the neck vein movement in health and disease, characteristic formations were shown in patients with tricuspid disease, pure pulmonary stenosis, constrictive pericardium, and endocardial fibrosis

Hæmodynamics and the Coronary Circulation

Prof C Heymans (Ghent) outlined the history of our knowledge of the control of blood-pressure and heart-rate by the baroreceptors of the carotid sinus and the aortic arch, from Astley Cooper's first observation of the pressor and accelerator effect of carotid compression to his own work in progress today The mechanism can be reset, he said, to function at other levels of pressure, and he gave new details of the depressor action of noradrenaline applied to the artery wall in the receptor zone

Prof Gustav Nylin (Stockholm), like Harvey, was concerned with the measurement of stroke and minute volume He described his experiences of angiocardiographic assay and of dilution techniques He had tried to find the volume of blood in the chest and its separate organs, but the calculations were difficult and uncertain

The changes in the circulation at birth, said Dr G S Dawes (Oxford), have received little attention in the past three hundred years Indeed Harvey appreciated the main facts Modern work on sheep and goats attached by the cord to the intact placenta had shown the distribution of the blood with regard to oxygen tension although the ventricles worked in parallel there were inequalities, the head getting more oxygen than the lower extremities Just before birth the fœtus was on the verge of oxygen lack The closure of the ductus, he has found, is delayed a week or more this may be an advantage in anoxic conditions occurring then, and indeed he has found that the diameter is a function of the oxygen tension, and so are the murmur and thrill

Coronary Circulation and Control

Dr Claude S Beck (Cleveland) showed how the distribution of the blood in the coronary arteries might be more important than its amount His striking film of the operation which he has developed [1] was an impressive testimony to the care and patience of his work in this field He felt that the small intercoronary anastomoses formed allow enough blood to reach the right place to prevent the trigger effect of acute local ischæmia in producing lethal ventricular arrhythmia

Pulmonary Circulation

Dr Andre Cournand (New York) described methods of measuring the pulmonary circulation It is not yet certain, he said, where the increase arises in pulmonary hypertension, but he inclined to the view that it might be a local effect of the blood itself in the vessels as in hypoxia, he had found that when one lung was supplied with 8% or less oxygen in nitrogen, though there was not as a rule any change in pressure, the blood flow fell on the affected side after 10 minutes Acetylcholine, which normally did not affect the pressure, caused a profound fall under hypoxic conditions, though the systemic blood-pressure was unaffected He had shown that these effects were independent of the sympathetic nervous system

Prof C V Harrison had studied the structural changes accompanying pulmonary hypertension in mitral and congenital heart disease The most constant change was narrowing of the segmental arteries of the lower zone of the lung, usually diffuse and due to muscular hypertrophy, but sometimes localised and of atheromatous appearance

Cardiac Surgery

A session was devoted to the results of cardiac surgery, with Sir Clement Price-Thomas in the chair Several surgeons outlined their present experiences, and at the end another team spoke by wireless from New York. The growing-point in heart surgery at present is clearly operation on the open heart, made possible by hypothermia Most speakers felt that the extracorporeal machines were here to stay As Sir Russell Brock said, in a masterly account of his experience of the correction of pulmonary stenosis, we must consider the opportunity to improve on the simple, indirect, and often incomplete remedies with which such good results have been gained For each of the subtypes he described the method which he had found suitable in the past

Earlier Dr Maurice Campbell had spoken on coarctation of the aorta The danger time was the third decade, after this the case for operation was not quite so strong He showed the impressive grouped blood-pressure figures in the Guy's series, and gave the reassurance that patients maintained the figure obtained at their first outpatient visit after operation for five years and more With regard to pulmonary stenosis he felt there was still a place for the anastomotic operations with their good results and lower mortality

Cerebral Circulation

Dr Seymour S Kety (Bethesda) described work at the National Institutes of Health on the factors thought to affect cerebral circulation It had been found that mostly intrinsic mechanisms of humoral type were involved, carbon-dioxide tension in particular the flow fell with hyperventilation and rose with inhalation of carbon dioxide The blood-pressure determined the rate of flow only when this was quite low, and then it was the limiting factor Sympathetic denervation, sleep, alcohol in normal doses, and even hypertension did not change the normal value, which was about 50 ml per 100 ml brain per minute Arteriosclerotic cerebral disease reduced it particularly in psychotic cases Papaverine, as in the pulmonary circuit, relaxed vasomotor control and gave up to 25% increase

Prof Th Alajouanine (Paris) had studied the normal and morbid appearances of the cerebral vessels by angiography in both the dead and the living He recognised that transient hemi-phenomena resulted from partial occlusion of any of the big cerebral arteries The intracerebral vessels, he showed, have a great deal of collateral overlap

Dr E H Botterell (Toronto) spoke on his experience of surgery in the treatment of cerebral aneurysm He felt that the limitations of neck ligation operations were severe, particularly in the poor-risk patient The present tendency was to use the protection afforded by hypothermia to cover the risks of an intracranial attack He emphasised the danger of unrecognised mechanical complications of the hæmorrhage hydrocephalus, a large lateral clot resembling a middle meningeal compression in its behaviour, arterial spasm, and, of course, recurrent bleeding He showed some impressive cases of arteriovenous malformation and their cure, and of traumatic arteriovenous fistula in which the patient was becoming semisyncopal from the shunting back of his carotid blood As in the limbs proximal ligation in such a case would often make things much worse because the remaining blood beyond the fistula rushed back into the vein Distal ligation or clipping must therefore be added

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[1] See *Lancet*, May 18, 1957, p 1025

Splanchnic Circulation

Sir JAMES LEARMONTH suggested that the time was ripe for the introduction of a unit of blood-flow and that we should follow the physicists and make it an eponym · he felt that we should think in terms of one or more "Harveys"

Dr SHEILA SHERLOCK showed that however the portal pressure had been measured in the past, there was fair agreement on normal and pathological values She noted that the degree of collateral-vein formation was not necessarily an indication of the severity of the portal hypertension—for example, in some very acute cases there had not been time for them to form and in others the very profusion of them might be the means of keeping the pressure down Indeed the spleen might shrink again and even the patent portal vein might not show on a further phlebogram There could be a reversal of the flow

Prof R. MILNES WALKER (Bristol) spoke mainly on the pathology of portal hypertension In the healthy if the portal vein was compressed the pressure beyond rose from 10 to 40 mm Hg This was the level encountered in patients who bled but as Dr Sherlock had said, some with very large veins might not have so high a pressure This did not prevent them from bleeding however Also, children with extrahepatic block had a normal liver and no ascites Their liver was fed only by arterial blood and was often very red in consequence Portal blood was therefore not essential to the liver Ascites though not an indication for portacaval shunting, was not a contra-indication, indeed since it was likely to be aggravated by portal hypertension it would sometimes respond favourably to the shunt in cases meriting the operation because of bleeding Like Dr Sherlock he felt that the spleen should shrink, and had not seen much evidence of any continued hypersplenism once a good shunt had been provided Fibrosis of the liver had little to do with the degree of hypertension but the regeneration nodules had been blamed He drew an important distinction between pre sinusoidal obstruction in which the outlook with a shunt was very good and the various other forms in which post sinusoidal lesions were present—for example the Budd Chiari condition and veno-occlusive disease seen in Jamaica, and in centrilobular necrosis after healing In each of these ascites and rapid liver failure tended to develop and the patients were not helped by a shunt Some damage might be secondary to vascular insufficiency and mixed types did occur The fact remained however, that in severe bleeding forms of the disease only a wide direct end to side portacaval anastomosis could stop the decline of the patient.

Peripheral Circulation

Prof HENRY BARCROFT, F R.S , took the delegates on an imaginary tour of the several laboratories where the normal peripheral circulation is being investigated, and modestly gave credit to everyone but himself for the advances he described The release of vasomotor tone on body-heating had now been shown to be wholly cutaneous, the forearm, physiologically "skinned" by adrenaline iontophoresis, showed no response when only the muscle flow was being measured Edholm had recently shown that ring block with local anæsthetic abolished the forearm response to heating, this was strong evidence for the existence of vasodilator fibres, and Greenfield had produced evidence that these were cholinergic

Prof W D M PATON, F.R S discussed the pharmacological action of ganglion-blocking drugs Some practical points emerged concerning the danger of a fall in blood-pressure in preventing the clearance of relaxants and other drugs He felt that autonomic overactivity might be a serious liability in injury or prolonged operation and that blockade by spinal or splanchnic anæsthesia might protect against shock and hæmorrhage

Prof J H DIBLE distinguished clearly between ischæmia of central or large-vessel origin and the much rarer form in which the distal small vessels are thrombosed With regard to Duguid's revival of the Rokitansky theory of atheroma, there was, he felt, evidence that thrombus could change in this way, but that mural abnormalities could develop at the same time.

In discussing treatment, Prof C. G ROB emphasised that arterial disease is always generalised, and that only when the local features predominate to a disabling extent should surgery be undertaken Of several hundred patients with aortic, iliac, or femoral arterial occlusion only a minority were suitable for operation, and this was particularly true of the femoral type The development of gangrene might lead to a decision to operate, and when arterial reconstruction had been done for this reason the majority of patients had done well Professor Rob ended by reviewing 26 cases of occlusion of the internal carotid artery Where the lesion was localised to the first $^1/_2$ inch or so and obstruction was incomplete, reconstruction had always abolished the symptoms

Other Events

Sir RUSSELL BRAIN's concluding address to the congress in London appears on p 1235 of this issue

On Saturday a historical session was held in Folkestone under the chairmanship of Sir GEOFFREY KEYNES

TRICHOMONAS INFECTIONS

AN international symposium on trichomonas infections, organised by the Societe Française de Gynécologie, was held at Rheims on May 28–30

It was concluded that the apparent increase in the incidence of such infections is probably due to increased awareness and improved diagnosis of the condition In infected women the urethra is usually involved, but other extension beyond the vagina is exceptional Acute trichomonas vaginitis may cause dyspareunia which persists as a psychological condition after the infection has been cured In men infection is much commoner than is generally supposed, and it may extend beyond the urethra to the prostate and seminal vesicles.

A commission was appointed to examine the question Is trichomoniasis a venereal disease? The commission reported that this infection should not be designated as a venereal disease, but its transmission is usually coital, and, as far as public health administration is concerned it should be regarded as a venereal disease

Wherever possible, both partners should be treated in order to prevent reinfection

In a session on pathology, it was concluded that there was no evidence of the existence of any sort of cystic or other resistant form of the organism, and it was emphasised that intestinal trichomonads cannot infect the vagina

The final session was devoted to treatment It was agreed that there is still no satisfactory remedy, many agents appear to be promising in vitro, but in practice there remains the problem of bringing the remedy into contact with the parasite A B Kupferberg (U S A) declared that in clinical trials nothing less than complete parasitological cure should be accepted as a criterion of cure Asymptomatic cases should be treated

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Special Articles

THE INCIDENCE OF INFECTION FOLLOWING GYNÆCOLOGICAL OPERATIONS

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SENIOR REGISTRAR

W A W DUTTON
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POSTOPERATIVE wound infection is still a major problem Colebrook (1955) wrote "There is still much more infection transmitted in our operating-theatres and wards than we should accept" Recent reports suggest that sepsis is actually increasing Strahan (1951) reported an incidence of 4 3% following elective operations for hernia Howe (1954) reported that 7 2% of clean surgical cases became infected Blowers et al (1955) noted a gradual increase in postoperative infection in a thoracic unit, which was closed and reorganised after the infection-rate had risen to 10 9%

After certain changes in the ward and operating-theatre for gynæcological patients at the City General Hospital, Sheffield, the postoperative infection of wounds appeared to be reduced This improvement, however, was not maintained, and a more detailed investigation of the infection-rates before and after these changes was made. The results are reported here

Before July, 1952, two gynæcological units (unit A and unit B) were housed in a single ward, where there were often as many as 42 beds occupied at one time, and all the operations were performed in the general operating-theatres of the hospital, which were often in use continuously day and night After July, 1952, unit A moved into a newly equipped 18 bed ward, and unit B remained where it was, its beds, however, being reduced to 24 Two labour wards, which had been converted into a small gynæcological operating-theatre, were opened for the use of both Units

TABLE I—ADMISSIONS AND ABORTIONS

Period	Unit	No of beds	No of admissions	No of abortions
I	A and B	42	1317	507
II	A	18	580	224
	B	24	771	345
III	A	18	554	205
	B	24	709	330

TABLE II—DISTRIBUTION OF 651 CASES ACCORDING TO PERIOD AND TYPE OF OPERATION

Period	Group 1 (total hysterectomy)	Group 2 (abdominal operations)	Group 3 (pelvic floor repair, &c)	Group 4 (vaginal operations)	Total
I	63	54	53	23	193
II	75	47	73	43	238
III	68	57	68	27	220
Total	206	158	194	93	651

Material

Three one year periods were chosen for study The first period was the year before the above mentioned changes (from July 1, 1951, to June 30, 1952), the second (from July 1, 1952, to June 30, 1953) and the third (from July 1, 1953, to June 30, 1954) covered the two years after the changes

The total gynæcological admissions in the periods under review are given in table I, which shows little difference between the two units as regards the total admissions and the number of abortions

651 cases are reviewed, comprising 193 in period I, 238 in period II, and 220 in period III

Only major gynæcological procedures were studied, as being more likely to provide useful data than the minor procedures and abortions The 651 cases were grouped according to the type of operation (table II) as follows (1) abdominal total hysterectomy, (2) gynæcological abdominal operations other than total hysterectomy, (3) pelvic-floor repair and other vaginal operations in which the peritoneal cavity was not opened, and (4) vaginal operations in which the peritoneal cavity was opened—e g, vaginal hysterectomy, and prolapse *with* pouch-of-Douglas hernia

All cases showing evidence of preoperative infection were excluded from the study The age distribution of the patients operated on in each unit was similar in all the groups We recognise that comparisons between the results in the two units and even between the three different periods need to be made with caution because of sources of bias, known and unknown For instance, the two wards were not at all alike in design, in one unit for some time the skin temperature was recorded instead of the oral temperature, the proportion of very serious cases dealt with varied with the units and with the periods, the standard of the case documentation varied, and the quality of nursing was not uniform throughout

TABLE III—INCIDENCE OF INFECTION (ALL OPERATIONS)

Period	No of patients	No of infections	
		All cases	With chest and urinary infections excluded
I	193	81 (42%)	51 (26%)
II	238	116 (48%)	57 (24%)
III	220	115 (52%)	76 (35%)
Total	651	312 (48%)	184 (28%)

Criteria of Postoperative Infection

A case was considered to be infected after operation if it showed any one of the following pyrexia (100 4°F or more at any time or 99°F on three or more postoperative days), chemotherapy for an infective condition, wound sepsis, secondary hæmorrhage, paralytic ileus, thrombophlebitis

Cases were counted only once, even if several criteria of infection were present simultaneously In the preparation of tables III, IV, and V a case with a chest or urinary infection was not omitted unless this was the only infection present

Results

All Patients

When all the patients were considered together, the infection-rate was found to have risen in period II and again in period III (table III) The overall incidence of infection at 48% was high, but it fell to 28% when urinary infections (which were very numerous) and chest infections (which were very few) were excluded

Table III also shows that, after excluding urinary and chest infections, there appears to be a reduction in the incidence of infection in period II. The reason for this is not clear (see below)

By Units

The incidence of infection in the two units was studied separately (table IV) When all infections are considered, it is seen that the high incidence of infection and the deterioration with succeeding periods were common to both units The results in unit B were affected much more than those in unit A by the exclusion of chest and urinary infections Patients in unit B ran a particular risk of urinary infection (see below)

TABLE IV—INCIDENCE OF INFECTION (ALL OPERATIONS) BY UNITS

Period	Unit A			Unit B		
	No of patients	No of infections		No of patients	No of infections	
		All cases	With chest and urinary infections excluded		All cases	With chest and urinary infections excluded
I	85	33 (39%)	24 (28%)	108	48 (44%)	27 (25%)
II	126	57 (45%)	43 (34%)	112	59 (53%)	14 (13%)
III	124	63 (51%)	53 (43%)	96	52 (54%)	23 (24%)
Total	335	153 (46%)	121 (36%)	316	159 (50%)	64 (20%)

Abdominal operations (groups 1 and 2)—The incidence of infection in each unit was determined for abdominal operations only (table V) This revealed that unit B experienced a significant reduction in the amount of postoperative sepsis in period II, and that the amount of infection was less than in unit A in periods II and III

Vaginal operations (groups 3 and 4)—The incidence of infection in each unit after all vaginal operations was determined (table VI) This revealed that the postoperative infection-rate in unit B was almost twice that of unit A, but this was almost wholly accounted for by urinary infections, and, when these were excluded, unit B appeared to fare very much better than unit A

Frank sepsis—Lastly, it was decided to get some idea of how much of the sepsis recorded amounted to frank abdominal or vaginal suppuration The data for all infected abdominal cases for unit A were therefore re examined (table VII), from which it seemed that just over a quarter of these infected cases showed frank suppuration A few of these patients had serious infections and were very ill

TABLE V—INCIDENCE OF INFECTION (ALL ABDOMINAL OPERATIONS) BY UNITS

Period	Unit A			Unit B		
	No of patients	No of infections		No of patients	No of infections	
		All cases	With chest and urinary infections excluded		All cases	With chest and urinary infections excluded
I	44	18 (41%)	13 (30%)	73	26 (36%)	23 (32%)
II	56	22 (39%)	16 (29%)	66	16 (24%)	12 (18%)
III	62	33 (53%)	28 (45%)	63	24 (38%)	19 (30%)
Total	162	73 (45%)	57 (35%)	202	66 (33%)	54 (27%)

TABLE VI—INCIDENCE OF INFECTION (ALL VAGINAL OPERATIONS) BY UNITS

Period	Unit A			Unit B		
	No of patients	No of infections		No of patients	No of infections	
		All cases	With chest and urinary infections excluded		All cases	With chest and urinary infections excluded
I	41	15 (37%)	11 (27%)	35	22 (63%)	4 (11%)
II	70	35 (50%)	27 (39%)	46	43 (93%)	2 (4%)
III	62	30 (48%)	27 (44%)	33	28 (85%)	4 (12%)
Total	173	80 (46%)	63 (36%)	114	93 (82%)	10 (9%)

Discussion

The results were surprising in two respects Firstly, a postoperative sepsis-rate of 48% (table III) was much higher than was expected. Even when chest and urinary infections were excluded, the incidence was 28% (table III) The incidence of suppuration (unit A) was 12%

Secondly, the less crowded conditions in the wards and the provision of a separate operating-theatre for gynæcological cases were expected to decrease the incidence of postoperative infection but did not do so Although the sepsis-rate after abdominal operations in unit B fell significantly in period II (table V), it was difficult to believe that this was due to the new arrangements, especially when the incidence of infection after vaginal operations in the same unit in the same period was extremely high—93%.

This suggested a fundamental difference in the management of the abdominal and vaginal cases in unit B, and such proved to be the case after vaginal operations an indwelling catheter was left in situ for the first four days and subsequently the patient was catheterised thrice daily until the residual urine was less than 1 oz This may well have largely caused the high incidence of urinary infections despite prophylactic chemotherapy in 25% of these cases The effect was that nearly every vaginal case in this group ultimately received chemotherapy, and this, so far as we can say, was responsible for the decrease in vaginal infection in the old ward - thus the total sepsis-rate, which was 82%, falls to 9% when urinary infections and 1 chest infection are excluded (table VI) This reduction in potential sources of infection could explain the better results obtained with abdominal cases in unit B in periods II and III (table V) when compared with unit A

TABLE VII—INCIDENCE OF FRANK SEPSIS (ABDOMINAL OPERATIONS) IN UNIT A

—	No of patients	No of infections
All infections	162	73 (45%)
Frank suppuration	162	20 (12%)

Because of differences in management of cases in the two units, the apparent difference between them shown in the tables cannot be taken as certainly due to the new arrangements after July, 1952, but suggests that the facilities may have conferred some temporary benefit in period II This suggestion is reinforced by the fact that in the infected abdominal cases in unit A only minor sepsis was observed, during the six months immediately following the new arrangement (first half of period II) All the major sepsis developed in the second six months of period II Unit B, on the other hand had almost an equal number of major and minor infections in both halves of period II.

The average incidence of postoperative infection was very high throughout the survey. What were regarded as substantial improvements in the ward and theatre facilities for the gynæcological patients did little to alter the amount of infection. Several factors may have been responsible. The most important may be that the clean and the septic cases were operated on in the same small theatre, and, through lack of isolation cubicles, were nursed by the same nurses in the wards; and all the surgical wounds were dressed in the open ward, with the inevitable result that cross infection took place. Moreover, there was still a rapid turnover in the wards, with little chance of resting the beds and the wards; and the staff were often shorthanded and overworked. Conditions in the wards, though much improved after the changes in July, 1952, were still not ideal for maintaining a high standard of nursing. Again, any improvement in the incidence of postoperative infection that resulted in the wards may have been offset by the small size and the construction of the new operating-theatre. This was very small, with a high risk of contact infection; there was no special ventilation or air conditioning; sterilising and sluicing were carried out in a small adjacent room through which the staff had to pass after scrubbing up; and the patients were wheeled into the theatre almost directly from the corridor.

Since the results have shown that the provision of a new ward and an additional operating-theatre did not reduce the incidence of postoperative infection, the question arises: how can this incidence be lowered?

As regards the wards, it is clear that much of the old open-ward system is inefficient: more cubicle-type wards are required, and better isolation facilities are needed for the care of infected cases. (It is in obstetric practice, with its special risk of fœtal and maternal morbidity and mortality from sepsis, that such fundamental knowledge has often been used to good purpose.)

The provision of cleaner air in the wards is obviously desirable. Bourdillon et al. (1948) has suggested a built-in suction system which may with justification be included in the hospitals of the future.

Wright et al. (1944) have shown that the sterilisation and oiling of blankets, screens, and floors in surgical wards can cut down the air content of bacteria-contaminated dust. Such a system is not always followed by a reduction in the incidence of infection (Clarke et al. 1954), because different organisms adopt other ways of dissemination.

Another approach to the same problem reverts to the principle of the old carbolic acid spray—i.e., chemical air-hygiene, which apparently can be safely achieved with various aerosols (MacKay 1952). Bourdillon and Colebrook (1946) showed that, every time wound dressings are disturbed, thousands of particles carrying pathogenic bacteria are released into the air, and these workers recommended the setting aside of a surgical dressing room, which, ideally, would be air conditioned.

Operating theatres should be spacious, well planned and should include satisfactory ventilation.

Positive pressure ventilation with filtered air has been shown to be very valuable in preventing infection by airborne organisms (Colebrook 1955).

Such ventilation, modified to produce a down draught of filtered air over the table to avoid still air zones where dust particles could settle over the wound, was considered by Shooter et al. (1956) as beneficial in preventing possible postoperative infection.

Electrostatic air cleaning (Lidwell 1951) is said to reduce bacterial penetration easily to less than 1%.

Bourdillon and Colebrook (1946) showed that the movements of gowned theatre staff increased the number of airborne organisms, and Blowers et al. (1955) found the bacterial content of the air in the theatre greatest during the disturbance caused by the arrival and departure of patients to and from the operating table, the air taking some time to settle after these movements.

Twin theatres would be a big advantage, because the operator alternates between them, thus allowing time for thorough cleaning of the resting theatre and for the air to settle between cases.

Whatever efforts are made to avoid infection from airborne organisms it is essential that the accepted theatre ritual is always closely observed. The origin of the infection and the bacteriology of the organisms involved are often obscure, as is the subsequent spread. In many hospitals planned and built years ago far more work is being done than they were intended for, and such conditions are ideal for the spread of infection. Again "carriers" of infection among the many persons employed in hospitals are an ever-present focus of infection.

Sterilisation must be efficient, and much evidence is accumulating to show that often it is not.

Bowie (1955), from a survey of sterilising apparatus in British hospitals, considered about 90% to be obsolete, and found numerous faults in design and installation—e.g., unsatisfactory mechanisms for the discharge of air and condensate from the steriliser chambers, the superheating of steam in the sterilisers, leading to ineffective sterilisation and damage to heat-sensitive articles, the absence of any means of recording the air condensate temperature, and the connection of steriliser chambers with the underground drains and with the main hospital water supply.

Recontamination of the contents of the sterilisers during drying is considered by Howie and Timbury (1956) to be a possibility where air filters are absent or improperly constructed.

The containers (usually metal drums) in which the articles are sterilised should be of the correct design and not packed too tightly, to allow proper steam penetration. In a busy hospital with an overworked steriliser the strong temptation to overfill drums has to be resisted. Howie and Timbury (1956) point out the importance of liaison between hospital engineer, theatre sister, steriliser attendant, surgeon, and bacteriologist in order to have a complete understanding of the particular sterilising apparatus and thus the maintenance of an efficient unit for sterilisation. Readers are also referred to the authoritative monograph by Perkins (1956), who goes into great detail and gives a most helpful account of the *Principles and Methods of Sterilisation*.

Hospital discipline must be high if minor sepsis is not to reach serious proportions. There may be a high incidence of infection in the hospital unnoticed or perhaps "accepted" until a unit suddenly becomes involved in a serious outbreak. A continual watch on the amount of sepsis not only in each unit but over all the hospital would be ideal: this may be done in various ways—e.g., a "wound book" (Shooter et al. 1956) in which all details of every infected surgical case are recorded and examined.

Colebrook (1955) recommended the establishment of full-time infection-control officers, and even a systematic check year by year on infection in hospital. By such means early action can be taken when infection becomes significant. The closure of wards and theatres at the beginning of each spate of sepsis should improve matters; but often, unfortunately, this cannot be achieved without increasing the pressure of work on the other wards and theatres still functioning. Clearly methods must be sought whereby wards and theatres can be rested periodically for thorough cleansing so that a harmful concentration of bacteria cannot be built up.

The efficacy of chemotherapy and antibiotics is almost a drawback in the prevention of cross infection, for they take away a stimulus and, as a result, "many hospitals have not yet applied all the methods of reducing cross infection which were shown to be of value in earlier studies" (Clarke et al. 1952). These methods cannot be ignored if the control of postoperative infection is to be satisfactory, and they are probably of as much value as ever in dealing with resistant bacteria To prevent the growth of resistant strains, widespread use of prophylactic drugs should be avoided

Many of these measures to reduce postoperative infection are urgently required, for it is only by technical and structural improvements, great care on the part of each individual concerned in the treatment of the patient, and a continual watch for infection that sepsis in surgical wards can be reduced to its proper minimum

Summary and Conclusions

An investigation was made into the incidence of postoperative infection following 651 major gynæcological operations before and after improved theatre and ward facilities had been provided for two gynæcological units in a busy general hospital

The total infection-rate was 48% The criteria of postoperative infection were rigorous, but about a quarter of the total infection included either abdominal or vaginal suppuration

The provision of a new ward and an additional operating-theatre converted from two labour wards did not improve the sepsis rate, which even rose in the latter part of the survey

Some of the means by which postoperative infection may be reduced are discussed

We wish to thank Dr W J Clancy, of the City General Hospital, Sheffield, for permission to study cases under his care

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CENTRAL HEALTH SERVICES COUNCIL

THE Minister of Health has appointed or reappointed the following doctors to the council and standing advisory committees for the period ending March 31, 1960

Central Health Services Council

Prof R V Bradlaw, Prof Digby Chamberlain, * T M Cuthbert, O M Duthie, * Prof Robert Platt, P R C P, F M Rose, J G Scadding

Standing Advisory Committees

Medical —Professor Chamberlain, O M Duthie, * Sir Arthur Gemmell, * Professor Platt, F M. Rose, J G Scadding, G W H Townsend

Dental —Professor Bradlaw, A M. Horsnell, J A Moody, T G Ward

Ophthalmic —J H Doggart, O M Duthie, * A B Nutt

Nursing —A Elliott

Maternity and Midwifery —Arnold Walker

Mental Health —John Bowlby, * T E Pilkington

Tuberculosis —Frank Ridehalgh, J G Scadding, G W H Townsend

Cancer and Radiotherapy—Sir Harold Boldero Cuthbert Dukes, Prof R Milnes Walker, J A Stallworthy, Sir Clement Price Thomas, C J L Thurgar, Prof B W Windeyer

* New appointment

INCREASED REMUNERATION OF FAMILY DOCTORS

THE Ministry of Health announces that, after discussions with the medical profession, it has been agreed that the 5% increase in remuneration as from May 1 last shall be distributed among family doctors under the National Health Service as follows

1 The capitation fee will be increased by *6d* to *17s 6d* per annum
2 The loading in respect of the 501st to the 1500th patient on doctors' lists will be increased by *1s 6d* to *11s 6d*
3 Initial practice allowances will be increased by 25%
4 Hardship payments and supplementary annual payments will be increased by 20%

It has also been agreed that the maximum allowance in respect of the salary of a trainee general practitioner will be increased by £75 to £850 a year

The increase in the capitation fees and loadings for the months of May and June will be paid not later than July 31 The other increases will be paid at the end of that quarter (Sept 30) but all will take effect from May 1

Occasional Survey

IRRADIATION OF THE TESTIS

IRRADIATION of the testis is now an established experimental method of investigating the timing of the events within the tubules which add up to spermatogenesis—i e, the development of mature spermatozoa from spermatogonia (stem cells) The assessment can be based either on regular cytological examination of the tubules after irradiation,[1–3] or on genetical analysis of the incidence of dominant lethals in successive matings after irradiation [4–5]

It is well known that the sequence of cell changes in the lining epithelium of the seminiferous tubules which constitutes spermatogenesis passes as a wave of activity along the tubules, thus not only will any one section of the testis at any given time show tubules at different developmental stages, but the phase of the cycle varies along the length of the individual tubule Spermatogenesis is made up of (1) the cycle of the seminiferous epithelium, with the successive cell types spermatogonia A, intermediate spermatogonia, spermatogonia B, and primary spermatocytes, (2) meiosis (reduction division), and (3) spermiogenesis (development of spermatids to mature spermatozoa) Leblond and Clermont[6] describe nineteen stages of spermiogenesis in the rat, based on the structural changes in the acrosome system Using a similar classification, Oakberg[7] gives sixteen stages of spermiogenesis in the mouse, and finds that the seminiferous epithelial cycle extends over the first twelve of these stages, which are used as " markers " to determine the characteristic cell-associations of its different phases

Spermatogonia have a high radiation-sensitivity, which increases through the developmental sequence (intermediate and B types spermatogonia) The division of spermatogonia B to form primary spermatocytes is accompanied by a dramatic shift to the radiation-response characteristic of spermatocytes Following a single dose of 100r to the mouse testis, there is severe depletion of spermatogonia with complete loss of the B type after 5 days, repopulation begins in 10–15 days Loss of spermatogonia is, according to Oakberg,[7] caused by cell death, rather than inhibition of mitosis, though

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[1] Hertwig, P *Arch exp Zellforsch* 1938, 22, 68
[2] Oakberg, E F *Rad Res* 1955 2, 369
[3] Oakberg, E F *Amer J Anat* 1956, 99, 507
[4] Auerbach, C, Slizynski, B M *Nature, Lond* 1956, 177, 376
[5] Bateman, A J *Ibid*, 1957, 179, 727
[6] Leblond C P, Clermont Y *Amer J Anat* 1952, 90, 167
[7] Oakberg E F *Ibid*, 1956, 99, 391

some of the spermatogonia obviously survive to restart the epithelial cycle. By examining the irradiated testes at intervals up to 38 days and noting the times of disappearance and reappearance in sequence of the different cell types,[8] Oakberg determined the time-limits of the epithelial cycle in the mouse and so the total length of spermatogenesis. According to his reckoning, the seminiferous epithelial cycle takes on average $8^1/_2$ days, and thus the time required for the maturation of one generation of spermatozoa (in the mouse) is 34 days. Earlier estimates of 26 days for spermatogenesis based on the uptake of labelled material,[8 9] are probably due to errors in cell classification and confusion of spermatocytes with spermatogonia, giving an underestimation of 25%.

By ascertaining the relative frequency of a given stage of the cycle in a random sample of mouse tubules, it was possible to assign time-limits to each tubule-stage and thereby to each phase of cell development. On the basis of genetical evidence, Bateman,[10] gives an estimate of 6–7 weeks between spermatocytes and ejaculation of sperm, but following data supplied by Sirlin and Edwards[11] he agrees[5] that this is probably an over-estimate, and represents the total time of spermatogenesis plus an average of 7·5 days for the *transit* of mature sperms from testis to ejaculate.

With the information now available "it should be possible to select tubule stages and post treatment time in such a manner that the radiation sensitivity of any given spermatogenic cell may be determined".[3] Auerbach[12] believes that there is a parallel radiation sensitivity pattern of testis in drosophila and mouse, and thus that we may be dealing with a fundamental property of male germ-cells.

Oakberg[7] reports an incidence of degenerating cells, particularly spermatogonia A, in the normal mouse testis. He regards this as a selection against the more drastic chromosomal aberrations and possibly even genic changes during cell multiplication and growth. Such cell-necrosis is not, however, a normal feature of other actively mitotic epithelium, and it is tempting to relate it to the high radiation sensitivity of these stem cells. As cytological techniques improve, it should become possible to detect with some assurance non-lethal chromosomal damage of cell types, denoting potential mutated sex-cells.

It seems that there must be some local mechanism integrated with the general hormonal control to maintain the timing and spacing of the cycle of cell differentiation in the different tubules, and the recurring cell associations characteristic of each stage of development.

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8. Glucksmann, A., Howard, A., Pelc, S. F. *J. Anat., Lond.* 1955, 89, 13.
9. Sirlin, J. L., Edwards, R. G. *Exp. Cell Res.* 1955, 9, 596.
10. Bateman, A. J. *J. Genet.* 1956, 54, 400.
11. Sirlin, J. L., Edwards, R. G. *Nature, Lond.* 1957, 179, 725.
12. Auerbach, C. *Ibid*, p. 725.

Parliament

The Government and the Piercy Report

In an adjournment debate on June 7 Mr Robert Carr, parliamentary secretary to the Ministry of Labour and National Service, reported progress on the implementation of the Piercy report.[1] Dealing with the group of recommendations on the hospital and medical services he said that all the departments concerned and representatives of the medical profession itself were considering what could be done to give general practitioners and consultants more information about the scope, nature, and potentialities of rehabilitation. The health Ministers were shortly to advise hospital authorities on points raised by the committee's support of planned and purposeful physiotherapy and of the tendency of occupational therapy to offer more realistic occupations and advice and help on how to live with a disability. Each hospital would be asked to consider setting up a rehabilitation committee of its own, and every large hospital would, it was hoped, set up a resettlement clinic to review difficult cases of disablement. These clinics had proved valuable not only in dealing with the problems of individual patients but also as a means of drawing together the different agencies concerned in rehabilitation and resettlement. Hospital boards would also be asked to have regard to the needs of rehabilitation departments in drawing up their capital programmes. But clearly development must be conditioned by the availability of funds and staff. It was essential that we should make the best use of existing resources before seeking to expand them.

Pharmaceutical Services Committee

The Minister of Health has set up a committee with the following terms of reference:

Having regard to the increased cost of prescriptions issued in the National Health Service, to investigate the factors contributing to this cost and to make recommendations.

The members of the committee are:

Sir Henry Hinchliffe (chairman), a member of St Mary's Hospital, Manchester, H.M.C. and director of the Manchester chamber of commerce; Dr William Brockbank, dean of clinical studies and lecturer in medicine, Manchester University; Mr K. E. Capper, PH.D., editor of the *British Pharmaceutical Codex* and joint secretary of the National Formulary Committee; Dr H. C. Faulkner, member of the General Medical Services Committee and assistant M.O.H., London County Council; Dr F. E. Gould, member of the General Medical Services Committee and secretary of the Birmingham local medical committee; Dr D. V. Hubble, physician, Derby Royal Infirmary; Dr C. A. Keele, professor of pharmacology and therapeutics in London University at Middlesex Hospital Medical School; Mr M. G. Kendall, SC.D., professor of statistics, London University; Dr A. M. Maiden, a rural practitioner and member of the General Medical Services Committee; Dr A. D. Stoker, a rural practitioner and member of the General Medical Services Committee; Dr A. P. Thomson, dean of the faculty of medicine and professor of therapeutics, Birmingham University.

One appointment is outstanding. It will be filled by another general practitioner, and it is expected that he will be from Wales.

QUESTION TIME

Influenza Precautions

Sir Frank Medlicott asked the Minister of Health what steps were being taken by his department and by the public health authorities generally to deal with the possibility that the new form of influenza which was now raging in the Far East might spread to Europe and reach Great Britain.—Mr Dennis Vosper replied: The outbreaks of influenza in the East are being caused by a new variant of the virus, but all reports are that the illness is clinically mild in character. There are standing arrangements for information to be supplied about outbreaks of influenza in this country through general practitioners, industrial medical officers and others, and port medical officers report epidemic influenza among persons arriving in this country. As a precaution, practitioners are now being reminded of these arrangements. The characteristics of this new strain of virus are being investigated at the World Influenza Centre and in other research departments.

North Staffordshire Royal Infirmary

Dr Barnett Stross asked the Minister of Health whether he was aware that the closure of the operating theatre in this hospital was causing pressure on the other hospitals in Stoke-on-Trent and that both patients and medical staff were inconvenienced; and when the new theatre would be completed.—Mr Vosper replied: I am aware of the difficulties which have unfortunately resulted from the closure of these theatres. The regional board has arranged for beds to be available in another hospital for certain surgical cases, and for extra operating sessions at two further hospitals. It proposes to provide a temporary operating theatre at the Royal Infirmary as soon as possible, and hopes to be able to provide a new permanent twin theatre suite within two years.

At the end of 1956, in England and Wales 6247 mental defectives were awaiting admission to institutions.

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[1] See *Lancet* 1956, ii, 985.

In England Now

A Running Commentary by Peripatetic Correspondents

THE life of a medical registrar in England to judge by the articles now appearing in a Sunday paper, has many drawbacks and is far from exciting How different things can be in tropical Africa Twice the amount of work, constant difficulties such as inadequate drugs and equipment, but always something out of the ordinary just around the corner, or perhaps—more accurately—a little further away

Last week my chief called me in and asked me whether I would care to see a patient for him as he was unable to do so, and would I contact the local G P ? From the G P I learned that the patient lay ailing far across Lake Victoria As money was no particular object, an aeroplane had been chartered to take the " specialist " (me), the G P , and two of the patient's relatives to the bedside There were a few seats vacant, said the G P , and would I care to take my wife along ? My wife had slipped another spool of colour-film into her new camera almost before the telephone was back on its stand

A rainy Sunday morning saw us setting out over the lake, the E C G machine tightly strapped into a seat of the aged de Havilland aircraft Visibility was limited by driving rain and black cloud I began to regret my eagerness to be airborne Suddenly a thin ribbon of blue sky appeared ahead of us and soon we were flying through brilliant sunshine, with small wooded green islands below and in the distance the green shores of Tanganyika Then over small thatched huts, each surrounded by its grove of banana trees, an occasional splash of colour from a woman's dress, and a peculiar three-dimensional effect as we passed over the tall palm-trees My wife's camera clicked furiously, while I wondered whether this was all in keeping with the serious nature of our mission and tried hard to look as if it was all her own idea anyway, and her camera Down to earth, where a large Mercedes-Benz whisked us into the small town nestling among dark green-brown hills which sloped down to the remarkably blue lake It seemed for all the world like a scene from a Western movie, rather ramshackle and a shade dusty, with figures sprawled idly on verandahs in the sunshine

The patient had responded rather well to the local doctor's treatment, and sat perched on his bed eagerly awaiting the visitation While I took his history, a steady flow of friends and neighbours passed through the room; a quiet hum of agitated whispering accompanied our conversation But it all seemed so accepted a procedure that I had not the heart to empty the room By the time it came to examining the patient the audience had grown Small children peered in at the doors and windows, and only by dint of persuasion could I thin the spectators to a respectable number for a rectal examination We soon discovered that the electrical fittings were unsuitable for the E C G machine, and after a hurried consultation the local electrician and his mate appeared Large quantities of wire and equipment strewed the floor and finally we were ready for the actual recording Once again the room was crowded, and it was all I could do to preserve my gravity amid the obviously admiring throng of men, women, and children I can hardly be blamed for using twice the usual amount of paper While I sat looking at the record, the patient's business partner decided that a little of the limelight should fall in his direction and amid sighs and groans prostrated himself gently on a bed in the next room, insisting that he be seen by the specialist as soon as possible I think he had visions of his partner's rapid retirement and wanted to stake his own claim to physical disability before it was too late

All this time my wife had been on a sightseeing tour of the district On her return it was only proper that she should be brought in and introduced to the patient and his friends To the joy of the assembled gathering and to my wife's embarrassment she was solemnly presented with a beautifully embroidered handbag After all this there could be no unceremonious rush to the airfield, but a gentle drive into the hills above the town, through the coffee-plantations and past the beach where a notice warned one to be careful of the hippopotami which came out of the lake in the evenings and wandered through the gardens A quiet lunch at the hotel looking over flaming cannas and gleaming yellow cassia trees to where the waves broke on the sandy bay, and then the time had really come to leave

Flying back I reflected how different this all was from the daily routine I had known in England, and looking down on the sparkling waters, the small canoes paddling between the islands, and the white birds circling slowly below, I gave thanks for the opportunities that still exist to lead a life that is just that little bit different

* * *

My patients used to come into the waiting-room worried, depressed, and sometimes bored, only to find others in the same unhappy state Some picked up the torn and dog-eared magazines on the table to while away the time Others chatted in lugubrious tones with their fellow sufferers All were concerned with their own ailments more than anything else

Since I have hung on the wall an example of abstract art all is changed Two patients look at it and after some strongly worded criticism agree cordially that it is all nonsense But they go on making comments as they continue to look at it, and for the moment at least forget their troubles Another patient looks at the picture and wonders if there could be something in it which is not readily apparent He studies it, compares it with conventional pictures, and forgets the pain in his leg To another patient the painting comes as a refreshing shock Perhaps to another it tells a story Another seeks to justify it, either to himself or to his neighbour, as a work of art

Whatever one may think about it as " art," my picture has banished apathetic gloom from the waiting-room

* * *

The pathologist's report on an unremarkable appendix read (perhaps somewhat less than ceremoniously) " vermiform appendix " The surgeon, who was temperamentally non-vermiform, read the two words and, turning to the small company which had forgathered to savour his counter-attack, declared " What did I tell you ? Worms in the appendix Bad things, worms " His last word may have been his counter-attack

* * *

For the patient life in hospital is curiously unreal Doctors make sporadic appearances The H S acknowledges the fact that you're human and makes encouraging remarks from time to time about getting up The Registrar appears in the middle of evening ablutions and does not stay He promises to return The Consultant, accompanied by the H S looking serious, looks at you briefly and then at your case-notes at the end of the bed and goes away talking about an entirely different patient

You begin to believe that you're not who you thought you were This thought is encouraged by the arrival of two ominous-looking visitors in black, with black ties You can almost feel them measuring you up to see if you will fit into one of their existing coffins or whether they must make another However, they introduce themselves obviously under the impression that they know who you are, but this doesn't help at all One is someone's father, which is fairly reasonable, and you make conventional remarks about how nice to see them and how good of them to come They say that they expect your parents will return to Ashby de-la-Zouch in the morning, you're not quite clear-headed enough to say that perhaps you're not the person they think you are and mutter something about your parents not living in Ashby de-la-Zouch They take their leave suddenly and you wonder whether, perhaps, you do not come from Ashby de-la-Zouch after all

* * *

I m a sittin at ease in me parlour
On Sunday, the second of June,
Takin Elgar s " The Dream of Gerontius "
It's a luverly arternoon,
When they calls me to see Mrs Uxtable
—A thing wot they frequently do—
So I ops to er elp as per usual
—And when I gets ome the Dream's through
Now I ain't one to grouse about hours,
Don't ask to be paid overtime,
But when they cuts into me culcher
I calls it a perishin crime

Letters to the Editor

RADIATION AND INFLUENZA MUTATION

SIR,—The wise suggestion in your annotation of June 8 that we should get ready for a winter epidemic of infection by the new variant of influenza virus A that is now ravaging South-east Asia, prompts some consideration of the possible origin of the variant. Viruses share with more elaborate organisms the ability to mutate under the influence of radiation. Mutations in all organisms are more likely to be detrimental than advantageous, but the probability of advantage becomes greater the simpler the organism. It is among the viruses therefore that increased radiation is most likely to lead to an improvement in performance. One aspect of improved performance is the ability to circumvent the specific immunity of the population that is being attacked and this is what the new variant of influenza seems to be able to do.

Mutations, whether in people or viruses, do not carry labels explaining their origin. What is expected as a result of increased radiation from nuclear bombs or other sources is simply an increased frequency of mutation. East Asia is the area that has already suffered most from "fallout" coming from both Siberian and Pacific tests. There is therefore no intrinsic improbability in the idea that this influenza epidemic is yet another evil consequence of these tests.

Harpenden. N. W. PIRIE

HYPERTENSION: PRESYMPTOMATIC DIAGNOSIS AND TREATMENT

SIR,—I was interested to read Professor Sanjivi's letter of Feb. 2 and would like to comment on some controversial points he raised.

He says "we are not unduly nervous about telling a patient that he is suffering from tuberculosis, valvular heart-disease, or diabetes. Why should then we continue to teach that it is best not to tell the hypertensive patient that his blood pressure is raised?" Professor Sanjivi perhaps ignores the fact that we know little about the pathogenesis of hypertension. It may be a psychosomatic disorder, where stress and psychological upsets play a big part. If so, telling the patient that he has "hypertension" will still further trouble his already agitated psyche. By telling his patients that they have hypertension, Professor Sanjivi may have done great harm and made them more conscious of their mercury levels. Patients with slightly raised blood pressure, as in the case he quoted, seldom complain of symptoms apart from those of "anxiety neurosis." These symptoms respond readily to reassurance, regulation of life, avoidance of hurry and worry, and a sedative. To measure a patient's health by his mercury column is to do him the greatest disservice. Professor Sanjivi is happy about his results, but he should realise that the patients he is treating with hypotensive drugs could have equally well responded to reassurance and sedation.

He continues, "The classification of essential hypertension into benign and malignant is completely misleading. It should be given up." I think this is going too far. Malignant hypertension has a poor prognosis and requires aggressive treatment by ganglion-blocking agents or by sympathectomy. If Professor Sanjivi does not like the word "benign," he may call it "non-malignant" hypertension. I think the classification of hypertension into benign, accelerated, and malignant forms might satisfy him.

I think that the benign and malignant types are in fact two different diseases having in common only the raised blood pressure. The characteristic lesions of benign hypertension are hyaline degeneration of intima of small arteries and medial hypertrophy of muscular arteries. The essential lesion of malignant hypertension is fibrinoid necrosis of arterioles. Clinically the brunt of benign hypertension is borne by the coronary and cerebral arteries, the patient usually dying of congestive heart failure, coronary thrombosis, or cerebral thrombosis. Not more than 10% of patients die from renal failure. But in malignant hypertension, the disease runs a very acute course, most patients dying of renal failure. Hypertensive encephalopathy and cerebral hæmorrhage are not uncommon. Cardiac involvement, however, is uncommon, though acute left ventricular failure is sometimes seen. The patients with benign (non-malignant) hypertension may live about a normal span, but without treatment patients with malignant hypertension seldom survive more than eighteen months. The occasional transition of benign into malignant hypertension may be taken as evidence against this concept. I believe that, pathologically and clinically, benign and malignant types of hypertension are so different that it is not very logical to regard them as different varieties of one disease of unknown ætiology. If the course of benign and malignant hypertension is analysed in many cases, the two types of hypertension may turn out to be two different diseases, as in nephritis types I and II. Occasionally type I nephritis may become "nephrotic," and the clinical picture resembles type II nephritis; perhaps, in the same way, benign hypertension occasionally becomes malignant.

Professor Sanjivi writes: "Of the many fallacies surrounding essential hypertension, perhaps the most serious is that there is no hypertension in the rice-eating people of the East." I believe he underestimates the significance of the rice diet. Its hypotensive qualities are essentially due to its low salt content. Hypertension may be common in Madras where people take too much salt and spices, but its incidence is certainly very low among rice-eating people in the East—e.g., in the Hyderabad division of West Pakistan, where salt intake is not so great. Indeed, the lower incidence of hypertension in the tropics (mostly backward countries of the world) may partly be explained by excessive loss of salt in sweating, especially during the summer, which lasts for about eight months a year in Pakistan and India. In most patients from the countryside with hypertension the disease is secondary to pyelonephritis, renal calculi, or other disorders. In my experience in Pakistan, the prevalence of essential hypertension is directly proportional to the stresses to which a person is exposed, and the incidence is enormously high in educated people holding executive or professional jobs; and the disease is more prevalent in big cities than in villages.

Liaquat Medical College,
Hyderabad, West Pakistan. ALI MUHAMMAD

STEATORRHŒA AND HYPERPARATHYROIDISM

SIR,—I have read with interest Professor Dent's letter (June 8) in which he expresses surprise at the simultaneous occurrence of the biochemical features of hypoparathyroidism and the radiological features of hyperparathyroidism. He proposes to call this condition "hypo-hyperparathyroidism," and believes that it can be explained only by destroying "one of our present concepts."

In your annotation of May 25, however, you draw attention to the fact that tetany (with the biochemical features of hypoparathyroidism) may occur in rickets and which suggests a possible explanation for this course of events—namely, that parathyroid overactivity, giving rise to rickets, may go on to parathyroid "exhaustion," giving rise to tetany.

This explanation adequately accounts for the contradictory features of Professor Dent's two cases without destroying any of our present concepts and without introducing a self-contradictory neologism.

Gardiner Institute,
Western Infirmary,
Glasgow, W.1. JAMES CROOKS

SIR,—In his letter of May 25 Dr. Jackson suggests that the simultaneous occurrence of steatorrhœa and *idiopathic* hypoparathyroidism, described by several authors and also by Salvesen and Boe,[1] cannot be fortuitous, and he believes, that this combination is a definite "syndrome." He also mentions our analysis of 85 cases of steatorrhœa, in which we concluded that hypoparathyroidism often exists in this condition, because the serum-calcium remains low, instead of being raised by increased activity of the parathyroids, whose function it is to keep the serum-calcium at a normal level. But this is a *secondary* hypoparathyroidism, which we have seen in relation to the effect of undernutrition on the endocrine glands, so apparent in sprue.[2]

The hypocalcæmia in ordinary cases of sprue is primarily caused by vitamin-D insufficiency and by loss of calcium as calcium soaps with the fatty stools. In the "syndrome" cases mentioned by Dr. Jackson the hypocalcæmia is primarily due to an existing *idiopathic* hypoparathyroidism and the development of steatorrhœa with fæcal loss of calcium should tend to aggravate the hypocalcæmia. These two different kinds of hypoparathyroidism in sprue should not be confused.

We have pointed out[1] that bone lesions of osteomalacia seem to be more pronounced in the cases with a normal or nearly normal serum-calcium and a low serum-phosphorus, indicating a high activity of the parathyroids with resultant loss of calcium from the bones. The secondary hypoparathyroidism in other cases in a certain way protects the bones, but exposes the individuals to the dangers of tetany.

University Medical Clinic B,
Rikshospitalet, Oslo, Norway
H. A. SALVESEN.

FATAL CARDIAC ARREST WITH FLUOTHANE

SIR,—Dr. C. A. Foster has given a timely warning (June 1) that 'Fluothane' (halothane) is an extremely powerful anæsthetic, and if pushed to high concentration will cause a dangerous fall of blood-pressure, and, in an unatropinised patient, rapid cardiac arrest.

Fluothane allows a quiet trouble free induction without laryngeal or bronchial irritation, and stabilisation of anæsthesia is quickly obtained; and, so long as the patient breathes automatically, and there is no excessive fall in blood-pressure, there is no safer non-explosive volatile agent. But it is essential to keep constant record of the blood-pressure, preferably by an oscillometer, as apart from the lengthening of expiration which, with the quiet breathing associated with halothane anæsthesia, may be difficult to detect, the falling blood-pressure is the most important warning of increasing blood concentration.

Owing to the present cost, closed circuit techniques have naturally become popular. Using a Waters' canister, completely closed, a flow of not exceeding 1 litre of oxygen blown over the surface of a fully open Boyle's bottle, containing 40 c.cm. of fluothane, will produce adequate light anæsthesia with practically no fall in blood pressure.

Bronchial relaxation is so complete that respiration is easily controlled. It must be remembered, however, that under such conditions it is only too easy to reduce venous return to the heart by increasing intrapleural pressure and so lower the blood pressure; if at the same time the concentration of fluothane has been in any way increased, cardiac arrest is possible.

This is no condemnation of fluothane, but of the technique. Fluothane is an excellent anæsthetic agent. Its ease of administration is perhaps its greatest danger because with a powerful drug a demand is essential for greater vigilance.

Christie Hospital & Holt
Radium Institute,
Withington, Manchester 20.
W. B. BACON.

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[1] Salvesen, H. A., Böe, J. *Acta med. scand.* 1953, 146, 290.

[2] Perloff, W. H., Lasché, F. M., Nordin, J. H., Schneberg, N., Wieillard, C. B. *J. Amer. med. Ass.* 1954, 155, 1307.

IMMUNOLOGY OF THYROID DISEASE

SIR,—Professor Wyburn (June 1) has drawn attention to the pioneer and apparently forgotten work of Leo Loeb in the field of tissue transplantation and organ specificity.

This prompts me to point out that Loeb[1] also invented tissue culture, ten years before the classical paper of Ross Harrison[2] who is usually credited with the discovery. Furthermore, Loeb and Fleischer[3] were the first to culture adult mammalian organs in vitro. In this work they discovered the importance of using a gas phase of oxygen rather than air, when adult, as distinct from embryonic, tissues were to be cultivated. Even today this latter point is not fully appreciated.

M.R.C. Radiobiological Unit,
Harwell, Berkshire.
O. A. TROWELL.

SIR,—In your leading article of May 25 you suggest that the initial event in Hashimoto's disease is a leakage of thyroglobulin from the acini; and that the complement fixing antibody is specific for extracts of thyrotoxic glands.

If this is true a high incidence of Hashimoto's disease should be found among cases of hypothyroidism following partial thyroidectomy, and the search for antibodies and the histological examination of the thyroid remnants in these cases would be rewarding.

Supporting this idea is the fact that postoperative hypothyroidism is much commoner in Graves's disease, where thyrotoxic tissue must be cut across, than in toxic nodular goitre, where the toxic tissue is usually removed intact.[4] Bartels states also that a high incidence of "strumitis," defined as "excessive lymphocytic infiltration and fibrosis," is found in the resected specimens in cases where hypothyroidism subsequently develops.

Perhaps it is stretching the idea too far to suggest that the rather surprising success of partial thyroidectomy in Graves's disease may be partly due to the "Hashimoto process" initiated by surgery.

Boscombe, Hants.
A. POLLARD.

ANÆSTHESIA FOR CÆSAREAN SECTION

SIR,—I am interested in the anæsthetic implications of the article on elective cæsarean section and neonatal deaths by Dr. Strang and his colleagues (May 11).

While there are no anæsthetic details, the phrases "The times taken to establish normal respiration (mean 5 minutes) are longer than after vaginal delivery. This delay was probably due to the maternal anæsthesia" and "The baby is usually anæsthetised" deserve comment.

In the Blackburn Hospital Group we have for some time used a method of anæsthesia for cæsarean section which does not anæsthetise the infant, and spontaneous normal respirations usually occur within a minute of delivery.

The mother is visited by the anæsthetist on the day before operation for the usual preoperative examination, and a full explanation of preoperative procedure. She is given a barbiturate sedative the night before operation and where the operation is to take place in the afternoon, she might also be given methylpentynol three to four hours before coming to theatre. Atropine gr. $^1/_{100}$ is given 45 minutes before operation, and in theatre all the skin preparation, towelling, &c., is done before the anæsthetic induction. When all is ready 0.3 or 0.4 g. of a $2^1/_2$% solution of thiopentone mixed with 80 mg. of gallamine ('Flaxedil') is injected intravenously, followed by 25–30 mg. of pethidine. A syringe containing 0.5 mg. ergometrine is attached to the same needle, and strapped to the arm so that it can be injected immediately the baby's head is born. The incision is made as soon as the thiopentone gallamine injection is completed. The maternal lungs are inflated with a mixture of 50% nitrous oxide in oxygen. The infant is delivered usually within 3 min. The longest time taken has been $3^3/_4$ min., and the shortest $2^1/_4$ min. from the anæsthetic injection. Most infants are a good pink colour and cry lustily immediately and even before separation from the placenta.

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[1] Loeb, L. Über die Entstehung von Bindegewebe, Leucocyten und roten Blutkörperchen aus Epithel und über eine Methode, isolierte Gebewesteile zu züchten. Chicago, 1897.

[2] Harrison, R. G. *Anat. Rec.* 1907, 1, 116.

[3] Loeb, L., Fleischer, M. S. *J. med. Res.* 1919, 40, 509.

[4] Bartels, E. C. *J. clin. Endocrin.* 1953, 13, 95.

Since we have been using this method, I have not known it to be necessary to use resuscitative measures, apart from dry suction of mucus from the nasopharynx, which is done by the surgeon or his assistant before the baby is handed to the waiting midwife.

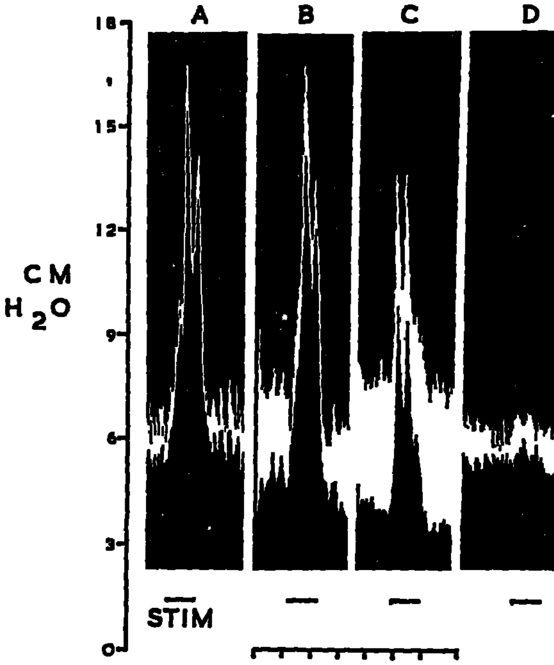
Once delivery is complete, anæsthesia proceeds as for any abdominal operation, an endotracheal tube being passed if necessary. As a rule, the mother is allowed to recover consciousness as soon as the last stitch is inserted, and she knows the sex and weight of her baby before she returns to the ward.

Blackburn MARGARET C. WATKINSON

DUODENAL ULCER

SIR,—As long-term studies of vagotomy and gastroenterostomy come to be published, it seems that this operation may prove to be better than gastrectomy in the treatment of chronic duodenal ulceration. Mr. Hindmarsh (June 1) stresses the importance of complete nerve section, and it would seem that section of all nerve trunks is of crucial importance in the operation. Hitherto no method has been available for testing completeness before the abdomen is closed.

We have developed a simple and safe technique which records quantitatively gastric motor function in response to vagal nerve stimulation. Used initially on animals, it has now been successfully applied to man. The method (later to be published in detail) consists in recording intragastric pressure changes in response to vagal nerve stimulation applied by an electrode around the lower end of the œsophagus. Not only can major trunks be demonstrated in this way, but so too can fine trunks which might have been otherwise overlooked (see figure).



Effects of vagal stimulation on stomach motility. Fluctuations in baseline are due to respiratory movements. At each mark vagus nerves were stimulated for 1 min. with 2 msec. shocks at a rate of 10 per sec.

A, Before nerve section.

B, After cutting the posterior nerve.

C, After cutting a large anterior nerve. A rise in pressure was still obtained, showing that a nerve trunk remained undivided. This was found and cut.

D, The effect is abolished, showing that no trunks remain in continuity.

We would like to thank Professor Sir Lindor Brown for his advice and Dr. E. H. L. Harries for his help in the early stages of this work.

West London Hospital, W.6, and Department of Pharmacology, Royal College of Surgeons of England HAROLD BURGE J. R. VANE

INJURY DUE TO ATOMIC EXPLOSION

SIR,—The reporting of the American Surgical Association's meeting, in *The Lancet* of May 25 (p. 1071), has gone astray in the first two paragraphs.

None of the Marshallese died. The 50% mortality at 200r (which none of them suffered), even if it be only a misprint for 5%, is probably excessive in any circumstances.

In the subsequent paragraph, which deals with facts as to the effects of radiation on dogs, there is included an opinion as to surgery for humans which is, to say the least of it, open to doubt. It is only too easy to extrapolate from limited experimental experience to dicta as to probable happenings in man.

London, W.1 E. ROCK CARLING

THE CHILD'S RIGHT TO ADOPTION

SIR,—Adoption is a controversial subject on which many people express strong views. Some points, however, are so delicate, or are thought to be so much at variance with public opinion, that they are rarely discussed openly. For instance, although there is no legal bar to the adoption of legitimate children, it is in fact difficult to achieve, because most adoption societies and children's officers reflect public opinion and refuse even to consider such a proposal.

The arguments usually put forward against it are that parents must be made to accept their responsibilities, that relieving them of their unwanted children would encourage them *to have more*, and that it would encourage irresponsibility, and be a threat to family life. All these arguments may be valid, but by taking this view society is surely sacrificing the real interests of many children—perhaps in order to gratify its own desire to punish the parents.

Anyone who works with children knows that there is no more pathetic and tragic group than those who are, and always have been, unwanted. Though they may suffer no overt neglect or cruelty, they present problems of disturbed behaviour, delinquency, and psychosomatic illness which are intractable; for if a child is unwanted no amount of outside help can ever make him feel wanted. If we admit that to be unwanted is about the greatest misfortune which can befall a child, are we not under an obligation to avert it whenever possible by making adoption easier?

If such children were accepted for adoption, society would benefit by the decrease in the number of misfits and delinquents; the adopting parents, who now wait years on the lists of adoption societies, would benefit by gaining a child sooner; and the actual parents would benefit by relief from a burden which they resent. Most important of all, the children themselves would have the chance of a happy family life.

As it seems to be so much to everyone's advantage, why is it not allowed? Partly, perhaps, because the public does not understand the extent of the problem, but also because society seems to think that it is a sin for parents not to want or love their children and that somehow they can be made to do so. It would be more realistic to accept the regrettable fact that some parents do not, and never will, love their children. It is fruitless to argue that they should not have them if that is how they feel about it; for despite admonition, censure, and moralising, unwanted legitimate babies will continue to be born

It will inevitably be argued that this change would open the gates to abuse and complications But an abuse does not invalidate a principle, if the principle is generally accepted The rules governing all good adoption procedure would naturally have to be applied, and care taken to weigh carefully the best long-term interests of each baby, its real parents, and its adopting parents It would be naïve to pretend that adoption is always successful, but it seems the best possible means of dealing with this tragic situation

A second point which is seldom discussed, because we have in this country a deep respect for each other's religious beliefs and differences, is the denominational bar There is at present a shortage of Roman Catholic adopting parents and as a result many illegitimate babies of Roman Catholic mothers are denied the chance of adoption and are brought up in baby homes A mother's wishes about the religious upbringing of her child must be respected, but where mothers only claim denominational membership for form-filling purposes and have no real feeling about it, it seems to me wrong to allow this label to prevent babies from being adopted when there are so many parents waiting to give them a home

Manchester 14

B M HUNTER
Almoner

HOME CONFINEMENTS

SIR,—About this time last year you assisted the London Regional Obstetric Committees by publishing a letter of mine[1] to the effect that, save in exceptional circumstances, practitioners who qualified after Jan 1, 1931, and who wished to be included in the London list of general practitioner obstetricians would, as a condition of admission to that list, be required to have held a resident house-job in obstetrics for a period of six months It was then indicated that any applications received prior to May 1, 1957, would be considered in the light of the conditions which obtained prior to that date

At the instance of the London Obstetric Committees I would again ask for the hospitality of your columns to remind all prospective applicants that the new requirements are now being put into effect

Public Health Department
County Hall
London, S E 1

J A SCOTT
Chairman
London Local Obstetric Committee

CHILDREN IN HOSPITAL

SIR,—As a layman whose occupation includes the reading of medical journals, but also as a parent, I was surprised to find that it was necessary to use six of your columns to demonstrate, in Dr Vaughan's article of June 1, what any intelligent parent could have told your readers—namely, that a simple, reassuring explanation given to children admitted to hospital will almost inevitably satisfy them Indeed, very much could be learned by the staffs of our hospitals if they would consider, more rationally, the need for reassuring even then adult patients It takes very little imagination to realise that people admitted to hospital are almost invariably frightened and disturbed, and that by overcoming this very real upset in their lives as far as possible, much will be done to ease their suffering So much good is done that it makes the notable lapses much more difficult to understand

Surely it can now be accepted that nearly all patients are much happier to know what is going to happen to them and to be relieved of the many and largely unfounded fears with which, quite understandably, they torment themselves

One simple solution, already used, I believe, by the more enlightened, is to have printed cards telling patients or relatives as much as they need know to give them some degree of reassurance It would be a rather grave indictment of those responsible if it should prove necessary to have hospital staff whose sole duty was to reassure patients and make their hospital experience less frightening

MEDICAL ABSTRACTOR

SEASONAL INCIDENCE OF MEGALOBLASTIC ANÆMIA OF PREGNANCY AND THE PUERPERIUM

SIR,—The results in Dr Thompson's interesting article of June 8 might not represent the true seasonal incidence of the disease unless all the cases which occurred during the period under review, were diagnosed Dr Thompson has reviewed a series of 105 patients, collected from three hospitals during a period of twenty-three years, but it seems probable that the total number of cases occurring during this period would be considerably higher than this

During 1956, 30 cases of megaloblastic anæmia of pregnancy and the puerperium were diagnosed at Whiston Hospital, Lancashire, and it is unlikely that there were any other cases, in which the diagnosis was missed The monthly incidence of parturition in these cases can be obtained with accuracy and the results agree closely with those of Dr Thompson (see accompanying table) The seasonal incidence of the onset of the anæmia cannot be determined with sufficient accuracy to give exact figures for each month However, the figures are sufficiently accurate to confirm Dr Thompson's findings that the highest incidence of the onset of the anæmia is during the late winter and spring

SEASONAL INCIDENCE OF ONSET OF MEGALOBLASTIC ANÆMIA AND OF PARTURITION

Month	Jan	Feb	March	April	May	June	July	Aug	Sept	Oct	Nov	Dec	Total
Delivered	1	3	3	7	7	1	4	0	0	1	1	2	30
Onset	17			8			2			3			30

Liverpool, 18

J W B FORSHAW

EFFECTS OF CARBUTAMIDE ON CARBOHYDRATE METABOLISM IN DIABETES

SIR,—Professor Bastenie's findings[1] seem to indicate that under treatment with carbutamide (B Z 55) both outflow of glucose from the liver, and resynthesis there, decrease We have studied, in the rabbit, the effect of carbutamide, with or without cortisone acetate, on the rise of blood sugar following the fall induced by 10 units of insulin given intravenously With insulin by itself, such a high dose ensures a significant rise of the blood-sugar—i e , outflow of glucose from the liver

Mild alloxan diabetes responds to carbutamide, but grave alloxan diabetes and diabetes caused by cortisone remain uninfluenced[2] Cortisone may inhibit the peripheral effect of insulin, but increases glucose production in the liver If carbutamide is really capable of decreasing the outflow of glucose from the liver, the post hypoglycæmic blood sugar rise must also be decreased

Male rabbits of the same breed, weighing about 3 kg , were used in the experiments We had previously observed, on administration of 10 units of insulin, a significant fall followed by a rise in the blood sugar level The effect of the insulin lasted four hours, and it rarely caused hypoglycæmic shock Blood sugar curves after giving 10 units of insulin intravenously are, accordingly, well suited for comparative examinations

Relatively high (therapeutic but not toxic) doses of carbutamide were administered—viz , 1 5 g daily for three to four days On the last day of the experiment, four hours after the morning dose, the insulin was given to the fasting rabbit The rabbits treated with cortisone acetate were given 5 mg intramuscularly at 8 A M , and 10 mg at 4 P M Hypoglycæmic attacks were seen in no case during the experiments

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[1] *Lancet* 1956 i 150

[1] Bastenie P *Lancet*, 1956, ii 628
[2] Peters G *Dtsch med Wschr* 1957, 82 311

The morning blood sugar of the control animals (also during carbutamide therapy) was around 108 mg per 100 ml , and in the animals treated with cortisone acetate 142 mg per 100 ml , whether or not carbutamide was administered When carbutamide was given there were moderate rises as well as falls in the blood sugar in the early hours In the cortisone-treated rabbits, the average fall in blood sugar after insulin was 91 mg per 100 ml and the following rise 63 mg When carbutamide was given the average fall was 69 mg and the rise 68 mg The corresponding figures in the controls were 85 mg and 58 mg without carbutamide, and 60 mg and 49 mg with carbutamide

This means that, in spite of carbutamide treatment, there was a significant outflow of glucose from the liver

First Department of Pædiatrics
Budapest University Medical School

L BARTA
G SIMON

NEW METHOD OF PROMOTING LABOUR

SIR,—We have developed a new and natural method of promoting labour based on Verney's experiments with antidiuretic hormone in dogs[1,2] For this purpose we use an intravenous infusion of hypertonic saline solution on the assumption that this may stimulate the posterior lobe of the pituitary gland Our first results have been good

CASE 1 —A primigravida, aged 23 (last menstruation Aug 8, 1956), was admitted on May 6, 1957, at 6 A M The membranes had ruptured spontaneously half an hour earlier She had had an uneventful pregnancy A vaginal examination then revealed only 3 cm (2 fingers) dilatation She was put to bed without therapy At 1 15 P M another vaginal examination was made and revealed exactly the same situation as at 6 A M , she felt no labour pains, and we could feel no uterine contractions At 1 35 intravenous infusion of 1000 ml of a 2 5% *saline solution was begun and completed at 3 35* At 3 P M we felt the first weak uterine contraction The labour pains became progressively more frequent and stronger, and at 7 55 a baby weighing 3080 g (6 8 lb) was born spontaneously

CASE 2 —A primigravida, aged 33 (last menstruation July 26, 1956), was admitted on May 1, 1957, at 6 45 A M Labour *pains had begun at midnight, after an uneventful pregnancy* At 10 30 A M a vaginal examination revealed 3 cm (2 fingers) dilatation There were only weak contractions of a short duration At 4 45 P M a second vaginal examination revealed 4 cm dilatation, and at 7 45 P M a third vaginal examination showed the same situation , practically no contractions could be felt An intravenous infusion of 1000 ml of a 2 5% saline solution was administered from 8 45 to 9 20 P M At 9 P M the contractions began again, and became stronger and more frequent At 11 30, at full dilatation, the membranes were ruptured artificially, and at 12 25 A M a baby weighing 3060 g (6 7 lb) was born spontaneously

CASE 3 —A primigravida, aged 29 (last menstruation July 3, 1956), was admitted on April 4, 1957 Pregnancy had been uneventful despite the fact that she had had serious diabetes mellitus since the age of 4 (88 units of insulin a day) On April 7 we concluded that the child was dead, for the fœtal heart sounds suddenly ceased On April 11, and again on April 15, we tried unsuccessfully to induce labour by means of castor oil, quinine, and oxytocin On April 17 she was discharged At home she took stilbœstrol 20 mg hourly for 10 hours Since this also failed to bring about labour, she *was again admitted on April 23 From 3 30 to 4 20 P M we* gave an intravenous infusion of 1000 ml of a 2 5% saline solution At 4 30 P M we noticed the first contraction of the uterus, and these became progressively more frequent and stronger At 1 00 A M , at full dilatation, the membranes were ruptured artificially At 1 32 a macerated female fœtus weighing 3620 g (8 lb) was born spontaneously

All three mothers had a *slight sensation of thirst after* the infusion During and after the infusion the blood-pressure and urine were regularly observed We could find no proteinuria and only a slight rise in blood pressure

The injected hypertonic saline solution probably stimulated the neurohypophysis, *so that the posterior* lobe of the pituitary gland produced not only more antidiuretic hormone but also more oxytocic substance This may afford a powerful and natural means of stimulating labour We are now trying to work out a dosage scheme more thoroughly The method is, of course contra indicated in hypertensive toxæmia and cardiac disease

Department of Obstetrics and
Gynæcology, State University,
Utrecht, Holland

T L A DE BRUINE

HIRSCHSPRUNG'S DISEASE

SIR,—I was very interested to read the remarks of Mr Daintree Johnson and his colleagues (June 1) upon continence after abdomino-anal anastomosis It has always appeared to me that normal bowel control is an involuntary process and does not depend upon voluntary contraction of the sphincters or of the levator ani muscle Indeed, if what we are taught by physiologists is true, it is not possible to contract striated muscle for long periods

Normal continence depends upon a normal sensory mechanism in the lower rectum and the involuntary internal sphincter The latter thickened portion of the internal circular muscle of the bowel is the normal mechanism of continence The *voluntary external* sphincter is only brought into play to prevent the short lived sensation of the call to stool It can contract voluntarily for about a minute allowing " plastic adaptation " to occur in the rectum and the internal sphincter time to regain control

It is for this reason that abdomino anal operations may give disappointing results The reason why they may be successful is more difficult to understand

London, W 1

IAN P TODD

CARDIOGRAPHIC TECHNICIANS

SIR,—*Your annotation of May 18 draws attention* to the plight of radiographers Cardiographic technicians are much fewer, but their financial position also needs emphasis

In 1952 Mrs X was a trained medical secretary when appointed technician in charge of a very busy department In 1954 she was put on grade II of the cardiographic technicians' scale, £360 rising to £485 plus London weighting By 1956 a small award had increased the scale to £390 rising to £520 p a , plus London weighting My medical secretary at the hospital, twelve years her junior, was then earning £12 a year more (and medical secretaries are by no means overpaid in the health service) In view of the obvious disparity between her salary and her value to the hospital, it was twice *recommended to the Ministry of Health* that Mrs X should be given accelerated increments to her salary These recommendations were both rejected She would have preferred to continue in the hospital where she had worked for seventeen years, but she has recently accepted an appointment as medical secretary and cardiographer to an industrial firm, where her salary is £500 plus emoluments amounting to £39 per annum, and her promotion prospects are much better

Under the N H S , a trained cardiographer (who needs to understand her patients as well as her machines) earns no more than many shorthand typists of 19 in industry

While pressing our demands for increased remunerations for ourselves, it would be sad if, as a profession, we failed to press effectively for the improved *pay of* our technical assistants

Central Middlesex Hospital,
London, N W 10

KEITH BALL

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1 Verney, E B *Lancet*, 1946, ii 739
2 Verney, E B *Ibid*, 1948, ii 108

POSSIBLE CONTROL OF RADIOACTIVE-STRONTIUM DEPOSITION IN BONE

SIR,—The accumulation in bone of radioactive strontium from nuclear explosions raises the question of whether it is possible to restrict the absorption of strontium by the body or to eliminate what has already been absorbed

The deposition of "calcium phosphate" in bone, in agreement with Robison's experiments,[1] can be interpreted in terms of the solubility-product principle, though not necessarily in terms of an initial deposition of trivalent phosphate Since the physical chemistry of strontium and calcium is very similar, it is reasonable to expect that the mechanism of their deposition will be the same It can also be reasonably assumed that strontium phosphate already deposited in bone—being, like calcium phosphate, "insoluble"—will be in a state of dynamic equilibrium with the surrounding tissues, in the same way as calcium phosphate This concept may be used to try to restrict the deposition of radioactive strontium or to remove existing deposits in bone

(1) Chemically, radioactive strontium and ordinary strontium are practically identical Consequently, for the limited amount which can be carried by a *saturated* transporting enzyme system, the higher the ratio of the concentration of ordinary strontium to the concentration of radioactive strontium, in a given intake sufficient to saturate the transporting system, the smaller will be the quantity of radioactive strontium eventually deposited Hence, addition of ordinary strontium salts to the diet, below toxic levels, should decrease the absorption of radioactive strontium, other factors being equal Accurate data concerning human toxic limits, however, are apparently unavailable

(2) For a limited and saturated phosphatase concentration—which may be expected to be responsible for the deposition of strontium in bone—the quantities of $[Ca^{++}]$ and $[Sr^{++}]_{ord} + [Sr^{++}]_{rad}$, by the solubility product principle, must also be limited. Now, the higher $[Ca^{++}]$, the more likely is calcium phosphate deposition and therefore the lower is the soluble phosphate ion concentration, this decreases the chances of strontium phosphate precipitation Hence, increase in the intake of calcium salts should decrease the uptake of both ordinary and radioactive strontium

People drinking very hard water or taking calcium salts should therefore deposit less radioactive strontium in their bones But absorption of calcium from the duodenum is dependent on pH (absorption takes place in slightly acid media, whereas in neutral or slightly alkaline conditions calcium phytate or phosphate may be precipitated) For this reason, people taking large doses of alkaline powders should be considered separately In such circumstances increased calcium salt absorption would require complex ions such as those found in the presence of citrates The presence of precipitated calcium phosphate in the duodenum, however, may not be without advantage, as will be seen presently

Some experiments I have performed suggest another approach Strontium ions are removed from solutions containing strontium salts when the solutions come in contact with calcium or magnesium phosphate, and the action depends on surface area and duration of contact The findings can be ascribed to initial adsorption followed by ion exchange and some precipitation of strontium phosphate This raises the possibility of removing strontium isotopes from the gut on a large scale and therefore of considerably restricting their absorption by adding calcium and magnesium phosphates to the diet

Methods of control involving increased calcium absorption are particularly applicable to the young, who take up considerably more radioactive strontium than older people, because in this case high calcium absorption is well tolerated When low calcium absorption is advisable, control may have to rely on gut precipitation and ion exchange methods

To remove existing deposits of radioactive strontium, other methods may be necessary Those used for the removal of lead and other metals give a guide Thus, lead deposited in bone can, by the injection of parathyroid hormone, be eluted and eventually excreted with bone calcium,[2] and it is likely that strontium elution will also follow A less drastic method involves the use of sodium calciumedetate, which combines strongly with heavy metals[3] Its administration leads to the formation of the lead salt, which is then excreted by the kidney[4] Sodium calciumedetate may reasonably be expected to form the radioactive strontium analogue and thereby hasten removal of strontium If so, the urine of persons treated in this way could be used to detect deposits of radioactive strontium in bone

Further details and physical biochemical considerations of the above and of the restriction of radioactive strontium transference in the food chain ending in man will be published elsewhere

Physical Chemistry Laboratory,
South-West Essex Technical College,
London, E 17

S LEWIN

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[1] Robison R *Biochem J* 1923 17 286

HÆMOGLOBIN E IN A NEPALESE SOLDIER

SIR,—Hæmoglobin E has so far been found in Thais, Siamese, Indonesians, Veddas from Ceylon, Malaysians, Persians, and Philippinos Recently[5] it was not found in 199 Nepalese Indian soldiers In a study of the hæmoglobin types in Nepalese soldiers (Gurkhas) stationed in Malaya, one case has been found showing a combination of hæmoglobins A and E (hæmoglobin-E trait) On electrophoresis, using veronal buffer pH 8 8 by the evaporation-prevented technique,[6] the mobility was identical with that of an A and E sample supplied by Dr Lie Injo Luan Eng of the University of Indonesia Since this finding was recorded a similar example has been observed

The conclusion is warranted that hæmoglobin E does occur in Nepalese, but that its incidence is very low

Department of Biochemistry,
University of Malaya
Singapore

F VELLA

NEW WAYS WITH TAR OINTMENTS

SIR,—Tar ointments are still regarded as widely useful in dermatology but their disadvantages generally are that they are "messy," and that "elegant" and smooth preparations are difficult and expensive to make Also tar ointments, because of the large and irregular tar particles, are frequently irritant

Carney and Zopf[7] described their experiences using 0 5% polyoxyethylene sorbitan monolaurate ('Teen 20'), which is a non-ionic surfactant, to help "break up" the tar particles He found that teen 20 (0 5%) and crude coal tar (1%) in zinc paste gave a very satisfactory ointment, in which the tar particles were uniformly small

For the past two years we have used a similar substance, cetamacragol, in tar ointments, and found it very successful With the aid of cetamacragol which is, I understand, widely used in cosmetic preparations, it is possible to break up the tar so that a very smooth and elegant preparation is obtained, and the tar can even be incorporated in ung aquosum if necessary These tar preparations are less messy to use than the ordinary ones, and spread more easily

We have used two types of base for the tar one very thick preparation in equal parts of Lassar's paste and 'Vaseline,' and a thinner one in ung zinc et ol ric

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[2] Hunter D *Lancet*, 1930 i 897 947 999

[3] Schwarzenbach G, Ackermann H *Helv chim Acta* 1948, 31, 1029

[4] Sidbury J B *Amer J Med* 1955 18 932

[5] Aksoy M Bird G W G Lehmann H Mourant A E Thein H Wickremasinghe R L *J Physiol* 1955, 130 56P

[6] Chernoff A I *New Engl J Med* 1955 253 322

[7] Carney R G Zopf L C *Arch Derm Chicago* 1955 72, 266

Keining and Weber[8] have advocated the use of 'Nobecutane' sprayed on as a film after tar has been applied. We have recently tried this on patients with only a few fairly large plaques of psoriasis, and have found it very useful. It not only keeps the tar off the patient's clothes, but also stops the clothes from rubbing against the patches, and it often makes tar treatments acceptable when they would otherwise be refused.

We have found that nobecutane works well if applied over the Lassar's and vaseline but not over ung. zinc oxide, on which it does not dry. Care must be taken to apply the nobecutane thinly and from a distance of about one foot.

I would like to thank Dr. Alice Carleton for allowing me to treat the patients and Mr. W. Trillwood for making up the ointments.

The Radcliffe Infirmary,
Oxford.
SUZANNE ALEXANDER.

ACUTE SPONTANEOUS MEDIASTINAL EMPHYSEMA

SIR,—In your issue of March 9, Dr. Watts discusses five types of therapy for acute spontaneous mediastinal emphysema. A sixth which, I think, has merit when other techniques cannot be applied, is the inhalation of pure oxygen for a sufficient length of time to absorb nitrogen in the air dispersed through the mediastinal tissues.[9,10] This method was applied successfully to intestinal distension some 20 years ago, before the advent of the Miller-Abbott tube, and, in particular, for the absorption of the nitrogen in the air injected into the ventricles for encephalography. In the latter case, most of the injected nitrogen could be resorbed in three or four hours. Mention was then made of its possible application to mediastinal emphysema.

Boston, Mass.
JACOB FINE.

CONSULTANT AND SPECIALIST

SIR,—In your leader of June 1 you stated that the consultant might get along well if relieved of some of his outpatients. As a general practitioner who held a senior-registrar post for four years, I have come to the conclusion that in a high proportion of cases the general practitioner could do without the outpatient department or the services of a consultant if he could have access to diagnostic facilities. The outpatient problem could thus be solved and result in an all-round saving in consultants. The general practitioner and the long-suffering patient would both benefit.

If the ability of the general practitioner received proper recognition and he was given better facilities for practice, more doctors might seek the comprehensive field of general practice and fewer the limited ground of the specialist, who generally sees only a part of every case. The whole standard of medical care might be improved and the cost of hospital care be greatly reduced.

Farnham Royal,
Bucks.
MARY HERFORD.

SIR,—I wish to condemn in the strongest possible terms the suggestion both in your leader and in the article headed "Reconstruction" (June 1) that a new grade of "specialist" of an assistant nature, with pay less than the consultant rate, should be introduced.

One of my main reasons for opposing this grade is your naive and implicit faith in the Minister of Health. The fact that he would use the grade to obtain a cut-price consultant service you say is baseless. In your article under "Reconstruction" you state that the representatives of the profession have ensured that the S.H.M.O. appointments have not been misused. In both articles you show yourself unaware of, or are conveniently casting a blind eye at, the abuse of the S.H.M.O. grade. Anyone who cares to look into the question can find scores of people in this grade, with higher qualifications and adequate training, who are doing work of a consultant nature and without supervision. It is ludicrous to suggest that the Ministry has been honest in its use of the S.H.M.O. position. A cut-price consultant service is at present in existence and its further extension should be vigorously opposed.

The answer to the problem posed under "Reconstruction" is simple—the creation of more consultant posts. By all means have assistant physicians, surgeons, &c., but pay them as consultants, and then, as you remark with regard to such posts in the North West Metropolitan Regional Hospital Board, the holders will work contentedly.

CUT-PRICE CONSULTANT.

SIR,—At the inception of the National Health Service general physicians and surgeons wisely refused to accept the grade of senior hospital medical officer (S.H.M.O.) in their specialties. In your leader you recommend the introduction of such a grade under a new name without any reference to the problems and frustrations experienced by S.H.M.O.s.

Their status has suffered all along from inadequate definition embracing, as it does, both part-time general practitioner and full-time hospital specialist. Most full-time hospital specialists have entered the grade as a step in the training ladder via senior house-officer, registrar, and senior registrar. Although almost all full-time S.H.M.O.s are doing consultant work when they apply for consultant posts, the strongest candidates against them are teaching-hospital senior registrars, lecturers, and research men. In numerous instances the S.H.M.O. fails to get the appointment.

It is extremely doubtful if any significant number of full-time S.H.M.O.s working as assistants in a specialty would wish to remain in that state. Not all will want to become departmental heads, but that should not prevent their reaching consultant status.

Much of the present difficulty might be resolved if the S.H.M.O., after four or five years' service, were given the right to make application to his hospital staff committee for a review of his grading. This review should be carried out by a committee of the regional board and the hospital concerned. The undue preference for academic distinction now shown by appointments committees can there be tempered by personal knowledge of the applicant's work and effectiveness in his hospital.

For the future, consideration might be given to the suggestion that no one be appointed consultant without having served as a S.H.M.O. for at least four years.

Peripheral hospitals can show that a 1 : 1 ratio of consultants to registrars is unnecessary and this should not be used as an argument against creating new consultants where needed.

The trained personnel to remedy the shortage of senior staff is available and with a little honesty all round the required establishment can be worked out.

S.H.M.O.

Appointments

DRAWNEEK, WALDERMAN, M.B. Lond., D.P.H.: M.O.H., Redditch, Worcestershire.

PHILLIPS, C. H., M.R.C.S., D.P.H.: M.O.H., Bromsgrove, Worcestershire.

The Hospital for Sick Children, Great Ormond Street, London:

BUCK, MAVIS, M.B. Lond., D.A.: junior resident anæsthetist.
GARRETT, KATHARINE R., M.B. Lond.: house-physician.
GLOVER, W. J., M.B. Belf., F.F.A. R.C.S., D.OBST.: resident anæsthetic registrar.
KOHORN, E. I., M.B. Camb., D.OBST.: house-surgeon.
LEES, M. H., M.B. Lond., M.R.C.P.: house-physician.
MARTINS, A. G. DA S., L.M. Lisbon: house-surgeon.

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[8] Keining, E., Weber, G. *Derm. Wschr.* 1956, 133, 393.
[9] Schwab, R., Fine, J., Mixter, W. J. *J. Amer. med. Ass.* 1937, 37, 1271.
[10] Fine, J., Hermanson, L., Frehling, S. *Ann. Surg.* 1937, 107, 1.

Obituary

GEORGE FREDERICK BUCHAN

M D Glasg, F R C P, D P H

Dr Buchan, whose death we announced last week, was medical officer of health for Willesden for thirty-five years But this formal description of his career is misleading, for it gives no idea of the extent of his influence on public-health thought and practice both inside and beyond this country

He was born at Kilmaurs near Kilmarnock, in 1878 and graduated M.B with distinction from the University of Glasgow in 1901 He at once decided to specialise in public health and the following year took the D P H He served his apprenticeship in his specialty in junior appointments in Birmingham and at Heston and Isleworth, and when in 1912 he became medical officer of health for Willesden, though he was still young in years he had a background of varied practical experience In those days Willesden still had areas of pleasant pasture and there was a forge in Neasden Lane The new M O H toured his district in a horse-drawn carriage The medical superintendent of the fever hospital visited his convalescent branch at Kingsbury on horseback The ambulances and school-buses were still drawn by horses The thirty-five years that Buchan spent at Willesden brought many changes The care of physically defective children of the maternity and child-welfare services were his special concern and the subject of many far-seeing reports to his council Willesden early offered immunisation against diphtheria to its school-children, home nurses to its invalids health centres to its families, a maternity hospital to its mothers Buchan was insistent that the agencies dealing with health and disease should be coordinated and his success in implementing this principle drew visitors from all over the world to Willesden He lost no opportunity to study work in other countries and his peace-time visits to the United States and Canada led to his being asked by the Canadian Wartime Information Board to visit the Dominion to tell the people there about Britain's health in war-time He was an honorary fellow of the Canadian and American public-health associations It was characteristic of his concentration on the future that when he retired in 1947 he closed his own record of his work at Willesden with the words "Little remains to be written but much has still to be done"

Elliott & Fry

But though Willesden was his parish his work was not circumscribed by its limits He lectured at Guy's Hospital, St Mary s Hospital, and the London School of Hygiene He took endless pains to arrange every detail of the programmes of the students sent to him at Willesden He examined for the Universities of Bristol and London He took a notable part in the revision of the curriculum for the D P H in 1946 He was a member of the Commission on Vaccination which sat from 1926 to 1930 and he was a member of the B M A. planning committee which reported in 1942 The Royal College of Physicians made him a member in 1927 and in 1933 he was one of the first medical officers of health to be elected to the fellowship For long he was also chairman of the council of the Royal Sanitary Institute, now the Royal Society for Health.

But his chief interest and perhaps the main channel of his influence was the Society of Medical Officers of Health He became treasurer in 1919 and laid down this office to serve as president in 1925, only to resume it Soon after the 1914–18 war he realised that if the expanding public-health service was to attract the right type of entrants, the conditions and remuneration of its appointments must be reconsidered, and for the next ten years he was the tenacious and moving spirit of the campaign sustained by the Society and the British Medical Association which ultimately led in 1929 to the recognition of the Askwith scale After Buchan retired from the treasurership of the Society in 1946 he continued to serve it as chairman of its council and in 1947 he was elected to its honorary fellowship Another task of his energetic retirement was the chairmanship of his local hospital management committee, and he conducted its business with his usual competence.

A L W, who for twenty years was associated with him in his maternity and child-welfare work at Willesden, writes

Buchan was a great teacher and trainer of medical administrators He drew a sharp line between administration and clinical medicine and did not expect his assistants to be expert clinicians nor his clinicians to dabble in administration It was the duty of his assistant medical officers to seek out those that appeared to require expert attention and to bring them before the appropriate consultant who attended regularly at his clinics and to see that the consultant's advice was carried out His medical officers were trained to be public health experts responsible for an area and he never approved of dividing them into M. and C W officers, school medical officers, and so on At this moment the most important measure to reduce maternal mortality is considered to be improvement in the standard of antenatal care Responsibility for seeing that a pregnant woman obeys instructions should rest on one person or clinic and the importance of following up defaulters is being stressed George Buchan stressed this in 1931 and any pregnant woman who failed to keep an appointment was visited the same day to find out the reason

Buchan was one of the clearest thinkers I have ever met However leafy the trees he saw nothing but the wood and not only steered a straight course through a problem but also convinced others without dominating them He had no use for woolly thinking yet he dealt with others whose brains were slower so gently that he rarely caused resentment

W J recalls that Buchan began his career among the giants of the public-health service

The two Hills, Bostock of Warwickshire and Eustace of County Durham Robertson of Birmingham, Hope of Liverpool, Shirley Murphy of the London County Council Newsholme of Brighton, and Newman of Finsbury to mention only a few were still in office Young though he was he soon took his place among them and proved himself of equal stature He held strong views regarding the status of the various kinds of health authorities and, indeed, of public health administration generally, and he was in no doubt that an area such as Willesden which he served with distinction for thirty five years, was well able to look after its own affairs without any supervision from a county council There was great competition among young people for appointments on his staff, and most foreign visitors studying British methods of public health administration were directed to Willesden where they found much to interest them In particular, the Ministry of Health made frequent use of his services and many a tentative official scheme was discussed or given a trial in Willesden He was a fluent speaker and a most determined advocate of any cause he had at heart He and the late Charles Porter of Marylebone together with James Fenton of Kensington (happily still with us) were a most formidable trio—not that they always agreed, but if they did they usually carried all before them

George Buchan was a striking figure—tall always immaculately turned out, and a lover of the good things of life He was a delightful and generous host If he promised to do anything he always did it in the appointed time and to the very best of his ability He was completely reliable Many members of the public-health service all over the world whom he had helped in one way or another though they will mourn his death, will be proud to have known and worked with him His elder brother, John Buchan of Bradford no less outstanding a character, survives him

Dr Buchan leaves a widow and a daughter

Births, Marriages, and Deaths

BIRTHS

SUDBURY —On June 9 at Brentwood to Mary (nee Sadler), wife of Dr J R. Sudbury—a son

DEATHS

FISHER —On June 4 at the Memorial Hospital Chipping Norton Oxford Donald Fisher M B

Notes and News

MEDICINE AND LETTERS

A collection of essays lately published[1] is united by the belief that, in medical writing, clear thinking must precede simple, concise exposition Dr R L Cecil discusses the editing of a medical textbook, and makes the point that editorship, as well as authorship, is tending to become multiple Plain words are called for by Dr Morris Fishbein and Dr Joseph Garland Dr Douglas Guthrie writes on medical history, and Dr J F Fulton on bibliography Dr F Marti-Ibanez gives an account of some famous men who combined the professions of medicine and letters Some essays are instructive, others discursive, all will interest those who know (or need to know) how great is the need for lucidity, precision, and conciseness in medical writing

NUTRITION OF URBAN CHILDREN

A joint committee on health policy of W.H O and Unicef has reported that the health of city children in rapidly growing countries is often poor The new populations have often crowded into fringe areas where sanitation is worse than in the villages The mothers acquire a harmful modicum of sophistication which leads them to abandon traditional ways of caring for children though they cannot follow modern ways In an Indian study infections and deficiency diseases were *found to* be commoner in urban than rural children

University of Cambridge

Lord Adrian, O M, has been elected vice chancellor of the university for 1957 58

On June 1 the following degrees were conferred

M D—G A Gresham, M C Joseph J J McMullan, David Scott

M B, B Chir—*C U Abengowe, *J P Clayton, *R M Pollock

* By proxy

University of London

Mr M J H Smith, PH D, F R I C, senior lecturer in chemical pathology at King's College Hospital Medical School, has been appointed to the university readership in chemical pathology at the school

Lung Function in Respiratory Illness

A postgraduate course on this subject will be held at Sully Hospital, Penarth, Glam, from Sept 9 to 13 Further particulars may be had from Dr Harley Williams, Tuberculosis Educational Institute, Tavistock House North, Tavistock Square, London, W C 1

Conference on Adoption

The standing conference of Societies Registered for Adoption s to be held on Oct 17 and 18 at the Church House, Dean's Yard, London, S W 1 Further particulars may be had from the hon secretary of the conference, Gort Lodge, Petersham, Surrey

Ciba Foundation

The first of the foundation's lectures on research on ageing will be given by Dr Nathan W Shock, chief of the gerontology branch of the National Institutes of Health, Baltimore, on Tuesday, July 9, at 5 P M, at the Zoological Society, Regent's Park, London, N W 1 He will speak on age changes in physiological functions in the total animal Admission will be by ticket only, obtainable free from the assistant secretary of the foundation, 41, Portland Place, W 1

College of Physicians and Surgeons of South Africa

In October this college will hold its first examinations for its fellowships in surgery, medicine, and obstetrics and gynæcology The South African Medical and Dental Council have in principle recognised these fellowships as "*additional qualifications*" Their titles will be F C S (S A), F C P (S A), and F C O G (S A) The council has approved the inclusion in the college of a division of obstetrics and gynæcology, equal in standing with the divisions of surgery and medicine It is intended to alter the title of the college to give effect to this change

National Hospitals for Nervous Diseases

Sir John Woods has been appointed chairman of the board of governors of the National Hospitals for Nervous Diseases, London

Poliomyelitis Vaccine for Malta

The minister of health for Malta has announced (*Times*, June 6) that the British Government has agreed to make poliomyelitis vaccine available for the island Enough vaccine to vaccinate 5000 children has been received and the same amount will now be supplied monthly

World Health Organisation

On June 15 a building erected by the *Danish* government in Copenhagen will be formally placed at the disposal of the World Health Organisation The building will house the regional office for Europe, which has hitherto been housed in the Palais des Nations in Geneva

Success of Campaign against Bovine Tuberculosis

Speaking at the Royal College of Veterinary Surgeons on June 5 (see *Times*, June 6) Mr D Heathcoat Amory, Minister of Agriculture, said that he hoped Britain would be free of bovine tuberculosis within five years Already nearly two thirds of the dairy herds in Britain were artificially inseminated and 90% of the population drank tuberculin tested pasteurised, or sterilised milk

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Diary of the Week

JUNE 16 TO 22

Monday, 17th

Postgraduate Medical School of London Ducane Road, W 12
4 P M Dr William Evans Pulmonary Heart disease

Institute of Obstetrics and Gynæcology
3 P M (Queen Charlotte's Hospital, Goldhawk Road, W 6) Prof W C W Nixon Disordered Uterine Action
4 30 P M Prof James Walker Fœtal Anoxia

University of Liverpool
5 15 P M Prof Ernest Sachs (Washington University) Sir Victor Horsley—Pioneer of Neurosurgery

Tuesday, 18th

Institute of Dermatology, Lisle Street, W C 2
5 30 P M Dr H T H Wilson Erythroderma

Wednesday, 19th

Royal Society of Medicine 1, Wimpole Street, W 1
2 15 P M *Proctology* Dr Cuthbert Dukes, Mr Lawrence Abel Mr W B Gabriel, Mr O V Lloyd Davies Mr C N Morgan Major Surgery in Carcinoma of the Rectum with or without Colostomy excluding the Anal Canal and including the Rectosigmoid

Institute of Diseases of the Chest, Brompton S W 3
5 P M Dr R V Gibson Pulmonary Heart disease

Institute of Dermatology
5 30 P M Dr Arthur Tickner Epidermal Proteins

Thursday, 20th

Institute of Neurology, National Hospital Queen Square, W C 1
5 30 P M Prof K B Corbin (Minnesota University) Analysis of 100 Cases of Protruded Cervical Discs with Compression of a Single Root

Royal Society of Tropical Medicine and Hygiene, 26, Portland Place, W 1
7 30 P M Dr A J Haddow The Work of the Virus Research Institute at Entebbe

Hypnotherapy Group
8 P M (1 Wimpole Street, W 1) Dr George Newbold Dr Denys Kelsey, Dr Gordon Davies, Dr Gordon Ambrose Brains Trust

Nuffield Orthopædic Centre, Wingfield Morris Orthopædic *Hospital Oxford*
8 30 P M Mr H Jackson Burrows West Indian Orthopædics from the Touchline

Friday, 21st

Postgraduate Medical School of London
10 A M Mr G H Macnab Intestinal Obstruction in the Neonatal Period
4 P M Dr Malcolm Thompson Principles and Practice in the Management of Rheumatoid Disease

St Mary's Hospital Medical School Paddington, W 2
5 P M Sir Heneage Ogilvie Shock

Faculty of Radiologists
11 A M (Royal College of Surgeons, Lincoln's Inn Fields W C 2) *Diagnosis Section* Dr F L Ingram *Differential Diagnosis* of Tumours of the Jaw Dr J H Middlemiss Tropical Radiology *Therapy Section* Discussion on Genetic Leukæmogenic Hazards of Radiotherapy
4 30 P M Sir Arthur Porritt Surgery or Science in Breast Cancer (Skinner lecture)

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[1] Medicine and Writing Edited by Dr F Marti Ibanez M D International Symposia, no 4 M D Publications Inc, 30 East 60 Street, New York 22, N Y, U S A New York. Pp 65

ATRIAL SEPTAL DEFECT AND ITS SURGICAL TREATMENT

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THORACIC SURGEON

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E M M Besterman
M A , M D Camb , M R C P
SENIOR REGISTRAR

MIDDLESEX HOSPITAL

Atrial septal defect (A S D) is the most frequent single congenital malformation of the heart encountered in clinical practice, yet its clinical diagnosis has only been accomplished during the past twenty years In 1875 Rokitansky gave a masterly account of the pathological anatomy of A S.D and its embryological basis, distinguishing two main anatomical forms—namely, defects of the septum primum and of the septum secundum Moreover, he stated explicitly that, in certain septum-secundum defects, the inferior vena cava opened partly or mainly into the left atrium, a fact which has been much ignored until surgeons became aware of it quite recently The association of A S.D with mitral stenosis was described by Corvisart (1811) and later by Lutembacher (1916), whose name is now linked with this combined lesion

Little was known of the clinical signs of A S.D until Assmann (1921) first identified its radiological features and thus paved the way to its clinical diagnosis When Roesler, in 1934, analysed 62 recorded necropsy cases, only 1 of them had been correctly diagnosed during life (by Maude Abbott) Within the next few years, the clinical diagnosis was being made with assurance (Bedford, et al 1941), but anatomical confirmation of the diagnosis, in this relatively benign lesion, was of necessity infrequent, and its distinction from various forms of pulmonary hypertension remained difficult The advent of cardiac catheterisation has now provided a means of verifying the diagnosis of A S D during life, and of elucidating its pathological physiology

Thus the stage was reached when surgical correction of A.S D could be envisaged, and in 1947 Cohn suggested suturing the right atrial wall to the margins of the defect In 1948 Murray, after experiments on dogs, closed an A S.D in a child by external suturing and in 1952 Bailey introduced the operation of atrio septopexy Another method of closing the defect without opening the heart has been introduced by Sondergaard and modified by Björk and Crafoord (1953), and by Edwards et al, (1955) Direct suturing of the A S D by opening the heart was introduced by Gross et al (1953) using an " atrial well," but this did not allow visual control Closure of the A S D under direct vision with the heart open was first accomplished by Lewis and Taufic (1953) employing hypothermic anæsthesia and this method has since been developed by Swan et al (1953 1955) and employed by Brock and Ross (1955) in this country and by Derra (1956) in Germany

To anyone who has studied the anatomical complexities of A.S D the advantages of direct vision must seem decisive, and now that hypothermic anæsthesia has become safe (Swan and Blount 1956) we believe that open heart surgery is the method of choice in the closure of uncomplicated A S D s

The indications for surgical treatment have to be considered in relation to the anatomical variety of the A S D and to the clinical findings and complications Therefore we shall briefly review the clinical features and complications encountered in 100 consecutive cases of A S D which we have investigated since commencing its surgical treatment at the Middlesex Hospital a year ago

Anatomy of Atrial Septal Defect

It is essential to relate the septal defect to the main anatomical landmarks visible within the right atrium—namely, the two caval openings, the eustachian valve the orifice of the coronary sinus and the tricuspid valve Unfortunately, all of these can rarely be identified in published pathological figures but Rokitansky's exquisite illustrations are an exception and his book is still our best guide to the anatomy of A S D However a purely embryological classification is inadequate for the surgeon, and the following anatomical classification is based on examination of pathological specimens on published necropsy findings, and on the surgical experience of ourselves and others

Atrio-ventricular defects (Persistent ostium primum , endocardial cushion defect , partial common atrio-ventricular canal) (Fig 1B)—This form of A S D overlies the tricuspid orifice and is crescentic in shape, its base being formed by the upper part of the ventricular septum and the attached mitral and tricuspid valves The aortic leaflet of the mitral and the septal leaflet of the tricuspid valve are often cleft and malformed, causing valvular incompetence An associated ventricular septal defect is common, as Rokitansky showed, and there may be a common atrio-ventricular (A-V) canal

Fossa-ovalis defects (Persistent ostium secundum)—The normal fossa ovalis is bounded above by a muscular annulus and its floor is covered by a membrane or so called valve which may be partly or wholly defective, or fenestrated Small defects occupy the upper part of the fossa ovalis but larger defects may extend to the orifice of the inferior vena cava in 8 of Rokitansky's cases the inferior vena cava opened either into both atria equally or mainly into the left atrium When the A S.D lies astride the inferior caval orifice its anterior limb may be continuous with the eustachian valve which thus forms the lower margin of the defect (fig 1E) In such cases, if the anterior and posterior margins of the defect are sutured together at operation, the vena cava will be shut off from the right atrium and so will communicate only with the left atrium The following forms of fossa ovalis may be recognised

(a) Defects of the upper part of the fossa ovalis below the annulus (widely patent foramen ovale) (fig 1C)

(b) Large fossa ovalis defects surrounded by a complete margin of atrial septum, and separated from the inferior caval orifice (fig 1D)

(c) Defects astride the inferior caval orifice which thus opens into both atria or mainly into the left atrium if there is a large eustachian valve (fig 1E) Occasionally small defects overlie the caval orifice leaving the fossa ovalis intact (Hickie 1956)

(d) Large fossa ovalis defects in which the posterior septal rim is lacking or rudimentary, so that the right pulmonary veins communicate virtually with both atria (fig 1F)

Superior caval defects (Sinus-venosus defect , high defect) (Fig 1G)—These are located immediately below and adjacent to the orifice of the superior vena cava, and above and separate from the fossa ovalis which may be intact or may contain a second defect Anomalous right pulmonary veins may open into the superior vena cava or into the right atrium adjacent to the septal defect

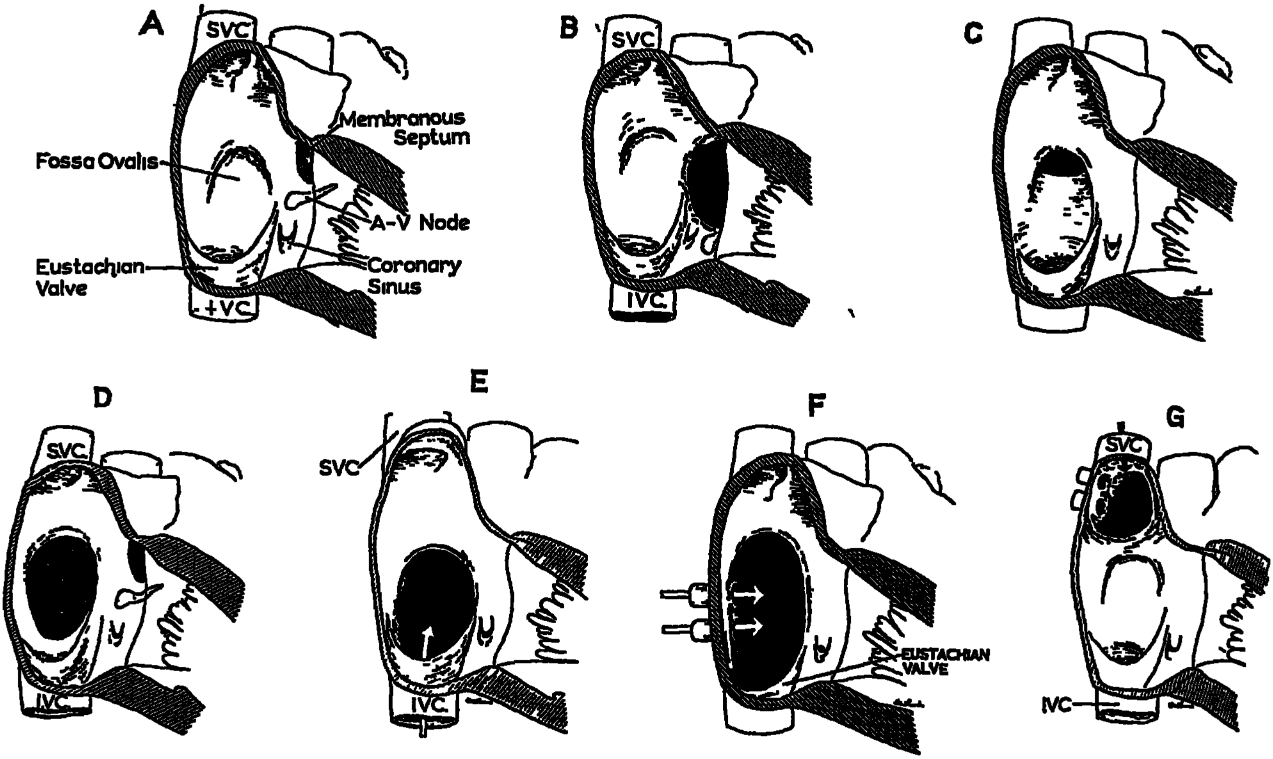


Fig 1—Anatomy of atrial septal defect, viewed from right atrium

(A) Normal atrial septum (B) A V type of defect (C) Widely patent foramen ovale (D) Fossa-ovalis defect with complete septal rim (E) Low fossa ovalis defect astride inferior caval orifice with large eustachian valve (F) Large fossa ovalis defect without any posterior septal rim, pseudo anomalous right pulmonary veins (G) Superior caval type of defect, showing entrance of right upper pulmonary veins

This type of A S D is probably less common than the A-V type, it was found once in 10 necropsies reported by one of us and was diagnosed in 3 of our 100 clinical cases It has been fully described by Hudson (1955), by Lewis et al (1955), and by Ross (1956)

Combination of defects—The three main anatomical types may occur in combination, thus an A V defect or a superior caval defect may be associated with a fossa-ovalis defect, or a single large defect may extend from the superior to the inferior caval orifice

Physiology

In uncomplicated cases, blood is shunted from the left to the right atrium so that the output of the right ventricle is increased, and the pulmonary blood flow usually reaches two to four times the systemic flow which is normal or slightly reduced As long as the vascular resistance in the lungs remains normal, the pulmonary arterial pressure does not rise appreciably unless the pulmonary flow is very large, when a moderate degree of hyperkinetic pulmonary hypertension results Obstructive pulmonary hypertension, due to an increased resistance in the small arteries, or to thrombosis of the larger arteries, or both, occurred in 15% of our cases As the vascular resistance rises, the shunt through the A S D is reduced, balanced, or sometimes reversed A bidirectional or reversed shunt is recognised by the appearance of central cyanosis, by the clinical signs of pulmonary hypertension, and by a reduced arterial oxygen saturation

Cardiac catheterisation was performed in 87 of our 100 cases, including all those submitted to surgery The diagnosis of A S D was confirmed by (*a*) a significant increase in oxygen saturation of blood samples from the right atrium and beyond compared with those obtained from the superior vena cava, (*b*) easy and usually repeated passage of the catheter from the right into the left atrium through the septal defect, accomplished in 50 cases

Estimation of the actual shunt through the defect must be regarded at the best as an approximation In 83 cases, the calculated pulmonary blood-flow was less than twice the systemic in 9, twice or more in 39, thrice in 21, and four times or more in 5 cases In 9 cases the shunt was balanced or reversed, and the arterial oxygen saturation reduced (63–89%) The pulmonary arterial pressure, recorded in 85 cases, was below 30 mm systolic in 59 cases, 30–50 mm in 15 cases, and over 50 mm in 11 cases in which the vascular resistance was elevated Anomalous pulmonary veins entering the right atrium or superior vena cava, or both, were demonstrated by catheterisation in 10 cases (11%)

Incidence

Wood (1956) found A S D in 18% of 900 cases of congenital heart disease investigated, of which it was the most frequent single lesion In regard to sex incidence, females predominated and constituted 69% of our cases In the past, A S D was not often diagnosed until adult life, but today it is more frequently recognised in childhood often at routine radiography, and 57% of Wood's patients were under twenty A recent paper entitled Atrial Septal Defect in the Aged (Coulshed and Littler 1957) indicates that it is occasionally compatible with longevity The ages of our patients were

Age (years)	1–9	10–19	20–29	30–39	40–49	50–59	60–69
Cases	11	23	28	12	13	9	4

Clinical Diagnosis

The usual clinical signs of A S D are now well established (Bedford et al 1941 Barber et al 1950, Leatham and Gray 1956) and therefore need only be enumerated briefly The cardiac impulse is of right ventricular type and often displaced to the left, there is a systolic lift over the outflow tract of the right ventricle and pulmonary artery, and in 20% of our cases there was a pulmonary systolic thrill The stethoscope reveals a pulmonary systolic murmur loudest in mid systole, sometimes a systolic ejection sound, and an obviously split second sound which varies little with respiration A diastolic murmur of relative pulmonary incompetence was heard in 20% of our cases and occurred when the pulmonary artery was grossly dilated or when there was pulmonary hypertension A short delayed tricuspid diastolic murmur was present in over half of our cases, and is due to an increased flow through the tricuspid valve The pulmonary systolic murmur is often audible at the apex The pulse is small or normal in volume, and the blood-pressure normal or rather low

Radiological findings include enlargement of the right atrium and ventricle, dilatation of the pulmonary trunk and main branches, and pulmonary plethora The aorta is usually small and the aortic knuckle may be invisible in the anterior view Exaggerated pulsation of the right ventricle and pulmonary trunk, sometimes accompanied by a hilar dance, is valuable evidence of a large shunt Calcification of the hilar branches was seen in 4 of our cases and in 3 a dense immobile right branch indicated thrombosis

The electrocardiogram showed partial or complete right bundle-branch block in 72 cases, and right ventricular hypertrophy without bundle-branch block in 18 cases In 8 cases the electrocardiogram was unusual, showing left axis deviation in 7, and right axis deviation combined with left ventricular hypertrophy in the chest leads in one case In 2 cases the electrocardiogram was normal

Clinical Diagnosis of Atrioventricular (Ostium primum) Defects

An A-V type of A S D may be associated with malformed mitral and tricuspid valves, with a ventricular septal defect, or with a common atrioventricular canal, and it is mainly by these complications that it can be recognised Its surgical repair is hazardous and usually needs more time than is available under hypothermia, so that its clinical recognition has become a major diagnostic problem

The A-V defect is not common, for it was found only once in 10 necropsies by Bedford et al (1941), and in 5 cases, verified by operation or necropsy, out of 85 cases investigated by Blount et al (1956), and its incidence at operation in America has been estimated at 10–15% (Brandenburg and DuShane 1956) We made the diagnosis of an A-V type of defect in 13 of our present 100 cases, and so far we have successfully excluded it in all cases submitted to surgery

Generally the heart enlarges early, symptoms appear in childhood, and pulmonary hypertension is common Those with a common A V canal usually die in infancy or childhood, but those with less complex types of lesion may attain adult life Rogers and Edwards (1948) mention 5 patients who survived the age of thirty, Bedford et al (1941) a patient aged forty four, and Cahen et al (1952) one aged forty-nine, and one of Rokitansky's attained the age of sixty one So an A-V type of defect cannot be excluded by age

The diagnosis has been discussed by Cahen et al (1952), by Blount et al (1956), by Brandenburg and DuShane (1956), by Toscano Barbosa et al (1956), and by Wakai et al (1956) In any case of A S D, an A V type may be suspected on one or more of the following grounds (1) unusual cardiac enlargement in childhood, (2) physical underdevelopment and mongolism, (3) pulmonary hypertension occurring below the age of twenty, (4) pansystolic murmur of mitral (or tricuspid) incompetence, (5) evidence of left ventricular hypertrophy in the electrocardiogram, (6) a left to right shunt at both atrial and ventricular levels, (7) bacterial endocarditis, (8) complete heart block

The most characteristic clinical finding is a loud pansystolic murmur, sometimes with a thrill, heard at the apex or left sternal edge, and due to mitral or tricuspid incompetence, or possibly to a ventricular septal defect There may be both systolic and diastolic murmurs, in which case mitral stenosis is simulated the term *faux syndrome de Lutembacher* has been coined (Cahen et al 1952) A left ventricular thrust may be appreciable at the apex-beat Bacterial endocarditis occurred in 1 of our cases and in 3 of those analysed by Rogers and Edwards (1948), whereas it is exceptionally rare in fossa ovalis defects

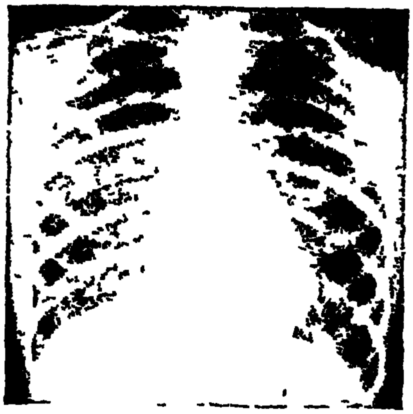


Fig 2—Radiograph showing localised dilatation of superior vena cava in case of high atrial septal defect.

The electrocardiogram showed *left* axis deviation and horizontal heart pattern in 7 cases, in 5 of which there was also partial right bundle-branch block in the chest leads In 2 cases the chest leads showed left ventricular hypertrophy as reported by Blount et al (1956) A prolonged P–R interval is common, left bundle-branch block and complete heart-block have also been reported (Cahen et al 1952)

Cardiac catheterisation may suggest a low atrial shunt, a shunt at both atrial and ventricular levels, or (we believe) a shunt mainly at ventricular level The catheter may pass readily into the left ventricle and its track through the A S D is said to be peculiar, though this should be interpreted with caution

Diagnosis of Superior Caval Defects

Radiographs may show a localised dilatation of the superior vena cava just above the right atrium (fig 2) Cardiac catheterisation may show arterialised blood in the superior vena cava compared with samples from the innominate vein, or samples from the upper part of the right atrium may be more oxygenated than those from the lower part Sometimes the catheter can be passed directly from the superior vena cava into a pulmonary vein (fig 3)

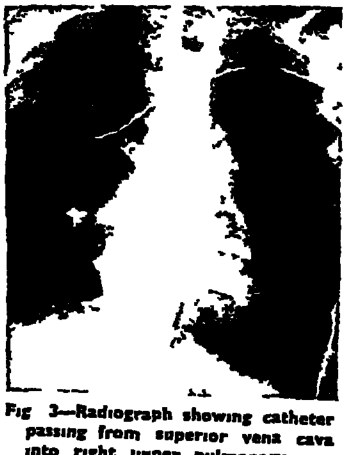


Fig 3—Radiograph showing catheter passing from superior vena cava into right upper pulmonary vein in case of high atrial septal defect

Complications of Atrial Septal Defect

Obstructive pulmonary hypertension occurred in 15 of our

100 cases, in 7 of which the shunt was reversed, in 3 balanced, and in 5 from left to right 2 with thrombosis and calcification of large pulmonary branches were not catheterised, and in another cyanosed patient the diagnosis was made by angiocardiography The pulmonary systolic pressures ranged from 50 to 118 mm Hg, and the vascular resistances from 3 5 to 38 units (1 unit = 80 dynes per sec per cm^{-5}) All showed clinical signs of pulmonary hypertension 2 patients were under twenty years of age and both probably had A-V defects 4 were between twenty and thirty, 3 between thirty and forty, and 6 over forty years Only 1 patient was submitted to surgery, namely a woman aged forty with a pulmonary systolic pressure of 75 mm and a vascular resistance of 3 5 units, but there was a 4 1 shunt from left to right and the hypertension was mainly hyperkinetic

Pulmonary stenosis —Wood (1956) found mild pulmonary stenosis in 10–15% of all cases of A S D , and it was diagnosed clinically or suspected from catheter findings in 11 of our 100 cases, in 2 of which the diagnosis was confirmed at operation However, we are sceptical of the diagnosis of mild pulmonary stenosis, based on a pressure gradient across the pulmonary valve, in cases of A S D with a large pulmonary flow when a condition of "relative stenosis" exists

Mitral stenosis —There is much discrepancy between post mortem statistics and clinical or surgical experience in regard to the incidence of mitral stenosis in A S D Thus mitral stenosis occurred in 4 of 10 necropsies but in only 4 of 43 clinical cases of Bedford et al (1941), and Burrett and White (1945) estimated its incidence as over 50% of all cases of A S D at necropsy It was diagnosed on clinical or other grounds in 6 of our 100 cases of A S D , in 3 of which the diagnosis was confirmed at operation

Atrial fibrillation was present in 10 of our cases, in 1 of which it developed after operation 5 of them had mitral stenosis, and all were over the age of forty except 1 with mitral stenosis aged twenty-four

Anomalous pulmonary veins opening into the right atrium or superior vena cava were recognised in 10 of our 100 cases at catheterisation and once at operation In 1 case where a right pulmonary vein was thought to open into the right atrium at catheterisation, it was found at operation to be just on the left side of the small posterior septal margin of the A S D It is especially in the high superior caval defects that anomalous right pulmonary veins are of surgical importance We are not considering here total anomalous pulmonary venous drainage which, of course, is invariably associated with an A S D

Clinical Course

According to post mortem statistics, the average age at death is between thirty six and thirty seven years (Burrett and White 1945), over half surviving the age of forty In A S D complicated by mitral disease, Bouvrain and Sibille (1954) give the average age at death as forty years

Although A S D is a congenital lesion, its consequences are acquired and develop gradually over the course of years as a result of the right heart being overloaded In uncomplicated cases, cardiac symptoms are usually mild or absent up to the age of twenty, after which some cardiac enlargement is common, and a grossly enlarged heart was found in 20% of our cases aged between twenty and forty, and in 60% of those over forty

Congestive heart failure occurred in 15 cases, 3 of them under thirty, and the remainder all over forty 5 of these have already been operated on, and another may become fit for surgery, but the rest are unsuitable because of their age and general condition, or of complications

To summarise, serious cardiovascular changes begin to develop after the age of twenty, and after the age of forty gross cardiac enlargement is present in over half

Indications for Surgical Treatment

With a heart lesion whose course is benign up to the age of twenty and sometimes even up to the age of forty the indications for surgical treatment are obviously related to the operative risk Wood (1956) expresses this view as follows "Until the mortality is under 5%, uncomplicated cases with 2 1 shunts should certainly be left alone" Accepting this view, we believe that today the operative mortality in uncomplicated cases should not exceed 5% at a centre dealing with a large number of cases and where a safe hypothermic technique is in routine use

It is true that published statistics indicate an overall operative mortality of about 10% for fossa ovalis defects, but these statistics are already out of date, and in properly selected cases the operation has now become far safer In A-V defects, of course, the operative mortality is much higher (probably over 50%), and we have not attempted to close them under hypothermia

The proper time to close an A S D is surely before the right ventricle and pulmonary vasculature have become irreversibly damaged, so that normal function may be restored to a relatively intact heart We believe, therefore, that uncomplicated fossa-ovalis defects with a shunt of 2 1 or more should be closed as soon as the diagnosis is established and preferably before the age of twenty, even in the absence of cardiac symptoms In practice, we are often faced with the problem of older patients with advanced heart disease, or even heart failure, and these patients have to be operated on unless there are contra indications to surgery

Mitral stenosis is no contra indication to closure of an A S D provided that the stenosis is relieved at the same time by valvotomy, and we have performed this combined operation in 3 cases with excellent results Slight pulmonary stenosis is likewise no bar to closing an A S D , and if necessary a valvotomy can be done at the same time

Pulmonary hypertension of hyperkinetic type, due to a large flow and without a seriously elevated vascular resistance, is no contra indication, but obstructive pulmonary hypertension is another matter When the shunt is balanced or reversed, closure of an A S D can only do harm Even when the shunt is still from left to right, closure of an A S D in the presence of serious pulmonary vascular disease removes the safety-valve action of a potential right-to left shunt during exertion and virtually reproduces a state of primary pulmonary hypertension Surgical experience indicates that closure of an A S D complicated by obstructive pulmonary hypertension is hazardous (Bolton et al 1957, Blount, personal communication), and we believe that the reward is unlikely to be great When an A S D is associated with systemic hypertension, as happens occasionally in older patients, its closure is likely to lead to left heart failure and is therefore, we believe, contra indicated

The A-V type of A S D is a complex anatomical lesion and its surgical repair is not only hazardous but must usually require more time than is available under hypothermia Atrio-septopexy has proved unsuccessful in this type of defect (Bolton et al 1957), so its closure requires open heart surgery by means of an artificial circulation Closure of high superior caval defects under hypothermia has been described (Lewis, et al 1955, Derra 1956) but we have not yet attempted it

To sum up, our contra-indications to closing an A S D under hypothermia are at present (1) A V type of defect, (2) reversed shunt with cyanosis, (3) obstructive pulmonary hypertension with high vascular resistance, (4) systemic hypertension, and (5) advanced age and poor general condition On one or more of these grounds 39 of our 100 cases of A S D were rejected as unsuitable for surgery

Surgical Experience

Closure of an A S.D by open heart surgery under hypothermia has been performed during the past year at the Middlesex Hospital in 40 patients (28 female and 12 male) aged six to fifty-five years

Age (years)	1–9	10–19	20–29	30–39	40–49	50–59
Cases	6	8	16	3	6	1

The heart was grossly enlarged (cardio-thoracic ratio over 60%) in 8 cases, considerably enlarged in 10 cases, and in the remainder moderately or slightly so, the right atrium being mainly involved 5 patients had congestive failure before operation, and 3 had atrial fibrillation Shunts, calculated in 38 cases, were less than 3 1 in 21 cases, 3 1 or more in 14, and 4 1 or more in 3 The pulmonary arterial systolic pressure was normal in 32 cases, 30–50 mm in 6 cases, and 75 mm in 1 case The pulmonary vascular resistance was normal in all but 2 cases where it was slightly elevated

All those submitted to operation had fossa-ovalis defects separated from the tricuspid valve, though some very large defects extended beyond the normal confines of the fossa ovalis, reaching the inferior caval orifice in 9 cases, and also the superior caval orifice in 2 There was no posterior septal residue in 2 cases

Hypothermic Anæsthesia

This was administered by Dr Sellick in all cases employing surface cooling and following the method developed by Virtue in Swan's clinic, with certain modifications (Sellick 1957) The important points in our technique are that an œsophageal temperature of 30°C at the time of circulatory arrest is regarded as ideal, and that rewarming by plastic water blankets is started as soon as the patient leaves the cold bath This degree of cooling permits circulatory arrest for at least seven minutes with safety and probably for a maximum period of ten minutes Neostigmine is injected into the coronary circulation via the proximal aorta before opening the heart and this we believe to be an important protection against ventricular fibrillation

During hypothermia the heart-rate was usually slow (about 40) Atrial arrhythmias were common and complete heart-block was sometimes encountered, but ventricular fibrillation occurred only twice and was due in both cases to technical errors In one it was brief and responded at once to electrical defibrillation, in the other it occurred when the heart was open and the circulation arrested, so that it could not be dealt with until closure of the A S D had been completed when it responded to electrical defibrillation combined with transfusion of blood directly into the right ventricle

Surgical Technique

The patient is removed from the bath after cooling to 31–32°C (œsophageal temperature) and placed supine on the operating-table, lying on and also covered by plastic water blankets through which water at 40°C is circulated by a pump Even with immediate rewarming, the temperature continues to drop another 0 5–2 C, and the maximum drop to about 30°C is timed to coincide as near as possible to the period of circulatory arrest Lower temperatures are unnecessary and predispose to dangerous ventricular arrhythmias

We have largely followed the technique introduced by Swan of suturing the defect under direct vision through the open right atrium during temporary arrest of the circulation Simple suture is sufficient to maintain closure; for, once the shunt has been eliminated, the tense and distended right atrium becomes retracted and flaccid so that the suture line is not under tension or likely to cut out

Operation

A bilateral thoracotomy is used for exposure of the heart A long transverse incision is made from one axilla to the other across the chest in the submammary region. The skin and underlying muscles are retracted to expose the fourth intercostal spaces and the pleural cavities are opened through these intercostal muscles Internal mammary arteries are secured between ligatures and the sternum cut across before opening up the incision with rib spreaders at each end of the wound.

The extrapericardial fascia and fat is divided and dissected free to the upper limit of the pericardium which is then opened along its left border and across the lower border as far as the level of the right phrenic nerve This triangular flap of pericardium is retracted to the right and sutured over the lung The superior vena cava is then encircled by a tape below the level of the azygos vein, a procedure which involves incision of a posterior pericardial fold which lies just in front of the right pulmonary artery The inferior vena cava is similarly controlled by a tape after incision of the pericardium where it is reflected on to the diaphragm The tapes are threaded through lengths of rubber tubing which, when pressed downwards, can act as tourniquets A special clamp is then placed with one blade through the transverse sinus and the other lying across the base of the pulmonary artery and the aorta (fig 4) A small incision is made into the lateral wall of the right atrium and the bare index finger inserted into the heart The edges of the defect are explored and the presence and size of the eustachian valve estimated The finger is passed through the defect into the left atrium where the mitral valve can be palpated, should it be stenosed valvotomy is carried out Next, the finger is passed through the tricuspid valve and through the right ventricle into the pulmonary outflow tract In nearly every case it is possible to feel the pulmonary valve itself and estimate any stenosis The atrial wall is clamped as the finger is withdrawn and the incision enlarged within the confines of the clamp to 2½–3 inches.

The heart is occluded from the circulation by tightening the tape tourniquets completely on both venæ cavæ, after which it is allowed to beat 10–20 times to empty itself of blood before the arterial clamp across the aorta and pulmonary artery is closed Neostigmine, 0 03 mg. per stone (14 lb) body-weight, is then injected into the aorta proximal to the clamp so that it reaches the coronary circulation, and the clamp is then shifted downwards

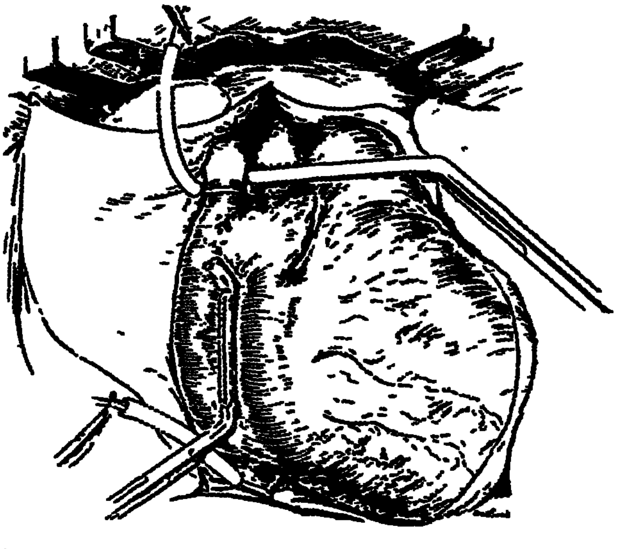


Fig 4—Method of arresting the circulation by tape tourniquets round both venæ cavæ and a clamp across aorta and pulmonary artery. Incision in right atrium controlled by clamp

to occlude the orifices of the coronary arteries The right atrial clamp is now removed and a *quantity of blood* gushes out which is sucked away while the edges of the atrial incision are retracted Continuous suction is required to keep the atrium free of blood so that the septum is visible The lower margin of the defect is then picked up by a suture (000 plastic or silk suture), and, using traction on this first stitch, the suture is continued upwards to the upper end of the defect, any bands or Chiari network can be included in the suture The end of this continuous suture is tied to a separate suture and two or three small interrupted reinforcing stitches are added

Before closure of the defect is completed, the anæsthetist inflates the lungs and distends the left atrium with blood, so excluding all air from the left heart The right atrium is then filled with Ringer's solution and one of the caval tourniquets is released As the right atrium quickly fills with blood, the edges of the incision are held upwards and clamped when all air has been expelled The second caval tourniquet is released and the clamp on the great arteries is removed The heart, which has been blue for some minutes, becomes pink in patches and as the circulation is restored rapidly regains its normal colour The incision in the right atrial wall is closed by continuous suture The pericardium is loosely closed and the chest incision is sutured after insertion of closed drainage tubes into each pleural cavity

The operation in most cases has been straightforward and the defect has usually been closed in four to five minutes Difficulties may occur in the case of low defects astride the inferior caval orifice without any lower septal rim If the defect is closed from above, a lower border or ridge is produced which overlies the caval orifice so that it communicates with both atria The lower edges of the defect must be sutured to the posterior margin of the caval orifice or to the adjacent floor of the left atrium so as to direct the caval flow into the right atrium Another problem arises if the lower border of the defect is formed by a large eustachian valve which is continuous with the anterior limb of the defect and merges into the posterior atrial wall (fig 1D) If the valve is included in the suture line, the defect will have been closed but the inferior vena caval flow will be directed entirely into the left atrium, causing central cyanosis

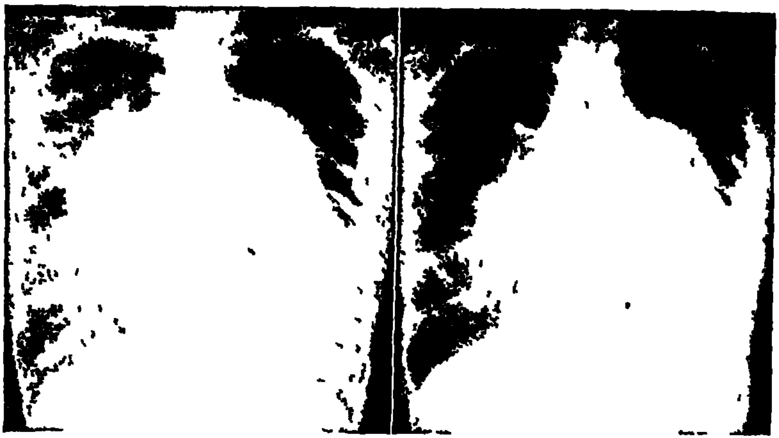
This happened in 3 of our cases

In the first, nothing unusual was noticed until some time after operation when central cyanosis developed

In the second, cyanosis was recognised on completion of the operation, the chest was reopened, and the circulation was again arrested for four minutes at 33°C On reopening the right atrium, the eustachian valve was found to have been *sutured into the edges of the defect* The stitches were removed, the valve cut across, and the defect was then reclosed

In the third case, after closure of a very large defect a postoperative examination of the arterial blood showed a reduced oxygen saturation suggesting that some of the inferior caval blood was entering the left atrium A second operation under hypothermia was undertaken later, and the right atrium was explored It appeared that the inferior vena cava had not been excluded from the left atrium, and the lower end of the defect was resutured However cyanosis persisted and seemed to be relieved by temporary occlusion of the vena cava The inferior vena cava was therefore divided and transplanted into the anterior wall of the right atrium, but the patient's condition *deteriorated and death resulted* At *necropsy*, it was found that the upper sutures had stenosed the superior vena caval orifice and directed it partly into the left atrium

In order to overcome some of the technical difficulties in cases of *low* defects, an obturator has been designed for insertion into the inferior caval orifice, which is thus held open instead of being buckled or narrowed by the tape *tourniquet* The *eustachian* valve is held *anteriorly* so that the lower edge of the defect can be more accurately defined This manœuvre is now carried out in all cases where the defect lies astride the inferior caval orifice and where a eustachian valve is palpated at preliminary digital exploration



(a) (b)

Fig 5—Radiographs (a) before and (b) six weeks after closure of atrial septal defect and mitral valvotomy Female aged 40 with Lutembacher syndrome Note diminution in size of right atrium

Postoperative Complications

Apical pneumothorax occurred in 10 cases but has now been avoided by the routine use of apical drainage tubes Small pleural effusions, mainly on the left side, developed as a rule but always resolved spontaneously Pericardial and pleuro pericardial friction usually persisted for seven to ten days after operation In one patient the rub persisted for three weeks with some pyrexia, and in another a febrile episode resembling the mitral post valvotomy syndrome occurred two months after operation Partial collapse of the left lower lobe occurred in 4 cases, paralysis of the left diaphragm in 1, and a transient Horner's syndrome was observed twice Postoperative abdominal pain, sometimes accompanied by nausea and vomiting, and suggestive of mild ileus occurred in 4 cases and these symptoms have been reported by others Cerebral symptoms occurred in 2 cases, one described later, and also in the last patient to be operated on who is improving

Postoperative arrhythmias were recorded in 15 cases—namely, atrial fibrillation in 3, atrial flutter in 3, ectopic supraventricular tachycardia in 6, and nodal rhythm in 3 cases Sinus rhythm was restored in all but 2 in one with a very large heart fibrillation has persisted, and in another recent case flutter is still present

Results

There was no operative or postoperative mortality apart from the one fatality, after a second operation, already described The immediate benefit to those with very large hearts and heart-failure or serious cardiac symptoms was remarkable Failure disappeared, effort tolerance increased, and the heart became much quieter There has also been a gain in weight and improvement in general health in poorly nourished patients In those without seriously enlarged hearts, the benefit of closing the A S D can be assessed only in future years, but most of them are less conscious of an overactive heart and feel better There is every reason to expect that restoration of normal cardiac function will prevent the progressive cardiac and arterial changes which usually occur in older patients, and that their expectation of life has been prolonged

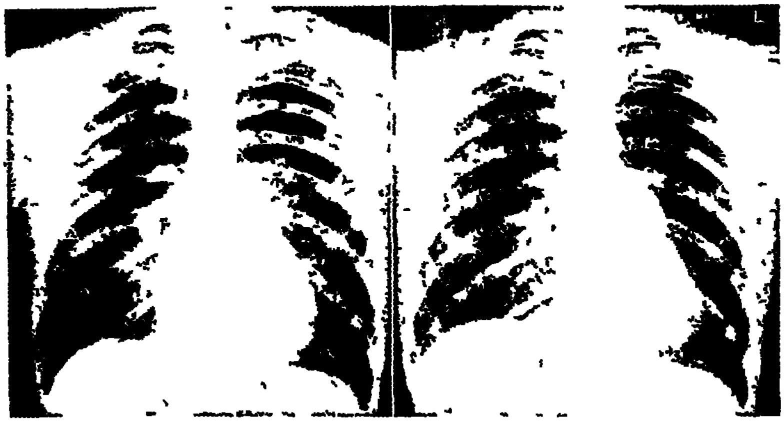


Fig 6—Radiographs (a) before and (b) six months after closure of atrial septal defect Male aged 20

There were two unsatisfactory results in which, as already stated, the inferior caval blood was deflected into the left atrium in closing low septal defects

In one, a boy aged 15, nothing untoward was noticed until after operation when there was a transient cerebral disturbance followed by tachycardia Four months later, there was slight central cyanosis and clubbing of the fingers, and pyrexia due to infected tonsils Following tonsillectomy, an angiocardiogram was performed, contrast medium being injected through a catheter into the inferior vena cava This showed that most of the inferior caval blood entered the left atrium The patient is now convalescing from tonsillectomy after which it is planned to operate again and resuture the A S D

The second case has already been described

Postoperative cardiac catheterisation has so far been performed in 12 cases In 7 of them catheter findings were completely normal and in 3 of them compatible with an insignificant residual shunt In 2 cases appreciable shunts persisted, in one a shunt of 9 litres per minute was reduced to 3 litres, and in the other an 11 litre shunt to 4 5 litres Curiously enough the last patient was the one who showed most dramatic benefit from operation Before it, she had a very large heart and was completely incapacitated by failure, but her heart became much smaller and she is now back in full time employment Anomalous pulmonary veins, recognised at operation in this case, were directed into the left atrium, but others may have been overlooked

Postoperative Clinical Signs

The most obvious change was that the overactive heart became much quieter, the right ventricular systolic lift diminished or disappeared and the apical impulse became less forcible A pulmonary systolic thrill, present before operation in 7 cases always disappeared and the systolic murmur diminished or sometimes disappeared Splitting of the second sound usually became closer or confined to inspiration, but in 10 cases wide splitting persisted unchanged The tricuspid diastolic murmur always disappeared, but a mitral diastolic persisted in 3 cases with mitral valve disease A pulmonary systolic ejection sound when present always persisted, and in 9 cases it only appeared after operation It was difficult to compare heart size in preoperative and postoperative chest films, owing to cardiac displacement and a higher level of the diaphragm postoperatively, but large hearts became obviously smaller and the right atrium was always less prominent (figs 5 and 6) Changes in the electrocardiogram often indicated a diminution of right ventricular predominance in chest leads V1 and V6

Summary and Conclusions

The anatomy of atrial septal defects is described with special reference to their surgical repair

The clinical features, hæmodynamic findings, and complications in 100 consecutive cases of atrial septal defects are briefly given and the indications for and contra indications to surgical treatment are discussed

Uncomplicated fossa-ovalis (ostium-secundum) defects can be closed under hypothermia with little operative risk, and this should be done preferably before the age of twenty years, when the heart and pulmonary vessels are intact, but even after the age of forty, and when the heart is grossly enlarged, operation may still give good results

Atrio-ventricular (ostium-primum) defects cannot safely be closed under hypothermia, and their clinical diagnosis is discussed Obstructive pulmonary hypertension with a seriously elevated vascular resistance is regarded as being usually a contra indication to surgical closure of an atrial septal defect

The closure of atrial septal defects by open heart surgery under hypothermia is described and the results of operation in 40 cases are given There was only one fatality, following a second operation undertaken to resuture the defect In another case, an unsatisfactory result was due to deflection of the inferior vena cava into the left atrium In the remaining cases the immediate results have been satisfactory

We are indebted to numerous colleagues for referring cases of A S D to us, especially to Dr J W Brown and Dr R Kemball Price Some of our cases were investigated at the National Heart Hospital and we are grateful to Dr Paul Wood, director of the Institute of Cardiology, and to Dr N A J Hamer and other registrars for their valuable help and cooperation We also wish to thank Mr J W Jackson who has assisted at all operations, Mr E Bridger, chief cardiological technician, and Miss E Hewland, medical artist, who have always been present in the operating theatre

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SLEEP AND WAKEFULNESS IN THE ARCTIC

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ON the British North Greenland Expedition of 1952–54 there was an opportunity to study the effect of the polar environment on the twenty nine men who were exploring an area at about latitude 77° N, some 800 miles from the North Pole (Lewis and Masterton 1955) There were two laboratories, one at the edge of the inland ice at Britannia So, and the other (a smaller station "Northice"), almost 300 miles out on the inland ice and manned by three scientists

There are two main climatic phenomena in the polar circles—the extreme cold, and the periods of light and darkness which are seasonal and not diurnal as in the lower latitudes At 77° North there is a summer period of continuous sunlight and a winter period of darkness, each lasting about 3 months

The effect of the environment was studied on the sleep pattern of men used to a diurnal cycle, observations being made on the number of hours slept over the seasons, the effect of specific duties, and the relationship of disturbed sleep to the taking of naps In this study artificial situations were not imposed experimentally, the records being made in natural surroundings

Each member of the expedition was issued with a specially printed sleep-card (fig 1) which he filled in daily At the end of every month the completed card was exchanged for a new one, and at the end of the expedition the information was transferred to a punch card system and the results extracted, each month being adjusted to 31 days Sleep/wakefulness patterns were plotted for groups and individuals (fig 2) after the method adopted by Kleitman and Engelmann (1953)

Periods of sleep not longer than 3 hours, and separated by at least 1 hour from the main sleep of the day, were defined as "naps" This implied that a nap was "sleep taken with the clothes on" It could usually be identified on the sleep card as an isolated line Interrupted sleep appeared on the cards as a discontinuous line on which the interruptions represented the time awake Recording of either naps or interruptions was not difficult, for the cards were usually well-documented with regard to time, frequency, and suggested causes of sleeplessness Examples are seen in fig 1

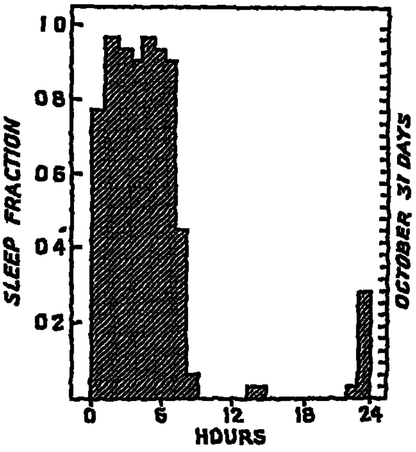


Fig 2—Sleep/wakefulness pattern derived from the sleep-card (fig 1) The hatched areas represent the fraction of the month spent in sleep There is a steep descent of the line which separates sleep from wakefulness, and the hours after 0900 are not involved in sleep, except for the nap at 1300 (After Kleitman and Engelmann 1953)

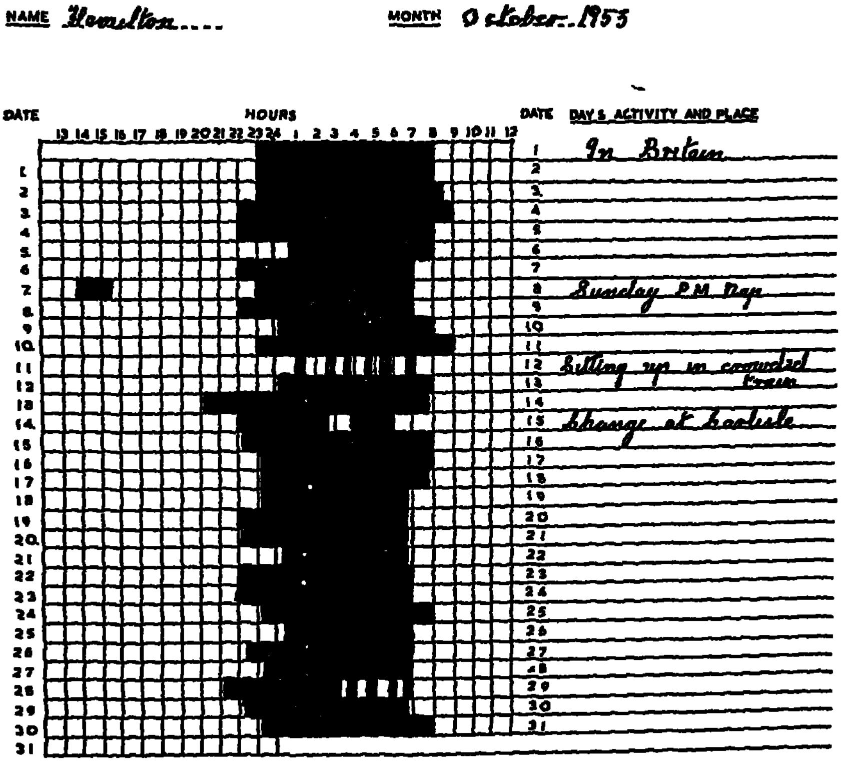
Results

The results are shown in figs 3–9

Total sleep —In a group of five men whose sleep cards were complete for 24 months, the mode was at 229 hours per month (7 4 hours sleep per night) If all available sleep-cards from the whole expedition were included, the mode was at 220 hours per month (7 1 hours per night) (fig 3) The mean sleep of individual subjects was 7 9 hours per night (S D =0 82) There was no relation between the age of the subject and his hours of sleep

Time of awakening —There was great variation in the time at which members awoke (calculated as a monthly mean) Greenwich Mean Time (G M T) was observed throughout, the local noon being 1430 hr G M T In the first 2 months the time of awakening ranged between 0600 and 1000 hr, but as the winter proceeded the range increased until the month of January which showed the widest dispersal from 0800 to 1600 hr In early spring the range contracted again, but in midsummer became large, from 0500 to 1300 hr In the autumn there was contraction The variations were considerably less in the second year, but the mean time of getting up was later—namely, nearer 1200 hr Fig 4 shows that the variation of awakening was due to the random time at which individual members awoke

Time of going to sleep —In the first two months the times of going to sleep were between 2100 and 0100 hr,



NAME Hamilton.... MONTH October 1953

DATE HOURS DATE DAY'S ACTIVITY AND PLACE

1 In Britain

8 Sunday PM Nap

12 Sitting up in crowded train

15 Change at Carlisle

SLEEP RHYTHM PLEASE DRAW A LINE ACROSS PERIOD YOU SLEPT EACH 24 HOURS
MEDICAL RESEARCH COUNCIL DIVISION OF HUMAN PHYSIOLOGY 1955

13 14 15 16 17 18 19 20 21 22 23 24 1 2 3 4 5 6 7 8 9 10 11 12
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31

Fig 1—Sleep-card This shows the typical distribution of sleep during a month for a man in the U K.

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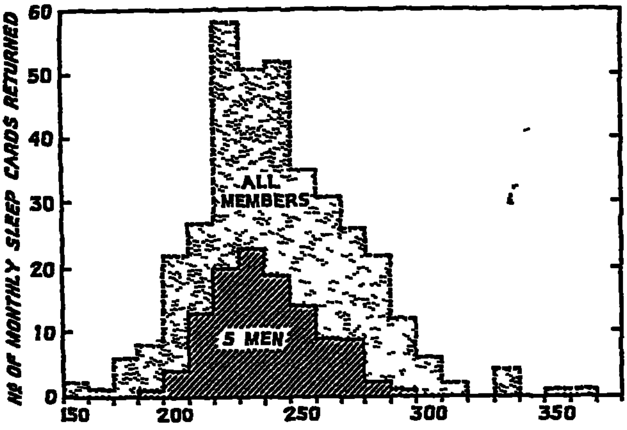

Fig 3—Distribution of total monthly sleep of all members, and of a group of five whose cards were complete for 24 months

with the onset of the winter this range widened, so that in January the mean times ranged from 1300 to 0300 hr The range contracted in the spring, but in the summer it broadened again to 1900–0100 hr The pattern was repeated in the second year

Fig 4 shows that the variation in the group was due to individuals' random time of going to sleep, likewise calculated as a mean time over the days of each month

Effect of continuous darkness—Sleep-wakefulness graphs, drawn for the group over the winter months, showed deviations from the conventional pattern illustrated by fig 2 An example is the card shown in fig 5

Effect of continuous sunlight—In the summer months there was rearrangement of sleep An example is shown in fig 6 As with the winter darkness, the total sleep per month was not appreciably altered

Effect of specific duties—Radio and weather observation were two duties at 0600 hr Fig. 7 shows the differing sleep rearrangement in two men (A and B) who had to be awake at that time As the season progressed, B (but not A) took the bulk of his sleep each night after the duty A slept 1·4 hours longer than B (nightly average)

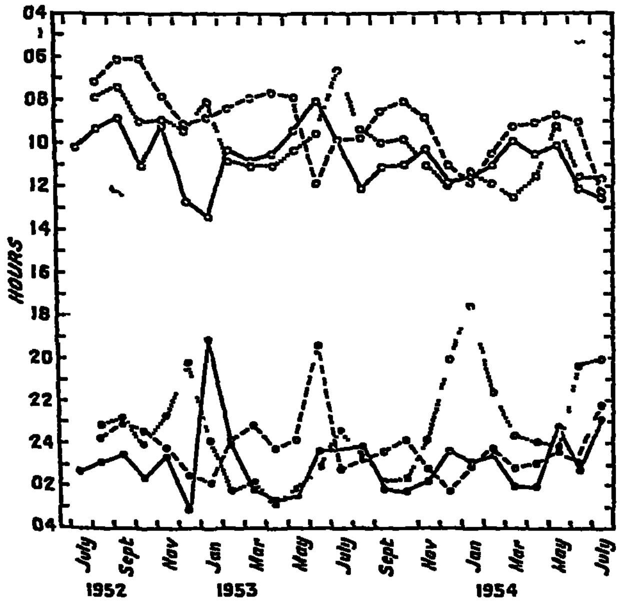

Fig 4—Times of awakening and going to sleep for three individuals Open circles represent times of awakening closed circles times of going to sleep The variation of the times for the group is seen here to be caused by variation in individuals' times

Monthly variations—As a group, the members slept longer in the first 12 months than in the second, a statistically significant difference of 0·4 hours a day, but this did not apply to individual subjects month by month for the 2 years

There was also a slight though statistically significant difference between the months, the general tendency being for longer hours in the autumn and shorter in the spring (fig 8) The pattern was repeated in the second year, though at a slightly lower level

Interrupted sleep—Fig 9 shows the monthly mean number of interruptions for the group There were fewest interruptions in August, 1952 Increases above the August level occurred in the winters of the 2 years The increases were smaller in the summer months, except for July, 1952, which gave a mean of almost 36 interruptions per man, due to seasickness on the voyage to Greenland

Naps—The monthly mean for the expedition was lowest in August, 1952, and in September, 1953 There were peaks in mid-winter, especially January, when the number of naps per person per month was over 25 (fig 9) In individuals, however, the taking of a nap did not closely follow nights of interrupted sleep

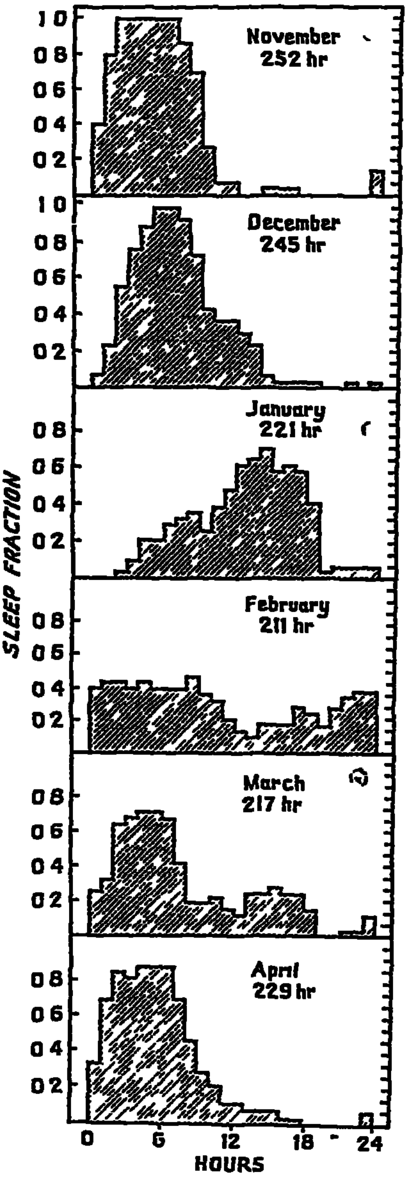

Fig 5—Sleep/wakefulness graph for one member

DISCUSSION

Living Arrangements

The cycles of sleep and wakefulness in man are determined largely by the influence of the community (Gesell and Amatruda 1945), which in turn has derived its pattern from the diurnal solar cycle of light and darkness Apart from other considerations it is economical—in the broadest sense—to sleep during the darkness and be active during the light hours

This is a perfectly reasonable arrangement in almost all parts of the globe In the polar regions, however, the period of light and darkness is not diurnal but seasonal

Visitors to Northern Norway during the summer often comment that there is much activity in the streets in the broad daylight of midnight but a careful study of the

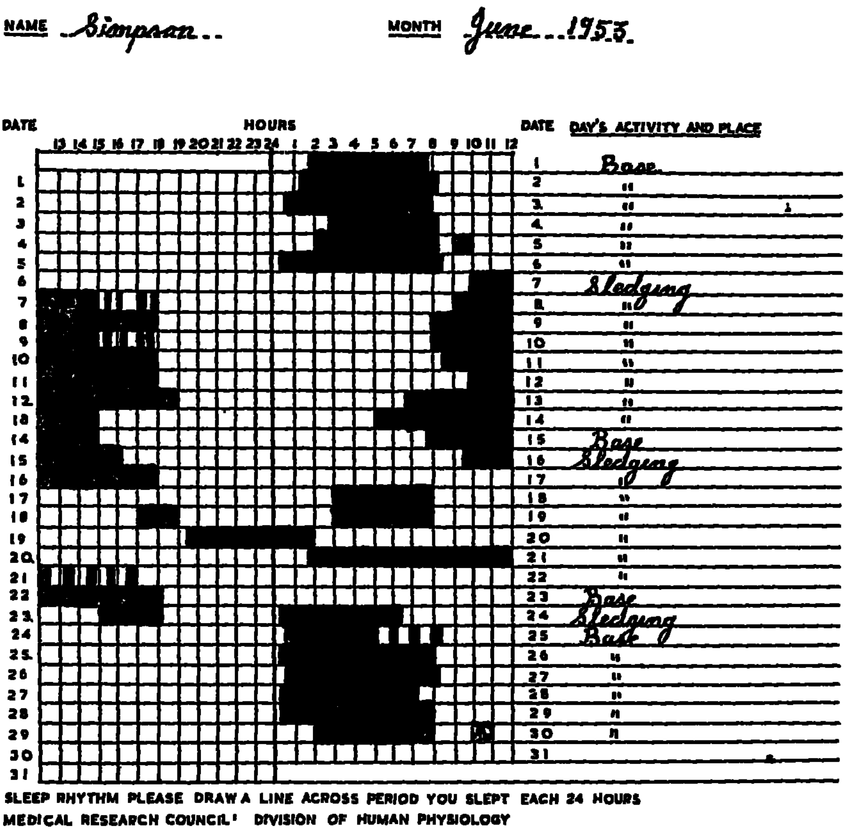

Fig 6—Sleep card for a member who slept mainly between midnight and 1000 at the base laboratory, but between 0800 and 1800 when sledging. He preferred to travel during the "night" when the snow surface was harder.

habits of the residents of Tromsø (Kleitman and Kleitman 1953) showed that this was not the case, and that in fact communally they did conform to the diurnal sleep/wakefulness pattern. The activity in the streets is usually associated with the departure of a ship, and soon afterwards the town is completely quiet, for they keep much the same hours as people in the rest of the civilised world.

There was confirmation of this when the ship of the British North Greenland Expedition arrived in Reykjavik, Iceland. It was broad daylight, and the members were surprised that the important harbour was so deserted and that the authorities did not immediately send a pilot when the siren was sounded. It was only then realised that the time was 2 A.M. and well out of normal working hours.

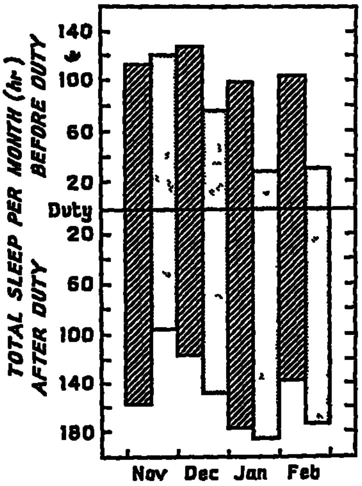

Fig 7—Relationship of sleep in two members to the 0600-hr meteorological duty at the Ice Cap Weather Station. A, winter 1952 (hatched). B, winter 1953 (stippled). As the season progressed, B took the bulk of his sleep each night after the duty, but A kept to his earlier pattern. On average, A slept 1.4 hours longer each night than B.

It appears, therefore, that despite months of darkness and of light the diurnal pattern is maintained, since the community is organised on this pattern. But if there is little or no control by community habit it is interesting to observe what happens to the sleep/wakefulness pattern of members. This might represent a truer *physiological* state of affairs than the conditioned pattern which reflects rather a *sociological* picture.

On the British North Greenland Expedition the men did not live as a strictly organised community. As long as the scientific programme or domestic work of the day was done, there was no reason why one should not take sleep at any time during the 24 hours. Some of the scientific programme required attendance at definite times, such as the weather observation and radio, whereas others required work to be completed over a period of months without necessarily a daily routine. The medical research programme was carried out at times convenient for the other scientists, without interfering with their routines.

In the winter their activity consisted mainly in calibrating and checking apparatus indoors, though a few men spent 2–3 hours outside tending the dogs. Physiological research was probably most active at this time, since most subjects were under one roof. Except for fortnightly estimations of basal metabolic rate early in the morning, their sleep was not interfered with.

Conditions of sleep were comfortable at base. There were iron bedsteads, each of which was covered with sponge rubber ($^1/_2$ in. thick) and a sheepskin. Each man had two down sleeping bags, and to make the beds more comfortable some slept on top of their spare sleeping bags, or other soft material such as parachute cloth, unused clothing, or canvas.

On the trail the men put one sleeping bag inside the other and lay on the sheepskin, which was placed directly on the snow. Inflatable air mattresses were not popular, because of their undue springiness. During cold weather, perspiration condensed and froze in the sleeping bags and sheepskins, considerably reducing their insulation; but the men slept well and only occasionally complained of sleeplessness due to cold.

During winter the men complained of sleeplessness which they attributed to comparative inactivity and to the stuffiness of the sleeping quarters. Windows and doors were kept shut to preserve the warmth, and as the building was draught-proof the air was so stagnant that tobacco smoke remained in layers at about 7 ft. There was a temperature gradient of 10°C between the air at the level of the upper and lower bunks, the upper often being uncomfortably hot.

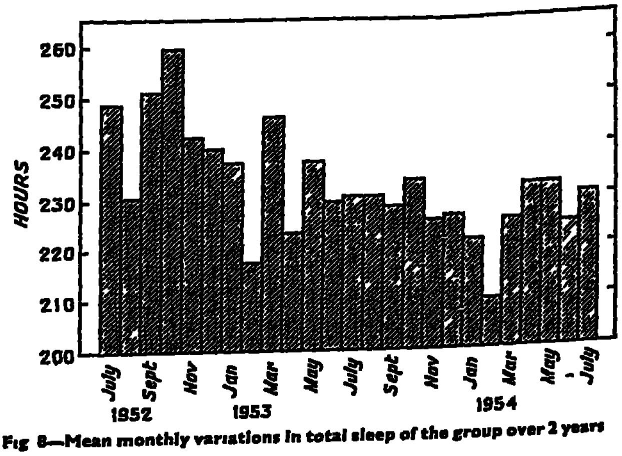

Fig 8—Mean monthly variations in total sleep of the group over 2 years

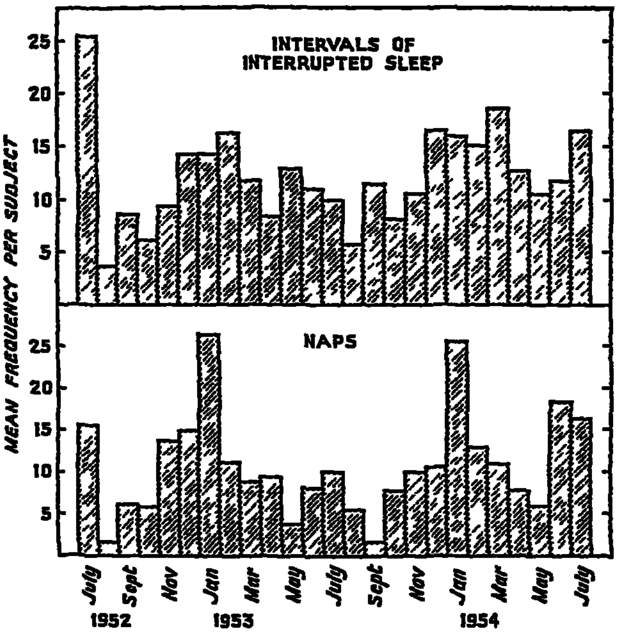

Fig 9—Intervals of interrupted sleep and naps

During the summer at the base laboratory complaints were made that the continuous sunlight made it difficult to sleep, even though there was outdoor physical work to tire the men Some curtained the window of their bunks, others blindfolded themselves One member asked for sleeping-tablets occasionally throughout the year, but this was not permitted. In spite of the complaints the total sleep of individuals was not significantly altered

Cooking duty was the main domestic chore, and it involved two men for a week at a time For the twenty other men the day began when the cook called them for breakfast About a quarter were usually awake when he came round, of the others, half responded at the slightest touch and half needed violent shaking Though mealtimes were set, this did not imply that the men had to be up and about after breakfast, and sometimes they went back to sleep—if they had been working late or celebrating the night before There was little social pressure to encourage being up early

During the winter men occasionally got up in the middle of the night to cook a snack, since all were familiar with the kitchen During the summer they would often be up very late, not realising the time, because of the continuous daylight, usually they cooked a snack before retiring, and this might represent “ breakfast ” if they chose to sleep late These examples show that they did not allow meals to interfere unduly with their chosen sleep habits Kleitman et al (1937) studied the effect of late snacks, which they found to produce a slight decrease in body movements during sleep, but no effect on the duration of sleep

If a man woke late he would have difficulty in getting to sleep at the conventional hour that evening, and would stay up working or reading until the early hours Then he would go to bed sleeping till next afternoon This arrangement tended to progress until the subject found that he was now on “ night shift ’ because he had indulged in sleep/wakefulness cycles of duration longer than 24 hours There were no landmarks of light and darkness to warn him that he had also lost a calendar date

The opposite might have been expected during sledging, because of the pattern of 8 hours’ work and 8 hours’ rest—namely 4 days’ activity in 3 In fact, this was not so Awakening on the trail was usually spontaneous, or by one’s sledging companion Other forces might include hunger, cold, a full bladder, or noise from the dogs Alarm clocks were used only occasionally

Other aspects of expedition life have been described elsewhere (Lewis 1954, Taylor 1955, Simpson 1957)

Methods

One of the approaches in the investigation of biological rhythms is to alter artificially the rhythm of the external environment—e g , to see what happens to men on an 18-hour or a 28-hour day (Lindhard 1910, Kleitman and Kleitman 1953, Lewis and Lobban 1954)

On the British North Greenland Expedition this was impracticable because many of the scientific duties involved radio and meteorological reports at strict G M T Time signals from the British Broadcasting Corporation were used continually to check chronometers, an essential part of navigation Because of this constant preoccupation with clock time, the observational approach was used, and though the filling-in of sleep-cards did rely on memory it was recent memory The men cooperated well

Seasonal Variations

During the times when the sleep patterns were disrupted, many men were going to sleep when others were getting up (fig 7) The casual observer would conclude that the men asleep were lazy, but the sleep totals showed that this was not so, and the impression of oversleeping was not confirmed Even though “ demand sleeping ” was possible (i e , whenever a man felt so inclined) the number of hours taken was not excessive and corresponded to the customary 8 hours

The environmental influences in Greenland affected the duties of the expedition During the darkness there was comparative inactivity and greater opportunity for sleeping , the summer was the season for outdoor work It was expected that more sleep would have been taken in the dark inactive period, but the difference was small Nor was there a significant change in the sleep totals during the periods of activity Less sleep was taken in the second year, but with little variation between months

Disrupted Sleep and Naps

In the first year, during the late summer and autumn, all men worked very hard to unload the aircraft and establish the base Because of near exhaustion each day, there were no sleep problems, but after this activity was over, with the onset of winter, some men started complaining of sleeplessness, and the taking of naps became a feature It is a common observation that, in ordinary circumstances of living, if after a sleepless night one takes a long nap, one’s sleep for the following night tends to be disturbed In Greenland there was a seasonal change in the number of sleepless nights, higher figures being found in winter and (to a lesser extent) summer In the other seasons the number of interruptions was very small.

An identical seasonal variation was found in the incidence of naps From this it might be presumed that they were taken to compensate bouts of interrupted sleep, but there was in fact no relationship. On the monthly basis only one nap was taken for every twenty interruptions of sleep, and there were only rarely direct coincidences of a nap within 48 hours of disturbed sleep In three members there were no coincidences at all

Specific Duties

It has been mentioned that the British North Greenland Expedition was a community only partially “ organised ” Provided the routine chores were done and one’s scientific programme was carried out, one’s spare time was not disciplined With such a background it is interesting to observe the effects of specific regular scientific duties on the sleep/wakefulness patterns of the members concerned For example, every morning at 0600 hr there was a weather observation, and this had to be transmitted by radio It was possible to compare the patterns of two meteorologists for 1952 and 1953

For one (A) in the winter of 1952, the duty caused his sleep to break up into two equal lengths, a pattern unchanged over 4 months In the following year, in identical circumstances, the other (B) showed that as the winter progressed he was taking most of his sleep after the meteorological duty—i e, he stayed up for this and then took his main sleep (fig 7)

It was possible also to study the sleep patterns of two radio-operators

During winter at the Northice, where he was one of three men, one radio operator took about a third of his sleep before the 0600 hr duty and the remainder afterwards, including a great number of naps at haphazard times, so that over a month almost every hour in the 24 was, at some time or other, used for sleep The next year he did the same duty at the main laboratory where over twenty men were working under conditions of greater communal organisation Despite this change of environment, his sleep pattern was disrupted as in the previous year If, however, the expedition had exerted social pressure on the members' off duty times, he would probably have conformed to the community timetable

His patterns may be compared with those of the other radio operator, who went to bed at a conventional hour, about midnight, woke just before 0600 hr to transmit the report, and then promptly went back to sleep for 2 hours before breakfast After that he was up for the whole day and only rarely took a nap

These two men, both petty officers trained rigidly in naval discipline, carried out identical duties on the expedition Whereas one's sleep was disrupted, the other showed no interference at all

These findings show that the conventional 8 hours may indeed represent a biological need, and is influenced neither by the absence of social pressures nor by the light darkness patterns Nor indeed is it influenced by physical work, although there are variations from day to day, the average hours of sleep during the month do not change

Summary and Conclusions

Members of the British North Greenland Expedition, living in the Arctic as a partially organised community, showed interesting disruption of their sleep/wakefulness patterns

The time of going to sleep and of getting up varied greatly, especially during midwinter (continuous darkness) and midsummer (continuous light), and without special preference to a particular hour

During the continuous darkness and continuous light more of the 24 clock hours were used for sleep, though the monthly total variations over the 2 years were slight, there were no great differences between months of out door activity and months when the men were confined to the hut The winter months were characterised by many interruptions of sleep, and by the taking of naps There was, however, no relationship or coincidence between interrupted sleep and naps

The effects of specific routine duties on sleep showed how men varied when there was no need to conform to a social pattern This varied response was seen in men whose backgrounds of Service discipline and training were identical

Though the men were at liberty to sleep almost as long as they liked, the mean duration of sleep was 7 9 hours The approximate period of 8 hours taken in temperate climates would indeed appear to represent a normal demand

We wish to thank Mr Roger Matchett and Petty Officer *D E Lee for valuable technical assistance*

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MAINTENANCE THERAPY IN PERNICIOUS ANÆMIA

CONTROLLED BY DETERMINING VITAMIN-B_{12} LEVEL IN PLASMA

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SINCE purified preparations of vitamin B_{12} became available in 1949, combinations of the pure vitamin + "intrinsic factor" have been widely used in the oral treatment of pernicious anæmia Their adequacy over long periods is, however, somewhat in doubt, and oral versus parenteral treatment of pernicious anæmia has been discussed (Berlin 1953, Mollin and Ross 1953, 1954, Spies et al 1953, Gerhartz and Koelle 1954 Heinrich 1954, Lowther et al 1954, Baker and Mollin 1955, Blackburn et al 1955, Begemann 1957, Ungley 1957)

Since low levels of vitamin B_{12} in the serum or in the plasma may precede clinical signs of vitamin-B_{12} deficiency in pernicious anæmia (Mollin and Ross 1954, Østergaard Kristensen and Søeborg Ohlsen 1956), determination of the vitamin B_{12} level in the plasma is likely to afford not only a specific but also the earliest method of disclosing whether pernicious anæmia therapy is insufficient To elucidate this problem we followed the vitamin-B_{12} levels in the plasma and the hæmatological values in twelve patients According to the ordinary principles of maintenance therapy prevailing in the department, they were treated by the oral preparation 'Cycoplex MCO,' which consists of vitamin B_{12} plus small quantities of hog pyloric mucosa (see below)

Material

The material comprises twelve patients from the Frederiksberg Hospital, medical department E ten women age 45–84 and two men aged 65 and 75 All presented typical pernicious anæmia megaloblastic bone-marrow, abnormally low vitamin B_{12} levels in the plasma, histamine refractory achlorhydria, anæmia, and normal absorption of fat

Before treatment the vitamin-B_{12} levels in the plasma averaged 57 μμg per ml (range 10–120 μμg per ml), the lower limit of normal being 150 μμg per ml (see below) The hæmoglobin (Hb) level averaged 49% (range 34–77%), the red cells 1,740,000 per c mm (range 1,130,000–2,890,000 per c mm)

Methods

The vitamin B_{12} levels in the plasma were determined (by H P Ø K) by the method using *Lactobacillus leichmannii* 313 (Østergaard Kristensen 1956) Normal values for adults are on an average 392 μμg per ml (range 150–950)

Sternal bone marrow was examined (by A S O) partly in sections after coagulation and mounting and partly in smears stained by the method of May Grünwald Giemsa

Other hæmatological studies—Hb level (100% = 14 8 g per 100 ml), red-cell counts, colour index $\left(\frac{\text{Hb \%}}{\text{erythrocytes (mill)} \times 21}\right)$, total and differential white-cell counts, and serum-iron determinations (by the method of Hoyer 1950)—were made by the Central Laboratory of the Frederiksberg Hospital.

The patients were admitted while the treatment was being instituted and then discharged for frequent out-patient control. The control period was 7–25 months on maintenance therapy. In most cases the vitamin-B_{12} levels in the plasma were determined at intervals of 1 or 2 months.

Initial Treatment

At the outset ten of the twelve patients had intramuscular injections of vitamin B_{12}, usually 30–60 μg daily for the first 10 days. In a few cases this treatment was then supplemented by weekly injections of 60 or 90 μg, in one up to 300 μg, of vitamin B_{12}. The total dose of vitamin B_{12} administered parenterally ranged from 300 to 1080 μg and was given over a period of from 10 to 51 days. In case 11 the treatment was instituted with 'Hepsol fortior MCO' (see below) 5 ml four times in the course of 20 days, and in case 1 cycoplex was given from the outset. A possible deficiency of other hæmatopoietic substances, primarily iron and ascorbic acid, was met by adequate measures (cf Pedersen et al 1957).

All the patients gave a satisfactory initial response—i e, a typical reticulocyte reaction and a satisfactory increase in erythrocyte-count.

Maintenance Therapy

After this initial therapy nine of the ten patients who had had injections of vitamin B_{12} were started on treatment with cycoplex MCO. The group with cycoplex as maintenance therapy thus comprised ten patients (cases 1, 2, 3, 4, 4a, 5, 7, 8, 9, and 10).

Case 12a, who initially had injections of vitamin B_{12}, was shifted to injections of hepsol fortior MCO, and in case 11 the treatment with hepsol fortior was just continued.

Preparation and Dosage

Cycoplex MCO.—Each capsule contains 5 μg of crystalline vitamin B_{12} + intrinsic factor corresponding to 50 mg of dried hog pyloric mucosa suspended in oil. The daily maintenance dose was two to four capsules daily; it was increased later in two cases to eight capsules daily.

Hepsol fortior MCO.—This contains liver extract corresponding to 10 "clinical units" plus 20 μg of crystalline vitamin B_{12} per ml. The maintenance dose for the two patients who served as "controls" of those treated with cycoplex was 5 ml of intramuscular hepsol fortior every 2 or 3 weeks.

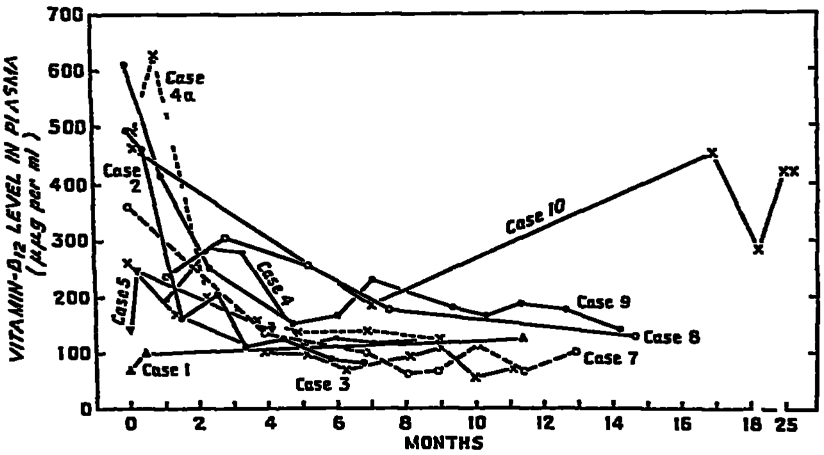

Fig 1—Vitamin B_{12} levels in plasma in 10 patients with pernicious anæmia on oral maintenance therapy with cycoplex MCO (vitamin B_{12} + hog pyloric mucosa). All but case 1 had initially received injections of crystalline vitamin B_{12} amounting to a total of 300—1080 μg, which had raised the vitamin B_{12} levels in plasma to normal.

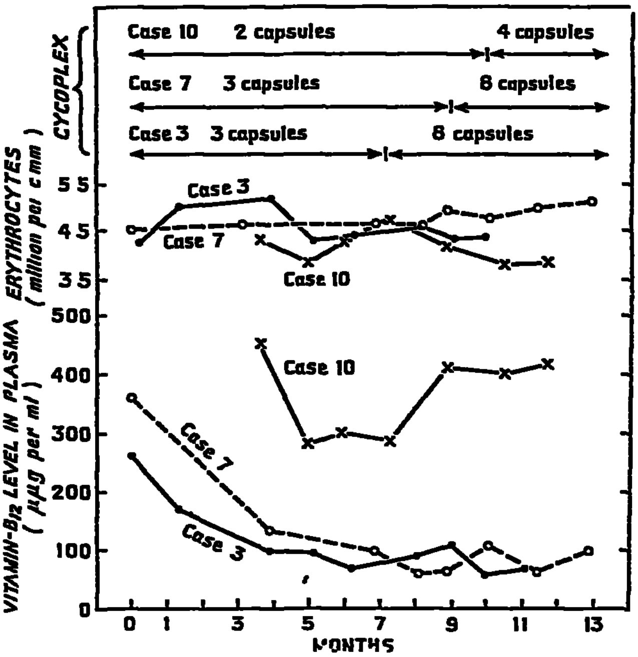

Fig 2—Vitamin B_{12} levels in plasma and erythrocyte-counts in 3 patients with pernicious anæmia on treatment with cycoplex MCO. After cases 3 and 7 had been treated for 7 and 9 months respectively, daily dose was increased from 3 to 8 capsules.

Results

Vitamin-B_{12} Levels in Plasma during Oral Maintenance Therapy with Cycoplex

Fig 1 shows the vitamin-B_{12} levels in the plasma during treatment with cycoplex. Case 1 (lowest curve on the left) did not have injections but was started at once on cycoplex. After a year's treatment his vitamin-B_{12} level in the plasma was only 125 μμg per ml.

In eight of the nine patients whose treatment began with injections of vitamin B_{12} the vitamin-B_{12} levels in the plasma had been raised to normal when cycoplex was started. In case 5 the vitamin-B_{12} level at that time was only 140 μμg per ml, but the first determination after cycoplex was started showed a value above 200 μμg per ml in this case too.

After 99–154 days—i e, after 3–5 months' maintenance therapy with cycoplex—the vitamin-B_{12} levels in the plasma had fallen, however, to abnormally low values—less than 150 μμg per ml in six of the nine patients. In six of them, who remained under control, this level remained unchanged or declined further.

Cases 8 and 9 showed for some time subnormal levels which, however, after 14–15 months fell below 150—140 and 130 μμg per ml respectively.

Only case 10 had an entirely normal level of vitamin B_{12} in the plasma after more than 2 years on cycoplex. Her initial level had been 50 μμg per ml—i e, decidedly in the range of pernicious anæmia, as in the other patients.

Dependence of Vitamin-B_{12} Level on Intensity of Initial Treatment

It might be presumed that the more intensive the initial treatment the longer is the period, during

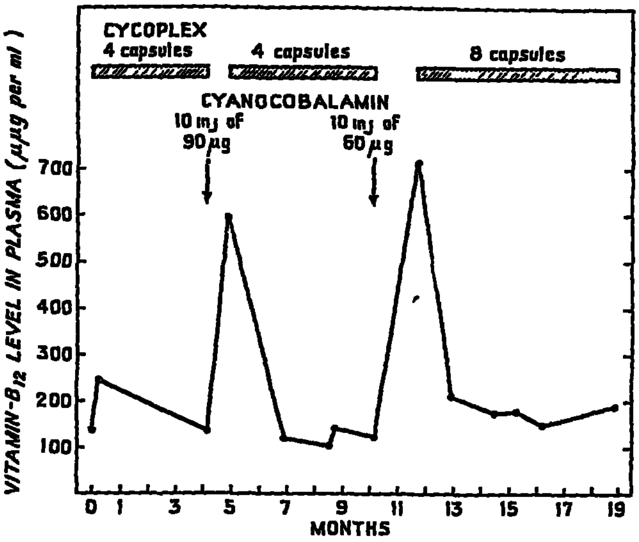

Fig 3—Case 5 vitamin B_{12} levels in plasma in pernicious anæmia treated with cycoplex MCO and intermittent injections of crystalline vitamin B_{1}

insufficient maintenance therapy, before the vitamin B_{12} level in the plasma falls to abnormally low values This question cannot be answered by the present study, but cases 4 and 4a, who had the most intensive initial treatment (1050 and 1080 μg of vitamin B_{12} respectively), showed levels lower than 150 μμg at the end of 5 months, whereas the patient who exhibited a normal level at the end of 2 years (case 10) had only received 540 μg of vitamin B_{12} initially

Dependence of Vitamin-B_{12} Level on Dose of Cycoplex

Case 10, whose vitamin-B_{12} level remained normal throughout 2 years on cycoplex, received two capsules daily during the first 10 months, and after that four capsules daily The two other patients (cases 8 and 9) whose vitamin-B_{12} levels also remained higher for some time than in the other patients, also had four capsules daily Their maintenance dose did not, however, differ from that in some of the patients whose vitamin-B_{12} levels soon fell to a low value

In two patients (cases 3 and 7) whose vitamin-B_{12} levels in the plasma were always low the dose of cycoplex was increased from three to eight capsules daily Fig 2 shows that, even after 4 months on this increased dose, the level of vitamin B_{12} in the plasma remained abnormally low—70 and 100 μμg per ml respectively The increase in the dosage did not raise the vitamin-B_{12} level

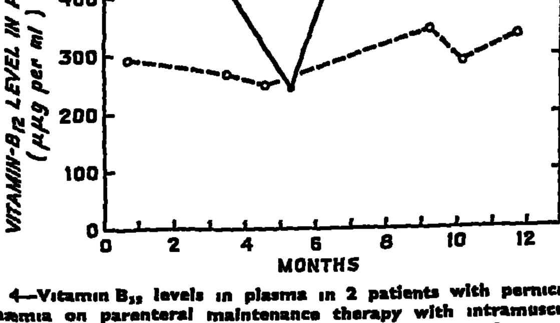

Fig 4—Vitamin B_{12} levels in plasma in 2 patients with pernicious anæmia on parenteral maintenance therapy with intramuscular injections of liver extract (hepsol fortior MCO) 5 ml about every 2 weeks Vitamin B_{12} levels were determined at least one week, and usually two weeks, after injections

Fig 3 illustrates the findings in case 3 Owing to a low vitamin B_{12} level in the plasma and the occurrence of paræsthesiæ during cycoplex therapy, this patient had injections of crystalline vitamin B_{12} in two periods, this led to a prompt rise in the vitamin-B_{12} level to normal and improvement of the paræsthesiæ

Vitamin B_{12} Level in Plasma during Maintenance Therapy with Injections of Hepsol Fortior

Fig 4 shows the vitamin-B_{12} levels in the plasma of the two patients (cases 11 and 12a) treated with injections of hepsol fortior At the end of 9–10 months both had vitamin-B_{12} levels within the normal range The estimations were made at least 1 week, and usually 2 weeks, after the last injection of hepsol

Vitamin B_{12} Level in Relation to Hæmatological Findings during Oral Maintenance Therapy

Table I gives these hæmatological findings in nine patients on cycoplex when the vitamin-B_{12} level in the plasma was first found to be less than 150 μμg per ml These patients had initially received injections of vitamin B_{12}

In six of these nine patients the vitamin B_{12} levels in the plasma continued to be estimated after the levels had fallen to less than 150 μμg per ml Table II compares the hæmatological values at the time shown in table I with those found after the vitamin B_{12} levels had remained low for a long time in these six cases

The tables show (1) that a vitamin-B_{12} level of less than 150 μμg per ml was found in the plasma when the *Hb* was entirely normal and the number of red cells satisfactory (averaging about 4,500,000 per c mm and being less than 4,000,000 per c mm in only one case), (2) that a low vitamin B_{12} level in the plasma for an average of $5^1/_2$ months did not involve a decrease of either Hb or red cells One patient with a low vitamin B_{12} level in the plasma was followed up for nine months without any signs of recurrence of the anæmia

TABLE I—VITAMIN B_{12} LEVEL IN PLASMA, HB, RED CELLS, AND COLOUR-INDEX DURING MAINTENANCE THERAPY WITH CYCOPLEX WHEN VITAMIN B_{12} LEVEL WAS FIRST FOUND TO BE LESS THAN 150 μμG PER ML

Average of 9 patients

Vitamin B_{12} level in plasma (μμg per ml)	Hb (%)	Red cells (million per c mm)	Colour index
126 (range 110–145)	91 (range 80–104)	4 29 (range 3 57–5 18)	1 01 (range 0 93–1 17)

Fig 2 shows the vitamin-B_{12} levels in the plasma and the number of red cells for three of the patients (cases 3, 7, and 10) on cycoplex In case 7 the number of red cells was normal despite an abnormally low level of vitamin B_{12} in the plasma In case 10 the number of red cells was on several occasions less than 4,000,000 per c mm despite a normal level of vitamin B_{12} in the plasma This combination of a low vitamin B_{12} level and a normal number of red cells in one patient and of a normal vitamin B_{12} level with a low number of red cells in another emphasises the fact that the number of red cells is not an ideal indicator of a possible vitamin B_{12} deficiency

Vitamin B_{12} Level in Plasma in relation to Erythropoiesis

In seven of the ten patients on cycoplex and in one of those on hepsol sternal puncture was repeated during the treatment The bone marrow could be described as *completely normal* in only two of them the one who had a normal level of vitamin B_{12} in the plasma after more than 2 years on cycoplex (case 10), and the one who was treated with hepsol (case 12a) and also had a normal level of vitamin B_{12} in the plasma

Of the remaining six patients on cycoplex in whom sternal puncture was repeated (cases 2, 3, 4, 4a, 5, and 7)

TABLE II—VITAMIN-B_{12} LEVELS IN PLASMA, HB RED CELLS, AND COLOUR-INDEX DURING MAINTENANCE THERAPY WITH CYCOPLEX *a* WHEN VITAMIN-B_{12} LEVEL OF LESS THAN 150 µµG PER ML. WAS FIRST FOUND, *b* AFTER AN AVERAGE OF 162 (RANGE 97–270) DAYS WITH VITAMIN-B_{12} LEVELS OF LESS THAN 150 µµG PER ML.

Average of 6 patients

Vitamin-B_{12} level in plasma (µµg per ml)		Hb (%)		Red cells (mill per c mm)		Colour index	
a	*b*	*a*	*b*	*a*	*b*	*a*	*b*
120 (range 110–145)	95 (range 55–120)	94 (range 89–104)	94 (range 85–105)	4.56 (range 4.13–5.18)	4.53 (range 4.17–5.14)	0.98 (range 0.93–1.02)	0.97 (range 0.91–1.06)

four (cases 2, 3, 5, and 7) showed a few typical (Ehrlich) megaloblasts despite a normal amount of Hb and a normal erythrocyte-count 3–6 months after an abnormally low level of vitamin B_{12} had first been found. The two others (cases 4 and 4a) had no characteristic megaloblasts but one of them had "macrometamyelocytes."

Neurological Signs

Before the treatment four patients (cases 4, 4a, 10 and 11) had shown slight signs of myelopathy, which disappeared or subsided perceptibly during the initial treatment.

In case 4, who had lost the Achilles-tendon reflexes before treatment, these reflexes became normal when the vitamin-B_{12} level in the plasma had been abnormally low for several months. Two patients (cases 1 and 5) with no pre-treatment signs of myelopathy, complained during cycoplex therapy of paræsthesiæ. At that juncture the peripheral blood was normal, whereas the vitamin-B_{12} level in the plasma was low. After injections of vitamin B_{12} the paræsthesiæ disappeared in case 1 and improved in case 5.

Discussion

At our present stage of knowledge, and with our present diagnostic methods the maintenance therapy of pernicious anæmia must keep normal the amount of Hb, the number of red cells the bone-marrow and the vitamin-B_{12} level in the plasma. Our results show that the oral administration of cycoplex MCO, which consists of vitamin B_{12} and small quantities of hog pyloric mucosa, did not keep the bone marrow and the vitamin-B_{12} level normal: in nine of ten patients the vitamin-B_{12} level in the plasma was abnormally low, in four of seven patients the bone-marrow was "partially megaloblastic", and in a fifth case "pernicious-anæmia neutrophils" were found. This maintenance therapy is therefore insufficient, although the amount of Hb and the erythrocyte-counts were normal.

The doses of vitamin B_{12} injected initially were probably not sufficient to restore tissue reserves in our patients (see below), but even in the two patients who received more than 1000 µg of vitamin B_{12} initially the vitamin-B_{12} level in the plasma fell to below normal within 5 months on cycoplex.

Our investigations confirmed that patients on maintenance therapy for pernicious anæmia can have a low vitamin-B_{12} level in the plasma for months without showing clinical signs of vitamin-B_{12} deficiency. Determinations of the vitamin B_{12} level in either the plasma or the serum are therefore necessary for assessing the efficacy of maintenance therapy.

Since the various combined preparations for oral treatment of pernicious anæmia differ in composition and in degree of purification of the intrinsic factor, the experience with one preparation (cycoplex MCO) does not permit conclusions regarding the efficacy of others. Whether any of the commercial preparations for oral use can maintain normal vitamin B_{12} levels in the plasma in long-term therapy is a question which calls for further study. The failure of a threefold dose of our preparation to raise the vitamin-B_{12} level suggests that simple underdosage of intrinsic factor is not the whole explanation.

In discussing oral versus parenteral treatment of pernicious anæmia it is important to realise, as Mollin and Ross (1953) and Ungley (1957) point out, that the quantities of vitamin B_{12} required to afford "satisfactory" increases in reticulocyte and erythrocyte counts in anæmic patients constitute only a very small fraction of the quantities required to restore normal tissue reserves of vitamin B_{12}. Since in untreated pernicious anæmia the deficit in liver-tissue reserves presumably amounts to about 1500 µg of vitamin B_{12} (cf. Ross and Mollin 1957, Swendseid et al. 1957) and since studies of vitamin B_{12} labelled with radioactive cobalt (Glass et al. 1954, Baker and Mollin 1955, Callender and Evans 1955) have proved that the amount of vitamin B_{12} which can be absorbed from the intestinal tract is very limited (1–2 µg after the administration of 50 µg of vitamin B_{12} + intrinsic factor) the depleted reserves can certainly not be replaced within a short time by the usual oral treatment.

In patients with a low level of vitamin B_{12} in the plasma indicating small or depleted tissue reserves the risk of hæmatological relapse or of the development of neurological deficiency signs must be high. This applies particularly under conditions in which either the requirement is increased (infection, hæmorrhage, &c.) or the absorption is decreased. In treating pernicious anæmia, therefore, one must try not only to increase the Hb and the red cells to normal but also to replace the depleted tissue reserves.

The initial treatment should therefore be by the parenteral route. In view of the considerable vitamin-B_{12} deficiency in the tissue reserves of these patients this initial treatment must also be much more intense than that in current use. Most patients will probably require about twenty injections of 100 µg of vitamin B_{12}, if normal tissue reserves are to be restored.

Maintenance therapy.—If oral therapy is chosen, it seems absolutely necessary to control the state by determinations of the vitamin-B_{12} level in the plasma and by the appearance of the bone-marrow. In the absence of facilities for determining the vitamin-B_{12} level in the plasma it seems wise at present to use parenteral treatment also for maintenance purposes. The cheapest form is injections of vitamin B_{12}—e.g., 100 µg every two weeks. Using this procedure the physician knows that he can maintain not only normal erythrocyte-counts but also normal vitamin-B_{12} levels in the blood.

Summary

Ten patients with pernicious anæmia were treated initially with injections of vitamin B_{12} (cyanocobalamin), which brought the vitamin-B_{12} level in the plasma up to a normal value. Nine of these patients were given oral maintenance therapy with 'Cycoplex MCO,' which consists of vitamin B_{12} and small quantities of dried hog pyloric mucosa. During this treatment the levels of vitamin B_{12} in the plasma fell to abnormally low values in eight of the nine patients, and in one patient,

who also had received cycoplex as initial therapy, the level remained low At the same time the bone-marrow showed signs of insufficient therapy, whereas the amount of Hb and the erythrocyte-count mostly remained normal

It proved impossible to restore the vitamin B_{12} in the plasma to a normal value by increasing the dose of cycoplex, but the injection of vitamin B_{12} immediately did so

In two patients treated with intermittent injections of a preparation of liver extract supplemented with crystalline vitamin B_{12} ('Hepsol fortior MCO') the level of vitamin B_{12} remained normal

The control of maintenance therapy of pernicious anæmia should include, in addition to determination of Hb and erythrocyte count, determination of the vitamin-B_{12} level in the plasma and examination of the bone marrow Only in this way can insufficiency of the therapy be disclosed at an early stage

As initial treatment of pernicious anæmia, injections of vitamin B_{12} are recommended, and this initial treatment should be more intensive than usual, the total dose being about 2000 µg of vitamin B_{12}

The oral preparation cycoplex MCO, which consists of vitamin B_{12} and small quantities of hog pyloric mucosa, appears to be insufficient, because it does not keep the bone-marrow and the vitamin-B_{12} level in the plasma normal

The efficacy of other oral preparations should be studied by determining the vitamin-B_{12} level in the plasma and by examining the bone-marrow

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" The present generation of consultants have never been general practitioners They have planned their own careers and applied their own labels Further, most of them have found that the way to success has been through increasing limitation They are one tool technicians or one disease diagnosticians On the whole they have had a simpler training and they lead an easier life than the general practitioners, and they often have less ability and certainly less wisdom The practitioner needs a consultant for advice about a particular problem in a particular patient He chooses the consultant either for his well known familiarity with that particular problem, or for his probable ability to handle, and to impress, that particular patient The choice of a consultant is one of the most important decisions of general practice There is, unfortunately, a tendency today for patients to choose their own consultants, usually on the advice of an acquaintance at a cocktail party, the doorkeeper at the hotel, or the gossip writer in an evening paper "—Sir HENEAGE OGILVIE in *Medical Ethics*, edited by Dr Maurice Davidson London, 1957, p 65

SERUM-LIPIDS AND ATHEROSCLEROSIS AMONG YEMENITE IMMIGRANTS IN ISRAEL

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Israel's population is composed of immigrants from East and West differing widely in their cultural background and ways of life Each group is reluctant to change its habits of eating, so that in Israel there is a unique opportunity for a long-term experiment on the influence of diet upon serum cholesterol levels and the incidence of atherosclerosis

Apart from the higher atherosclerosis mortality rate in Israel among immigrants from Western countries (Dreyfuss 1953, Toor et al 1954), a striking difference has been found between Yemenites who had immigrated over twenty years ago ("early" Yemenite immigrants) and those who had immigrated within the previous five years ("recent" Yemenite immigrants) After assembling statistical data on atherosclerosis mortality rates among different communities in Israel during the years 1953–55, we studied 528 recent and early Yemenites to determine their social conditions, diet, nutritional status and serum levels of cholesterol, phospholipids, and total lipids We then tried to correlate the findings with the atherosclerosis mortality rate

All the Yemenites were examined by one of us (J A) with the help of their local physician Those with a history of cardiovascular disease or other abnormality liable to affect the serum cholesterol level were excluded from the inquiry, and so were those with a blood pressure higher than 140/90 mm Hg, those who were very underweight, those with enlarged spleen or liver, and those with low blood cholesterol levels in the presence of impaired liver-function tests Pregnant and lactating women were also excluded The sex and age distribution of the 274 recent and 254 early Yemenites selected are shown in table I

TABLE I—AGE AND SEX DISTRIBUTION OF RECENT AND EARLY YEMENITES

Age (years)	Recent Yemenites		Early Yemenites	
	Male	Female	Male	Female
35–44	52	42	43	47
45–54	57	43	48	51
54–64	56	24	37	25
Total	165	109	128	126

Social Conditions

Data about social status were collected with the help of the local physician and social worker and are set out

TABLE II—OCCUPATIONS OF RECENT AND EARLY YEMENITES

Age and sex		Yemenite immigrants	No of cases	Farm workers (%)	Industrial workers (%)	White collar workers small artisans, pedlars (%)	Housewives (%)	Dependent on social relief (%)	Other dependants (%)
Males	35–44	Recent	52	80·8	9·6	5·8		3·8	
	45–54		57	45·6	3·5	12·3		38·6	
	55–64		56	21·4	5·4	8·9		64·3	
	35–44	Early	43	62·7	30·3	7·0			
	45–54		48	62·5	20·9	10·4			6·2
	55–64		37	54·1	16·2	10·8			18·9
Females	35–44	Recent	42	26·2			73·8		
	45–54		43	18·6			81·4		
	55–64		24	8·3			41·7	50·0	
	35–44	Early	47	31·9	4·3		63·8		
	45–54		54	24·1			75·9		
	55–64		25				76·0		24·0

in table II The recent immigrants were living in transit camps under poor conditions, whereas most of the early immigrants lived in their own houses under better economic circumstances The number of children was highest and monthly income lowest among recent Yemenites Among the recent immigrants the mean number of persons per family was 6·5, compared with 5·0 in the early Yemenites (Yemenite children leave their families to fend for themselves at an early age and only children dependent on the support of their families are included in these figures) The mean monthly income per person in the recent Yemenites was I L 19 (I L 1·80 = $1), compared with 38 I L in the early immigrants

Dietary Survey

The survey was conducted during the clinical and laboratory investigation and includes additional data, collected by the social worker, on the nutritional habits and consumption and composition of food of 55 recent and 21 early Yemenite families The figures in table III represent average daily values

The diet of recent Yemenites contains a lot of *pita*, a type of flat yeastless bread They also eat large quantities of vegetables, very little meat (once weekly), and very little fat (table III), which is mainly in the form of *samne** (boiled butter with *hilbe*, the seed of fenugreek (*Trigonella fœnumgræcum* L)) As the quantity of ingested fat is very small, the nature, composition (Bronte-Stewart et al 1956), and/or preparation (Sinclair 1956) of this fat probably has little influence on the pathogenesis of atherosclerosis † Both early and recent Yemenites make abundant use of sunflower seeds, chick-pea seeds, nuts, and almonds

Though the data collected on recent and early Yemenites express long-term nutritional habits, they cannot be as accurate, of course, as those provided by a controlled nutritional experiment Our results are, however, closely similar to those obtained by Strauss et al (1954) (table III)

Among males, 94% of recent and 92% of early Yemenites consumed more than a litre of alcohol monthly There was no striking difference in tobacco consumption between the two groups

Clinical and Laboratory Findings

Height and Weight

There was no significant difference in the average height of the two groups, but the weight of the recent Yemenite immigrants was significantly lower The weight/height ratio ‡ (table IV) was thus lowest in recent Yemenites In the 35–44 age group the weight/height ratio was normal among early Yemenites and fell with increasing age In recent Yemenite women the ratio was rather higher than in men of the same age and did not drop with increasing age

TABLE III—DAILY DIET OF YEMENITES

Group	Total calories per day	Animal proteins (g)	Fats (g)	% calories derived from fats
Recent Yemenites	1750	12	30	16
Early Yemenites	2350	20	55	21
Yemenites (overall) (Strauss et al 1954)	2296	19	51	20

Blood-pressure

Recent Yemenites had the lowest systolic and diastolic pressures The mean diastolic values of the early Yemen-

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* *Samne* is prepared by boiling ordinary butter, which contains about 82% fats, with small amounts of *hilbe* for its flavour The water thus extracted is discarded, so that the new product contains about 95–98% fats As the cooking of the butter is not performed under pressure, it is doubtful if all fatty acids undergo complete oxidation

† During the period of rationing, when the government supplied fats and animal proteins cheaply and equally to the whole population, the recent Yemenite immigrants were accustomed to selling their rations and restricted themselves essentially to food rich in carbohydrates

‡ $\frac{\text{Weight in kg}}{\text{Height in cm} - 100} \times 100$

TABLE IV—MEAN AND STANDARD DEVIATIONS OF TOTAL CHOLESTEROL, PHOSPHOLIPIDS, CHOLESTEROL/PHOSPHOLIPID RATIO, TOTAL LIPIDS, AND WEIGHT/HEIGHT RATIO IN RECENT AND EARLY YEMENITES

Age and sex		Yemenite immigrants		(1) Total cholesterol (mg per 100 ml)	(2) Phospholipids (mg per 100 ml)	Ratio (1)/(2)	Total lipids (mg per 100 ml)	Weight/height ratio
		No	Arrival					
Male	35–44	52 43	Recent Early	146 ± 28 189 ± 29	207 ± 23 217 ± 39	0·72 ± 0·15 0·88 ± 0·10	556 ± 67 634 ± 111	94 ± 9 99 ± 10
	45–54	57 48	Recent Early	158 ± 32 193 ± 37	212 ± 52 233 ± 40	0·76 ± 0·14 0·85 ± 0·13	*607* ± 103 *674* ± 104	92 ± 8 96 ± 12
	55–64	56 37	Recent Early	158 ± 29 206 ± 40	*205* ± 48 *233* ± 50	0·79 ± 0·12 0·89 ± 0·13	*594* ± 93 *655* ± 101	87 ± 10 92 ± 9
Female	35–44	42 47	Recent Early	172 ± 26 194 ± 30	237 ± 47 228 ± 37	*0·75* ± 0·12 *0·84* ± 0·11	*618* ± 72 *664* ± 93	94 ± 8 104 ± 14
	45–54	43 54	Recent Early	172 ± 29 209 ± 28	*219* ± 39 *245* ± 37	*0·80* ± 0·12 *0·87* ± 0·11	615 ± 89 694 ± 97	95 ± 10 108 ± 18
	55–64	24 25	Recent Early	190 ± 26 228 ± 36	233 ± 37 253 ± 31	0·83 ± 0·11 0·90 ± 0·11	633 ± 65 722 ± 97	*95* ± 11 *107* ± 17

Figures in bold type show highly significant differences (critical ratio > 3·5)
Those in italics show significant differences (critical ratio > 2·5)

ite immigrants were significantly higher As those with high blood-pressure were not included in this study, no definite conclusions on "coronariness" (Gofman et al 1954) could be drawn from these figures

Blood

Blood samples were collected in the morning from fasting subjects and separated three to four hours later Every blood examination was performed in duplicate, and results diverging by more than 5% were discarded Our method was described in an earlier communication (Toor et al 1954)

Hæmoglobin—The mean hæmoglobin values (determined with Sahli's apparatus) were slightly lower in both groups than the accepted values in Western countries (Berry et al 1952) In females these values were lower than in men for all groups In men the hæmoglobin values dropped with increasing age, but not so in women The hæmoglobin values of early Yemenite immigrants were significantly higher than in recent Yemenite groups The gap between the two decreased with increasing age There was no significant difference in hæmoglobin values of early and recent female Yemenite immigrants

Cholesterol—The mean and median serum cholesterol value was lowest for recent Yemenites in both sexes and in all age groups (table IV, fig 1), and the difference was statistically significant (males, t=7 35–5 15–6 30, females, t=3 71–6 35–4 21)

Phospholipids—The values were higher among females in all age-groups

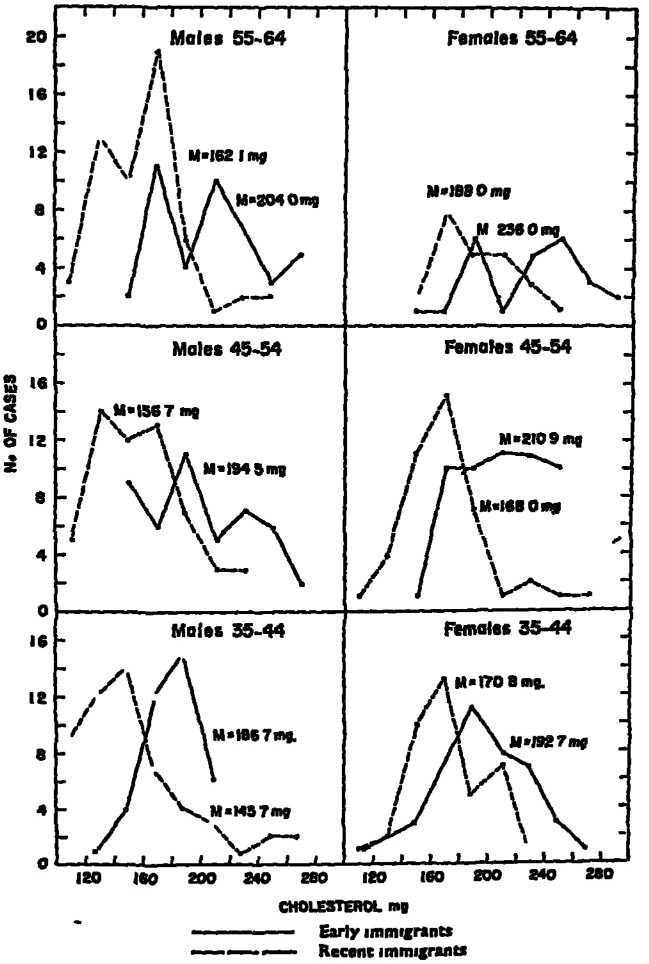

Fig 1—Distribution of serum-cholesterol values in early and recent Yemenite immigrants in Israel M = median value

TABLE V—ATHEROSCLEROSIS MORTALITY OF EARLY AND RECENT YEMENITES (1953–55) (RATES PER 1000 INHABITANTS PER YEAR)

Age and sex		General population		Yemenite immigrants			
				Early		Recent	
		No of deaths	Mortality rate	No of deaths	Mortality rate	No of deaths	Mortality rate
Males	35–44	47	0 44				
	45–54	203	2 26	6	3 3	2	0 49
	55–64	393	8 56				
	65 +	945	32 2	15	23 6	8	6 3
Females	35–44	20	0 19	1	1 8		
	45–54	82	1 04	3	1 8	2	0 51
	55–64	262	5 9				
	65 +	932	26 5	12	20 0	6	4 7

Cholesterol/phospholipid ratio—This ratio remained within normal limits, but was lowest among recent Yemenites

Total lipids—The mean values were lowest among recent Yemenites, and the differences were significant in both sexes

The mean of the results for each age group and the standard deviation are set out in table IV

Mortality from Atherosclerosis

To minimise the errors due to detailed clinical diagnosis, we have used the group diagnosis of "atherosclerosis" in which we did not include deaths due to hypertension or heart failure induced by causes other than atherosclerosis Most of the death certificates from which mortality figures were derived were based on clinical rather than on post mortem examination But our main object was a *comparative* study of atherosclerosis mortality-rates in the different communities in Israel As most of the Jewish population in Israel get their medical treatment through the Sick Fund of the General Federation of Labour, the proportion of errors due to death certificates based on clinical diagnosis is likely to be the same in all sections of the community

The atherosclerosis mortality-rate in 1953–55 was about four times higher among early Yemenite immigrants than among recent ones (table V) In fig 2 the rates are compared with those for European Jews (Toor, Katchalsky, Agmon, and Allalouf) It should be stressed that the body build of Yemenites, both early and recent, remained the same Both groups obeyed religious laws and conformed to social customs to the same extent Their ways of life were practically unchanged, and no mental stress could be incriminated in the early Yemenites The mortality rate from infectious diseases was similar in both groups The mortality-rate from malignant tumours was lowest among the recent immigrants The mortality rate from all causes in recent Yemenites over 65 was practically the same as the over 65 rate among other national groups in Israel The lower mortality-rate from atherosclerosis among recent Yemenites cannot therefore be ascribed to death from other causes at a younger age

Discussion

Keys et al (1950, 1954) established a relation between the amount of fat in the diet, the serum cholesterol level, and the frequency of atherosclerosis Katz (1953) pointed out that the differences in the incidence and severity of atherosclerosis "tend to correlate with culturally conditioned variations in nutrition and diet rather than with racial, climatic or other factors" Most of the Yemenites we studied were manual workers or clerks of limited income, and the recent immigrants were the poorest Their nutritional status was lower

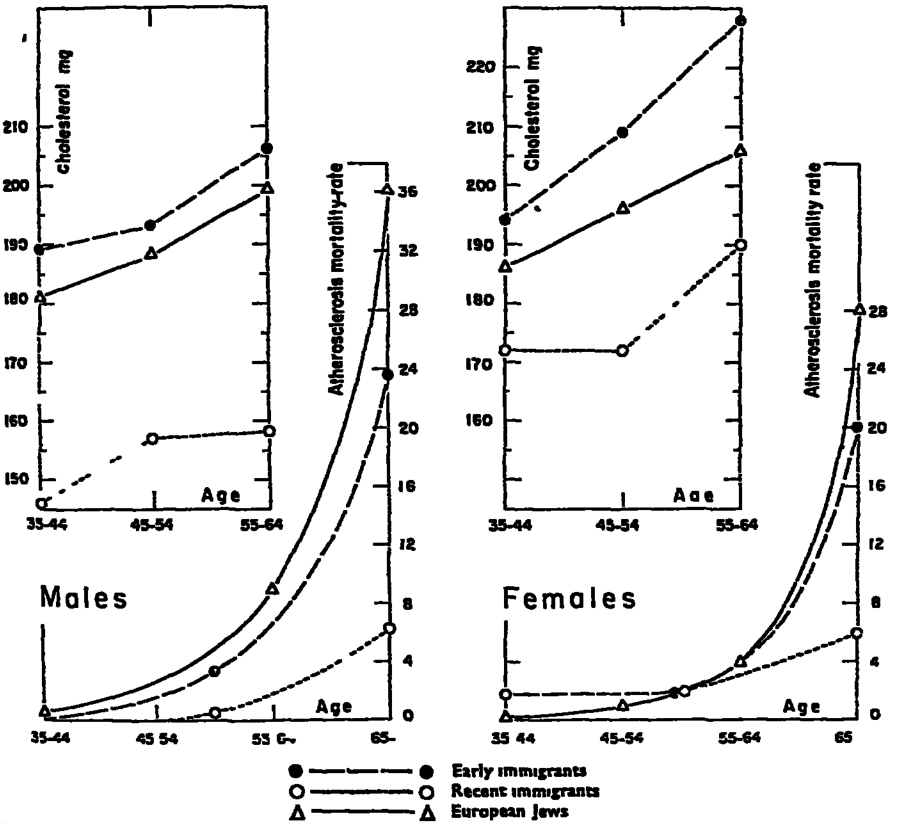

Fig 2—Atherosclerosis mortality and mean serum-cholesterol values in early and recent Yemenite immigrants in Israel

than that of the early immigrants, and their serum-cholesterol, phospholipid, and total-lipid values were also lower and were in accordance with the values reported in Guatemalan farm-workers (Mann et al 1955) and in South African Bantus (Bronte-Stewart et al 1955)

The lower mortality from atherosclerosis among Yemenites in Israel has attracted much interest during the past few years In a series of 967 post-mortem examinations, including 123 Yemenites, Shalom (1954) found a third coronary artery in 0 83% of European Jewish immigrants as against 2 44% in Yemenite immigrants—a possible explanation for the lower incidence of myocardial infarction in Yemenite Jews But this explanation is unlikely because of the increased atherosclerosis mortality among the early Yemenite immigrants

Our own observations indicate that varicose veins and thrombophlebitis are uncommon among Yemenite immigrant women, even in those who have had many pregnancies Berman-Yeshurun (1956) found that the incidence of atherosclerosis and thrombophlebitis was low among Eastern Jewish immigrants These findings raise the possibility that these people are less liable than others to intravascular clotting The rarity of thromboembolic phenomena among the Bantus (Keys 1956) and the Dutch East Indians (Van Unnik and Straub 1953), however, and the decrease of thromboembolism in Norway during the late war (Strom 1954), suggest a relation between low-fat diet, thrombosis, and atherosclerosis

It is also difficult to explain the low serum cholesterol values on the basis of a metabolic genetic factor in recent Yemenite arrivals, because, with increased consumption of food, particularly fats, cholesterol values and atherosclerosis mortality-rates approach those of Europeans The possible effect of sunflower seed oil on serum-cholesterol levels does not seem to be relevant, since both groups eat sunflower seeds

The cholesterol levels in both early and recent Yemenite women aged 45–64 were significantly higher than in men of the same age We can suggest no satisfactory explanation for this interesting finding and we are investigating it further

The differences in the incidence of atherosclerosis among early and recent Yemenite Jewish immigrants can best be explained by the differences in total food intake determined by differences in income Furthermore, the recent Yemenite immigrants work harder, and remain in a state of caloric imbalance at the age when atherosclerosis is commonest

Summary

The nutritional status, serum-cholesterol values, and incidence of atherosclerosis were investigated in recent (within past five years) and early (over twenty years ago) Yemenite immigrants in Israel Serum-cholesterol and total lipid levels were significantly less in recent immigrants On the other hand, the atherosclerosis mortality-rate was four times higher, for the same age and sex, in the early Yemenite immigrants and approached the rate for European Jews Among the early immigrants, the average income per head was double that on which the later arrivals were living

This study, undertaken as a part of the research programme on morbidity and mortality from atherosclerosis among the various communities in Israel, has been made possible by a grant from the Kupath Holim, Workers' Sick Fund of Israel We wish to thank Dr G Kalner, chief of the statistical department, Israel Ministry of Health, for providing the data on mortality rates of different age groups, and we gratefully acknowledge the aid of Mrs S Seligson, head of the medical statistical department of the Sick Fund, for the statistical analyses

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VENTRICULO-SUBDURAL DRAINAGE IN INFANTILE HYDROCEPHALUS

ANALYSIS OF EARLY RESULTS

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MANY operations may relieve hydrocephalus, but none is suitable for all types of the disease In an attempt to fill this gap, the present procedure was devised by one of us (D M F) as a drainage from a lateral ventricle to the supratentorial subarachnoid space A brief announcement in these terms was made (Forrest 1955), but it became obvious soon afterwards that the method was in fact a ventriculo subdural drainage—a method which has been used before with different materials (Taylor 1909)

Thus founded in error, the operation would have been abandoned had we not observed that in a high proportion of the early cases the disease was becoming arrested This led us to persist with a longer trial The patients operated on in this series have now been followed up for between twenty and thirty-two months, and the effect of the operation can be seen in reasonable perspective

Material

To give the method a comprehensive trial, it was decided to perform the operation in all cases of progressive hydrocephalus, even in those with an apparently hopeless prognosis The present series comprises all cases of hydrocephalus seen in one unit at the Westminster Children's Hospital and The Hospital for Sick Children, Great Ormond Street, between October, 1954, and August, 1955 During this time there were 70 new cases at all ages up to 6 years Of these, 20 appeared to be arresting spontaneously, so were not operated on Of the remaining children, 4 died before operation could be done, and in 10, though treatment was required, it was abandoned because of active infective ventriculitis (8) or very gross thinning of the cortex (2)

In the 36 cases coming to operation, blockages were demonstrated at all the common anatomical sites (table I), and were of varied ætiology Many patients were in an advanced stage of the disease

Investigations

Only those tests used in selecting cases for this operation or in assessing the results will be discussed here, though all the usual *investigations for hydrocephalus* have been carried out

Circumference of head.—This is the most useful gauge of progressive hydrocephalus in all cases which still have some elasticity of the skull It is estimated weekly, if possible by the same observer on each occasion

Ventricular pressure.—This is estimated with the child quiet (if necessary, sedated) but not anæsthetised, and under these conditions we have achieved consistent results It is less informative than measurement of circumference, but, taken in conjunction with this, it offers a satisfactory means of assessing improvement or deterioration in comparison with previous readings

Subdural fluid should be sought at the time of ventricular tap Its presence may be due, among other causes, to a *hæmatoma or a natural ventriculostomy*

Thickness of cortex.—is estimated during ventricular puncture and confirmed by air studies

Analysis of ventricular fluid.—Evidence of recent hæmorrhage or active infection are indications for delaying or abandoning the operation

Dye studies.—Estimations of urinary excretion of dye after ventricular or thecal injection are mainly used for localising the block (Laurence 1957) and are not essential in an operation where this is not important They have been used in a few cases to demonstrate improved excretion after a successful operation

Method

Design of Apparatus

Drainage is achieved by means of a plastic tube passed through the cerebral cortex from a lateral ventricle to the supratentorial subdural space On several occasions, where various forms of drainage from a ventricle to another part of the body had failed, it was observed that failure was usually due either to blockage of the *distal* end of the tube (the proximal end remaining patent), or to displacement of the *proximal* end from the ventricle Accordingly, the tube was made with a deeply grooved cover on the distal end and a self-retaining proximal end (fig 1)

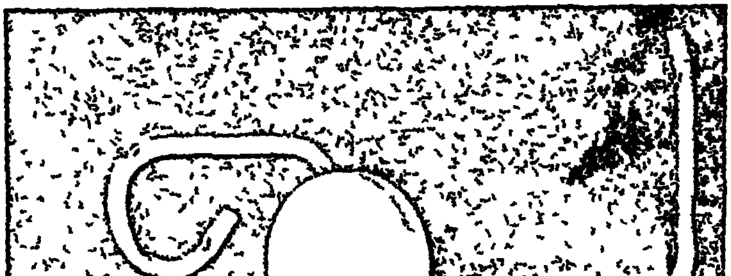

Fig 1—The Forrest disc with and without stylet in place

Plastics are the obvious materials to use, but there is some difficulty in choosing one with the required characteristics of flexibility, elasticity, and ease of moulding and of sterilisation Most important of all, the material must not produce a foreign-body reaction, or the tube will become blocked 'Polythene' has been widely used in similar procedures, and the first 11 operations were performed with discs of this material In those cases which failed, however, the discs were seen to be blocked by heavy deposits of fibrinous or collagenous material, and polythene was discarded in favour of nylon, a much more physiologically inert plastic All the remaining operations in this series were done with nylon discs, but more recently an even better material, polytetra fluoro ethylene, has become available This is almost completely chemically and

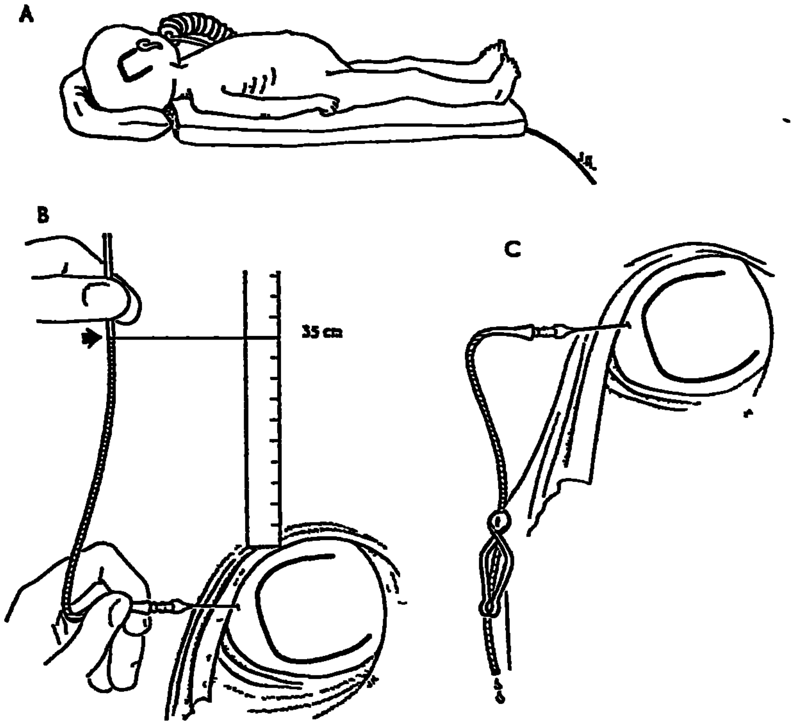

Fig 2—Stages of the operation as described in the text

physiologically inert, has a high softening temperature, and is unwettable The discs are now being manufactured of this plastic under the name of the 'Forrest Disc' *

With all these materials the method of construction has been the same The tube is shaped by passing a malleable wire through the lumen, bending to the required shape and then heating to the softening point of the plastic After cooling, the wire is withdrawn, whereupon the tube resumes the curved shape (This general method has wide applications in other surgical procedures where a tube of a certain curve or angle is required) The disc portion of the device is turned up from solid plastic rod

Operative Method

The actual insertion of the disc presents few difficulties it is straightforward (fig 2), and well tolerated by the patient Since the first 2 cases we have found it unnecessary to provide intravenous fluid or blood during operation

First, a short lumbar-puncture needle is inserted into the dependent lateral ventricle A half-metre length of polyvinyl chloride tubing of 2 mm bore is connected to it, and used as a manometer to measure the ventricular pressure (fig 2B) The tube is then lowered to drain the ventricles (fig 2C) While the dura remains intact, fluid is allowed to drip until the pressure falls to atmospheric, and this rapid decompression has been found not to disturb the patient

An osteoplastic flap is next reflected, usually in the right posterior parietal region (fig 2A) Sometimes the bone is thin enough to be cut with stout scissors but often it must be sawn in the usual manner The posterior limb of the bone section should be made about a centimetre anterior to the occipito-parietal suture If it is

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* Manufactured by Crane Packing Ltd Slough, Bucks

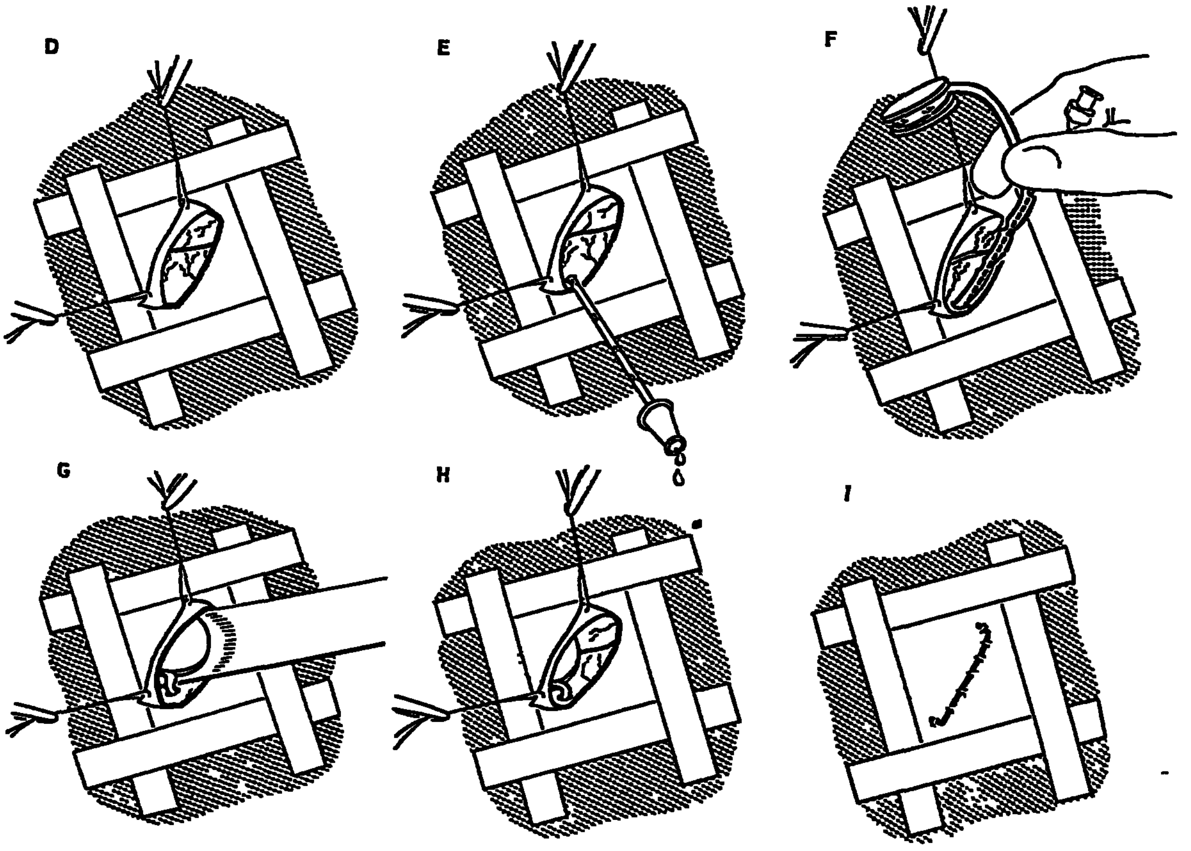

Fig 3—The operation continued and concluded

too close, the dura, which is adherent to the suture, may be inadvertently lacerated

The dura should not be opened until the ventricular pressure has fallen to a low level and the dura is seen to be indrawn If the skull is very thin this may not happen, because *the sutures override and the skull* collapses as fluid escapes In these cases it is helpful to elevate the parietal bone by means of a blunt hook placed under the bone edge

When the dura is incised the brain should fall away, leaving a space about 1 cm deep Thus the dural incision can be enlarged to 3 cm and the disc inserted without risk to the cortical vessels (fig 3D) When the brain has fallen away sufficiently, the lumbar-puncture needle may be withdrawn from the fontanelle

Selecting a bloodless area of the cortex near one end of the dural incision, the operator next passes a Jefferson's brain cannula into the lateral ventricle, to form a track for the insertion of the tube (fig 3E)

Before the device is inserted *it* is absolutely essential to make sure that there is no bleeding and to rinse away with Hartmann's solution all blood and clot which may have collected in the subdural space The *disc*, which has been sterilised by boiling or autoclaving, is next prepared by the insertion of a blunt ended hollow needle to straighten the tube, which is then passed down the track made through the cortex (fig 3F) When it enters the ventricle, fluid is aspirated and then reinjected as the stylet is withdrawn, thus ensuring that the tube is not blocked with clot or brain tissue The end of the tube then resumes its curled shape within the ventricle

TABLE I—DESCRIPTION OF THE 36 CASES COMING TO OPERATION

A Type	
Communicating	17
Non communicating	10
Unknown	9
Total	36

B Site of Block	
Aqueduct	5
4th ventricle foramen	2
Basal cistern	12
Arnold Chiari malformation	15
Unknown	2
Total	36

With the aid of a brain spatula (fig 3G), the disc is now rotated under the dural flap (fig 3H), well away from the operation site When hæmostasis is certainly complete, the dural flap is closed (fig 3I)

Postoperative Course and Complications

The postoperative course is usually smooth, though the temperature is often elevated for a few days The infant should be nursed flat for twenty-four hours, but supportive therapy is usually unnecessary The fontanelle does not often collapse in the dramatic way seen after some drainage operations As it is almost impossible to make a watertight closure of the dura, there is a risk of a collection of cerebrospinal fluid forming under the skin flap The risk is minimised by application of a firm dressing, but, if fluid does collect, it should be aspirated before it becomes infected

TABLE II—OPERATION RESULTS

—		No of cases	%
Operation successful (arrest immediately after operation)		13	36
Operation not successful		23	64
Arrested subsequently	5		
Still progressive	1		
Dead	17		
Total		36	100

TABLE III—FATE OF THE WHOLE SERIES

—	Arrested	Progressive	Dead
Operation	18	1	17
No operation			
Natural arrest	18		2
Persistent (i e , infection)		1	7
Thin cortex		1	1
Death before operation			4
Total	36 (52 %)	3 (4 %)	31 (44 %)

The only other complications we have seen were repeated slight intraventricular hæmorrhages in 1 case, and massive fatal cerebral thrombosis in 2 cases Most of our patients were well enough for discharge fourteen days after operation if drainage appeared satisfactory

Results

In following up cases of a disease characterised by insidious progress or spontaneous arrest, it is not easy to assess the effect which an operation has had Some of our cases which were steadily progressive before operation have remained static for between twenty and thirty-two months since It is this group alone which has been classed as successful A few of the cases seemed to progress for a time after operation but have since arrested *These have been classed as failures in our* series, though operation may possibly have prevented too much deterioration before spontaneous arrest

Assessment has been by frequent checks, in which clinical impression, head measurement, and (in the majority) repeated ventricular-pressure readings have made a decision possible In a few cases, dye-excretion tests and air studies have been used, and improved absorption or thickening of the cortex has been demonstrated

The problem of classification was simplified by the fact that all the cases which failed after having drained did so within four months of operation, and nearly all within two months All cases which succeeded for that length of time are still arrested, though *of* course it is impossible to say whether the arrest will be permanent

TABLE IV—CAUSE OF DEATH IN OPERATED CASES

Related causes	
Progressive hydrocephalus	7
Intracranial infection	3
Intracranial vascular thrombosis	2
Operative	1
Unrelated causes	
Gastro-enteritis	1
Inhalation of vomit	1
Intestinal obstruction	1
Unknown cause	1
Total	17

Of the 34 babies not operated on, hydrocephalus was arrested naturally in 20, as predicted *All these* are alive and well now, except 2 who died, 1 congenital heart disease and 1 of meningitis from an infected myelocele Of the 14 progressive cases, 12 are dead, and 2 not expected to survive long

Of the 36 babies operated on, hydrocephalus was arrested immediately in 13 and later in 5 These 18 are all still well (table II)

Tables III and IV show the survival-rates of the whole series and the causes of death in the cases operated on

Discussion

Little would be gained by comparing these results with those of other workers The criteria of success must differ widely in different series (here we are taking only the narrowest meaning—i e, arrest definitely coinciding with operation) Also, we have made no selection of cases, operating on all with progressive disease in whom it was technically feasible to do so This must have prejudiced results since many patients coming to operation were in an advanced stage of the disease We think, however, that this approach was the correct one, for the experience gained in treating these children is now proving of value in a more discriminating selection for a new series

In an attempt to devise a reliable method of selection, a dye excretion test for the subdural space has been worked out It was not used in the present series, but more recent work has shown a correlation between the percentage of dye excreted and the potential absorptive power of the space, and hence the prognosis for the operation in any particular case

The operation has a wide field of application, being suitable for the treatment of obstructive hydrocephalus wherever the site of the block Its sole requirement is a subdural space which will absorb sufficient cerebrospinal fluid and will continue to do so Therefore, success cannot be expected in the presence of a subdural effusion, and the space will rapidly lose its absorptive power if operation is performed in the presence of recent ventricular hæmorrhage or infection We have operated on patients whose cortex is almost paper-thin but, apart from other considerations, the technical difficulty of placing the disc without damage to the cortex makes these cases almost hopeless

In failed cases, it has usually been found that the disc, and sometimes the subdural space itself, have become occluded by adhesions More rarely, the disc has been found patent but the subdural space lined by a membrane and filled with unabsorbed fluid In either case, the cause can usually be shown to be due to the presence of blood or low grade infection

The fate of all the cases seen during the period of this series has been analysed to show that the success of the operation does not depend to any significant degree on natural arrest, since these cases have largely been eliminated before operation The figure of 36% success for the operation series, not in itself very striking, must be considered in the light of the total arrest rate of 52% for the whole series, and it must be remembered that the successes in the operation series were obtained from material from which many of the more favourable and only a few of the worst cases had been eliminated

In the next series we hope to be able to show that selection of cases will lead to more predictable arrest The number of operations performed is already large enough to show that, in a wide variety of hydrocephalic infants, arrest for a considerable length of time can be produced

Summary

An operation for hydrocephalus is described and a previous report amended The operation consists in the insertion of a plastic device through the cerebral cortex to provide drainage from the lateral ventricle to the overlying subdural space

A series of 36 operations on cases selected from 70 hydrocephalic infants is presented and the results discussed 13 of the operations seem to have arrested the disease

The results suggest that the method may be of value in many types of hydrocephalus, especially after selection by subdural dye excretion studies

We wish to thank our colleagues at both hospitals for their coöperation One of us (K M L) acknowledges the support of the research committee of The Hospital for Sick Children, Great Ormond Street Thanks are also due to Mr D Martin of The Hospital for Sick Children for fig 1 and to Miss J Hassell, the medical artist at the Westminster Medical School, for figs 2 and 3

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THE TRANSFER OF BLOOD BETWEEN BABY AND PLACENTA IN THE MINUTES AFTER BIRTH

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IN 1801 Erasmus Darwin wrote

> " Another thing very injurious to the child, is the tying and cutting of the navel string too soon, which should always be left till the child has not only repeatedly breathed but till all pulsation in the cord ceases As otherwise the child is much weaker than it ought to be, a part of the blood being left in the placenta, which ought to have been in the child "

Since then many estimates have been made of the amount of additional blood which a baby may receive if the cord is not tied immediately Assessments have been made by weighing the baby (Haselhorst 1929, Allmeling 1930) and from blood volumes, and from the amount of blood obtainable from the placenta (DeMarsh et al 1942) Each investigator has found that a considerable proportion of the placental blood may flow into the baby or be trapped in the placenta according to the time of tying the cord

Present Investigation

Continuous records were made of the baby's weight in the minutes after birth so that not only the amounts of blood but also the events determining its flow could be examined

A semi automatic weighing machine was adapted to give a continuous record on a constantly moving drum indicating weight gain and loss The machine stood on an adjustable trolley and could be raised and lowered As soon as the baby was born he was put on to the pan in warmed blankets, and the recording pen was quickly brought near the centre of the chart by putting weights on the other pan. There was inevitably a delay, usually of 10–20 seconds, between the completion of birth and the start of the record

The instrument was so sensitive that the baby s movements caused an oscillation and a thickened record This had the advantage of showing the vigour of the baby's movements without obscuring the weight trend Large oscillations and interruptions in recording were inevitable during resuscitation and were sometimes also caused by the baby's movements

No attempt was made to hold up the flow of blood by constricting the cord while the record was interrupted or during the initial phase of getting the baby on to the pan Since at this stage the blood usually flowed rapidly to the baby, the total gains recorded were probably less than might have been obtained by holding up the flow then Recording usually continued until just before the birth of the placenta

Changes of weight were recorded in 39 babies born by vaginal delivery and 11 born by cæsarean section There were 33 boys and 17 girls The boys outnumbered the girls possibly because weighing was stopped at the outset through anxiety for the baby more often in the case of girls than boys

Pulsation in the cord was taken to indicate partial or complete patency of the cord arteries Because this was not seen to recur once it had ceased, blood was considered to flow only through the umbilical vein after cessation The records of weight change after vaginal deliveries showed that though the flow was mostly towards the baby, rapid loss from the baby to the placenta also often took place, sometimes but not often

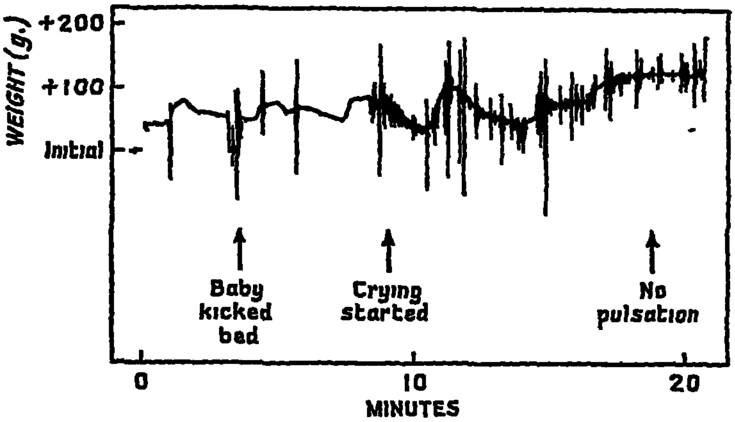

Fig 1—Weight changes in baby lying at level of vulva, with cord pulsating for 19 minutes Note weight changes induced by uterine contraction and relaxation

equalling or even exceeding the gain When the umbilical arteries were open, such loss may have been due to the pumping up of the placenta from the arterial side or be due to venous loss and no distinction could be found to indicate which was happening, except that where pulsation was present loss was more frequent

To find whether siphonage played any part in the interchange of blood, the weighing-machine and the baby were racked up and down to about 15 cm above and below the level of the mother's vulva when the baby's weight was steady

Figs 1–3 illustrate the events in three instances where the cord was pulsating during all or nearly all the period of tracing

In fig 1, with the baby kept at the level of the vulva, the successive gains synchronised each time with a uterine contraction, which was shown by the small increased loss at the introitus In this record the dominant effect of uterine tone is so clear that the baby's weight record had become virtually *a plethysmograph of uterine activity*

In the record shown in fig 2 two gains were accompanied by uterine contraction, but there was no weight loss even though the baby was raised and lowered, once stability had been reached

Fig 3 shows an instance where a baby who was slow to cry gained and lost and gained again before crying was established, the timing of the changes being different from those in figs 1 and 2

Fig 4 shows part of a tracing where pulsation had ceased and the weight, though still slightly increasing, was almost steady The baby was then raised above the level of the vulva (the broadened record represents the vibration of winding the pan up) *It will be seen that a loss of weight started as the baby's position was altered* and continued until the pan was quickly lowered to below the original level The succeeding gain when the baby was below the level of the vulva slowed as the baby started an outburst of crying, the subsequent tracing shows a slow steady gain The loss of 26 g and the gain of 58 g brought about by small hydrostatic changes due to the baby's position show how a baby may lose blood through being held above the level of the placenta In this instance the loss was cut short by altering the baby's height and was not necessarily maximal Clear evidence of loss and gain through venous siphonage was seen in 5 cases in the 19 where trial could be made

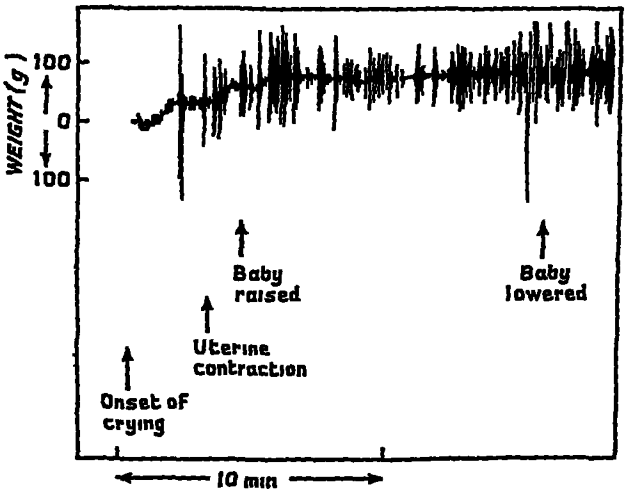

Fig 2—Stepwise weight gains associated with uterine contractions Cord pulsation throughout. No change resulted from raising or lowering baby.

The weight changes in 11 babies born by cæsarean section were recorded despite the difficulties of the circumstances The baby was put on to the pan and the weight charted intermittently between frequent phases of resuscitation (fig 5) (after its delivery the placenta was put in a tilted kidney-dish and taken, together with the baby and the apparatus, to another part of the theatre) These records are therefore less detailed They fall into two contrasting groups (fig 6)

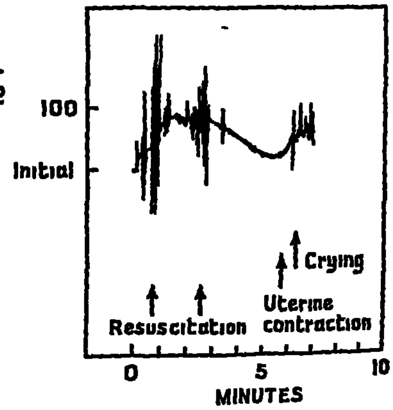

Fig 3—Large early weight gain succeeded by loss and small gain Cord pulsating throughout Baby at level of vulva

(1) 3 babies were large and vigorous and recording was continued conveniently The *increases observed* included 3 of the 4 greatest seen in this investigation (125, 130, and 180 g)

(2) In the other group the birth weights were, with one exception, under 3 5 kg , and the signs of vigour were delayed , so the recording was cut short, but even in the period of observation a stationary phase appeared to have been reached *None of these babies received more than 55 g* of blood

Discussion

These records confirm once more that, if the cord is left untied, a baby will usually increase his blood volume by a significant amount The weight of blood received by these babies, as in Haselhorst's (1929) and Allmeling's (1930) work, was roughly correlated to the baby's weight (fig 6), ranging from 0 8 to 4 7% of the body-weight If the blood of the neonate weighs about 10% of the body-weight the amount of blood involved can probably be more than 40% of the baby's blood volume

Little is known of what determines how much blood the baby's body will accept The amount of blood passing into the baby may be correlated to the baby's size because the size of the placenta is similarly related, and the amount of blood in the placenta depends on the size of the placenta The changing resistance of the pulmonary vessels at the onset of respiration in the maturing embryo (which has been found in sheep by Born et al [1955]) may be another contributary factor. Thin cords appear to go white and cold sooner than thick ones, and transfer ceases soon after the cord is white

The baby's size is not the only determining factor, because some of the records showed a cessation of flow while the cord vessels were still functioning, as if a main reservoir had been filled For instance, fig 4 shows that, after siphonage out, the blood flowed in fast at first when the baby was put below the level of the placenta, but, when the gain reached a point lying more or less on the projection of the original weight line, the gain slowed suddenly and continued as before from there In that case the loss and gain were known to be venous and the inflow was at a rate of 60 g a minute If the circulation time in a neonate is about 10 seconds (Lesser et al 1952), this addition to, and the earlier subtraction from, the circulation are relatively small, but the definite limit observed suggests that the filling may have been partly set, perhaps, by the capacity of liver, lungs, and spleen

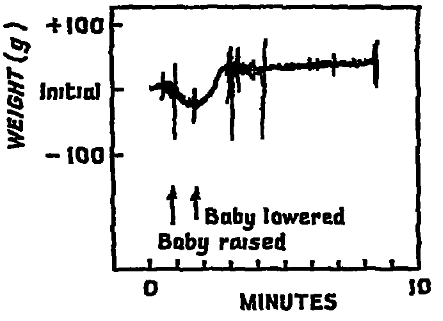

Fig 4—Loss of weight from siphonage when baby was raised and restoration when baby was lowered No pulsation of cord

The intake was also seen to be limited on a small scale by a certain sequence of events In many records a relatively steep gradient showing flow into the baby, as in fig 1, was followed by a burst of crying rather as, in transfusing a baby, crying is often induced by quickness of flow Sometimes the crying had little apparent effect on the rate of inflow, but more often the raised intra-thoracic pressure of crying could be seen to be damming back the venous flow or even to be driving blood into the cord vein at the umbilicus when the cord had been previously empty The immediate effect of crying may therefore be to slow the intake, yet the contrast between the two groups of babies born by cæsarean section implies that the lusty crying baby gains much while the baby not quickly putting its lungs into use gains little

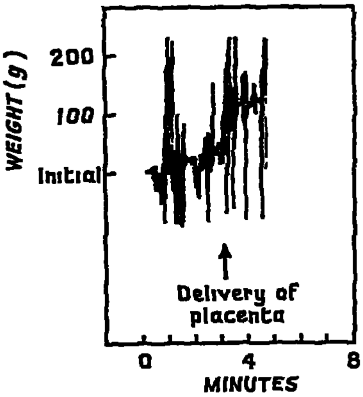

Fig 5—Weight after cæsarean section

We have, then, a picture of complicated hydrodynamics After vaginal delivery the force of the uterine contractions, known to be about 60 mm Hg in the second stage (Moir 1936), may squeeze the placenta The baby's systolic arterial pressure of 69 mm Hg (Holland and Young 1956) tends to distend the placenta and does so rapidly while the umbilical arteries are patent and the uterus is relaxed The blood in the umbilical vein is hastened towards the baby by uterine contraction but, when uterine tone is poor, may flow in either direction, which is determined by small changes in pressure, such as those induced by 15 cm difference in height (12 mm Hg) and by changes in intrathoracic pressure

In addition it is probable that the physiological mechanisms in newborn lambs described by Dawes et al (1953, 1955, 1956) and Born et al (1955, 1956) have their counterpart in man, and that the interplay of pressure changes and the patency of the foramen ovale and the ductus arteriosus and the calling up of autonomic effects by asphyxia with quickened umbilical arterial flow alter and are altered by the nett flow of blood

Most important of all, presumably, are the interaction and interdependence of the inflation of the lungs and the increasing circulation in them Jäykkä (1957), who subjected the lungs of stillborn babies to constant inflation down the trachea and constant reduced pressure surrounding the lungs, showed that the distension of the lungs was greatly aided by distending the pulmonary arteries (in his work at 80 mm Hg) It seems that, for the establishment of breathing, the ample filling of the right side of the heart and also perhaps reversed flow in the ductus should occur with the phases of attempts to distend the thorax Although the venous inflow is halted by the expiratory efforts of crying, over a period of time the distension of the lungs would be promoted by the existence of a reservoir to feed into the circulation

If the inflow is important not only for increasing the amount of blood but also for expanding the lungs, delay in tying the cord has to be viewed slightly differently With a brief delay the obstetrician may be helping the baby to 50 g of blood, with a longer delay there may be an alternation of events which benefits the child even more Possibly there is here a principle of intermittency.

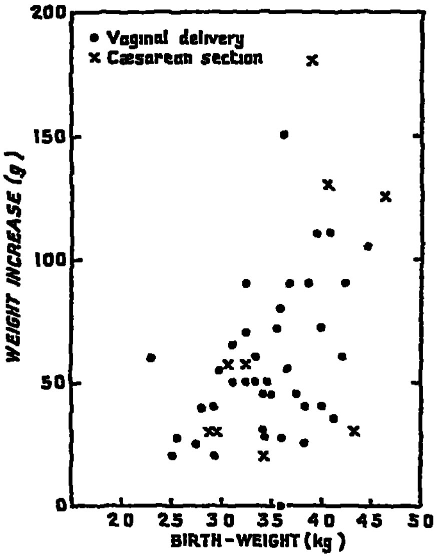

Fig 6—Relation of weight gain to birth weight.

Further work should show whether the incidence of pulmonary syndrome of the newborn can be reduced by allowing this reservoir to operate Bonham Carter et al (1956) have already shown that the child who survives the condition has the capacity to increase his caval pressure The added risk of pulmonary syndrome in delivery by cæsarean section (Bound et al 1956) may be due to the draining to which nearly all babies so born are subjected, because at cæsarean section the baby is usually held well above the mother's abdomen,

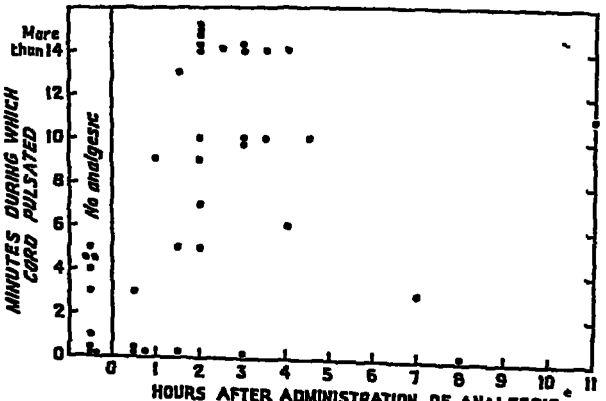

Fig 7—Relation of duration of pulsation of cord to administration o analgesics in labour

the intra uterine pressure being roughly that of the atmosphere The cord vessels are conspicuously distended Loss of blood into the placenta is almost certainly fast and large, and the baby loses not only what would have been transferred to him if tying had been delayed but also an additional amount flowing in both cord vein and arteries into the unsqueezed placenta Usually the cord is *cut near the baby*, a practice which deprives him also of the 10–15 ml of blood in it Many surgeons now hold the baby at table level to avoid siphonage Landau et al (1950) suggested delaying the tying of the cord and slinging the placenta in a towel above and beside the baby in the cot to allow passive transfer to continue

Siphonage and arterial loss are also almost inevitable when the mother is delivered in the lithotomy position and the baby placed on her abdomen, unless an oxytocic drug has been given Lohne (1943) recommended that babies delivered by forceps should be put below the level of the vulva This procedure is also probably very important to the first born of twins, at their birth the large relaxed uterus cannot be treated with oxytocics, for them the cord should be left untied until it is white and the uterus contracted, the baby lying below the level of the placenta

Holland and Young (1956) describe persisting low blood pressure in infants after breech and forceps deliveries and, more especially, after cæsarean section Their findings may well be a measure of the draining to which the babies are subjected where an analgesic is keeping the cord arteries patent, anæsthesia has relaxed the uterus, and the position of the baby is allowing siphonage I have been repeatedly surprised that the baby's condition gives no indication of the loss of blood into the placenta Obstetricians can so easily be unaware that blood is draining from the baby, and none would consent to the visible removal of 30–50 ml

One argument often put in favour of delayed tying of the cord is the tradition that the baby born before the arrival of assistance thrives In such a case the baby usually lies at a level lower than the placenta, the tying of the cord is not immediate, and the placenta (and the blood going to the baby) is kept warm in either the uterus or the vagina

In most deliveries nowadays we cannot imitate what appears natural, because analgesics (pethidine and chloral in this work) given to the mother during labour prolong the duration of pulsation in the cord Fig 7 relates the duration of pulsation to the administration of analgesics Since analgesics have such a definite action on the umbilical arteries, their possible effect on the closing of the ductus arteriosus and their effect on uterine arteries need to be reconsidered The incidence of postpartum hæmorrhage among women receiving one analgesic should be compared with a group receiving none rather than with those receiving another The delay between administration and its effect on the umbilical vessels presumably prevents the use of analgesics in the treatment of prolapsed cord

This investigation was first undertaken to determine whether delayed tying of the cord would provide fluid to tide the baby over the period of dehydration No clear evidence was obtained on this point, but certainly the additional blood is enough to be a significant contribution to the baby's nutrition 100 g is more fluid than a baby usually takes from the breast in the first two days, and the iron content is as much as the baby might be expected to get from milk in his first month

Fear has been expressed that the increased intake of blood would cause severe jaundice, but only 1 of the 50 babies developed severe jaundice It is unlikely that jaundice was prevented by increased renal secretion induced by greater fluid intake, because the weight losses in the first days of life were not unusual

Summary

The transfer of blood between baby and placenta was studied by continuous records of the baby's weight after normal deliveries and after birth by cæsarean section.

The transfer of substantial amounts of blood to the baby was confirmed, but large losses were also observed and were attributed to loss through patent umbilical arteries and by siphonage when the baby was held higher than the placenta

Three large vigorous babies born by cæsarean section gained very much, but the others little

Pulsation in the cord was prolonged if the mother had received analgesics

The findings are considered in relation to obstetric practice and neonatal respiratory physiology

My thanks go to Sister K M Billing and to the obstetric staff of University College Hospital for their help in this work, which was assisted by a grant from the Medical Research Council

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ACUTE SUPPRESSION OF URINE AND LIVER FAILURE ACCOMPANYING ECLAMPSIA

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SUPPRESSION of urine may have many causes, and we do not always understand its pathogenesis It is a well recognised complication, but we do not know why anuria following eclampsia has hitherto been almost invariably fatal either directly or through further complications

Many cases of anuria treated conservatively have been described Most of those from departments of obstetrics and gynæcology have followed abortion, incompatible blood-transfusion, antepartum hæmorrhage, or postpartum hæmorrhage[2, 9–11, 16–19, 21, 23, 24, 26, 28–30, 34–37] Few detailed reports of anuria in eclampsia have been published, and a large proportion of the patients died[12, 19, 21, 24, 25, 29, 35, 36]

In the present case the patient developed anuria during eclampsia and was treated conservatively and recovered, probably because the renal failure was recognised early and conservative treatment, based on the lines of Borst, Bull, and others,[3–7, 13, 39] was started at once We have been unable to find any published report of a case of this type treated in this way

Case-report

The patient, aged 29, was admitted with severe pre-eclampsia at 9 20 P M on Feb 10, 1956 This was her third pregnancy, and she had borne two children Her two previous pregnancies had been normal and both deliveries spontaneous

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There was no relevant medical history. She was 34 weeks pregnant and had had ankle œdema for the past three weeks and one episode of spots before the eyes. Both symptoms had subsided with rest in bed. She had had headaches during the past two days.

Examination

The patient was conscious. Her pulse and temperature were normal, and blood-pressure 220/120 mm. Hg. Œdema caused generalised puffiness of her face, and her finger rings were immovable. There was gross pitting on pressure from her ankles to half-way up her thighs. She had gross albuminuria, and her urine became solid when boiled. A single fœtus was palpable, with its breech presenting in the left sacro anterior position, and its size was consistent with the duration of amenorrhœa. The fœtal heart was regular. No abnormality was found in the other systems.

Treatment and Course

A basal anæsthetic dose of bromethol 6·3 ml. (0·09 ml. per kg. of estimated body-weight) in 217 ml. of water at 110°F was given rectally and repeated five hours later. Seven hours after admission the patient had an eclamptic fit, and a further 6·3 ml. of bromethol was given. There was a second fit at 7.45 A.M., and a further 6·3 ml. was given.

The blood pressure had fallen to 130/110 mm. Hg (fig. 1), and at 10 A.M. a stillborn female was delivered spontaneously.

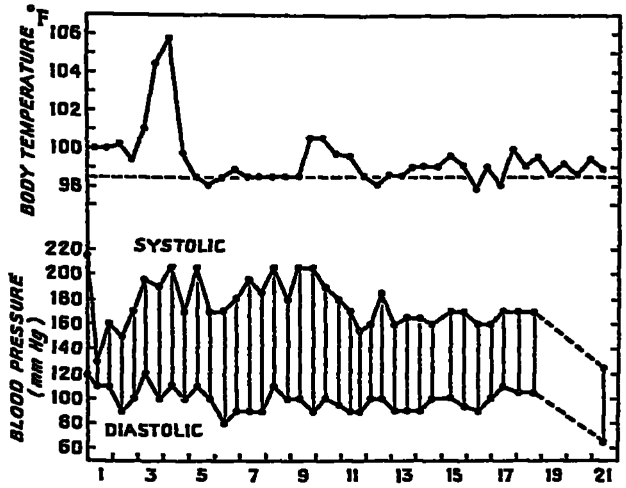

Fig. 1—Temperature and blood pressure.

The third stage was completed in five minutes, and there was no abnormal retroplacental clot. There was therefore no evidence of accidental hæmorrhage.

Post Partum

Large doses of sedatives (phenobarbitone sodium gr. 3 and paraldehyde 10 ml.) were given intramuscularly in the next few hours, and the blood pressure remained 130/100 mm. Hg. Seven hours after delivery the patient was jaundiced and had passed only about 8 oz. of urine since admission. Next day her blood urea level was 55 mg. per 100 ml. (fig. 2) and serum bilirubin level 22 mg. per 100 ml. (see table). The van den Bergh test gave a direct biphasic reaction. There were numerous red blood cells but no crystals or casts in the first specimen of urine examined in the ward by us. Subsequent laboratory examinations revealed casts in addition to the red cells.

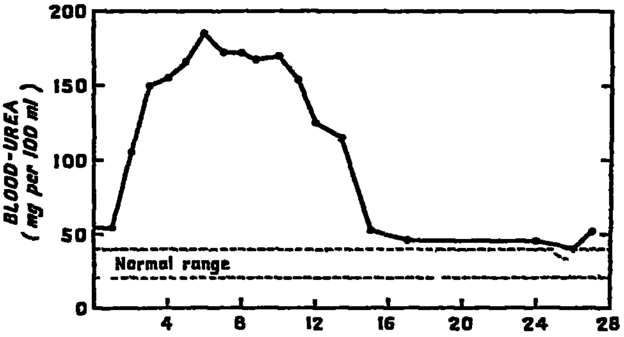

Fig. 2—Blood urea levels.

The day following delivery the patient remained unconscious. A catheter was kept in situ and was released hourly, to see whether urine was being secreted. It was felt that repeated catheterisation would be necessary, and that this would be more likely to provoke urinary infection than would a catheter kept in the bladder. The facts that the patient was unconscious and that it was necessary to save and measure all the urine influenced this decision. No urine was obtained in eight hours in spite of intravenous fluids, which were given as 25% dextrose 1 litre plus a quantity equivalent to the previous day's output (fig. 3). The blood chemistry was estimated daily (fig. 4). For the intravenous transfusions into the arm was substituted a polyethylene cannula in the inferior vena cava by way of the sapheno-femoral junction. Fluid requirements were calculated as before except that 40% glucose was used. Treatment with intravenous 40% glucose 1 litre a day provided 1600 calories. Amounts in excess of 1 litre were given as 5% dextrose. When the CO_2 combining power remained low, 1/6 molar sodium lactate was given from the sixth to the ninth day instead of some of the 5% glucose. An attempt was made to correct anæmia by transfusing packed cells. Intramuscular calcium gluconate was given because of the low serum calcium level.

On the third postpartum day the patient's temperature rose to 105·6°F. This was first treated by tepid sponging, which proved ineffective. She was then cooled with damp sheets, the draught from electric fans, and ice applied to her body and extremities. Aureomycin 250 mg. was given into the drip. Her temperature remained raised for five days before settling to normal.

On the fifth postpartum day diuresis began, the patient passing 1300 ml. of urine in twenty-four hours. The jaundice was noticeably less (serum bilirubin level 5 mg. per 100 ml.), and the patient spoke to the nurse for the first time. Her hæmoglobin was 55% (Haldane) (8·1 g. per 100 ml.) and 1 pint of packed cells was given slowly. This was not counted in the daily intake requirements.

Next day her general condition was improved and serum-bilirubin level was 2·2 mg. per 100 ml. She could take fluids by mouth, and the amount so taken was allowed for in calculating the daily requirements. From then on the amount of fluid given orally was increased until the intravenous route was discontinued on the ninth day post partum. A light diet was allowed but no protein until the blood urea level fell below 100 mg. per 100 ml. on the fourteenth day post partum. A low protein diet was then allowed. The jaundice disappeared, and the serum electrolytes and serum bilirubin levels returned to normal values.

LIVER-FUNCTION TESTS AND BLOOD-SUGAR LEVELS

—	Day after onset of failure									
	2	3	4	5	6	7	9	10	12	16
Liver function Tests										
Total protein (g. per 100 ml.)	4·9	4·5	3·5	3·2	3·2	3·8	4·3	4·8	5·1	6·2
Albumin (g. per 100 ml.)	2·5			1·7						
Globulin (g. per 100 ml.)	2·4			1·5						
A : G ratio	1·1 : 1			1·1 : 1						
Thymol turbidity (units)	2·5			2·5	2·5					
Thymol flocculation (units)				0	0					
Serum bilirubin (mg. per 100 ml.)	22·0	12·0	8·0	5·0	2·2	1·5				0·4
Prothrombin activity (% of normal)	70		81	72	72	72				
Plasma specific gravity		1·018	1·017	1·016	1·016	1·018	1·019	1·020	1·027	
Alkaline phosphatase (K-A units)	13·5			11·8	11·7					
Blood sugar (mg. per 100 ml.)	112			168	281	381	144	110	175	132

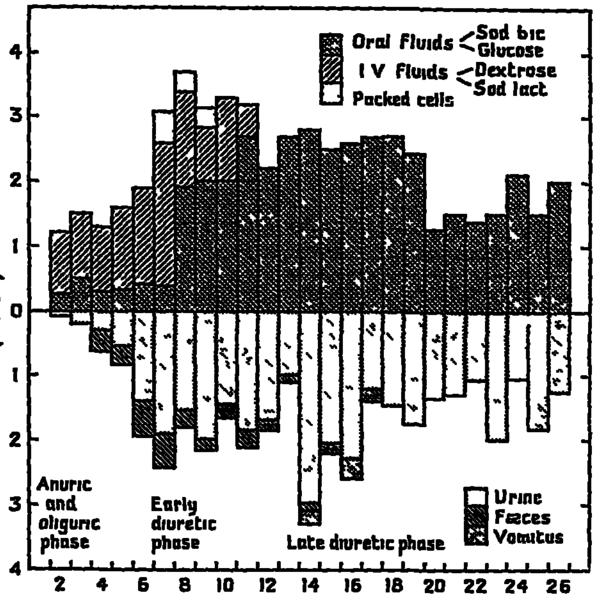

Fig 3—Fluid balance chart

On March 7 the blood urea level was 39 mg. per 100 ml., and the urea clearance test showed 45% of normal function in standard urea clearance. The specific gravity of the urine was 1·000–1·008. The patient was discharged on March 8, her blood pressure being 160/80 mm. Hg.

Follow up

The patient was readmitted a month after discharge. She was feeling well and had maintained her low-protein diet. Her blood-pressure was 125/90 mm. Hg. Her serum electrolyte levels and liver function tests were all within normal limits; her blood urea level was 35 mg. per 100 ml. Her standard urea clearance was 34% of average normal function, and her urine was concentrated up to 1·012.

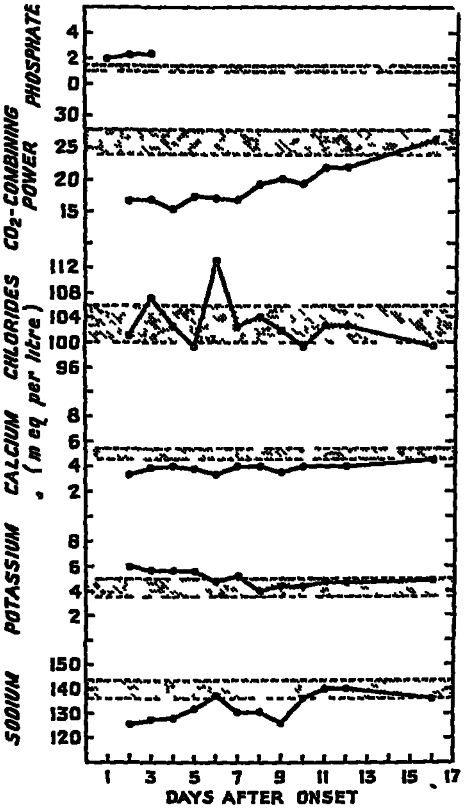

Fig 4—Serum-electrolyte levels. Shaded areas represent normal range.

Three months afterwards the specific gravity of the urine was 1·002–1·020 and the standard urea-clearance test 51% of normal function.

DETAILS OF TREATMENT

Liver and Kidney

The patient was first noticed to be jaundiced and oliguric seven hours after delivery, while still comatose. The small amount of heavily blood-stained urine and the accumulation of bile pigments in the plasma indicated renal and hepatocellular damage. To protect the liver and kidneys, a 25% glucose infusion was started into an arm vein, and 1 litre was given in twenty-four hours. Digoxin was added to this because of the congestive failure shown by the raised jugular venous pressure and gallop rhythm.

Thirty-six hours later it was realised that this situation might continue for some time, and the infusion into the arm vein would not be able to continue indefinitely because of the risks of local thrombosis and inadequate caloric intake. Accordingly it was decided to give fluids into the vena cava. Therapy by glucose/peanut oil intragastrically was not contemplated, because of coma and possible vomiting. The inferior vena cava was chosen because access to it by cutting down on to the saphenous vein close to the sapheno-femoral junction was thought to be easier for those inexperienced in the technique. Moreover only ordinary polyethylene tubing was available, whereas a proper cardiac catheter was thought to be essential to pass the subclavian arch to reach the superior vena cava. However, since then it has been pointed out (G. M. Bull, personal communication, 1957) that it is quite easy to put a polyethylene tube into the superior vena cava via the antecubital vein. It is just pushed until roughly the right length is in, and then its position is checked by manometry as follows: if there is an inspiratory lowering of pressure it is in the thorax or the neck; if an inspiratory rise it is too far (in the inferior vena cava). If it is in the neck a Queckenstedt sort of test will reveal this; if in the right ventricle there will be a higher mean pressure than there should be.

It is neither hazardous nor difficult either to set up or to *maintain an infusion into the inferior vena cava*. Considerable discussion and speculation preceded our use of it, but experience soon showed it to be quite simple.

Since the patient was not fit to be moved, the operation was done, with her in bed in her side ward, under fully aseptic technique. Through a two-inch incision the upper end of the left saphenous vein was exposed and the distal part ligatured. A no. 4 polyethylene tube was introduced into the proximal end for about ten or eleven inches and tied in with a double catgut ligature. A further deep nylon suture was inserted and tied over a gauze pad. By this means the patient's intake of fluids and calories was maintained for seven days. Heparin 2500 units per litre was added to the drip as a harmless and necessary precaution. Prophylactic aureomycin 250 mg. daily was given, sometimes by direct injection into the polyethylene tube, and at other times it was added to the transfusion bottle. It has since been realised that we gave too much aureomycin and risked getting dangerously high blood levels in a patient whose glomerular filtration mechanism was not working. A more rational régime, which would be followed in a future case, would be to give a loading dose of 1 g. aureomycin and thereafter 250 mg. every four days, or alternatively to stick to the simpler and safer penicillin, given as 1 mega unit followed by 0·25 mega unit on alternate days. The need for preventing infection at this stage has been emphasised by Bull[5] and others.

In dealing with a case of this severity for the first time it is necessary to keep very accurate fluid balance charts; and it is important that one member of the team should be responsible for sending specimens of blood to the laboratory at the same time each day, receive the results personally, and provisionally order treatment for the next twenty-four hours. This minimises the chance of confusion, as has been pointed out by Scott Russell et al.[27]

Renal failure was recognised early, but a prompt decision to start treatment cannot be overemphasised. This is more likely to succeed when the complication is anticipated.

Hyperpyrexia

When her temperature reached 105·6°F on the third day the patient appeared moribund. Energetic measures were needed because ordinary tepid sponging had not helped. She was stripped and covered with a wet sheet, and the draught from open doors and windows was augmented by electric fans. Her limbs and trunk were then packed with plastic theatre caps filled with ice cubes. As the covering sheet became dry it was easily moistened by cold water from the ice bags.

A small brain stem hæmorrhage following the eclampsia was considered to be the cause of the hyperpyrexia.

Eclampsia

The only deviation from the usual therapy of bromethol and general nursing was that bromethol was repeated on three occasions after the first dose—i.e., a total of 26·2 ml. in about twelve hours, including an unknown amount that was not retained. This was possibly excessive and may have been responsible for some damage in a liver already affected by eclampsia Slow detoxication of the bromethol may have added to the subsequent coma

Morris[22] did not find evidence that oliguria was a complication of bromethol treatment

Electrolyte Balance

The deviation from normal of the blood electrolyte levels was fairly severe, but they never reached levels of extreme danger Some were nevertheless abnormal enough to merit comment

Potassium —The initial hyperkalæmia was effectively controlled by the protective action of the hypertonic glucose,[5] and alternative measures were not required Hyperkalæmia is always to be feared, it prolongs the PR interval and lengthens and elongates the Q R S segment An electrocardiograph is necessary to demonstrate these changes[33, 38] Hyperkalæmia may be minimal, but the excess potassium in the blood may have been sufficient to act harmfully on the heart Such damage may be detected electrocardiographically, whereas estimation of the serum potassium level alone might not show sufficient abnormality to suggest myocardial changes resulting *from* it *Digoxin* should then *only* be given if congestive failure is severe and there is no sign of reduced myocardial conductivity

Alkali reserve —The acidosis persisted until sodium lactate was given intravenously Sodium lactate could perhaps have been given at an earlier stage to this patient, but the question arose of administering sodium to an œdematous patient It was considered wiser not to give it as lactate intravenously in the early stages but to wait and see if the acidosis would correct itself When this did not happen, even after concentrated sodium bicarbonate had been given orally, we decided to observe the effect of 1/6 molar lactate, estimating the alkali reserve daily The response was good (fig 4), and there was no sign of retention of sodium, but much of the œdema had subsided by the time this stage was reached There is controversy *about* whether *sodium lactate should* be given to correct acidosis in the presence of œdema, we steered a middle course without disadvantage We feel that each case should be judged on its merits, and, if sodium lactate is given, one should be ready to stop it whenever signs of retention of sodium appear

Calcium —The serum calcium level fell and tetany was feared Therefore 10% calcium gluconate 40 ml was given daily The intramuscular route was chosen as being safer than the intravenous The hypocalcæmia is compensatory to retention of serum phosphate when there is no renal function, and was to be expected Calcium has an effect on the myocardium about opposite to that of potassium, it therefore seemed logical to give calcium to the patient

Blood transfusion

When the hæmoglobin was found to be *55%* (8 1 g per 100 ml), a pint of packed cells was given Opinions differ about whether this should be done, Bull[8] being in favour and Sheehan[33] against No rise or fall in serum potassium level was detected after the transfusion

Vena cava Infusion

The vena cava infusion was stopped after seven days, when the patient had recovered clinically but the specific gravity of the urine was still only 1 010, showing that selective reabsorption had not yet been restored, although glomerular function was adequate Subsequent renal function may have been improved had this infusion been maintained another week, but some authorities suggest that concentrated glucose solution may have toxic effects on the kidneys For that reason it was discontinued as soon as possible

Signs of liver failure following eclampsia are uncommon, and the cause is obscure, but a large supply of glucose is known to exert a protecting influence An adequate intake of vitamins was given, as recommended by Bull[5]

PROGNOSIS

Eclampsia

The recurrence rate of eclampsia alone is about 10%[14]

Renal Function

Since the patient can concentrate urine to 1 020 and the urea clearance rate is rising, the prognosis for the renal lesion is favourable Eclampsia does not appear to cause permanent renal damage[15] An insufficient number of women have yet recovered from acute suppression of urine for a more accurate prognosis to be given

Liver function —This quickly became normal, and the regenerative capacity of the liver is well recognised

Discussion

It is now generally agreed that the conservative régime should be started as soon as anuria is recognised, so that the patient's *milieu interieur* never becomes so abnormal that she dies before renal function is restored This treatment is rational because the kidneys of patients who die on the eighth to twelfth day of anuria commonly show active regeneration of tubular cells in the injured areas Anatomical and functional repair of the kidneys may take place if the patient can be kept alive long enough Treatment aims at reducing the breakdown of cell protein to a minimum, thereby diminishing the rate of accumulation of metabolites—e g, urea—and of potassium in the blood It is the increase in extracellular potassium which usually kills the patient[5]

Ætiology of Anuria

The general medical and surgical causes of anuria have been enumerated,[13] and the obstetric ones analysed[8, 33, 35] Terminology used in defining anuria has varied between anatomical, symptomatic, and ætiological Among the names used more or less synonymously have been the following acute renal tubular failure, lower nephron nephrosis,[20] acute tubular necrosis, acute nephrone nephrosis,[1] crush syndrome, transfusion kidney, and traumatic uræmia Possibly the name of choice, when eclampsia is involved, is merely " acute suppression of urine," because it involves no theory of pathogenesis

When anuria in obstetrics is classified into ætiological categories of shock, excretion of abnormal pigment, and circulating nephrotoxic substances,[35] it is at once seen that all the causes except eclampsia would easily find their place in a list of the general medical and surgical causes of anuria some (e g, accidental hæmorrhage, postpartum hæmorrhage, ruptured uterus, incomplete abortion, and ectopic gestation) are similar to such causes, and others are medical conditions that happen to obstetric patients (e g, incompatible transfusion, hæmolytic drug-reaction, sulphonamide or quinine sensitivity, mercurial poisoning, and septicæmia) Thus pathogenesis of the " shock " causes may be explained as renal ischæmia and its nine grades of lesion according to degree and severity,[31, 32] that of the other causes being damage to tubular epithelium by pigments and toxins preventing selective reabsorption of the glomerular filtrate, but where eclampsia comes in this classification is uncertain Slowinsky[35] puts it among the nephrotoxic agents as " ? toxins of eclampsia and pre eclampsia " But what the toxins are is unknown, and where they exert their influence is undiscovered Until further light is shed on the subject, it could be suggested that renal failure in the present case of eclampsia followed the pattern of that in shock, the renal ischæmia arising from spasm of the renal arterioles and capillaries

The rôle of the hypothetical toxin is unknown We are certain that our patient did not suffer enough shock to make her anuric, because her blood-pressure was always above normal There was no evidence of concealed accidental hæmorrhage[40] either before she became unconscious or after delivery, and she did not have a postpartum hæmorrhage Blood-transfusion, sulphonamide, and quinine therapy were never used, and there was no evidence of any other intoxication We conclude that her renal failure could only have been of eclamptic origin

The cause of renal failure is leakage of glomerular filtrate through the walls of the damaged tubules instead of being concentrated and transported by them

It has been said that the importance of oliguria and anuria in obstetric cases may sometimes have been unrecognised previously This may be due to the overwhelming nature of other aspects of the case, the speed with which patients succumbed, or the lack of standardised rational routine of treatment

Summary

A case of fulminating pre eclampsia progressing to eclampsia and stillbirth while under bromethol therapy is described

Renal and hepatic failure followed, the patient remaining unconscious for five days

Her brain-stem appears to have received damage, which was reversible

Concentrated glucose was given into the inferior vena cava, the electrolyte equilibrium was carefully controlled, and hyperpyrexia was reduced by physical cooling

We wish to thank Mr T. B FitzGerald for permission to publish, Dr D A K Black for helpful advice during treatment, and the nurses for the skilful attention they gave this patient

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Reviews of Books

William Harvey

His Life and Times His Discoveries His Methods LOUIS CHAUVOIS, Laureat de l'Institut et de l'Academie de Medecine London Hutchinson Medical Publications 1957 Pp 271 25*s*

IN this tercentenary year of Harvey's death, many doctors and medical students will want to learn more of his life and times, his discoveries and his methods, and in this book Dr Chauvois, a distinguished French physician and medical historian, has provided exactly what they want He has carefully studied and sifted all the available information, and he has inspected all the memorials of the great man An accomplished scholar, he has also examined the Latin texts of Harvey's published writings From these materials, his balanced judgment has produced a life-like portrait of the man and the scientist He has not hesitated to use deliberate fiction when that can be done without going too far from probability Thus, he describes a journey from Padua to Venice when, *as an* undergraduate, Harvey reviewed and criticised in his mind current ideas about the circulation of the blood, and there is an account of a typical day with Harvey in the year before *De Motu Cordis* was published There are some factual errors in the text, but they detract little from its merit

Much of the text is quoted from D'Arcy Power's biography, but Dr Chauvois is sometimes critical of Power's views For example, he insists that it is not enough to read Harvey's book to appreciate properly his teaching, and that the two letters to the unbelieving Riolan, written in 1649, are even more important Power and others believed them to be of secondary interest

> "In the Letters we have the same affirmations, the same demonstrations of the way the heart works, of the functions of the arteries, of the return of the blood by means of the veins—in a word, the same description of the circuit but with overwhelming answers to all possible objections Despite his seventy one years Harvey still shows himself to be an admirable dialectician, though one who always relied upon observation and upon carefully executed experiments"

This important and very readable book, written with much charm and well illustrated, deserves many readers

Methods in Enzymology

Vol III Editors SIDNEY P COLOWICK and NATHAN O KAPLAN, McCollum Pratt Institute, The Johns Hopkins University, Baltimore, Maryland New York Academic Press London Academic Books 1957 Pp 1154 $26 00

THE third instalment of this Herculean publication surpasses by some 200 pages the larger of its two predecessors A subtitle says that it is devoted to the preparation and assay of substrates, and this definition includes, of course, most of the organic compounds found in living matter Much of the book, therefore, has interest and application outside what might be regarded as the rather esoteric province of the pure enzymologist Thus, the discussions of analytical procedures for the nucleic acids, sugars, amino-acids, and lipids provide excellent introductory reading for anyone faced with estimating one of these substances for the first time Quite apart from forming a valuable new unit in the series to which it belongs, this book is a helpful source of information on many topics in quantitative biochemistry The final volume promises to deal with biochemical methodology in a still more general way

Dextran and its Use in Colloidal Infusion Solutions

ANDERS GRONWALL, M D professor of clinical chemistry, University of Uppsala Stockholm Almqvist & Wiksell Oxford Blackwell Scientific Publications 1957 Pp 156 20*s*

A PLASMA substitute must be a *harmless colloidal* solution of a substance whose molecular size gives it an appropriate osmotic pressure in the blood-vessels Dextran is a viscous polysaccharide produced in cultures by certain micro organisms, particularly some leuconostoc species By purification and degradation processes, dextrans can be prepared which are useful plasma substitutes for intravenous infusion, and this book is an excellent account of the development of clinically useful dextrans and of the historical background Chemical and physical theories are clearly enunciated, and clinical applications and toxic manifestations well described Despite some awkward passages of translation the style is generally very clear

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Current Therapy (Philadelphia and London W B Saunders 1957 Pp 690 £3 17*s*)—The new edition of this annual, edited by Prof Howard F Conn, has nearly succeeded in the almost impossible task of keeping itself fully up to date thus, though perchlorate for hyperthyroidism and hypophysectomy for breast cancer are not mentioned, there are good accounts of the hypoglycæmic sulphonylurea compounds and the newer hypotensive drugs Its scope encompasses all non surgical disease and a few surgical and obstetric conditions The authors' recommendations are in the main dogmatic and orthodox, though the account of treating venous thrombosis by surgical removal of the clot is intriguing The list of ingredients in commercial products could be invaluable in a poisoning emergency

THE LANCET

LONDON SATURDAY, JUNE 22, 1957

How Many are Chosen?

WITH the post-war ex-Service bulge behind them and with the prospect from 1960 onwards of a considerable increase in the numbers reaching the age of 18, the Committee of Vice-Chancellors and Principals has prudently taken stock of the relative numbers of successful and unsuccessful applicants for university entrance in the recent past. In 1952 they appointed a subcommittee, with Sir JAMES MOUNTFORD, of Liverpool University, as chairman, to investigate the nature and fate of applicants for entry; after careful planning, a detailed survey was made of applicants and entrants to almost every university in the United Kingdom for the session 1955–56. The main object was to ascertain "whether the number of places was inadequate, adequate, or in excess"—a matter of interest to parties as diverse as the Chancellor of the Exchequer and the heads of schools as well as to university staff. Fortunately the scope of the inquiry was widened to obtain "information about the previous educational background of the applicants, their social classification, the sources of their financial support, and the careers which at the time they made their application they proposed to pursue." The subcommittee's report[1] written by Mr R. K. KELSALL, and published last week is described in the *Times* by Sir JAMES MOUNTFORD[2] as "based on the first large-scale investigation of its kind ever attempted," and thus "a matter of considerable public interest." The figures now made available bring some precision into an area previously occupied only by opinion, or rather by opinions; for some thought that worthy applicants were being turned away in droves, while others thought that every suitable applicant would find a place, though not necessarily in the university of his first choice. As the preface to the report says, "Opinion, in a matter of this kind, is no substitute for facts."

Of 31,000 applicants, about 18,000 were admitted in October, 1955; the 13,000 applicants not admitted included 2000 from overseas. Of the 11,000 home applicants who did not succeed in 1955 no less than 4000 had been accommodated by October, 1956; and of the remainder, about half had failed to enter not as the result of an arbitrary decision, but through sheer lack of the minimum educational requirements for entry. There was, it is true, a residuum of 2000–2500 applicants who had obtained the minimum requirements for entry but had not gained a place; and there was a similar number of unfilled places; but unfortunately the vacant places were mainly square and the candidates round, or vice versa. A substantial number of places—over a thousand—was vacant only by default, having been offered to applicants who had gone elsewhere. The general picture, with 94% of available places filled, is not unsatisfactory. As Sir JAMES MOUNTFORD says: "It is not reasonable to expect that places and applicants can ever be so perfectly matched that there will be no vacancies; nor is it to be expected that universities will feel it right to accept every applicant who has secured just the minimum of marks to bring him into the category of 'qualified' as that term has necessarily had to be used in this inquiry." The *Manchester Guardian*[3] stresses the low proportion of "working-class children" among the applicants (28–30%, compared to 72% of manual workers in the adult male population). Fortunately, there was no material difference between the proportion of manual workers among the parents of those admitted and those not admitted; so discrimination by the universities could be ruled out. The report also gives evidence that hereditary factors are much less important than the combined effect of "differing environmental influences and parental aspirations"; and the *Guardian* draws one possible moral—that these are "circumstances that will have to be overcome."

The medical reader will naturally be curious to know how the applicant for a medical course compares with other applicants in his social background, his previous education, and—more critically—his hopes of admission. Those who claim that medicine is no longer a popular choice of career can draw no bitter confirmation of their views from the 1955 figures. Multiple application was commonest among medical applicants, and failure to accept a place when qualified to do so was rarest. Among the sons of doctors, 51% of those admitted were entering the medical course; and doctors' sons made up 17% of male medical students. Among medical students, a lower proportion had been to local-authority schools, primary or secondary, than among students of other faculties; and fewer medical students were receiving financial assistance. The percentage of manual workers among the parents of medical students is low (16–20%), compared with the parents of science students (33–35%). The chance of admission to the medical course in 1955 can be inferred from table I of the report which gives the required increase in places for admission of all applicants in medicine as 48%; in other words, 2 out of every 3 applicants were placed at the time and university of their choice. This is probably a reasonable figure, for many of the rejected applicants were placed in the following year, or were on the other hand lacking in the minimum requirements for entry. It would appear, in fact, that the medical schools are not at present compelled to turn away too many of their applicants, while on the other hand there is still a need and an opportunity for selection. The pressure for entry (and perhaps for expansion) can be expected to increase after 1960; but the number of applicants cannot be the sole criterion of the number of entrants. The staffing and accommodation of medical schools in general is scarcely adequate for our present numbers. This can no doubt be improved, but the process is unlikely to be sudden in its accomplishment or effects. Moreover, while we now have a better answer than ever before to the question "How many intending students are we likely to get?", we still have precious little solid information on the other end of the course—

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[1] Report on an Inquiry into Applications for Admission to Universities. By R. K. KELSALL. London: Association of Universities of the British Commonwealth, 36 Gordon Square, W.C.1. 17s. 6d.

[2] *Times*, June 14.

[3] *Manchester Guardian*, June 14.

"How many doctors do we need?" For that, we hopefully await the report of the Willink committee, set up in 1955 "to consider the future numbers of medical practitioners and medical students"

Night Vision

In peace-time the city-dweller has very little occasion to use his night vision and (as was revealed in the first few nights of the blackout in the late war) may suffer from some degree of night blindness without ordinarily being aware of the fact In the 1914–18 war poor night vision was apparently not a serious problem for the Allies, but it caused a good deal of anxiety in the armies of the Central Powers In the 1939–45 war the demands on night vision made by the rigid blackout and by night flying brought the problems of seeing in the dark into sharp prominence, and much work has since been devoted to the subject

When, in the years between the wars, the association between poor dark adaptation and vitamin-A deficiency was finally established, tremendous interest in night vision and the means of testing it suddenly developed Much work was done on dark adaptation and night vision in an attempt to find some satisfactory means of evaluating the extent of possible vitamin-A deficiency in various populations Unfortunately, by far the greater part of this work was unsatisfactory, owing to the incursion of workers from other specialties into the highly complex field of visual research Consequently a number of workers, notably in America, Denmark, and this country, concluded that large sections of the population had some degree of vitamin-A deficiency—a conclusion that was not supported by other workers[1] whose investigations were more carefully controlled One among the many causes of confusion was the uncritical use of two different criteria of dark adaptation One of these is the sensitivity of the eye to light as such—in other words, the ability to recognise whether a test patch is illuminated or not—while the other is visual acuity at very low illuminations More recent investigations[2] have revealed no correlation between the results obtained by these two methods, and the impression has gained ground that to estimate visual ability for some specific task it is necessary to devise a test bearing the closest possible similarity to the anticipated field conditions If correct, this means that there can be no one generally satisfactory test for night vision

The Medical Research Council has now published the report[3] of an extensive investigation of night vision in young subjects Both the absolute sensitivity to light and the visual acuity at low illumination were tested in the same people A carefully checked and rigidly controlled method of measuring the dark adaptation and the absolute sensitivity was found to give satisfactorily reproducible results and to be relatively simple in operation, but some training was necessary before reproducible results could be obtained with two very different visual-acuity tests After such training, however, there was a high correlation between the performances on these tests and those on the simple sensitivity test But this correlation held only for visual acuity at scotopic levels, at higher illuminations other factors complicate the picture The authors of the report therefore claim that a carefully devised sensitivity test can be used as a measure of night vision, or at least of potentiality for performing visual tasks at low illuminations after suitable training Their discussion of the reasons why they were able to obtain a correlation between visual sensitivity and what they call visual perception, whereas such careful and experienced workers as CRAIK and VERNON could not, is convincing

Obviously performance in the field—for instance, on the bridge of a ship—cannot be accurately predicted from knowledge of the person's visual sensitivity in the laboratory, too many extra psychological and other factors are involved As the authors themselves point out, a high visual sensitivity does not of itself ensure good perceptual efficiency On the other hand, a good perceptual efficiency requires a high sensory efficiency, and the latter can be measured in the laboratory It seems, therefore, that tests such as those described could at least be useful in picking out candidates with poor sensitivity who will always be unsuitable for exacting visual tasks at low illuminations

Serum-cholesterol and Myocardial Infarction

SEVERAL recent studies have added precision to our knowledge of the levels of cholesterol in apparently healthy men and women living in various countries In general, these studies have confirmed earlier views that myocardial infarction is often associated with high levels of serum-cholesterol, but they have added little to the understanding of the association between coronary-artery disease and disturbance of lipid transport in the blood

LAWRY et al,[1] in Boston, investigated 1508 men and 412 women, of whom most were resident in New England but a minority came from New York, Chicago, and other parts of the United States All were active and well by certain pre determined criteria Blood from 273 men who had had myocardial infarction and 141 men with definite angina pectoris was also examined In addition to serum-cholesterol the serum S_f 12–20 and S_f 20–100 lipoproteins were estimated by flotation methods LAWRY et al remark on the wide range of serum-lipid values in large groups of people of the same sex and age and with similar health status Individual values are thus of limited interest, but much can be learnt from mean values for groups For men the mean serum-cholesterol value at age 25–29 was 212 mg per 100 ml Thereafter the value rose steadily to a maximum value of 245 mg spread over the years from 45 to 59 After 60 there was a slight fall The mean values for women were about 20 mg lower than those for men up to the age of 45 Thereafter the means for women

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[2] Berry, W Review of Wartime Studies of Dark Adaptation, Night Vision and Related Topics Armed Forces National Research Council Visual Committee Secretariat University of Michigan, Ann Arbor 1949 Craik, K J W Vernon, M D *Brit J Psychol* 1942 32 206

[3] Pirenne, M H Marriott F H C O Doherty, E F Individual Differences in Night vision Efficiency *Spec Rep Ser med Res Coun Lond* 1957 no 294 H M Stationery Office Pp 83 8s

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[1] Lawry E Y, Mann G V, Peterson, A Wysocki A P, O Connell, R, Stare F J *Amer J Med* 1957, 22, 605

continued to rise, and for the age-group 60–69 the mean was 263 mg. For men aged 30–39 with acute myocardial infarction the mean level was 301 mg.—74 mg. above the mean for the healthy group of the same age. As age advanced, mean levels in the patients fell: the difference between the means of the patients and the healthy subjects diminished and was only 18 mg. at 50–59 years. The means for patients with angina pectoris were only slightly above the normal values. Only in patients with myocardial infarction who were younger than 40 were the mean figures very much higher than those for the controls. Tables show that after a myocardial infarction many older men have a serum-cholesterol value no higher than the mean for the control group. A smaller study in Malmö, Sweden, gave very similar results.[2] Apparently healthy Swedes have slightly lower values than the Americans, with a maximum of 230 mg. per 100 ml. in the age-group 50–59. Patients with myocardial infarction have a much higher serum-cholesterol than the control group up to the age of 50, but between 50 and 59 the difference is only just over 10 mg. In a large study in New York[3] the sera of 1200 apparently healthy men and women were examined. The cholesterol levels for the men were very similar to those in the Boston series, with the mean reaching a maximum of 247 mg. per 100 ml. at the age of 40. In the New York series girls up to the age of 20 have higher levels than boys; then up to 45 years the figures for men are higher; but after the menopause the figures for women continue to rise, with a maximum of 260 mg. at 60 years.

The Boston group point out that, although all these figures have been obtained on apparently healthy people, they do not necessarily represent normality, for myocardial infarction is endemic in the United States, as it is in Sweden. They add that a strong argument can be developed for the contention that the normal serum-cholesterol level in men is 150 mg. per 100 ml. This view is supported by a study in Israel, by Dr TOOR and his colleagues, which appears on an earlier page of this issue. These workers show that, in recent immigrants to Israel from the Yemen, mean serum-cholesterol levels for men vary from 145 to 158 mg.; in women after the menopause a maximum of 190 mg. is reached. In Yemenite immigrants who have lived twenty years in Israel, levels are much higher and the means for men have a maximum of 210 mg. in the 55–64 age group. These early immigrants lead a life which resembles more closely that of the U.S.A. and Western Europe; they also have a high mortality from myocardial infarction. The recent immigrants, who are poor Asiatic peasants, have a very low death-rate from this cause. In a letter this week Dr BRUNNER and Dr LÖBL also report low levels of serum-cholesterol in Yemenite immigrants to Israel, whereas Jews whose ancestors had lived for many years in Europe, the United States, or South Africa and were habituated to the manner of life in these countries had much higher levels (mean at age 46 years 231 mg. per 100 ml.)—the same as those usually found in their country of origin.

The Boston group found that neither S_f 12–20 nor S_f 20–100 values had any clear superiority over cholesterol values in predicting manifestations of coronary heart-disease. Nor could any useful combination of the three values be found. They also found that in over-weight people the contribution of "body fatness" to lipidæmia was significant; but the magnitude of the contribution was small, and they conclude that it can scarcely be of more than minor significance in the overall regulation of serum-lipids.

These observations on serum-cholesterol levels come from well-planned surveys in different parts of the world. Each is consistent with the hypothesis that the level of blood-lipids in man is artificially raised in successful modern civilisations. This disturbance of the lipid transport system appears to be an essential condition for myocardial infarction to become endemic in a people. Clearly the disturbance does not cause infarction, but only predisposes to it; the immediate causes of infarction remain unknown. But these observations provide firm evidence that the many studies now being carried out to determine the effects of different dietary fats on levels of serum-cholesterol are relevant to the prevention of myocardial infarction.

Annotations

BREATHING EXERCISES

IF owning that we do not know is the beginning of knowledge, then such a beginning was evident at a meeting of the section of physical medicine of the Royal Society of Medicine on June 12. Whether the benefits of breathing exercises are due to the exercises themselves or to the encouragement and attention that goes with them is disputed, and no acceptable controlled trial has been published. It is hard to get homogeneous material in so variable a disease as emphysema, and a double-blind trial of exercises is impossible. Dr A. C. Dornhorst proposed the use of such objective measurements as vital capacity, tests of ventilatory capacity, and timed vital capacity. He said that patients with emphysema should start deep breathing when they expected exercise and dyspnœa. Dr J. L. Livingstone, a firm believer in breathing exercises, reported many cases in which cure of asthma had followed a course of exercises, and thought that teaching patients to use the lower chest and epigastrium improved their condition and, especially in children, helped to prevent deformity. Dr D. A. Brewerton was less impressed with the value of such exercises; he emphasised that breathing exercises were of little use for patients before abdominal operations, but that postural drainage was valuable after inhalation of isoprenaline.

Many speakers agreed that there was little or no change in objective measurements after a course of exercises; that advice was more important than exercises; that harder and consciously prolonged expiration, and slower breathing, were often helpful (especially in asthma, where they might abort an attack); and that singers could hold a note longer after training. There was less agreement about the possibility of diaphragmatic spasm or of learning to use any group of intrinsic respiratory muscles in isolation.

We can be sure that, by means of physiotherapy, many patients achieve better posture and coordination, are encouraged through feeling that something is being done, and learn when to breathe out and when to breathe deeply. But we remain ignorant of whether breathing exercises as such are helpful.

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[3] Adlersberg, D., Schaefer, L. F., Steinberg, A. G., Chun I Wang. *J. Amer. med. Ass.* 1956, 162, 619.

THE ELECTROCARDIOGRAM IN MITRAL-VALVE DISEASE

THE *electrocardiogram in disease of the mitral valve* reflects the effects of the lesion primarily on the left atrium, and secondarily on the right ventricle (in pure or dominant stenosis) or the *left* ventricle (in dominant incompetence) Appreciable left atrial enlargement and hypertension is reflected in the character of the P wave, which is widened and notched but of normal amplitude [1] This widening and notching is present in most severe cases of mitral stenosis in sinus rhythm, but not in slight cases [2] When pulmonary hypertension is present, the P wave may become augmented in amplitude, reflecting right atrial hypertension, and enlargement of both atria may be revealed by a tall, broadened, and notched P wave Persistent atrial fibrillation, however, is present in roughly 45% of all cases of mitral-valve disease [2]

Since mitral stenosis is one of the commonest causes of right ventricular hypertrophy in acquired heart-disease, the cardiogram often shows evidence of this [3] The pulmonary arterial pressure and arteriolar resistance has been shown to be related to the left atrial pressure,[4] *and to the severity of the mitral stenosis* [5] *It might* be supposed, therefore, that the degree of right ventricular hypertrophy apparent in the cardiogram would be a good guide to the severity of the mitral stenosis Wood [2] noted that the degree of right ventricular hypertrophy was correlated closely with the height of the pulmonary arteriolar resistance, while Goodwin et al [5] found poor agreement between the degree of right ventricular dominance on the one hand and the size of the mitral valve or degree of pulmonary hypertension on the other, but Wood and Goodwin agreed that severe right ventricular dominance indicated a high pulmonary arterial pressure and resistance and a small mitral valve The association of augmented, pointed P waves without proportionate evidence of right ventricular dominance should suggest the possibility of associated tricuspid stenosis [6]

The difference in the findings in the *two* series of cases may be explained by several factors The electrocardiographic assessment of the severity of right ventricular dominance is difficult The degree of pulmonary hypertension was measured by cardiac catheterisation in Wood's cases, but for the great part it was assessed radiologically *in those of Goodwin et al Moreover,* associated left ventricular hypertrophy may modify the picture [7], Goodwin et al claimed that some patients with critically *stenosed valves had no evidence of any right ventricular* hypertrophy, and only a third of these had any left ventricular hypertrophy

Extreme right ventricular dominance is associated with tall delayed R waves, sometimes preceded by Q waves and followed by inverted T waves, in right precordial leads, and deep S waves in *left* precordial leads These findings are common in congenital heart disease, such as pulmonary stenosis, but rare in acquired right ventricular hypertrophy, including *that* accompanying mitral stenosis [8] Morris and Whitaker [9] reported 9 such cases in 173 patients with mitral stenosis, and Pruitt and Robinson [10] found 41 cases in 93 patients with severe mitral stenosis, and 53 of extreme right ventricular dominance among 147 patients with mitral valve disease of all types

The evidence therefore suggests that critical mitral stenosis (if not severe pulmonary arterial hypertension) can exist without a corresponding *degree of right ventri*cular dominance on the cardiogram The presence of gross right ventricular dominance in mitral valve disease virtually *guarantees severe pulmonary arterial* hypertension, but does not exclude mitral incompetence associated with stenosis [5] When there is cardiographic evidence of abnormal left ventricular dominance, pure mitral stenosis cannot be the sole lesion, and dominant mitral incompetence, aortic-valve disease, or severe systemic hypertension is likely

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1 Wood, P Diseases of the Heart and Circulation London 1950
2 Wood P *Brit med J* 1954 i 1051, 1113
3 Trounce, J R *Brit Heart J* 1952, 14 185
4 Holling, H E *Brit med Bull* 1952, 8 358
5 Goodwin J F, Hunter, J D Cleland W P, Davies, L G, Steiner, R E *Brit med J* 1955, ii, 573
6 Gibson R, Wood P *Brit Heart J* 1955, 17, 552
7 Pagnoni, A Goodwin J F *Ibid* 1952, 14, 451
8 Campbell, M *Ibid*, p 201
9 Morris, T L, Whitaker, W *Amer Heart J* 1956, 52, 738
10 Pruitt, R D, Robinson, J G *Ibid*, p 880

TUBULAR DYSFUNCTION IN NEPHROSIS

RENAL biopsy in the nephrotic syndrome has shown that among the common renal lesions are subacute glomerular nephritis (membranous or proliferative), chronic glomerular nephritis, diabetic glomerulosclerosis, lupus nephritis (in systemic lupus erythematosus), thrombosis of the renal vein, and renal amyloidosis [1] But of 56 cases investigated in this way, 6 are described as "nephrotic syndrome with predominant tubular degeneration" [1] This is interesting because it has become widely accepted that in the nephrotic syndrome the primary lesion is glomerular, causing increased filtration of protein, and that the heavy proteinuria is only partly or else not at all due to defective tubular reabsorption Such histological changes as are present in the proximal tubular epithelium are related by some to maximal protein reabsorption, and simple tests, such as measurement of specific gravity range or *p* aminohippurate excretion, show normal tubular function in most cases

The primary importance of a glomerular lesion in nephrosis has now been challenged, however, by Freeman and Joekes,[2] who believe that there is "diminished tubular protein reabsorption, without necessarily any abnormal escape of protein through the glomeruli" By means of paper electrophoresis they studied the differential protein patterns in serum, urine, and œdema fluid of 6 nephrotic patients The patterns were very similar in urine and œdema fluid, which both showed a much higher proportion of albumin to globulin than did the serum Freeman and Joekes reason that the abnormal quantities of plasma lipoprotein and the consequent increase in the molecular size of the globulins led to a preferential loss of albumin into the tissue spaces and renal tubules Normal or raised ratios of serum-albumin to tissue-fluid albumin in these patients appeared *to* exclude an increased escape of albumin due to a generalised capillary lesion These findings are of interest, but the argument put forward by Freeman and Joekes is by no means conclusive

Stanbury and Macaulay,[3] who accept the glomerular lesion as primary, have recently discussed secondary renal tubular insufficiency in the nephrotic syndrome Renal glycosuria and amino aciduria, either singly or together, have been reported in nephrotic patients, and Tegelaers and Tiddens [4] have described a more complex combination of tubular defects in 2 nephrotic children in whom renal glycosuria and amino aciduria, acidosis, hypokalæmia, and polyuria developed The rather similar patient described by Stanbury and Macaulay was first seen at the age of 2 years with all the typical clinical and biochemical features of the nephrotic state and was treated with *cortisone for a week,* concentrated plasma infusions, low salt and high-protein diet, and, for several months, cation-exchange resin ('Katonium') The nephrotic *state continued, but* hypocalcæmic tetany developed when the patient was 4 years of age, and subsequently he was found to have renal glycosuria and amino aciduria, which had not been present at the onset of his illness

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1 Kark R M Cited by Findley, T *Amer Heart J* 1957, 53, 323
2 Freeman, T Joekes A M *Acta med scand* 1957 157 43
3 Stanbury, S W, Macaulay, D *Quart J Med* 1957 26 7
4 Tegelaers W H Tiddens H W *Helv pædiat Acta*, 1955, 10, 269

Next he had a frank hypokalæmic episode, with muscle weakness and confusion Hypokalæmia had been detected biochemically, but had been disregarded, shortly after administration of cation-exchange resin had been discontinued At the age of 5 the child was dwarfed and showed delay in the appearance of centres of ossification and osteoporosis, probably due to extreme protein depletion and inadequate intestinal absorption of calcium , he still had heavy proteinuria and hypoproteinæmia, polyuria, glycosuria, amino-aciduria, potassium deficiency, and metabolic acidosis were present and were ascribed to defects of renal tubular reabsorption These tubular defects might have been due to persistence of severe tubular degeneration, such as is known to occur in acute membranous glomerular nephritis An alternative suggestion by Stanbury and Macaulay is that the cation-exchange resin brought about potassium deficiency and tubular kaliopenic nephropathy with possible irreversible damage However it was produced, the combination of tubular defects in this patient is reminiscent of that in cystine-storage disease (Lignac-Fanconi disease) and in a varied set of tubular nephropathies generally grouped under the unsatisfactory title of "adult Fanconi syndrome" Obviously, renal tubular deficiencies can arise singly or in many combinations and may be due to congenital defect of tubular structure or function or to a wide variety of acquired diseases, among which we may now have to include the nephrotic syndrome, or, possibly kaliopenic nephropathy resulting from its treatment

THIOBARBITURATES IN ANÆSTHESIA

The synthesis of the thiobarbiturates was described in 1935,[1] and a year later the first reports of the clinical use of one of them, thiopentone, began to appear Since then, thiopentone has remained the most popular intravenous anæsthetic But knowledge of its side-effects and of its mode of breakdown in the body has led to the introduction of other thiobarbiturates, and more recently of other drugs

The principal side-effects are depression of respiration and circulation, and increased liability in some patients to coughing and laryngeal spasm The relatively brief anæsthetic action of thiopentone was early claimed as a major advantage, but by modern standards it is too long in certain circumstances Moreover the speedy return of consciousness that follows its use is due not to quick detoxication, but to a rapid redistribution of the drug in the body Thus for about 30 hours after an induction dose of thiopentone, enough of the drug remains in the body to affect the duration of action of a subsequent dose[2] Too large an initial dose prolongs unconsciousness , even a small dose leaves the patient unfit for responsible action for some hours (though he may not be aware of it himself), and repetitive doses are cumulative

Other thiobarbiturates were first introduced primarily to circumvent the side-effects Clinical reports appeared in 1946 of thialbarbitone ('Kemithal'), synthesised in 1938, and in 1950 of thiamylal ('Surital'), one of the original thiobarbiturates Neither of these drugs is sufficiently different from thiopentone to have achieved widespread use as an alternative

Interest in recent years has been concentrated on duration of action rather than on side-effects and two other thiobarbiturates have achieved some prominence One—methitural sodium ('Neraval,' 'Thiogenal')—seems to differ little from thiopentone[3] Favourable reports on the other—buthalitone sodium ('Transithal' 'Ulbreval' 'Baytinal')—have appeared in this country and a much briefer effect than that of equipotent doses of thiopentone has been claimed for it[4] But clinical assessment of the duration of effect of these anæsthetics is difficult and more objective measurement by means of the electro encephalogram suggests that buthalitone may in fact be active for even longer than thiopentone, though the difference between the two is slight[5]

The best hope of better intravenous anæsthetics may lie in investigation of drugs other than thiobarbiturates Hydroxydione ('Viadril'), a steroid with anæsthetic potency, has some advantages,[6] and a new substance—5 ethyl-6-phenyl-meta-thiazone-2,4 dione ('Dolitrone')—has been synthesised and used clinically for intravenous anæsthesia, but without striking advantages[7]

PELVIC TUBERCULOSIS

Chemotherapy has transformed the prospects for women with tuberculous infection of the genital tract This is not a common disorder, but the increasing investigation of women with minor gynæcological disturbances is revealing an unexpectedly large proportion of cases of pelvic tuberculosis A frequency of 5 3% has been found among nearly 2000 patients complaining of infertility, and this figure is regarded as a minimal estimate[8] Other common presenting symptoms such as pain, abnormal uterine bleeding, amenorrhœa, and vaginal discharge have led to the discovery of this underlying disorder, often without any palpable abnormality in the pelvis. Pelvic tuberculosis must always be borne in mind as a potential cause of persistent gynæcological symptoms, especially when infertility coexists Halbrecht[9] found that 40% of cases of blocked fallopian tubes (discovered on salpingography for primary sterility) were caused by tuberculosis The diagnosis is usually made by histological study of the endometrium , the specimen should be obtained as late in the cycle as possible to give the slow-growing tuberculous focus as long as possible to develop (Fewer cases of endometrial tuberculosis would be missed if routine curettage was more commonly timed for the premenstrual phase)

Before the advent of chemotherapy it was perhaps of academic importance whether the early case was diagnosed, for treatment was restricted to general health measures, a sanatorium regime, or X-ray therapy to suppress ovarian activity and rest the genital tract[10] The extent of the change that has taken place is indicated by the final report of the joint subcommittee of the British Tuberculosis Association and the Royal College of Obstetricians and Gynæcologists on the treatment of endometrial tuberculosis with streptomycin and *p* aminosalicylic acid (P A S)[11] This report analyses the results of a controlled trial in several centres in England and Scotland from 1950 to 1952, in which women with tuberculosis limited to the genital tract were allocated at random to a treated or an untreated group and followed up according to a prearranged schedule The treated patients received a three month course of streptomycin (calcium chloride complex) 1 g and P A S 12 g daily as outpatients

Of 43 treated patients who were observed for a year from the start of treatment, only 5 showed bacteriological evidence of recurrence, whereas of 44 untreated cases 11 had to be removed from the trial because of clinical deterioration and given immediate treatment, and 25 of the remaining 33 still had evidence of tuberculosis at the end of a year

Unfortunately, after treatment infertility usually persists[3] By the time the diagnosis is made, the tubal epithelium has already been damaged, and successful pregnancy is all too rare [12] At present relief of infertility depends chiefly on prompt diagnosis and treatment Further studies are in progress to determine what combination of drugs gives the best results, and to probe deeper into the all-important time factor Comparison with practice in pulmonary tuberculosis suggests that longer courses of treatment may still further reduce the incidence of recurrence, and that P A S and isoniazid by mouth are less likely to have serious side effects or to cause the patient to default

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[1] Tabern D L Volwiler E H *J Amer chem Soc* 1935, 57, 1961
[2] Dundee J W *Anæsthesia* 1955 10 139
[3] O Herlihy D B Nishimura N, Little D M Tovell R M *Canad anæsth Soc J* 1956 3, 326
[4] Nobes, P *Lancet* 1955 i 797
[5] O'Mullane, E J *Brit J Anæsth* 1957, 24 71
[6] Galley A H Rooms M *Lancet* 1956 i, 990 See *Ibid*, p 1002
[7] Tait, C A Davis D A Grosskreutz D C Boniface K J *Anesthesiology* 1956 17 536
[8] Sharman, A *Brit med J* 1947, ii 83
[9] Halbrecht I *Fertil Steril* 1951 2 267
[10] Jameson, E M Gynæcological and Obstetric Tuberculosis London 1935
[11] Sutherland, A M *Tubercle Lond* 1957, 38 46

Possibly in the future irreparable tubal fibrosis may be prevented by combining chemotherapy with cortisone or allied substances

QUARANTINE IN POLIOMYELITIS

THOUGH poliomyelitis is classed among the highly infectious diseases, secondary cases among family contacts are relatively uncommon In a statistical survey in this country, Spicer and McDonald,[13] using data obtained in the Medical Research Council's investigation of inoculation and paralysis, found that among 7782 households in which there was a primary case of paralytic poliomyelitis, in only 82 did another paralytic case follow They suggest that, as far as home contacts are concerned, quarantine and passive immunisation with gamma globulin have little value One course often followed in this country is to confine close child contacts to house and-garden quarantine for three weeks from the date of last possible exposure to infection, and to exclude *all* family contacts from school Only in exceptional circumstances are adults kept away from work [14] The W H O expert committee on poliomyelitis [15] recommended that "children with familial or intimate exposure should be confined to their homes for 21 days Adults need not be confined they should refrain from association with children other than their own and should avoid intimate contact with adults"

Strict quarantine measures, even if desirable, are not always practicable they need much organisation and take up a great deal of the public health department's time To be successful, they depend on the support of the public, and therefore on effective publicity and propaganda In a thickly populated area the task may be almost impossible, for one thing, interference with the work of the community may not justify the results achieved In a small isolated community, on the other hand, quarantine may be feasible and effective in stopping an outbreak [14], though Goffe and Parfitt [16] were not persuaded that quarantine measures did anything to stop community infection in the small winter outbreak they studied Agerholm,[17] however, was convinced of the value of quarantine she maintained [18] that the persistence of virus in the fæces was less important than many people supposed, and she believed that the real danger lay in pharyngeal carriage, which lasted for a much shorter period and would therefore be more susceptible to control by quarantine But not everyone is yet prepared to relegate the fæcal carrier to comparative insignificance

Further data about the influence of quarantine are therefore welcome, and the organisation and results of strict house quarantine in a housing estate in an isolated valley near Brighton have lately been described by Parker [19] Such elaborate measures had not been taken in the borough before, because, as is usual (and extremely likely in a town with a large floating population), the number of sporadic apparently unrelated cases did not seem to justify more than routine action But when 5 cases of paralytic poliomyelitis were notified in a week among children living on the estate, which had been free from the disease for at least five years, it was decided to impose house and garden segregation on everyone in the affected families This rule was relaxed only to allow the housewife to go shopping once a day, and she was instructed to wash her hands immediately before she went out Only 3 new cases were diagnosed on the estate later than twelve days after the diagnosis of the first case and four days after strict quarantine was begun 2 of these 3 cases were from houses already in quarantine In Brighton itself, however, sporadic cases continued to appear for more than two months There is no proof that quarantine protected the housing-estate from further attack, but the results are, to say the least, interesting

Public cooperation in the quarantine measures was sought in various ways A team was formed from members of the child welfare and school health services who were already familiar to those living on the estate The head teacher of the school "at once assumed the position of leader of the local population," and the school became the operational centre Public meetings were addressed by the medical officer of health, and the local press passed on information and advice [20] Those in charge appreciated that success depended on full public support It is noteworthy that, as a result of the crisis, barriers were broken down and a good community spirit sprang up where little had existed before

Experiments of this kind should be repeated elsewhere when conditions are favourable, and much valuable information could be gained by carrying out at the same time virus examination and antibody surveys in contacts and others (We refer on p 1305 to some preliminary details from a London borough where the fæces of contacts of a case of poliomyelitis have recently been examined) Good opportunities for such inquiries may present themselves in the next few weeks next year the picture may have been complicated by the immunisation of large numbers of children

BIRTHDAY HONOURS

THE barony accorded to Sir Horace Evans in the Birthday Honours list will give pleasure to the many colleagues who have observed his lightly borne wisdom in consultation and his cheering friendliness to all patients from king to commoner Mr Ralph Marnham, surgeon to St George's Hospital, London, is appointed K C V O for services to the Royal house Major General F K Norris, who is appointed K B E, is well known in Australia and beyond for his service in the Army, ranging from combatant duties in the 1914–18 war to the post of director general of medical services in 1948–55, and for many other useful activities Australia will also welcome the knighthood granted to Prof A B P Amies, dean of the faculty of dental science in Melbourne, who became known to a wider circle in the Western Desert in the late war Other doctors in the Commonwealth who are honoured include Mr J H Pierre, who has pioneered chest surgery in the West Indies, and who is now created a knight In this country knighthood is to be conferred on Prof G R Cameron, F R S, the author of distinguished work on cellular pathology, Dr R Brunel Hawes, who holds the important post of consulting physician to the Colonial Office at an exacting time, Prof G W Pickering, who, at his translation last year from London to the regius chair in Oxford, was already esteemed as a professor of medicine and as a person, and Colonel M Stoddart-Scott, M P, and Mr S T Irwin, M P, Northern Ireland, who are honoured for political and public services To these and others whose names appear on p 1295 we offer our congratulations

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[12] Halbrecht, I *Lancet* 1955 ii 1165
[13] Spicer, C C, McDonald J C *Ibid*, March 2, 1957, p 470
[14] Ministry of Health and Department of Health for Scotland Medical Memorandum, Poliomyelitis, July, 1954 See *Lancet*, 1954, ii 187
[15] *Tech Rep Wld Hlth Org* 1954, no 81 p 24
[16] Goffe A P Parfitt, E M *Lancet*, 1956, i, 1172
[17] Agerholm, M *Ibid* 1953 ii, 287
[18] Agerholm M *Ibid* 1955, i 1327
[19] Parker W S *Med Offr* 1957 97 107
[20] Gorringe, V P *Ibid*, p 109

The Wider World

REFLECTIONS ON MEDICAL TRAVEL

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AIDED foreign travel, like the aeroplanes we travel in, is part of the post-war way of life It goes with egalitarianism and new types of privilege, with high taxation and income tax rebates, with notional half-days and study leave It is a product of the past decade and the time has perhaps come to review its development

How enjoyable was the first small international congress of internal medicine in Basle in 1946 and how sadly congresses have deteriorated since! Indeed, their initial success was largely due to the fact that they manifested a world set free, they satisfied a need, and they were spontaneous and improvised Today, congresses are immense in size and they are organised down to the smallest item There were 1500 hæmatologists at the last congress of the International Society of Hæmatology, which is a relatively small specialty, and the expenditure for the congress exceeded 100,000 dollars[1] The attendance at symposia on some minute facet of medicine may be numbered in hundreds

One thinks of the long period of gestation, the delay between the acceptance of a paper and its delivery, which means that the material is already out of date by the time it is given, the concessions to international susceptibilities in the choice of programme, the ageing stage army of regular performers, the frequently deplorable level of presentation, the devitalised version of the addresses that comes over the Tannoy, the impossibility of discussion, the host of papers read by title so that participants can obtain currency allowances and tax reliefs, the inability to see one's friends unless one arranges a rendezvous beforehand, the banquets with the conventional references to the internationality of science, the expensive outings and the crowded sightseeing—and one wonders sadly whether medicine, too, has not come under the sway of Admass

Congresses have become too large and too frequent if their object is the advancement of medicine and the promotion of friendship among physicians The cost per head rises steeply when the attendance exceeds a few hundred, and the organisers become preoccupied with the physical problems of the meetings, the organisation of entertainments and the collection of subventions from the pharmaceutical and other industries However, the main subject of my paper is not these *omnium gatherums* but the growing stream of individuals who journey from our shores to all parts of the earth as visiting professors, lecturers, examiners, advisers, and so on This, again, is a new phenomenon Few, if any, of my teachers in Manchester and Cambridge, and few of my pre war colleagues on the staffs of London hospitals, had ever visited one of the Dominions or Colonies in peace time, and that indefatigable traveller, Sir Arthur Hurst, did not get farther than North America

Whereas international medical conferences might well be diminished in size and frequency, I believe that the more solitary migrants have an increasingly important part to play in the development of medicine and in the enhancement of England's status in the comity of nations Because aided travel is new, it is probably susceptible to technical improvement, and this must be my excuse for some notes on a term of absence in which I travelled around the world in 130 days A little mathematics shows that the average velocity was over 200 miles a day and the circumspection therefore somewhat superficial The journey is seen, however, against the background of previous trips to Europe and America

* * *

The human brain, particularly at the age when visiting professors are selected, is not a high-speed camera, and impressions soon blur if they are received in too rapid succession I believe a process of unconscious re remembering has to go on for some time until an imprint on the brain is fully developed This seems not to happen if the attention is closely focused on ever changing scenes, and the traveller should remember Wordsworth's dictum that emotion must be recollected in tranquillity if it is to issue again in a communicable form It is wise, therefore, to insist on a five day week, with one week out of every five off all duties, including social duties Moreover, it is foolish to travel round the world and to miss seeing the Barrier Reef, Alice Springs, Darjeeling, and the Khyber Pass In retrospect, the journeys along the interminable corridors and stairs of so many departments of anatomy and pathology have faded into a grey cloud, whereas a sunny afternoon at the races in Sydney, or a dinner by candlelight at the club in Melbourne, remains indelibly fixed in the mind "Not by eastern windows only, when daylight comes, comes in the light"

* * *

There are three types of academic foreign travel, the visit, the progress, and the sortie They are not mutually exclusive and in this recent trip a visit and a progress were combined The most profitable period, for others as well as myself, was the five weeks I spent in Sydney as McIlrath guest professor There we stayed in one place —actually in the hospital—long enough to get to know well the staff, the students, and in particular the hospital residents I was in charge of beds and took part in teaching, including the postgraduate fortnight, so that there was no need to collect special audiences, as sometimes has to be done for a visiting lecturer I had the opportunity to go out to near by centres such as Canberra and Orange, to visit practitioners in their homes and cottage hospitals, and to become familiar with the general social and economic background

The rest of our trip was what I have called a progress Here, to change the metaphor, one starts on a conveyor belt under the ægis of a sponsoring organisation, and the belt moves inexorably along Life is a succession of academic and social engagements and unrestful travel, and six weeks of this in Russia is said to destroy one's taste for caviare and champagne for the rest of one's life If you have a queazy stomach your travel will be one long dyspepsia, and, if you have not, you will increase your chances of bronchial carcinoma and coronary thrombosis, which have taken a heavy toll of recent medical travellers You are introduced as an expert in some small sector of medicine, and if you are a hæmatologist the same obscure cases of aplastic or hæmolytic anæmia, of lymphadenopathy, or leukæmia turn up wherever you go A longer stay is necessary to convince people that you are interested in medicine as a whole

The worst method of travel is the sortie, in which the holder of a travelling professorship, instead of taking long leave of absence, continues to look after his firm, his practice, or his department and makes brief dashes across the oceans like a water-beetle zigzagging across a pond This indicates a misguided sense of personal indispensability Any well established department should be able to spin for some months like a humming top without further application of the whip It is true that the current quip has it that the part time consultants are away part of the time and the whole time consultants away the whole of the time It is true, too, that some travellers return home to find that their subordinates have become dissident, but these are usually men like Richard I, for whom foreign excursions have become a perpetual way of life The ordinary man who cares for his personal work and therefore travels only at reasonable intervals is well advised to delegate his duties entirely and not try to fill two exhausting rôles at the same time

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[1] *Blood* 1957, 12 96

Short visits do, of course, have their rewards, for one makes many friends and receives abundant hospitality Centres which are often by-passed may be greatly stimulated by a visit and immensely grateful for the contact While, therefore, it is bad for a single individual to make a journey which consists of short visits to many different places, it would be good to try to satisfy the desire for more contacts with English medicine by encouraging more people to interrupt the flight to Australia or the Far East and to touch down and lecture at one centre at least A continuous flight to the Antipodes is exhausting if it is not interrupted by one or more breaks en route Again, it would be better for a Sims professor to spend six weeks at two of the six capital cities in Australia rather than two weeks at each of them Over the years it could be ensured that each capital city got a fair proportion of the professors'

* * *

A visit may be of any length, though anything more than the traditional sabbatical year would be unusual What I have termed the progress, where the visitor is travelling more or less continuously, should probably not be less than three weeks, to justify the expense of the journey, nor more than three months, to maintain peak performance In many people the return home is followed by a period of reactive depression which has been called the repatriation syndrome Some of the components of this are fatigue, the accumulation of tasks and problems during absence, and the switching-off of the limelight in which the traveller has basked so happily

* * *

A difficulty with a lecture tour through a variety of countries is the different character of the audiences which are encountered The same lectures will not be suitable for all of them With the growth of medical travel and writing, ideas travel quickly and modern audiences have become like the ancient Athenians who perpetually demanded some new thing It is idle to pretend that any of us possesses a large stock of unpublished information, and the preparation of a great number of lectures summarising current knowledge is a wearisome task

In the large centres in Australasia the doctors are right up to date and they complain that some recent visitors have talked down to them They require something sophisticated, with an element of personal research The men in the smaller centres in Australia are equally up to date, but they want something of a practical type which deals with the current problems of Western medicine In India and the Far East the medical setting is quite different It is important to note that the major problems are not those of tropical medicine in the accepted sense, in so far as they are, they can be left to experts in tropical medicine Most of the clinical material is identical with what Osler saw and described in North America over seventy years ago, but it is on a vast scale, it has to be handled on a doctor-patient ratio of 1 to 10,000, and it is presented against the background of modern chemotherapy and modern ideas about public health For example, all these Eastern countries are going through an epidemic of tuberculosis which is more severe than the one we experienced in Europe a hundred years ago, but today much more is known about the epidemiology and treatment of tuberculosis

Other common illnesses are nephritis, rheumatic heart-disease, and rheumatoid arthritis, anæmia and leukæmia, jaundice, cirrhosis of the liver, and splenic anæmia, bronchitis, emphysema, and heart failure, typhoid and the dysenteries Some diseases which are important in this country, such as pernicious anæmia, ulcerative colitis, and disseminated sclerosis, are almost completely absent, and there is little interest in geriatrics when half the population is under the age of 21 There are, of course, regional differences, lung cancer and peptic ulcer being common in Burma but uncommon in North India and Pakistan

The problem in the East is to smash these great epidemics of disease and to discover the best way of doing this with limited man-power and funds Expensive individual procedures—what I call millionaire medicine—are of much less practical importance than community programmes, and therefore lectures on field work, screening for disease by simple tests and therapeutic trials, should be successful, even though British experience is not immediately transferable This is not to say, of course, that the physician in the East does not enjoy the occasional purely scientific lecture as much as the physician in the West and there is always interest in material which can be presented dramatically or visually, such as plastic surgery, cardiac surgery, and thoracic surgery

(To be concluded)

Occasional Survey

THE ARCHITECTURAL FUNCTION OF PULMONARY CAPILLARIES

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RESEARCH has suddenly advanced our knowledge of the initial expansion of human lung The idea that the lungs first expand gradually over hours or days was never held by Potter,[1] who showed that inflation with either air or oxygen caused irregular expansion, with distension of the proximal parts of the lung and atelectasis of the distal parts She also showed that this histological appearance in the mature neonate proved that an attempt had been made at resuscitation by inflation In premature neonates weighing 1000–2000 g Potter found the same appearance produced by the infants' own respiratory efforts Lind and Wegelius,[2] in their exquisite ciné radiological studies, show how quickly the lungs expand in normal neonates with the first two or three breaths the lungs expand "like the lighting of a lamp," and the heart, which is initially large, diminishes stepwise with each respiration

Jaykkä [3] has shown that the extirpated lungs of full-term neonates cannot be fully expanded by the air-pressure difference resulting from a negative pressure of −20 cm of water applied outside the lung in a partially exhausted jar and a positive pressure of + 20 cm of water applied within the trachea This experiment produces a histological appearance similar to that shown by Potter [1] to be typical of the lungs of mature neonates in whom inflation by air or by oxygen had been tried as a means of resuscitation

More important is Jäykkä's finding that when a fluid pressure of 80 mm Hg is put into the pulmonary artery in addition to the above mentioned application of the air-pressure difference, the alveoli expand to their proper extent He considers that the pulmonary capillaries are erectile and help to hold out alveoli as a result of their distension with blood His inability to expand the lungs of fœtuses weighing 500–800 g by this method he explains on the grounds of immaturity of this erectile capillary system

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[1] Potter E L Pathology of the Fetus and the Newborn *Chicago*, 1952
[2] Lind J Wegelius C *Int Cong Pædiat* 1956
[3] Jäykkä S *Acta pædiat, Stockh* 1957, 46, suppl 112

Dawes et al [4] and Born et al [5] have shown in lambs that, before the lungs expand, the initial pulmonary vascular resistance is high and can be made higher by asphyxia produced by tying the cord before the onset of respiration The fact that the pulmonary resistance can be varied by asphyxia implies an ability on the part of this vasculature, probably the arterioles, to contract and so to raise the resistance and to impede the onward flow of blood to the capillaries

Bonham Carter et al [6] seem to have shown that a high venous pressure, measured in the inferior vena cava, is beneficial to premature neonates with respiratory difficulty at or shortly after birth, and these workers suggest that this benefit is derived from a high cardiac output (stroke volume) dependent on a high venous pressure

The foregoing work seems to show two things

(1) Initially the alveoli are expanded by the erectile pulmonary capillaries and the air pressure difference created by respiratory effort

(2) Where the peripheral pulmonary vascular resistance is very high, probably made so by asphyxia, a high cardiac output is necessary to overcome it, so that the pulmonary capillaries may be adequately filled with blood and play their part in the proper expansion of the alveoli

Gunther [7] shows how much the position of the placenta relative to the baby and other factors, with the cord intact, can vary the neonatal blood volume—up to 47% of the expected total She also shows how, with the cord intact, the baby acts as a plethysmograph, recording, by increases in weight, the effects of uterine contractions on the placenta during the third stage of labour Sharpey-Schafer and Wallace [8] have shown, in adults, what a great volume of fluid is required to raise the systemic venous pressure by transfusion, and how fast it has to be injected, but Gunther's findings indicate a fast transfusion of a relatively great volume of blood during the third stage of labour under certain conditions

From the visible evidence of Lind and Wegelius's film of the stepwise diminution in the size of the heart during the first two or three breaths and from Bonham Carter's work it looks as though the stroke volume of the heart during the onset of respiration is high, and that the capacity of the neonatal right auricle to withstand a high pressure must be great, for a caval pressure of 14 cm of 5% dextrose solution in water has been recorded with survival It seems likely also that the factors described by Gunther play a part in the production of this high stroke volume Perhaps Starling's law is being exercised at the time almost at the maximal stretch of cardiac muscle

The redirection of blood with the onset of respiration must be considered A high right-auricular pressure must tend to keep open the foramen ovale because of its anatomical structure Therefore, unless there is a high left-auricular pressure, the right to left shunt must persist Could the initial distension of the heart seen in the radiographic film, and implied by Gunther's work, provide for this shunt and for adequate right ventricular filling? Or must a sudden rise in left-auricular pressure be assumed? If the left auricular pressure rises thus, as well it may, as the result of the high right-auricular pressure and the foramen ovale shunt, a "backward" distension of pulmonary capillaries may occur (see below)

Barcroft [9] showed that the closure of the ductus arteriosus in lambs was related to the onset of respiration, probably by a mechanism involving an increase in systemic oxygen tension Lind [10] and Hultgren [11] have produced evidence that the duct can be reopened, in human neonates, by interference with respiration or by breathing low-tension oxygen It looks as though the duct closes with normal oxygen tensions and reopens or remains open with anoxia If the peripheral pulmonary vascular resistance is high, the pulmonary artery pressure will also be high, if the cardiac output is maintained Asphyxia if this produces the same effect in men as in lambs, will do this However, the direction of the flow in patent ductus arteriosus will depend on the relative pressures in the systemic and pulmonary circuits, if the flow is largely from pulmonary artery to aorta, the blood normally used to distend pulmonary capillaries will be diverted conversely, if the flow is the other way, the erection of pulmonary capillaries will be assisted by the shunt from the aorta

This conception of the architectural function of pulmonary capillaries and the part they play in the initial expansion of human lungs can be related to the clinical picture of neonates with difficulty in breathing—what Bound et al [12] called "the pulmonary syndrome of the newborn" These infants at, or shortly after, birth make desperate respiratory efforts They have episternal, lower costal, and even sternal recession, and yet achieve little or no ventilation They are commonly premature and born by cæsarean section The physiological explanation of this behaviour may be that of a premature infant rendered asphyxial by some accident of birth, with the result that the peripheral vascular resistance in his lungs rises with increasing asphyxia in a vicious spiral, until his cardiac output cannot overcome it, so his alveoli are never properly expanded Possibly this situation arises from, or is aggravated by, a blood volume diminished by the factors shown by Gunther and possibly by early tying of the cord

To explain on this hypothesis the ability of neonates with pulmonary atresia or with severe pulmonary stenosis to expand their lungs is difficult, unless the ductus arteriosus temporarily remains patent with a shunt from aorta to pulmonary artery and possibly with minimal assistance from the bronchial arteries Such infants, however, would remain anoxic and so might be expected to maintain the patency of the duct

If this hypothesis is acceptable, and the structural function of the pulmonary capillaries is maintained in later life, other concepts may follow Lung elasticity (rigidity), its ability to relax from the inspiratory phase, will in part be a function of pulmonary capillary pressure

Taussig [13] has drawn attention to the fact that children with congenital heart-disease and large left to right shunts have large lungs, a bowed sternum, and a flat diaphragm, and this has been our constant observation in the congenital-heart clinic at Great Ormond Street A large left-to-right shunt will result in overdistension of the pulmonary capillaries until or unless the peripheral vascular resistance increases sufficiently to reduce the blood-flow This, in a manner of speaking, is the "forward" form of pulmonary capillary distension giving rise to an inability of the alveoli to relax completely The measurement of residual air is impossible in little children, but we have found, by way of indirect evidence, a tendency in such cases without congestive failure to retain carbon dioxide with a shift of blood pH to the acid side, as if the mixture of gases was imperfect (unpublished data)

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[4] Dawes G S Mott J C Widdicombe J G Wyatt D G *J Physiol* 1953 121 141

[5] Born G V S Dawes G S, Mott J C Widdicombe J G *Cold Spr Harb Symp quant Biol* 1954 19 102

[6] Bonham Carter, R E Bound J P, Smellie J M *Lancet* 1956, ii 1320

[7] Gunther M *Ibid* June 22 1957 p 1277

[8] Sharpey Schafer F P Wallace J *Brit med J* 1942 ii 304

[9] Barcroft J Researches of Prenatal Life Oxford 1946

[10] Lind J M & R Pediatric Research Conference Ohio, 1955, p 27

[11] Hultgren H N *Ibid* p 53

[12] Bound J Butler, N R, Spector, W *Brit med J* 1956, ii 1191 1260

[13] Taussig H B Congenital Malformations of the Heart London 1947

Hellems et al[14] and Lagerlof and Werko[15] have shown how pulmonary capillary pressure reflects the pressure in the left auricle So a "backward" form of overdistension of pulmonary capillaries could arise from changes in left auricular pressure with similar effects on the alveoli The clinical picture here is that of cardiac asthma with its expiratory wheeze Christie and Meakins[16] and others since have shown that an increase in residual air is usual in patients with chronic congestive cardiac failure, and an inability of the alveoli fully to relax in expiration may be the cause

Finally, it must be said, that although *pressure, flow, and resistance in the pulmonary circuit* are interrelated according to Ohm's law and will therefore affect the rigidity and flaccidity of the capillary network, the property which is most responsible for this will be the tension in the wall of the capillaries This tension, as in a tyre, will be related not only to the pressure within the tube but also to the radius and diameter of the tube Under static circumstances this relationship can be expressed thus

$$\text{Tension} = \frac{\text{pressure} \times \text{radius}}{2}$$

So little of the original work on this subject is mine that I clearly owe a debt to all those whose writings I have read on this subject, and all the friends that I have bored with it, particularly John Bound, Mavis Gunther, and Jean Smellie of the Obstetric Hospital, U C H

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[14] Hellems H K, Haynes F W, Glovely J F *J clin Invest* 1948, 27 540

[15] Lagerlof, M Werkö, L *Scand J clin Lab Invest* 1949, 1 147

[16] Christie R V Meakins J C *J clin Invest* 1934, 13, 323

Special Articles

AN ATTEMPT TO COUNTER "INSTITUTIONALISATION" IN CHRONIC SCHIZOPHRENIC PATIENTS *

A R MAY
M B Lond, D P M
ASSISTANT PSYCHIATRIST,
NETHERNE HOSPITAL, COULSDON, SURREY

HABIT TRAINING is now a recognised method of dealing with the chronic deteriorated patient in a mental hospital As its name implies, it seeks to impose socially acceptable behaviour on the patient by a process of conditioning But though the patient's behaviour improves, he remains "institutionalised"[1], for the method is disciplinarian and does not sufficiently encourage the spontaneous development of social interaction and initiative Our experience among these patients led us to consider how we could counter the automatic pattern produced by conventional habit-training programmes

In 1955 and 1956 I was concerned with a male ward[2] and a female ward[3] of chronic deteriorated patients By habit-training we were able to improve their behaviour and to open both wards within a year Aggressive behaviour remained the greatest difficulty, but we noticed that at mixed parties of patients from both wards there were hardly any acts of aggression and that the spontaneity and interest of patients improved

This observation prompted us to consider extending this social contact by creating a mixed unit for deteriorated patients Our aims were roughly defined as investigation of the effect of community life on the behaviour and psychotic process of deteriorated schizophrenic patients, and the effect of this new therapeutic policy on the attitudes and beliefs of all the staff By treating this as a pilot study, we hoped to get some idea of the difficulties which would arise when extending this mixing of the sexes to other parts of the hospital

A Schizophrenic Community

At the outset we decided to make our intentions as widely known as possible to all grades of staff The first plans were made in September, 1956, at meetings with ward and administrative nursing and medical staff In general there was considerable enthusiasm among those directly concerned, but misgiving among those who distrusted the disturbance of the traditional dichotomy between male and female sections of both patients and staff Others saw it as yet another innovation which would upset the comfortable equilibrium of institutional life But after discussion it was eventually agreed to give the plan a trial In November, 1956, 44 men and 43 women patients were transferred from their wards to two adjacent villas in the hospital grounds

Patients

The criteria for selection of these patients were a diagnosis of schizophrenia, a history of treatment in a mental hospital for five years or more, and a maximum age of 50 Further details about them are given below

	Men	*Women*
No of patients	44	43
Average age	40 4 yr (range 26–50)	37 4 yr (range 20–50)
Average time in mental hospitals	14 3 yr (range 5–37)	12 3 yr (range 5–21)
No of patients who have had		
E C T	39	43
Deep insulin	7	14
Leucotomy	7	17

All patients had been rated on the Fergus Falls behaviour-rating scale by at least two independent raters before they were moved The senior ward staff had been with them for a year or more and knew them well

Pattern of Care

The actual move was made with the minimum of disturbance The villas are surrounded by a large railed garden, and for the first two weeks the gates were closed in case patients wandered away Thereafter they were opened, and they have remained open ever since The doors of the villas were opened from the start

The mixing of patients was at first allowed to develop spontaneously After four days a woman wandered into the male villa and was promptly handed a bucket and scrubbing-brush, she scrubbed the kitchen floor without protest, but has never done as well since In the first week about a dozen men and women patients began to meet inside and outside the villas

In the second week a more formal programme was started From both sets of patients were drawn two groups of 12 each, under one nurse The sister or charge nurse was responsible for the remaining larger group, some of whom were better preserved ward workers We were obliged to accept these unsatisfactorily large groups because we had so few nurses Nurses in charge of groups understood that they were expected to organise the social and working activities of their group as well as getting to know all the members From the start it was made clear that rigid adherence to the programme was not expected—more important was the opportunity for mixing given by the programme

Men and women share gardening work on most mornings, and an art class for half of each villa is supervised by the art master twice a week A mixed "movement

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[*] *Based on a paper to the Surrey Inter Hospital Psychiatric Association on Feb 21, 1957*

[1] Martin D V *Lancet* 1956, ii 1133

[2] May A R *Ibid* 1956, i, 500

[3] Folkard S *Proc R Soc Med* 1956, 49, 1030

with music" class is held one evening a week, and a ward social, with dancing and games, on another evening Both villas attend dances, concerts, and the cinema in the main hall Men and women who prefer to do so may watch television in the male villa in the evenings

If the weather is bad, there is always a group of men patients in the female villa and vice versa—where they are encouraged to share in simple occupational tasks

About three weeks after the move, one of the men patients visited the female villa and stayed to lunch He was well tolerated, and we decided to have mixed meals at separate tables We started with lunch and extended this to tea, behaviour at meals is excellent and there is virtually no disturbance, in sharp contrast to conditions in the original women's ward

Staff

The most fascinating and probably the most important aspect of all these developments has been the change in the attitude of the staff I hold a meeting with the ward-staff once a week, and once a month we have a larger conference with the medical superintendent, matron, and representatives from the administrative and training staff We keep a record of matters discussed at all these meetings, and they have developed into very lively affairs, with a refreshing lack of reserve Perhaps the best commentary on their success, or at any rate on their entertainment value, is the fact that although they started as lunch-hour sessions from 1 P M till 1 45 P M, we are now usually obliged to end them forcibly about 3 P M

The interaction between men and women staff, with mutual criticism, has changed our discussions out of all resemblance to the rather moribund meetings we used to hold on the separate male and female wards These discussions have been essential The gradual development of policy has been anything but smooth, and the unit has been the cynosure of the hospital as a whole The smaller ward staff meetings have been frankly therapeutic, and the attitudes expressed over the management of individual patients have been related to personal motivations, with a good deal of interpretation It has been most instructive to correlate the level of ward tension with the personal satisfaction or anxiety of the nurses

A major theme which has run through all these meetings has been the conviction of the female staff that the women patients are more active, more aggressive, and more difficult to manage than the apparently well-drilled or well trained men, and the equally strong conviction of the male staff that the women are not properly managed by the female nurses This is mainly because the men, who had followed a habit training regime for at least two years longer than the women, will *work* much better, though they are less spontaneous at social functions, and because the women are, by and large, as putty in the hands of the male staff But this rivalry seems to be gradually lessening

Response of Patients

Ten weeks after the move all patients were again rated on the Fergus Falls scale There was a strong positive correlation between these ratings and independent clinical assessments, but the scale is not precise enough to measure the more subtle alterations in social attitudes and group interaction which we have noticed

Though there has been no deterioration in the behaviour ratings since the move, neither has there been any significant improvement On the other hand, many patients have become more spontaneous in social situations, and disturbances in the ward have been noticeably reduced under the mixed regime Only 5 women, and none of the men, now require regular electroconvulsion therapy It has only been necessary to seclude 1 patient, a man who became disturbed by the presence of women patients and staff and eventually had to be transferred He was the sole casualty among the men 2 of the women patients had to be transferred, 1 because of persistent absconding, and 1 because she became disturbed and deluded as a result of the co education

The apathy which is the stigma of the institutionalised patient has almost disappeared The increased mobility and spontaneity is shown by the growing ease with which patients can be encouraged to perform fairly responsible tasks Most of the men can now be trusted to shave themselves, and many of the women can be sent on errands to the hospital shop The general bearing of patients has improved, they move more flexibly and with more purpose, and they can manage with less supervision than before Less time is spent on washing, dressing, and toileting All but about half a dozen will now answer when spoken to Some who were previously uninterested now speak of each other and the staff by name, and the isolating anonymity of ward life is partially dissolving

Conclusion

The experience of our first three months supports the view that change of environment towards a more normal community can have a therapeutic effect on chronic schizophrenic patients and can do much to combat institutional behaviour

The future development of this project depends on the staff, and therapeutic policy has now been directed to countering institutional attitudes in them, for only by some such reorientation can they (including the doctor) prevent the patient from sinking back once again into the amorphous mass of chronic schizophrenics

I wish to acknowledge the encouragement of Dr R K Freudenberg, physician superintendent, and to record my thanks for the cooperation and support of the nurses engaged in this project

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BIRTHDAY HONOURS

THE list of honours published on June 13 contains the names of the following members of the medical profession

Baron

Sir HORACE EVANS, G C V O, M D Lond, F R C P
Physician to H M The Queen, physician to The London Hospital

K C V O

RALPH MARNHAM, M CHIR Camb, F R C S

K B E

Major General FRANK KINGSLEY NORRIS, C B, C B E, D S O, E D, M D Melb
For services to medicine

Knights Bachelor

ARTHUR BARTON PILGRIM AMIES, C M G, D D SC Melb, F.R A C S, F R C S F
Dean of the faculty of dental science, University of Melbourne

GORDON ROY CAMERON, M B, D SC Melb, F R C P, F.R S
Professor of morbid anatomy in the University of London at University College Hospital Medical School

RICHARD BRUNEL HAWES, C M G, M B Lond, F R C P
Consulting physician to the Colonial Office

SAMUEL THOMPSON IRWIN, C B E, M CH Belf, F R C S E, M P Northern Ireland
Consulting surgeon, Royal Victoria Hospital, Belfast, for political and public services

GEORGE WHITE PICKERING, M D Camb, F R C P
Regius professor of medicine, University of Oxford

Joseph Henry Pierre, M B Lond, F R C S E
Specialist surgeon, General Hospital, Port of Spain, Trinidad

Colonel Malcolm Stoddart Scott, O B E, T D, M D Leeds, M P
For political and public services

C B (Military)

Surgeon Rear Admiral David Duncan, O B E, M D Aberd

Major General Philip Francis Palmer, O B E, M B Dubl

Surgeon Rear-Admiral Arnold Ashworth Pomfret, O B E, M B Manc

C M G

Frederick Roland George Heaf, M D Camb, F R C P
David Davies professor of tuberculosis, University of Wales, consultant in tuberculosis to the Colonial Office

David James Masterton Mackenzie, O B E, M B Edin
Director of medical services, Northern Region, Nigeria

C B E (Military)

Air Commodore James Hill, M B Glasg, R A F

C B E (Civil)

Archibald Simpson Anderson, M B Melb, F R A C S
Honorary consultant ophthalmic surgeon, Victorian Eye and Ear Hospital, Melbourne

Alexander King Bowman, M B Glasg, F R F P S
Senior administrative medical officer, Western Regional Hospital Board, Scotland

David Paton Cuthbertson, M D, D SC Glasg
Director, Rowett Research Institute, Bucksburn, Aberdeenshire

Benjamin Thomas Edye, CH M Sydney, F R C S
Honorary consulting surgeon, Royal Prince Alfred Hospital, Sydney

Sybil Gertrude Horner, M B Lond
Senior Medical Inspector of Factories, designate, Ministry of Labour and National Service

Donald Hunter, M D Lond, F R C P
Physician and director of the department for research in industrial medicine (Medical Research Council), London Hospital

Samuel Horton Oluwolé Jones, O B E, M B Manc
Director of medical services, Gambia

Edmund Oliver Lewis, M A Camb, D SC Lond, M R C S
Lord Chancellor's Medical Visitor in Lunacy

Ernest Steven Monteiro, M D Malaya, F R C P
Dean of the faculty of medicine and professor of clinical medicine, University of Malaya

M V O (*4th Class*)

Surgeon Commander Peter Geoffrey Burgess, B M Oxfd, R N

William Neil Maclay, M B E, B A Camb, M R C S

O B E (Military)

Squadron-Leader Peter Howard, M B Lond, R A F

Surgeon Commander James Lees, M R C S, R N

Lieut Colonel Alexander Robert Taylor Lundie, M C, M B St And, R A M C

Lieut Colonel Walter William McLellan, R A A M C

Lieut Colonel Maurice Irving Silverton, T D, M R C S, R A M C, T A

Squadron-Leader Arthur John Wainwright, M B Birm, R A F

O B E (Civil)

Joseph Antoine Hermann Andre, M B E, M R C S
Deputy director of medical services, Mauritius

Thomas James Biggs, M B Sydney
Senior physician, Mater Misericordiae Hospital Sydney

Humphrey Malomo Samuel Boardman, L R C P E
Assistant director of medical services, Sierra Leone

Archibald Turner Macleod Blair, M B N Z
A medical practitioner at the Queen Elizabeth Hospital, Rotorua, New Zealand

Mabel Alice Dobbin Crawford, M D Dubl, F R C S I
Medical officer, Ministry of Supply

Alfred John Craig, M D Malta, F R C S
Professor of surgery, Royal University, Malta, senior surgeon, government hospitals

Muthiah Doraisingham, L M
Deputy permanent secretary to the Ministry of Health and deputy director of medical services, Singapore

Mary Katherine Dorothy Douglas, M B Edin
For political and public services in Fife

John Richard Hertslet Fulton, M B N Z, M R C P E
Chairman of the Otago hospital board, Dunedin

Noel Gerald Carleton Gane, F R C S E
Consultant surgeon, Salisbury Hospital and Rhodesian Forces

John Mark, M B
Medical practitioner and surgeon, Tauranga, New Zealand

Otto Mastbaum, M D Cologne
Malaria medical officer, Swaziland medical service

Frederick Lubovius Richard, M B Glasg
Commissioner, St John Ambulance Brigade, Staffordshire

Thomas Haines Sims, M B Camb
Senior medical officer, Ministry of Pensions and National Insurance

Robert Stewart Slessor, M B Aberd
Senior medical officer, Falkland Islands

Arthur Wesly Sugunaratnam Thevathasan, M R C P
For public services in Singapore

William Wood, M B Durh
Head of virus research unit, Glaxo Laboratories

M B E (Military)

Squadron Leader Irwyn Morse Perkins, M R C S, R A F

M B E (Civil)

Frederick Esibi, M R C S
For medical services in the Western Region Nigeria

Frank Neville Grannum, E D, M B Edin
Lately senior medical officer of health, Barbados

Thomas Patrick Howkins, M R C S
Divisional medical officer, southern region, British Railways

Ivan Saja Kadama
Medical officer, Uganda

Manchersha Manekji Kutar, M B Bombay
Assistant medical officer, Aden

Petro Solomon Blandina Muganwa
Medical Officer, Uganda

Vilikesa Ramaqa
Senior assistant medical practitioner, medical department, Fiji

Medicine and the Law

Dispensing Doctor Issues Prescriptions

The Minister of Health is to withhold £1100 from the remuneration of a doctor because of a breach of the regulations.[1] It was alleged that, between June, 1955, and March, 1956, he had issued prescriptions to the value of £269 16*s* 11*d* to patients for whom he was receiving drug capitation fees In some cases the names could not be traced as National Health Service patients, in others the names were indecipherable Some of the forms had been issued by the doctor's partners The Kent and Canterbury executive council had at first recommended that £500 be withheld, but on considering events before June, 1955, recommended withholding £1500 The Minister has decided on £1100 The doctor has accepted responsibility, but attributed the discrepancies to "muddle and not wilfulness"

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[1] *Times,* June 13

Conferences

A TRUCE IN THE REMUNERATION DISPUTE

Special Representative Meeting of B M.A

A SPECIAL representative meeting of the British Medical Association decided on June 12 that the profession should give evidence to the Royal Commission and that a decision on withdrawal from the National Health Service should be deferred Dr SOLOMON WAND, chairman of the B.M.A council, summed up the situation by saying that a truce had been declared—an armed truce The profession's dispute with the Government remained unresolved and if it was not settled in a way that doctors could accept, then they must still be prepared to take vigorous action The breathing space, Dr Wand added, would give them an opportunity to strengthen finances and promote unity The need was for reunification, not recrimination

THE ROYAL COMMISSION

Early in the meeting, a representative suggested that everyone's minds were made up and that no arguments would change them Nevertheless, Dr G S R LITTLE (Greenwich and Deptford) pleaded forcefully for non-coöperation with the Royal Commission First thoughts he declared, were best and the first thoughts of the council had been not to give evidence to the Commission Whether the Spens reports were legally valid or not was unimportant Spens was not, as had been suggested, "in the melting-pot" it was in the incinerator Dr Little was sure that the Royal Commission would produce something much less attractive than Spens When the Commission had reported, the Government would accept only those recommendations which it was prepared to accept *now*

Dr C P WALLACE (Guildford) sadly reflected that, by reason of default, it had become inevitable to give evidence, and Dr A V RUSSELL (Wolverhampton) thought that, though the profession would not get very far by going to the Commission, there was now no alternative Mr H H LANGSTON (Winchester) was for a more cheerful approach ' if we are to give evidence, do not let us do so in this lukewarm way" But Dr C R G BARRINGTON (Bromley) saw little hope no other profession, he said, would put up with the treatment the doctors had received To give evidence to the Royal Commission was another step down the ladder and towards the state of mind in which " we do exactly what we're told "

PUBLIC-HEALTH DOCTORS

Anxiety about the future of doctors in the public health service found expression in an amendment declaring that evidence should be given to the Commission provided that either (*a*) all doctors in the public health service be included within the scope of the terms of reference of the Commission or (*b*) that an undertaking be given by the Government that an independent inquiry into the remuneration and status of all public-health medical officers be set up immediately Dr J A STIRLING recalled the view recently endorsed by the council of the B M.A —that coöperation with the Royal Commission should depend on the inclusion of public health doctors, and Dr J S G BURNETT spoke of the difficulties which faced those doctors in a service in which no cognisance was taken as far as remuneration was concerned, of postgraduate training and in which it was hard for doctors to get in the forty years' service necessary for full pension rights The meeting was clearly anxious to strengthen the position of colleagues in the public-health service but many representatives felt as did Dr A BROWN (Cambridge), that if they went on attaching impossible strings to the giving of evidence, they would do the public-health doctors a disservice

Dr J B TILLEY (Newcastle upon Tyne), chairman of the B M.A 's public health committee, said that they had tried hard to get the Minister of Health or the chairman of the Royal Commission to take one of these courses But not a shadow of a promise could be extracted The public-health committee had decided to leave the decision to the special representative meeting Dr WAND observed that general practitioners and hospital staff were in dispute with the Government the public-health doctors' dispute was primarily with local authorities The evidence of doctors in the public-health service would be presented to the Royal Commission, and this amendment would defeat the intention to give evidence Dr Wand could see no reason why the profession should not give evidence so long as their rights to seek fulfilment of the Government's moral obligations were not prejudiced By a large majority the meeting agreed that "the Association should give evidence to the Royal Commission on the understanding that it is given without prejudice to the profession's right to press for fulfilment of the Government's moral obligations inherent in the public and private assurances given by it and its predecessors to doctors taking part in the National Health Service '

WITHDRAWAL

This decision having been taken, there was no long debate on the issues concerning withdrawal from the National Health Service The meeting agreed to defer a decision on withdrawal, but the emphasis was on preparedness, and representatives insisted that the machinery and method of withdrawal be kept under constant review and that the council should also proceed urgently with preparations for an alternative health service

LEGAL ACTION ?

The possibility of taking action to test the validity of the Spens report as a legal contract for general practitioners again roused interest, as it had done at the special representative meeting on May 1[1] Dr WAND said that legal advice was firmly against such a course, and when some representatives seemed dissatisfied, he spoke more fully on counsels' views Dr I D GRANT, the chairman, ruled that this part of the discussion be private

Dr B BURNS (Sheffield) attributed this reluctance to go to court to fears that the public were "not on our side ' It was not public opinion, however, but editorial opinion that was against them "*The Times* has repudiated Spens Let no dog bark" A motion calling on the council to test in the courts the validity of Spens as a legal contract for general practitioners was defeated

PARALLEL DECISIONS

Dr A BEAUCHAMP, chairman of the annual conference of representatives of local medical committees, told the meeting of decisions taken at the conference on June 6 In view of the statements made publicly by the chairman of the Royal Commission and assurances given to Dr Wand by the Minister of Health, the conference recommended that evidence should now be given A decision on withdrawal should, it was agreed, be deferred, and another recommendation was that "the negotiating machinery be revised with a view to establishing effective coordination between the several branches of the profession and the prevention of unilateral action by any one branch" A motion was also passed instructing the General Medical Services Committee, in consultation with the council of the B M A, to prepare plans for an alternative national medical service

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[1] See *Lancet* May 11 1957 p 987

In England Now

A Running Commentary by Peripatetic Correspondents

ALL normal boys want to be engine-drivers when they have nannies. Later their ideas develop and the nannies have to go. My nanny went too, but something went wrong, something in me failed to develop, and I have only lately discovered what it was. All through my school years, through M.B., B.S. to M.D., through houseman, S.H.O., registrar, S.H.M.O. and consultant pathologist, through my military service, I wondered what was wrong with me. During all my years of dutiful seaside holidays with the family I wondered why I was unhappy. Now I know—I still wanted to be an engine-driver.

And so it is that every holiday now finds me a "passed fireman" on the books of an old-time, half-size, obsolete railway line in Wales, alongside dozens of others suffering from the same complaint. I light the engine-fire and watch "her" get up steam, I clean and polish her, and then move her along to pull her train out. I talk railway jargon. Sometimes I forget and the passengers become patients. My companions are a cross-section—professional railwaymen, tally clerks, fitters, solicitors, policemen, accountants, lorry-drivers, company directors, and of course clergymen. Occasionally I see a colleague and I tease him. Yes, he remembers the face. 1938? St Mary's? The engineman's cap and overalls, the covering of coal and grime, overwhelm his cerebral processes and they grind to a halt. How can a contemporary be working thus? Unless, yes, that must be it. It must be the work of the General Medical Council. After all it might happen to anyone. Volunteer, did you say? This is only a summer holiday hobby? Recognition dawns, freely, honourably, and obviously. Of course he remembers, and what a wonderful hobby. Reminiscences are interrupted by a shriek of the whistle. "Right away" it is, and the train moves off.

May I never grow up.

* * *

Occupational medicine in the North is a bit of a change. I now syringe ears to strains of *Music While You Work* and am no longer surprised by a "How do you do" in response to a proffered "Good morning." The uniformed gatemen have ceased to look grim and hostile, and their welcoming smile and wave compensate for the evil odours that assault me as I enter the factory. I drive past glistening rows of fitters' cars in my twenty-three-year-old vehicle, but realise that the display will save me a visit to the show-room when my ship comes home.

There are many surgery attendances on Mondays, when industrial hazards are eclipsed by football and Judo as sources of trauma. The chairman seems to burn as well as a shop-steward at the business-end of the cautery, and I find that the pain of a "strained back at work" may emanate from a renal calculus. I live in suspense lest patient and first-aider should meet before the former reaches the medical centre; the practical effect of some answers at a recent viva would best be untried. There is an abundance of monosyllabic Christian names and a pleasing democracy extends even to the golf-club. I lately arrived at the first tee to admire the drive of someone whom I had that very day restricted to sedentary work.—But perhaps the amended certificate next morning was an aid to productivity. No discussion was necessary and a "fit" note thus achieved might be considered a "knock-out" as against the "win on points" which is so much more exhausting to the doctor.

At first the impact of industry depressed me, but after a few months the sullen faces that greeted a first anonymous tour of inspection were replaced by those of friendly patients, whose foibles are appreciated and who have themselves learnt that a description of the terrible job they are doing does not fall on green ears and may elicit a rapid and conclusive visit to the site. I find that the girls on seemingly monotonous and soul-destroying packing operations wouldn't change jobs if they had the chance—"what, use my brains for the company?" They are far happier gossiping about boy friends and giving each other verbatim reports of the latest films. The greatest disturbance in their factory life is a change of working group. The art of evading leading questions is tested to the utmost, for in general practice I did not lunch daily with my patients and their associates. It is, however, possible to keep a check on the managerial coronaries by well-directed glances when the chipped potatoes are in range of unsuitable recipients.

Also I have a very nice pair of industrial shoes for which I paid 36s.

* * *

William, aged 12, represents the small line of pure-bred countryfolk still discernible among the welter of immigrant technicians in our Surrey town. Though by no means stupid, he is artless and all-trusting. His middle-ear infection had flared up a few weeks before his visit, and was now smouldering like a tired volcano, with an indolent lava-stream of pus lying on the meatal floor and the main furnace-flames visible, slowly pulsating, through the central perforation. The temptation to leave the healing to Nature was great, but the temptation to use an antibiotic was greater, and after a rapid twist of the mental roulette I settled for a well known topical preparation in propylene glycol. "Use these drops in your ear three or four times a day," I said, "right?—And come again in a week."

He came. "How is the ear?" I asked. "Much better, thank you, doctor" he replied. "No discharge any more?" I asked. "No, thank you, doctor," he replied. "Well, let's have a look," I said, "Let's see now, which one was it?" "This one," he answered, pointing to the right. "Are you quite sure?" I queried. My notes said definitely it was the left. "Yes, doctor," he replied, "you said put them drops down the right ear and that's wot I done like you said, doctor."

I clapped a mental hand to my psychological brow and groaned inwardly. Then picked up the auriscope and looked. Sure enough, the volcano was extinct, no lava, no fires. The drum and meatus were clean and dry.

My thesis on the value of contralateral topical antibiotics in otitis media will soon be in the Editor's hands.

* * *

My new secretary smokes cigarettes but reads all your articles and letters about cancer and types out all my P.M. reports on cases of secondaries in the brain. The result is she is developing an anxiety state, and smokes more cigarettes than before.

* * *

My wife's description of her first air trip. It's wonderful—everything is done for you. It's just like having an operation.

* * *

Little Nurse Delaney has been taken away
And oh! the difference to me!
She was the one who shook me pillows
Into a billow of cool white clouds
And when dawn came jade green
And the thrush began its lyric stave
On the chestnut tree outside my ward
She brought in the toast
Thin, hot,
No frame of tough crust.
Her fingers rested
Imponderably
On the fevered pulse
(The new wench grips your wrist
Like an officer of the law.)
And she was the nurse
(My own Delaney)
Who took my teeth away
To wash under the tap
And brought them back
Cleansed, fresh washed,
Pleasant to taste.
Oh where is my Delaney
Who pulled unruly ridge
From under draw sheet mackintosh?
And served me bed pan
Warm as her own heart?

Letters to the Editor

CONTROLLED TRIALS NEEDED

SIR,—I was delighted to read your annotation of June 15 about the need for controlled trials of therapy in hypertension, for this is a subject that has been causing us much worry in our hypertensive clinic

Up to the present time the medical control of hypertension has involved the use of drugs such as hexamethonium or pentolinium, together with reserpine, and the patient's life has been made difficult by the need for rigid control and the liability to side effects Under these circumstances we have felt it unjustified to treat symptomless or mild hypertension and treatment has been reserved for those patients who had severe hypertension marked symptoms and a bad prognosis

The recent introduction of mecamylamine may have altered this situation, for this drug appears to produce satisfactory control of blood-pressure with less risk of sudden hypotension and with little disturbance other than constipation It is preferred by almost all our patients who have been transferred on to it from hexamethonium

The group of hypertensive patients who cause us most concern are the young men, between 25 and 35 who are found, often by chance to have a raised blood-pressure due to essential hypertension The ultimate prognosis in these patients is poor, and many may develop serious symptoms or signs in the course of a few years

A controlled trial of medical treatment in this special group of patients is urgently needed As you say in your annotation such a trial requires a cooperative effort It presents far greater difficulties than the trial of streptomycin in tuberculosis for not only must it be continued for years, but the subjects will feel fit and will be at work and yet their full coöperation is essential So is that of their general practitioners Another difficulty is that such a trial cannot be a blind one for it will be obvious to both the patient and the doctor that an active constipating drug is being used

I hope that as a result of your suggestion, the Medical Research Council or some other body will investigate the possibility of organising such a large scale controlled trial We must find out whether the outlook for such patients can be improved by drugs but the trial will also have to answer the question as to whether the end results justify the anxiety that must necessarily be aroused by such early treatment

University College Hospital,
London W C 1

M L ROSENHEIM

CONSULTANT AND SPECIALIST

SIR,—On behalf of S.H.M.O.s I wish to thank you for so lucidly putting the case for an increase in the number of fully trained specialists in the National Health Service With the exception of the last paragraph of your leader of June 1 S.H.M.O.s are in sympathy with your views But the final paragraph is far from reality for instance the fear that the Ministry would swell ranks to get cut price consultants is not baseless this may not be the intention but in practice this is precisely what is being done throughout the country Where there is a limit on the expenditure of regional boards, S.H.M.O. posts are created in place of consultant posts On one occasion an administrative medical officer said "we cannot manage a consultant but we could run to a S.H.M.O."

The profession did suggest a definite ratio in the report on hospital medical staffing This ratio was deleted altogether in the final report when returned from the Ministry and the proposed new grade had absolutely no safeguard against its unlimited expansion in *all specialties*

Your statement that our representatives have had no difficulty in securing strict observance of the agreement for limitation of S.H.M.O. posts" is not true There has been gross abuse of the grade as follows

(1) There has been a big expansion of the grade as compared with the consultant grade especially in certain specialties such as chest diseases and psychiatry

(2) S.H.M.O. posts have been created where definite consultant work is to be done on the grounds of supervision" by a consultant who is miles away and who in certain cases never visits the hospital or clinic

(3) Figures of S.H.M.O.s as given in official lists are misleading as the general practitioner S.H.M.O.s who retire or leave the service are seldom replaced by S.H.M.O.s the positions are offered to G.P.s as clinical-assistant posts

Any new grade whether it is called assistant consultant, trained specialist or as at present, S.H.M.O. must be controlled by a strict ratio approved by the profession and accepted as a strict rule by the Ministry

Leicester

G WARING ROBINSON
Chairman, S.H.M.O. Group, B.M.A.

POSTOPERATIVE COLLAPSE DUE TO ADRENAL INSUFFICIENCY

SIR,—I was very interested in the paper by Mr Slaney and Mr Brooke (June 8) because their experience agrees closely with my own There are however, other relatively common causes of postoperative adrenal failure which are not generally recognised

The causes of adrenal failure may conveniently be classified as follows

Primary adrenal failure

Removal	adrenalectomy
Destruction	Addison's disease, traumatic adrenal apoplexy
Exhaustion	toxæmia and starvation
Dysfunction	virilising hyperplasia

Secondary adrenal (primary pituitary) failure

Removal	hypophysectomy
Destruction	Simmonds's (Sheehan's) disease pituitary tumours
Inhibition	therapy with cortisone and its analogues and with corticotrophin

I would like to comment on two of these

First Addison's disease may easily be overlooked, especially in an emergency in a patient with some other condition which requires surgery Operation is followed by peripheral circulatory failure which may well prove fatal In early or mild cases the first clinical sign of adrenal insufficiency may be severe prolonged hypotension after the stress of an operation In such circumstances if no cause can be found for the collapse and if there is no response to blood transfusion, adrenal insufficiency should be suspected and treatment with noradrenaline and hydrocortisone should be given at once The noradrenaline can be withdrawn when the hydrocortisone starts to take effect On several occasions this has proved life saving

Secondly, starvation which may cause 'adrenal exhaustion,' is not uncommon in patients who have to be "dripped and sucked" for long periods after an operation I have had two such cases in the past year—one following gastrectomy and one after transplantation of the ureters—in both of whom the systolic blood-pressure fell to about 80 mm Hg after 2 to 3 weeks Adrenal insufficiency was suspected in both hydrocortisone was given, and the blood-pressure was restored to normal within 24 hours

Death from adrenal failure must be regarded as a tragedy since it is largely avoidable Experience has led me to formulate the following rules

(1) The conditions which may cause adrenal failure must be borne in mind

(2) If time allows adrenal function should be assessed before operation in those in whom it may be deficient

(3) Supportive therapy should be given when necessary If in doubt it is better to give support than to withhold it

(4) The clinical picture of adrenal insufficiency must be recognised early and the condition should be suspected in any case of unexplained hypotension following an operation

(5) Treatment must be given as soon as the condition is suspected, otherwise it may be too late The therapeutic response to hydrocortisone is often the only way of confirming the diagnosis

A fuller account of this important subject was presented to the surgical section of the Royal Academy of Medicine in Ireland in February and is now in the press

The Queen's University of Belfast RICHARD B WELBOURN

SERUM-LIPIDS IN ISRAELI COMMUNITIES

SIR,—In view of the topical discussion on the ætiology of atherosclerotic coronary-artery disease and its relation to hereditary and nutritional factors, we would like to refer to our research in Israel [1]

Among the Jews in Israel, there is a homogeneous group of Ashkenasian Jews, whose ancestors lived in Europe for hundreds of years and, for the past 80 years, in the United States of America and South Africa On the other hand, the forefathers of the Sephardic community lived in the countries of the Middle East or among the Arabs The same mortality and morbidity from arteriosclerotic and from coronary-artery diseases prevails among Ashkenasian Jews as generally in England and the United States, Sephardic Jews, on the other hand, are much less prone to these disorders Among Sephardic Jews there exists one community, the Yemenites, of whom there are now in Israel 118,800 people Coronary-artery disease is practically unknown among Yemenites, and hardly any clinician can recall Yemenite patients with myocardial infarction in his ward

The Yemenites are Jews who have lived for thousands of years in the Yemen, in the peninsula of Arabia They lived in a secluded society having no relations with any other Jews in the world, they were also very little in touch with the Arabs surrounding them As a result they preserved the traditions and the way of living of biblical Jewry, and Hebrew remained the language of daily use during all the years of the Diaspora

We examined the serum-cholesterol, serum phospholipids, and cholesterol/phospholipid ratio in four groups of healthy males—recently arrived Yemenite immigrants, Israeli Arabs, Yemenites who had lived for 25 years in Israel, and Ashkenasian Jews Each group consisted of fifty men aged 35–50 Later we added another group of twenty-five men who had had myocardial infarction (clinical and electrocardiographic diagnosis) As the average age of these men was higher than that of the healthy groups, another series of matched controls (same age and community membership) had to be taken into account Most of the men in these two groups were Ashkenasians

The recently arrived Yemenite immigrants had a very low serum-cholesterol (see accompanying table) It was even lower than the average serum-cholesterol in the Bantu [2] On the other hand, the levels in Ashkenasian Jews were equivalent to those seen in Western Europe and the United States Between these lay the other two groups The serum-cholesterol and serum-phospholipids of patients with myocardial infarction were higher than those of the healthy Ashkenasians and resembled those cited in the literature The values of the matched controls were the same as those of the healthy Ashkenasians Thus it was not the age difference which caused the rise in the plasma lipids

The various differences in the serum-cholesterol from group to group were definitely statistically significant

The difference between the serum cholesterol in the recently arrived Yemenite immigrants and that in Yemenite residents was also definitely statistically significant, but there was almost no difference in the serum phospholipid levels between the two Yemenite groups As a result the cholesterol/phospholipid ratio in the Yemenite residents was much higher than in the recently arrived Yemenites and amounts even to a little more than this factor in the Ashkenasians Gertler et al.[3] thought that the cholesterol/phospholipid ratio was a more important measure of atherogenic activity than the level of either single lipid

The change in a Yemenite group in one generation is expressed in a rise in serum cholesterol without a corresponding rise in the serum phospholipids In general the way of living in Israel is the characteristic Western way, and we want to suggest the possibility that this change may give us a clue to the kind of acclimatisation that takes place in the lipid metabolism of Yemenite immigrants The differences between the two groups of Yemenites also contribute a point to the discussion whether the variations of lipid levels are the result of hereditary or of nutritional and other environmental factors The experience with Yemenites in Israel shows that there is no significant hereditary factor present

Lately we surveyed the nutrition of a group of recently arrived Yemenite immigrants

These Yemenites are peasants who live in a *moshaw ovdim* (a village with communal distribution of the soil) near Jerusalem They live by agriculture and most of them also partly on paid day labour The nutritional survey was done by Yemenite nurses who could make easy social contacts with the tested individuals The nurses lived in the village during the period of the survey and weighed the food of all male members of the families for a whole week Thus, twenty five men, 35–50 years old, were examined individually for a week The results showed that these Yemenites ate food yielding 2200–3000 calories a day The main part of their nourishment was bread (on the average 600–900 g a day), which means that they received the greater part of their calories and proteins from bread They ate on the average 30–50 g fat a day—i e, about 11–18% of their daily calories were derived from fat They ate many raw vegetables and very little cooked food They used much spice Cheese, margarine, and butter were entirely unknown to them They dipped their bread in olive oil or similar vegetable oils, and used them for cooking

The customary food of the Ashkenasians in Israel is similar, in its form and composition, to the usual food in England and the United States

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[1] Brunner D, Löbl, K, Fischer, M Schick G *Harefuah* 1955, 48 1 quoted in *J Amer med Ass* 1955 158 1305

[2] Bronte Stewart, B, Antonis, A, Eales, L, Brock, T F *Lancet*, 1956 i, 521

[3] Gertler M M, Garn, S M Bland, E F *Circulation*, 1950 2, 517

SERUM-LIPID LEVELS IN MEN OF VARIOUS COMMUNITIES IN ISRAEL

Group	Average age (yr)	Average serum cholesterol (mg per 100 ml)	Range	Average serum phospholipids (mg per 100 ml)	Range	Average cholesterol/phospholipid ratio	Range
Ashkenasians	46 1	231	148–346	305	235–415	0 76	0 52–1 07
Yemenite residents	46 3	194	128–279	251	185–358	0 77	0 60–0 95
Arabs	47 0	177	105–304	270	213–317	0 66	0 45–0 90
Recent Yemenite immigrants	44 9	149	98–208	251	182–416	0 61	0 35–0 93
Myocardial infarction	53 0	299	201–413	328	246–425	0 92	0 70–1 35
Matched controls	53 0	228	154–354	301	243–380	0 75	0 54–1 02

It seems to us that all these results may add a little more to our knowledge of the relations between nutrition, lipid metabolism, and coronary-artery disease

Government Hospital Dowolo,
Jaffa Israel

Daniel Brunner
K Lobl

X RAYS AND LEUKÆMIA

Sir,—Professor Sonnenblick's letter of June 8 asking for further information regarding the work of Dr Stewart and her colleagues in relation to possible risks attached to radiodiagnosis in pregnancy is a valuable contribution to this problem The greatest possible publicity should be given to all evidence which points in a different direction, lest patients be wrongfully deprived of life-saving information He is apparently unaware that a much more exhaustive survey is in progress here, at the instigation of the British group, and it is to be hoped that other countries may follow our lead

It is, however, deplorable that he should take exception to your publications on this subject as premature His pontifical and avuncular judgments read oddly in an age when freedom of expression of scientific opinion has been accepted, they would have been familiar to Galileo

I have no doubt that you, Sir, will continue to publish communications from qualified persons, and from departments of repute, regardless of the corns that may be exposed to trauma, on either side of the Atlantic

The quickest way to dispose of data wrongly interpreted is to publish them as soon as possible The sooner doctors learn of possible risks to their patients the better In an age bedevilled by political issues and vested interests in all aspects of radiation, nothing but harm can issue from attempts to impose a censorship on scientific and medical publications No important scientific fact has ever been established without honest contradiction by well-qualified experts

London, S W 3 **R J V Pulvertaft**

CIRCUMCISION WITH BONE-CUTTERS

Sir,—I was interested to read Dr Skeggs's contribution (June 8) towards greater safety in the technique of circumcision using bone forceps I agree that this method is employed only too seldom, and this is all the more unfortunate in view of its many advantages Few operations offer such economy of time or materials, with complete absence of bleeding, and by comparison with the conventional alternative it assumes a distinctly æsthetic nature (leaving strictly aside all controversy as to indications for operation)

There is no doubt that its lack of popularity in this country is mainly due to the very natural fear of injury to the glans Another important factor is failure to obtain separation of the two mucosal surfaces without disturbing the sealed mucocutaneous edge The resulting hæmorrhage and crestfallen call for sutures forms an embarrassing anticlimax to an impressive bloodless amputation

In order to prevent this latter complication I should like to describe another point of technique which I have found of help This is to insert a slip of corrugated rubber underneath the foreskin so that it lies alongside the glans The bone forceps are then applied On their removal, the corrugated rubber has sufficient resilience to spring apart and reveal the correct plane Further separation is then easily effected with a dissecting forceps with no risk of disturbing the mucocutaneous seal

A further word to nervous beginners one should not confuse the sensation as the bone forceps cuts through the rubber and think that the worst has happened! This has often given my younger colleagues an unnecessarily anxious three minutes

Glasgow Royal Infirmary **F T Crossling**

TOWARDS SAFER CLOTHING

Sir,—The marketing of flame-proofed materials and garments is at the moment in the stage of "teething troubles"—hence Dr Woodliff's difficulty (June 1) in getting pyjamas About a year ago several manufacturers became interested in one process of proofing, but the price was high and the makers ran into some technical difficulties when they started applying it on a large scale, with the result that some samples supplied to the shops were stiff and did not stand up to hard wear for children's clothes This was unfortunate and has given a set-back to the supply and demand

Meanwhile, at least two other processes have been undergoing trials but naturally the manufacturers prefer to go slow and not risk another false start It is hoped (but not certain) that one or both of these may be ready for the market by next autumn—and perhaps also an improved version of the original process

Other possibilities are also on the way For example, one firm has produced a very attractive "raised" nylon which may well become a serious competitor to proofed flannelette, but this has not yet completed its trials I gather

The best plan for the time being, to avoid unproofed flannelette, is to get pyjamas of a light weight woollen material, or of ordinary nylon or 'Terylene' (Mixed wool and cotton are almost as flammable as cotton alone)

Farnham Royal, Bucks **Leonard Colebrook**

AUTO-ANTIBODIES IN ADDISON'S DISEASE

Sir,—The claim made by Dr Anderson and his colleagues (June 1) that they have demonstrated an auto-antibody to adrenal tissue in patients suffering from Addison's disease is of considerable interest Although this was a preliminary communication, we feel that it is open to criticism

Firstly, no proof is produced that the complement-fixation reaction they have encountered is truly immunological—namely, that it is a property of the globulin fraction of the serum and that it can be inhibited by absorption of the serum with a specific antigen Secondly, their suggestion that two different antibodies are involved in the reactions between the serum and extracts of thyroid and adrenal is not supported by cross-absorption or gel diffusion tests, or by accurate titration of the serum against the two extracts Thirdly, the presence of an organ specific antigen, such as thyroglobulin, has not been demonstrated Failure to acquire immunological tolerance has been suggested as the explanation for Hashimoto's disease It is difficult to conceive of any derivative of the adrenal which is normally shut off from contact with sites of antibody production in a manner similar to thyroglobulin and which could therefore become an auto antigen Fourthly, there is no evidence, as yet, that the antibody detectable in Hashimoto's disease is actually responsible for the pathological changes, though it would appear that this is so in the rabbit immunised with its own thyroid gland [1] Fifthly, if the reaction is an immunological one, Dr Anderson and his colleagues have demonstrated an iso antibody rather than an auto-antibody This is true of the work of Roitt et al [2] in Hashimoto's disease, though it has subsequently been shown that an auto antibody occurs [3]

It is to be hoped that these questions will be answered soon and unequivocally Many unconfirmed claims of the presence of auto antibodies have been published in the past decade Some of these have been critically reviewed in your columns [4] and similar criticisms are applicable to other work With the exceptions of paroxysmal hæmoglobinuria and Hashimoto's disease, there has been no unequivocal demonstration of an auto antibody in human disease We feel that it is important that strict criteria, such as those laid down by Witebsky at the meeting of the British Society for Immunology last month, should be *fulfilled* before the presence of auto antibodies is claimed or accepted in any disease

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[1] Rose N R, Witebsky, F *J Immunol* 1956, 76 417
[2] Roitt I M Doniach D, Campbell, P N, Hudson, R N *Lancet* 1956 ii 820
[3] *Ibid* Mar 23 1957 p 1075
[4] Annotation *Ibid* Feb 16 1957, p 362

BRUCE CRUICKSHANK
A R CURRIE
T SYMINGTON

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SEASONAL INCIDENCE OF MEGALOBLASTIC ANÆMIA OF PREGNANCY AND THE PUERPERIUM

SIR,—I feel that Dr Thompson's reference (June 8) to a paper by Vinke and Van der Sar[1] should not pass without comment The statement made by these Dutch workers is "As the minimal quantity of folic acid required by man is 200 µg a day (Williams et al 1950[2]), the stock in the liver is sufficient for 15 or 30 days when the diet is completely lacking in folic acid" This is used both by Dr Thompson and by the Dutch workers as an explanation of why megaloblastic anæmia of pregnancy in temperate zones is due to deficiency of folic acid rather than vitamin B_{12}, it is generally agreed that the stores of vitamin B_{12} will last for months or even for years

The fact is, however, that this theory has not previously been accepted because the daily requirements of the human for folic acid are quite unknown They *may* be 200 µg per day, but even Williams et al[2] do not claim this Indeed on p 325 of this book they state that "The quantitative requirement (for folic acid) cannot be closely estimated from evidence now available" The figure of 200 µg per day is put forward by them on p 326 in a table as a recommended allowance in view of the lack of knowledge, and reference is made to a paper by Williams[3] which in fact says that it is not even known that folic acid is required for the human (This was in 1942)

It is easy to observe a human developing vitamin-B_{12} deficiency, since this will occur after total gastrectomy because of lack of intrinsic factor, but to produce folic acid deficiency alone is not practicable

However, some idea of the order of magnitude of the daily requirement of folic acid might be obtained by finding the minimum effective daily oral dose in patients with nutritional megaloblastic anæmia who had normal folic-acid absorption, a normal serum-vitamin B_{12} level, and normal absorption of labelled vitamin B_{12} Another less physiological method of approach would be to find the minimum effective daily injected dose in patients with idiopathic steatorrhœa and megaloblastic anæmia whose absorption of labelled vitamin B_{12} was normal and whose absorption of folic acid was impaired In both instances the possibility of complicating ascorbic-acid deficiency would require consideration, and in any case some of the administered dose might be deviated to functions other than restoration of normal erythropoiesis

It is likely that some cases of megaloblastic anæmia in pregnancy in temperate regions are due to folic acid *deficiency* and in some instances the output of folic acid after a test dose has been low[4] However, many patients with extremely poor diets do not develop megaloblastic anæmia in pregnancy, and some who do develop it are in good circumstances, eat a normal diet, and have no complicating factors such as vomiting, diarrhœa, or multiple pregnancy To complicate the matter even more, Okuda and his co workers[5] in Baltimore have claimed that very low serum vitamin B_{1} levels may be obtained even in normal pregnant women at the time of delivery, and consider that the fœtus deprives the mother of the substance

In summary, the theory of Vinke and Van der Sar is attractive, but we do not really know whether the body stores of folic acid will last for 30 days or for 600 As Dr Thompson says, dietary deficiency is probably an important contributory cause in megaloblastic anæmia of pregnancy even in temperate climates, but other unknown factors appear to play a part

Department of Medicine,
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R H GIRDWOOD

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[1] Vinke, B, Van der Sar, A *Docum Med geogr trop* 1956 8, 151
[2] Williams R J, Eakin R E Beerstecher E, Shive W The Biochemistry of B vitamins New York 1950
[3] Williams R J *J Amer med Ass* 1942 119 1
[4] Girdwood R H *Quart J Med* 1956 25 87
[5] Okuda, K, Helliger, A E, Chow B F *Amer J clin Nutr* 1956, 4, 440

DIVISION OF INTERCOSTAL ARTERIES

SIR,—In your report of the Anglo French surgical conference (June 8) the question of dividing intercostal arteries and the safety of doing so was raised by Jean *Cauchoix and Jean-Paul Binet* with the words "*there* is still no final answer in man"

Presuming the danger to be interference with the circulation of the cord, I should like to point out that the circulation of the cord was worked out by Kadyi in 1889 and his work confined by Suh and Alexander in 1939 The latter point out that Tanon emphasised the importance of the lumbar radicular vessels in the blood supply of the whole cord and that the middle thoracic section of the spinal cord has the *poorest local segmental* circulation

Our experience supports this in 106 cases of anterior fusion, Prof F E Stock and I have divided up to as many as eight intercostals in a single patient without any complications I think the most dangerous area is the lumbar and it is in the thoracolumbar region that the danger lies *I hope this will fortify those who might* be deterred from using this excellent approach to the thoracic spine by the words "there is still no final answer in man"

University of Hong Kong

A R HODGSON

MECHANISMS OF PERIODIC PARALYSIS

SIR,—It was with particular interest that I read your leading article of April 20 and the article by Professor Conn and his colleagues in the same issue

I agree entirely that the underlying mechanism of periodic paralysis is not identical in all cases At least one other condition can produce symptoms similar to *those of familial periodic* paralysis In April, 1956, I described[1] a disease which, like periodic paralysis, is characterised by attacks of paralysis, especially during rest after exertion The disease is hereditary and the inheritance is due to a single, autosomal, dominant gene with complete or almost complete penetrance Clinically the disease differs from periodic paralysis in the following respects it begins earlier in life (in 90% before the age of 10 years), the attacks are more frequent, shorter, and less severe (75% of the patients have at least one attack a week, and the attack lasts at most 1 hour, during which the patient is usually not completely helpless), the attacks are more liable to occur when *the patient* is hungry, and the intake of food, especially of bread, has a good prophylactic and therapeutic effect During an attack the serum-potassium is increased without any accompanying decrease in the urinary excretion of potassium, and the electrocardiogram shows high pointed T waves Like rest after exertion, 1–2 5 g of potassium by mouth will precipitate an *attack* The administration of glucose has a good prophylactic effect

Of the published reports of familial periodic paralysis, some, such as that of Tyler et al,[2] appear to fit in well with the picture of adynamia episodica hereditaria In other words, the description of the mode of inheritance, the clinical picture, the absence of decreasing serum-potassium during an attack, and the lack of response to potassium therapy suggest that the patients really had adynamia episodica hereditaria.

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[1] Gamstorp I *Acta pædiat Stockh suppl* 108 1956
[2] Tyler, F H Stephens F E, Gunn, F D, Perkoff, G T *J clin Invest* 1951, 30, 192

Since Tyler et al found vacuoles in the muscle-fibres, this finding cannot be pathognomonic of periodic paralysis. The mechanisms of the two diseases must be different, which does not, of course, exclude the possibility of vacuoles occurring in the muscle-fibres in both conditions. Microscopic examination of muscle-biopsy specimens from 3 of my patients, however, failed to reveal any such vacuoles.

Barnsjukhuset, Lund, Sweden. INGRID GAMSTORP.

CHILDREN IN HOSPITAL

SIR,—What a pleasure it is to read a paper like that of Dr Vaughan in your issue of June 1. The point of his investigation—the presence or absence of explanation to children, before admission, of what was going to happen to them in hospital—is an important one. As he points out, most of these children were confused and frightened on admission, and twenty-six weeks after discharge 11 of the children to whom no explanation had been given, as against 3 of those to whom matters had been explained, were still disturbed.

This inquiry raises a point very familiar to child psychiatrists—of the loss of confidence in their parents felt by children given lying statements by their parents about the reasons for their visit to a hospital of which inpatient admission is the (to the child) unexpected outcome. As Dr Vaughan reports, some parents are unable to explain what is to happen to their children and some are definitely frightened to do so. At present no provision is made for the preparation of children about to come into hospital in our outpatient and inpatient routine handling.

During two years spent in the wards of the Royal Hospital for Sick Children, Glasgow, under Prof Leonard Findlay on an M R C inquiry which involved direct contact with the children's families, I was much struck with the help that could be given, both to the progress of the child in hospital and to wise aftercare by his family, by simple explanations to both sides concerning the procedures the child was experiencing in hospital.

As Dr Vaughan points out three things are necessary: (1) explanation to parents of the importance to their future relations with their children of a truthful account of the reasons for the child's visit to hospital, (2) explanation to the child himself of what is going to happen to him in hospital (and in every case this should include explanation of the meaning of, to the small child, so mysterious a procedure as the use of the injecting needle), and (3) opportunity for the child to express his fears and receive comfort and reassurance.

Is not this a sound opportunity for coöperation between the psychiatric and the pædiatric branches of our children's services? And would something like the following not possibly meet the case?

(1) The psychiatric social worker, should there be one in the hospital, or if not a member of the nursing staff with special training to meet this need, should have a talk in the outpatient department with each mother whose child has been put down for admission to hospital. Such an interview should contain an explanation of what is to happen to the child while in hospital and persuasion of the mother to prepare her child for it. Fear is catching; children catch it from their mothers. Such a procedure would give an opportunity to the mother to ventilate her own fears about hospital admission for her child and to be reassured.

(2) In every children's department, and particularly in relation to surgical wards, it should be the duty of one of the resident medical staff to see all children for a brief period immediately after admission to explain to them carefully just what is about to happen, and to assure them of a future friendly visit and opportunity for a talk over anything that has puzzled or frightened them shortly after the completion of an operation.

(3) All outpatient children's physicians should be asked, on the child's reporting visit after discharge from hospital, to inquire specifically about symptoms of disturbance, and if these are present to refer the child at once to the psychiatric clinic.

(4) Simple leaflets should be prepared for use in the outpatient department and by general practitioners, setting out clearly the importance of explaining to children going into hospital what is awaiting them, and telling parents whom to ask if they are puzzled as to how to do this or if they later find their child upset by his experiences in hospital. The parent bringing the child to outpatients could be encouraged to take this leaflet home to discuss with the other parent and older members of the family, so that a period in hospital for a child could become more of a corporate event in which all the family is interested, instead of being, as so often at present, a mysterious experience in which the child feels afloat on a very small raft out of sight of familiar land or faces.

As a step towards the achievement of these objectives, would it not be possible for the child psychiatrist to the hospital to give short talks to nursing and resident staff, explaining the grounds for these additional, and which may seem to an over-worked staff tiresome, additions to routine and the good harvest that can be reaped by them in understanding home management of their small patients after discharge and an increase in mental health of the children?

London, W 11 MARGARET LOWENFELD

EPIDEMIOLOGY OF POLIOMYELITIS

SIR,—In your leader of April 20 you say "Recent studies have made clear the reasons for the striking differences in the incidence of paralytic poliomyelitis between countries with high and with low standards of living."

The evidence brought forward fully explains the rising age incidence in countries with a high standard of living but, as Dr Pease and I[1] recently pointed out, it does not explain the recent increase in paralytic disease in under-developed countries, nor the variation in the severity of attack in countries with a high standard of living (cf Denmark in 1952).

Hammon et al[2] have suggested that paralytic poliomyelitis in the Philippines may be due to the importation of "paralytic strains" from the United States, and a similar explanation *could* account for the epidemics in Malta and Madagascar during the late war and in many other countries, such as Israel and Kenya,[3] since then.

In other virus diseases, such as smallpox, strains exist of the same immunogenic type, but of varying virulence and giving rise to a varying severity of illness.[4] In smallpox the difference in virulence is so marked that two distinct forms are recognised and known as variola major and variola minor, or alastrim.

Clinical cases of poliomyelitis are most frequently associated with type 1 viruses, but evidence is accumulating that the severity of an epidemic depends more upon the virulence and neurotropism of the strain of the virus than upon its type.

Tanganyika is a country with a low standard of living and very poor communications, and yet in 1954 there was a severe localised epidemic of paralytic poliomyelitis among susceptible infants, with 99 cases among a total population of approximately 100,000, and in 1956 there was an even *more* severe outbreak at Kilonko with an incidence of 275 cases in a similar population.

The fact that paralytic poliomyelitis, or "polio major," has taken so long to penetrate Africa since its first appearance in the 1880s, is probably due to the high degree of immunity which has been developed there by repeated epidemics of "polio minor" and to the difficulties of communication. The existence of previous epidemics of the non-paralytic disease is shown by the immune state of the majority over the age of 5 and by the sporadic cases of paralysis that have occurred in the past. Their existence is further supported by the type of research carried out by Melnick et al.[5] to which you refer.

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[1] Kerr W G Pease M J *Brit med J* 1956 i, 1387
[2] Hammon W McD Ludwig E H Sather G E Schrack, W D jun *Ann N Y Acad Sci.* Sept 27 1955 p 979
[3] Walker A J *East Afr med J* May 1956 p 169
[4] Couchez D G *Ibid*, May, 1957, p 157

Ocean Road Hospital,
Dar es Salaam,
Tanganyika
W. G. KERR

CÆSAREAN SECTION

SIR,—Few of your readers interested in modern cæsarean section would endorse all the views expressed in your leading article of April 6. Many would be in fullest agreement with Prof. Dugald Baird and Mr. Terence Robinson (April 27) and Mr. Higgins (April 20). Merely to repeat the view that all other methods of delivery will become obsolete is to perpetuate an absurdity.

Dr. Salzmann's letter (May 25) calls for comment. In a symposium on general-practitioner midwifery services last year,[6] it was pointed out, in discussing the place of cæsarean section, that a survey of 30 large maternity hospitals, mostly teaching, for the five years 1951–55 showed the section-rates to vary from as high as 14% to as low as 1.5%. These units included all the well-known British teaching hospitals as well as prominent units in the U.S.A., Australia, New Zealand, and Eire. It may well be true, as Dr. Salzmann states, that some hospitals in this country show what may be deemed an unnecessarily high section-rate, but the average yearly rate for the group of hospitals analysed was 5.1%, and if the results of the group studied by Marshall and Cox[7] are re-examined for the period 1951–55 the average yearly rate is shown to be 6.1%, which is almost exactly the figure quoted by those authors for 1943–1947—i.e., 6.2%.

The criticism by the prominent member of the Royal College of Midwives, to which Dr. Salzmann refers, seems therefore a little ungracious without a fuller knowledge of the conditions obtaining in the particular hospitals to which she alludes.

Liverpool
H. VINCENT CORBETT

ANÆSTHESIA FOR CÆSAREAN SECTION

SIR,—The letter by Dr. Margaret Watkinson (June 15) has stimulated us to make a plea for the abandonment of the long established ritual of "slash-and grab" cæsarean section. For the obstetrician who stands beside his patient about to be delivered by cæsarean section, prepared with scalpel poised to extract the fœtus at a word from the anæsthetist, will allow his forceps cases to be anæsthetised whilst preparing the vulva, catheterising, and draping the patient before he is ready to commence vaginal delivery. Forceps extraction is then performed slowly and deliberately, without haste or rush.

It is our practice to anæsthetise patients for cæsarean section before subjecting them to the frightening experience of skin preparation and draping. The operation itself is unhurried and the benefit to the mother of the slower and gentler surgery has been achieved without increased risk to the fœtus.

The anæsthetic technique employed is briefly as follows:

Induced by the inhalation of cyclopropane and oxygen, the patient is maintained at the lightest possible plane of surgical anæsthesia with nitrous oxide and oxygen, augmented with a little cyclopropane if necessary. All cases are intubated, a cuffed Magill orotracheal tube being passed under suxamethonium (succinylcholine) induced paralysis. Respiration is controlled, relaxation being produced by intermittent administration of suxamethonium, and light plane anæsthesia is maintained with nitrous oxide and oxygen.

It is not our intention here to advocate any one method of anæsthesia for these cases, or to compare general with local, spinal, or extradural anæsthetic techniques. Neither is unnecessary slowness condoned; in cases of fœtal distress surgery is performed with expedition, as in forceps delivery for this condition.

We make no claim to originality in contending that no greater speed is required in delivery of the fœtus per abdomen than per vaginam, and that, with an anæsthetic technique embodying good oxygenation with a light plane general anæsthetic, "slash and grab" cæsarean section is a ritual to be abandoned.

St. George's Hospital,
London, S.W.1
DAVID SAVAGE

Queen Victoria Hospital,
East Grinstead
DAVID HUGHES

MECHANICAL FACTORS IN ATHEROSCLEROSIS

SIR,—I was very interested to read the article by Professor Duguid and Dr. Robertson in your issue of June 15. The importance of these factors was strikingly demonstrated during some work on post-mortem arteriography by Dr. K. D. Keele and myself.[1] One of the subjects had wasting of one of the lower limbs due to tuberculosis of the hip and knee as a child, and on this side the arteries were almost devoid of disease, whilst those on the other showed all the features of atherosclerosis.

St. Peter's Hospital,
Chertsey, Surrey
C. F. ROSS

INFLUENCE OF THE CEREBRAL CORTEX ON SODIUM EXCRETION

SIR,—A conditioned diuretic reflex in the dog was first described by Bykow and Alexejew Berkmann,[2] who administered water repeatedly per rectum in dogs. After a certain number of trials, taking the dog into the experimental room and putting it on the stand was enough to elicit an increase in diuresis.

In our own experiments, the conditioned diuretic reflex was obtained by giving water by mouth. Loading with water resulted in the well-known phenomenon of unconditioned water diuresis. After a suitable number of experiments the conditioned reflex was established and the diuresis increased without water intake when the dog was on the stand.

In this conditioned diuresis, the urinary excretion of sodium was very high, whereas in the unconditioned diuresis it was very low. To use modern terminology, the unconditioned water diuresis is characterised by a high positive free water clearance, with a negligible osmotic clearance. In the conditioned diuresis, the positive free water clearance is relatively low and the osmotic clearance is high. The "conditioned reflex" nature of the phenomenon is proved by differentiation. Creatinine excretion being virtually unchanged, the cause of the increase in the excretion of sodium is apparently a reduction in tubular reabsorption.

Our observations suggest that the conditioned reflex may differ from the unconditioned reflex, and that the cerebral cortex may also directly influence tubular reabsorption.

A detailed account of our experiments, in coöperation with *Dr. M. Gerbner and Dr. K. Altman*, will be published elsewhere.

Physiological Institute,
University of Budapest
P. BALINT

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[5] Melnick, J. L., Walton, M., Isacson, P., Cardwell, W. *Amer. J. Hyg.* 1957, 65, 1.
[6] Rogerson, J. P. G., Corbett, H. V. Transactions of the Liverpool Medical Institution, 1956, p. 39.
[7] Marshall, C. M., Cox, L. W. Transactions of the 12th British Congress of Obstetrics and Gynæcology, 1949, p. 30.

[1] Ross, C. F., Keele, K. D. *Angiology*, 1951, 2, 374.
[2] Bykow, K. M., Alexejew Berkmann, I. A. *Arch. ges. Physiol.* 1930, 224, 710.

Public Health

Training for the New Public Health

THE evolution of a specialty tends to follow a recognisable pattern There is the recognition of a need , the pioneer attempts to meet that need , the hiving-off of the pioneers' successors into a new caste with a special training, qualifications, rituals, and jargon , the inclusion of the specialty's basic content in the undergraduate curriculum , and eventually its expansion at the expense of others, its decline, or its modification Surveys of the status of training in the subject form milestones along the road

A milestone along the road of public health is the World Health Organisation's monograph by Professor Grundy and Professor Mackintosh [1]

To this an international character has been imparted by including summaries of W H O conferences at Nancy (undergraduate, 1952) and Goteborg (postgraduate, 1953), and by submitting the text to leading public-health educators in eight countries In addition there is a factual survey of the position in nineteen countries—perhaps too much compressed, however, for in the fifteen lines given to undergraduate training in London, for instance, it does not bring out the widely varying standards and the relative neglect of the subject in comparison with provincial schools and with many foreign countries Here a comparison with the similar survey by Prausnitz [2] in 1932 would have been interesting

The main theme is the change of emphasis from environmental public health to social medicine—from water-closets to welfare, in fact—which some may reckon a rash change when the subject is in a state of flux Perhaps, therefore, the words "social medicine" should have been included in the monograph's title, particularly as there is a school of thought, notably in Scandinavia and the Netherlands, which holds that public health and social medicine cannot be combined in one professorial chair

It is on such subjects as the three prevailing types of curriculum (traditional, intermediate, and comprehensive social), the problems of nomenclature, and the extent to which social medicine is a specialty that the authors are at their best All concerned should be grateful to them and to the World Health Organisation for their intelligent and important survey of where we are and whither we are likely to go in the ill-defined and almost hedgeless fields of public health, hygiene, and preventive and social medicine

Poliomyelitis

Uncorrected notifications for poliomyelitis in the week ending June 8 (23rd week of the year) were as follows (previous week in parentheses) paralytic 48 (42), non-paralytic 26 (25) , total 74 (67) The following figures compare this year's notifications with those in the preceding nine years

Year	*Total cases up to and including 23rd week*	*Cases in 23rd week*
1948	597	14
1949	383	19
1950	840	79
1951	591	52
1952	603	61
1953	766	73
1954	534	26
1955	419	44
1956	646	55
1957	1084	74

We have received preliminary details of the results of fæces examination of persons in contact with a case of paralytic poliomyelitis in a London borough The patient, a woman, was the first notified case (May 1, 1957) in the borough since February last (there had been 3 non-paralytic cases in children) The rest of the family had been ill with "colds" and "influenza" sixteen days before the mother was taken ill In 2 of her 3 children, as well as a classmate of one of the children, virus was present in the fæces The virus was still present twenty-eight days after the first examination No other cases of poliomyelitis had so far been notified in that district up to June 17 House quarantine was not begun until after the result of the fæces examination of the children was known before this, one of them had been to school

Similar inquiries should help to clarify the value of close quarantine in poliomyelitis, a subject which is discussed in an annotation on p 1290

Influenza

Influenza virus isolated from a traveller lately arrived at the Hague has been sent to the World Influenza Centre in London So far no spread has been reported in Holland Reports reaching the World Health Organisation suggest that the virus responsible for the epidemic in Asia has also arrived in Australia and North America, but no outbreaks have developed [1] The disease remains very mild Viruses sent to the World Influenza Centre from Hong-Kong, Singapore, Kuala Lumpur, Australia, and Japan have all been antigenically alike, belonging to the new so-called Far Eastern variety of influenza A The reported view [2] of Sir Macfarlane Burnet, director of the Walter and Eliza Hall Research Institute in Melbourne, is that the virus will spread throughout the world and that it will arrive in Britain when the cold weather comes

Vaccine against the new type of virus has been prepared in the department of virus research in the Wright-Fleming Institute, St Mary's Hospital, London [3] The first batch will be tested soon

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[1] *Times* June 15, 1957
[2] *Ibid* June 17, 1957
[3] *Ibid*, June 18, 1957

Diary of the Week

JUNE 23 TO 29

Tuesday, 25th

INSTITUTE OF DERMATOLOGY, Lisle Street W C 2
5 30 P M Mr A K Monro The Rôle of Surgery in Skin Diseases

Wednesday, 26th

INSTITUTE OF DISEASES OF THE CHEST, Brompton, S W 3
5 P M Mr J R Belcher Emphysematous Cysts of the Lung

INSTITUTE OF DERMATOLOGY
5 30 P M Dr R W Riddell Mycological Routine in Dermatology

Thursday, 27th

ROYAL SOCIETY OF MEDICINE 1 Wimpole Street, W 1
2 30 P M *Urology* Dr A G Lewis Disturbances of Renal Physiology Dr F M Parson, Mr R Shackman Uses of the Artificial Kidney

POSTGRADUATE MEDICAL SCHOOL, Ducane Road W 12
4 P M Dr A G Macgregor Hæmochromatosis

INSTITUTE OF DERMATOLOGY
5 30 P M Dr G C Wells Keratinisation

Friday, 28th

ROYAL SOCIETY OF MEDICINE
8 15 P M *Obstetrics and Gynæcology* Dr Francis Camps Medico legal Adventure and Misadventures in the Field of the Gynæcologist and Obstetrician

POSTGRADUATE MEDICAL SCHOOL
10 A M Mr Leon Gillis Amputations

Appointments

DAVIES G C, M B Wales F F A R C S consultant anæsthetist Merthyr and Aberdare H M C

REES ELISABETH M D Lpool S H M O in venereology, United Liverpool Hospitals

East Anglian Regional Hospital Board
- LAVY, G A D, M B Camb , F R C S surgical registrar Norfolk and Norwich Hospital
- LUCKHOO M S M B Aberd medical registrar North Cambridgeshire and Clarkson Hospitals, Wisbech
- MANTELL M C G M B Camb anæsthetic registrar West Suffolk General Hospital

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[1] Teaching of Hygiene and Public Health in Europe a Review of Trends in Undergraduate and Postgraduate Education in Nineteen Countries By F GRUNDY professor of preventive medicine Cardiff, and J M MACKINTOSH professor of public health London With an introduction by JACQUES PARISOT Geneva World Health Organisation Monograph series no 34 1957 Pp 254 25s Obtainable from H M Stationery Office

[2] Prausnitz C Teaching of Preventive Medicine in Europe London 1933 See *Lancet* 1932 ii 951

Obituary

MARINUS VAN DEN ENDE

M B Cape Town, Ph D Camb

Prof M. van den Ende, dean of the faculty of medicine in the University of Cape Town, died on June 4 at his home in Cape Town at the age of 45

He was born in South Africa of a family of Dutch settlers, and he was educated at the University of Cape Town, graduating M B in 1933 Four years later he came to this country to take up a John Lucas Walker studentship in the department of pathology of the University of Cambridge, and in 1940 he was awarded the PH D Camb Meanwhile, in 1939, he had joined the scientific staff of the Medical Research Council at the National Institute D G E, one of his colleagues there, writes

van den Ende was a born research-worker, both in the laboratory and in the field, with a highly critical mind and amazing energy, he seemed destined to reach the highest possible position. His researches during the war on cross-infection in hospitals and on typhus were quite outstanding Perhaps his greatest achievement in England was the organisation of the laboratory at Frant for the large scale production of scrub typhus vaccine, exacting and dangerous work which he carried out with tremendous speed and success

Although he was thoroughly at home in England, he never lost the desire to return to his own country, to which he had an intense loyalty, and in 1945 he accepted the chair in bacteriology at the University of Cape Town In this new position he built up a large and active research school in virology and bacteriology and was able to show yet another quality, that of a teacher both of the research-worker and the undergraduate

Apart from his ability as a scientist there were other qualities that will always first come to mind when thinking of van den Ende He was a most lovable person with great charm, he was kind and generous almost to a fault and when, four years ago, he was tragically struck down by his fatal illness he faced the consequences with unbelievable courage, working fervently and relentlessly right to the end Those of us who were with him during his time at Hampstead—which he often referred to as the happiest and most crowded period of his life—realise the great privilege we had in knowing such a man.

Prof van den Ende leaves a widow, two sons, and two daughters

ARTHUR CUBLEY

M R C S

Dr Cubley, formerly deputy medical superintendent of the North-Eastern Fever Hospital of the London County Council, died on June 2, after a long retirement at Ashover, Derbyshire He qualified from University College Hospital in 1900 and his whole career was spent in the fever service of the Metropolitan Asylums Board, and later of the L C C W E S writes

Dr Cubley was for long a well known figure to all the medical staff of a service which was notable for its active inter-hospital social life He had a kindly and unruffled bearing and was always ready to help his juniors from his great store of knowledge of the infectious fevers His upright figure, deliberate speech, and large moustaches perhaps gave an impression more of the countryman than the doctor He had a strong mechanical bent as shown by his invention of the Cubley tracheotomy tube, and he was a skilled woodworker

He leaves a widow

Dr G F BUCHAN

C M S, a county M O H, recalls the one occasion on which he met Dr Buchan

In the early days of the war, when this county had some 40,000 evacuee women and children with all the related multifarious problems, we had many requests from the evacuation authorities to do this and to do that The requests were all perfectly reasonable but nevertheless sometimes trying There was a great sense of relief and contrast when one afternoon a tall distinguished man came into my office and introduced himself as Buchan of Willesden "You have a large number of women and children from Willesden and you must be heavily pressed for health visitors Can I send you some help ?"

Notes and News

SMOKING AND LUNG CANCER

In 1954 a group of tobacco manufacturers in the United Kingdom decided to contribute £250,000 towards research into the cause of lung cancer, and asked the Medical Research Council to apply this fund A year ago the manufacturers set up a standing committee, with Sir Alexander Maxwell as chairman Sir Alfred Egerton, F R S, and Sir Ronald Fisher, F R S, were appointed scientific consultants The committee, which has now issued its first annual report, proposes to set up a new fund to promote research on any problem relating to smoking and health

Mr G F Todd, statistical adviser to the committee, has reviewed various statistical surveys in consultation with Sir Ronald Fisher They criticise studies of the relationship between smoking and lung cancer on the ground that the material was not randomised, the smoking classes being self selected No studies have been made of the causes which determine whether a person will smoke "It would be frankly incredible to assert that these smoking classes are not systematically differential, at least in respect of genotype, if not also in respect of environmental exposures not irrelevant to the subsequent incidence of cancer" If lung cancer were due to direct application of smoke to the bronchial epithelium, it should be commoner in those who inhale than in those who do not, but if it were due to a remote effect, then taking smoke into the mouth might be effective, and lung cancer would be as common in smokers who did not inhale The latter explanation is consistent with the findings of Richard Doll and Bradford Hill, but L Breslow and F Lickint found higher percentages of inhalers among their lung cancer cases than among their controls If both direct application and a remote effect caused lung cancer, the lower mortality rate in pipe smokers would be explained, but at least some increase in inhalers among lung cancer patients would be expected

Non causal explanations of the statistical relationships are considered A genetic factor might increase both the tendency to smoke and the liability to lung cancer The increase would then be explained either by an environmental factor (such as the increase in oxidation products of hydrocarbons in the atmosphere) or by an increase of the numbers of persons surviving into the lung-cancer age group who would, in previous eras, have died sooner and whose inherent resistance to lung cancer is lower than average

The impossibility is noted of measuring the extent to which any individual is exposed to atmospheric pollution, and studies of the different prevalence of lung cancer in large and in small towns are criticised Mr Todd concludes that nobody can say how far the estimates linking lung cancer mortality rates with smoking or with atmospheric pollution are applicable to the whole population

NEWS FROM KUALA LUMPUR

The Institute for Medical Research at Kuala Lumpur in Malaya has published a report on its work for 1955—a heartening document The list of papers covers work in microbiology, zoology, nutrition, and many other fields, and the collaboration between the institute and the U S Army Medical Research Unit continues to be fruitful

The work on malaria continues, "but at a lower ebb from the diversion of resources to the more challenging problems of filariasis" That the pressure of the attack on malaria can be slackened is an indication of its success The filariasis research unit, established in 1953, reports the discovery of sheathed microfilariæ in various local animals, but it is not yet known whether these are pathogenic to man Diethylcarbamazine has been given to carriers with success The same drug was given to the inhabitants of one kampong, while another kampong was sprayed with dieldrin, a *residual insecticide*, there was a striking decrease in the microfilaria rate and density in the drug treated population, but in neither was there any reduction in the proportion of mosquitoes infected

Much research has been done in virus and rickettsial diseases Volunteers were immunised against typhus by a live vaccine with appropriately timed doses of chloramphenicol 17 viruses (10 JE, 7 unidentified) have been isolated from 400,000 mosquitoes, and a dengue like virus was found to be responsible for a third of the undiagnosed fevers at Kuala Lumpur General Hospital

Research in nutrition includes the discovery of low thiamine levels in the milk of mothers of infants with acute respiratory disease, suggesting that the lack may reduce the infant's resistance to infection. Of 238 severely anæmic patients, most were found to be iron-deficient, and in many there was a superimposed megaloblastic anæmia Of 1200 patients whose stools were examined, hookworm infestation was much commoner in patients with a low hæmoglobin level, suggesting a cause for the high prevalence of iron deficiency

These examples give some idea of the impressive scope and quality of the work in progress in Malaya

EUROPEAN UNIVERSITY INTERCHANGE

A REPORT[1] by the Committee for Foreign University Interchange, whose chairman is Mr F W D Deakin, illustrates the value of university interchange as a means of promoting European understanding The 551 visits which have been arranged under the interchange scheme between this country and other European countries during the past eight years have produced a total of 985 contacts between the participating European universities In a foreword to the report, Sir James Mountford, vice chancellor of Liverpool University and chairman of the Universities Advisory Committee of the British Council, declares that the cumulative effect of these schemes has resulted in a "really impressive number of academic contacts," and that "the learned world owes a debt to the work that has been done"

The scheme for the interchange of short visits lasting one to three weeks by university teachers, which is administered with the help of the British Council, came into operation in 1948 between the United Kingdom and Belgium and has since been extended to include Austria, Finland, France, Germany, Iceland, Italy, The Netherlands, Norway, Portugal, Spain, Sweden, Switzerland, and Yugoslavia Each year 63 visits are made each way between these countries, and in the course of the current year there are plans to extend the scheme still further by the inclusion of Denmark, Turkey, and Poland.

The report describes a supplementary scheme, arranged between the United Kingdom, Belgium, France, Germany, and Yugoslavia, for assisting younger research workers to further their investigations by personal contact with others working in the same field abroad Belgium, France, Germany, and the United Kingdom also plan to introduce in the next academic session a new scheme for the exchange of longer teaching visits of one term or semester

In the field of postgraduate scholarships, 684 students from the Continent have been given awards by the British Council for study in the United Kingdom, whilst 549 British students have been helped by foreign governments or universities to study on the Continent The report also refers to the growing number of awards offered by such bodies as the Council of Europe, the High Authority of the European Coal and Steel Community, UNESCO, and NATO, and the interest shown by Western European Union in fostering coöperation between the universities of Europe

ELECTRICAL INCUBATORS

A REPORT to the East Anglian Regional Hospital Board[2] has drawn attention to the potential dangers of electrical incubators The report arose from a baby's death owing to overheating from an electrical fault, and it instanced several other cases where babies had been at risk

A draft British standard for electrically heated incubators and cots for babies has now been produced The adoption of this standard will eventually go far towards eradicating the dangers of incubators In fairness to the manufacturers it should be remembered that accidents have been extra ordinarily few, although in the past ten years very many babies have been nursed in incubators Trouble may some times have been due to lack of serviceing and overhaul, hospital attendants and junior nursing staff are not always as gentle as they should be when moving and cleaning incubators, and it seems likely that in some hospitals out of date amateur built incubators, and incubators made as proto types by firms not ordinarily engaged in building incubators, may still be in use These may be dangerous, and they should not be retained even for occasional use in a hospital where an incubator is rarely required

A GENTLEMAN'S LIBRARY

To buy books is always a pleasant hobby, to buy them for a definite purpose on a limited budget is also a skilled occupation Some fifty years ago Arnold Bennett in *Literary Taste* offered the man of modest means a useful guide to the books needed for a reasonably complete library of English literature His basic list included 562 volumes at a cost of £87 18*s* 6*d* In our more specialised (and expensive) days, Dr Iago Galdston, secretary of the medical information bureau of the New York Academy of Medicine, is seeking the help of his colleagues on both sides of the Atlantic in a more limited venture—though the cost will be about the same If you had no more than £80–90 to spend, what books, Dr Galdston asks, would you buy to form a modest working library on medical history? His putative readers have apparently studied only modern languages, for though the library may include books written in French, German, and Italian, he adds "We can count on very few who have a competence in either Latin or Greek" Lists of suggestions should be sent to Dr Galdston at the Academy, 2, East 103 Street, New York 29, N Y

NEW FILMS

Nutrition in Pregnancy (16 mm, sound, colour, 11 minutes, Great Britain, 1957) is designed to advise expectant mothers on diet both in the antenatal period and while breast feeding the baby

Emphasising that an adequate diet is the best foundation for the life of the baby, the film discusses the body's need of carbohydrates, fats, proteins, minerals, and vitamins and the foods that contain them The film consists of a talk illustrated throughout by animated diagrams Though well drawn, these tend to be fussy and the emphasis on dietary constituents is less helpful to a mother than suggested menus and recipes A lot of information is given in the film and this might have been better presented as an illustrated article or pamphlet.

The film is available free from the Nutrition Information Centre Vitamins Ltd, Upper Mall, London, W 6

Line of Defence, the third film of a series shown on B B C television recently, dealt with the international control of infectious diseases

A passenger from Asia where there has been a recent outbreak of smallpox, develops spots which though resembling those of chickenpox, are sufficiently atypical to make the ship's surgeon suspicious Through the World Health Organisation at Geneva, the port of London health authority is warned and the routine procedure on ship and ashore is shown. While the efficiency of the international organisation was well conveyed, the detail lacked balance such aspects as the differential diagnosis between variola and varicella by microscopy, egg inoculation and serum methods being shown at considerable length whereas the routine procedure as it affected the other passengers and crew of the ship was barely touched on.

THE LIVER

THE choice of subject for the second number of the *British Medical Bulletin* for this year[1] is timely in view of the many recent advances in our knowledge of the liver in health and disease The topics which have been selected for review cover a wide field, and will interest both physiologist and clinician

In his introduction, Sir Harold Himsworth, F.R S, emphasises that study of neither the normal alone nor the abnormal alone can supply the full information required for the comprehension of either Progress depends on our ability to integrate the knowledge gained on the two sides In the case of liver disease, the work which linked protein and fat metabolism with experimental liver injury was the stimulus which led to the development of much recent research In this respect, the article by J C Waterlow and G Bras on nutritional liver damage is especially interesting They point out that in man the only example of a direct effect of diet is the fatty liver of kwashiorkor In this condition recovery, both structural and functional, is the rule and earlier suggestions that the fatty change led on to cirrhosis cannot now be substantiated The rôle of protein deficiency in the development of permanent hepatic disease in underdeveloped countries is difficult to determine, but possibly malnutrition may have an indirect effect on the liver and predispose it to injury by other harmful agents

The place of protein in the dietary treatment of diffuse liver disease is becoming more clearly defined In acute hepatitis, J F Stokes and M L Rosenheim suggest an intake of about 100 g protein per day, and they remark that the advantages of a higher protein content are not clearly established In patients with ascites secondary to hepatic cirrhosis a high protein diet is often beneficial, provided that no neurological complications ensue The *mechanism* of the development of neuropsychiatric changes in liver failure is ably reviewed by Sheila Sherlock The condition depends on the absorption of nitrogenous material from the intestine, and in the acute stage it is essential to stop all dietary protein The liver has a remarkable ability to replace lost tissue, and the question of the stimulus to regeneration presents a fascinating and fundamental problem, which is discussed by R D Harkness Here again, protein may play a part, for there is some evidence that a fall in the protein concentration in the immediate environment of the hepatic cells may be responsible for setting in motion the regeneration of new tissue after partial hepatectomy Other features of protein metabolism are considered in several of the articles which make up this number In addition, many other aspects of hepatic function and disease are reviewed This admirable symposium can be recommended to all interested in recent progress in the study of the liver

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[1] University Interchange between the United Kingdom and other European Countries A report on the work of the Committee for Foreign University Interchange Issued by the British Council 65 Davies Street, London W 1

[2] *Cambridge Daily News*, May 16, 1957

[1] The Liver Some Physiological and Clinical Aspects *Brit med Bull* May, 1957, 13, no 2 20*s*

University of Oxford

On June 8 the degree of D M was conferred on John Swithinbank

University of London

On May 22 the following degrees were conferred

M D—Eunice Lockey, John Newsome
M S—Kenneth Owen

Royal College of Surgeons of England

At a meeting of the council on June 13, with Sir Harry Platt, the president, in the chair, Lord Webb Johnson, past president, was admitted as a member of the court of patrons

The following were coopted to the council for the year 1957–58, representing various branches of practice

Dr John Hunt, general practice, Mr A C H Bell, gynæcology and obstetrics, Mr G Gill Carey, otolaryngology, Dr Frankis T Evans, anæsthetics, Mr A B Nutt, ophthalmology, Dr E Rohan Williams, radiology

The Hallett prize was awarded to Dr R Y Calne, of Guy's Hospital Medical School

A gift under covenant which will produce £45,000 was received from Cerebos Limited

Diplomas of fellowship were granted to the following

J W Garraway, W J L Harries, E J Hargadon M D Lord, W K M O Watkins, G R Benett, P S Watson, D H Nixseaman, George Kazantzis, B L Whitaker, M W F Dunning, H E D Griffiths, H B Eckstein P E Huddy, †R A Williams, P H E Courtenay Peter Goodall, J W Goodfellow, G P C Orlay, Katharine M Fussell, Ernest Kirz, C R Griffin, B T Hammond †R V Tracy Forster, Anant Charan, Gobindadas Goswami Anand Mohan Ahuja, †G O Clark, Muneer Husain, N K G Mendis, †R K Roddie, D D Beard, J H Hodgson, A R Kirby, Mary K Marchant †A W Morrison, Mihir Kumar Senapati, C V Wijesinha, J A Wilkinson, Nabil Ahmed Allouba, A G Bond, †B W M Bushell Abdul Karim Chaudhry, Hansa Deva Perera Goonatillake, G A D Lavy, B K Madden, Arivaman Mahanama Mendis, Bernard Nolan, G J Smart, Oliver Wesley James, Elliott Bader Ranjit Basu, R G K de Castro, M H Flint, J R W Gleave, *P A Graham, Syed Zafar Haider, C D Levis, I J MacQueen, Salil Kumar Mukhopadhyay, Durgadas Sengupta Dhirajlal Chhelshanker Vora, B M Andrea, Shyam Kishinchand Bulchandani, Kedarnath Vasudeo Chaubal Harold Collinson, K B Cornwell, †Israr Hasan Jafri, Adrian Litton, J R McQuaide G M Nunn, *Ramachandra Pararajasegaram, Rasikbhai Ambalal Patel, J P Richardson, A G G Robson, Norman Samuels, Brahma Dutt Sharma, Kedar Nath Sharma Thomas Stack, Henry Sunderland, J G Sweeney Cyril Toker, R O Wise, F C O Allen J R Badger K S Brearley, *Madhav Ranchandra Chaudhary*, H J Done H L Duthie W J Eskdale, R K Greenwood, R S M Ling, D C Mackenzie, B R Meyerowitz, J F Newcombe Ishwarbhai Chaturbhai Patel, V M Rao, Fardoon Phiroze Soonawalla, D W Whiteway C A Cass, Jean A Evans, †V T Hammond N J Jackson, P R Knight Peter Knipe, A B Oliveira, Ratan Chandra Varma John Ludbrook

* In ophthalmology † In otolaryngology

A diploma of membership was granted to M B Rees Jones

Royal College of Physicians of Ireland

At a meeting of the college on June 7 with Dr F J O Donnell, the president, in the chair, the following were admitted to the fellowship

W A Gillespie M E Cheffins, J D Kennedy D J O'Callaghan, and H B Kelly (*in absentia*)

The following were admitted as licentiates and members

J P Alexander Thomas Haran, B J Lomass and J R McCarthy

National Institute of Mental Health, Washington

Dr J J Elkes is resigning the chair of experimental psychiatry in the University of Birmingham on his appointment as head of the clinical neuropharmacology research centre of this institute

Lebanon Hospital

The annual meeting of this hospital will be held on Thursday, July 4, at 5 P M, at the Cora Hotel, Upper Woburn Place, London, W C 1 The Earl of Feversham will be in the chair, and the speakers will include Prof Alexander Kennedy

Biochemistry Society

A meeting of this society will be held in the department of chemistry of King's College, Newcastle upon Tyne, on Friday, June 28, at 11 15 A M On Saturday, June 29, at 11 A M the society will hold a joint meeting with the *Association of Clinical Biochemists* when the programme will include a symposium on mucoproteins

Oxford Graduates' Medical Club

The summer dinner of this club will be held in Trinity College, Oxford, on Friday, July 5, at 7 30 P M, when Dr Maurice Campbell will be in the chair Members may bring medically qualified guests of either sex Tickets (37*s* 6*d*) may be had before June 28 from Dr Ronald Macbeth, department of otolaryngology, Radcliffe Infirmary, Oxford

Service Awards

On the occasion of the Queen's birthday, in recognition of distinguished services in the Near East, October to December, 1956, the following doctors received awards

M C—Captain John Malcolm Elliott, M B Birm, R A M C
Mention in despatches—Surgeon Lieutenant John Gwythar Bradford, M B Lond, R N, 45 Commando, Royal Marines, Surgeon Lieutenant Peter Gordon Harries M B Lond, R N, H M S *Diana*

Lady Tata Memorial Fund

For research on leukæmia and allied diseases, in the year beginning October, the trustees of this Fund have made the following awards

Grants for Research Expenses—Dr J Kieler (Denmark) Fibiger Laboratory, Dr M Seligmann (France), Institute Pasteur Dr M Simonsen (Denmark), Fibiger Laboratory, Dr B Thorell (Sweden), Karolinska Institute, Dr G Klein (Sweden), Karolinska Institute, and Dr M. Bessis (France), Centre National de Transfusion Sanguine

Scholarships—Dr G Marinone (Italy), University of Pavia and Dr A J Therkelsen (Denmark), Institute of General Pathology

Scholarship and Grant—Dr G V Seaman (England) Department of Colloid Science, Cambridge

Ross Institute of Tropical Hygiene

At a luncheon held at the London School of Hygiene and Tropical Medicine on June 12 to mark the centenary of Sir Ronald Ross's birth, Sir Eric Macfadyen, the chairman, recalled that the establishment of the institute named after Ross was mainly due to the efforts of the late Sir William Simpson and the late Sir Malcolm Watson, and Austin Chamberlain had been mainly responsible for the institute's incorporation with the London School of Hygiene and Tropical Medicine Dr M G Candau, director general of W H O, spoke of the Organisation's debt to Ross, who, forty five years before the introduction of D D T, established the principles that were now being followed in programmes of malaria eradication In May, 1955, W H O had decided to support steps towards achieving world wide eradication of this disease By the end of March this year 63 countries and territories had accepted eradication as a goal, in 10 this had been almost achieved, while in 15 the work was well advanced Mortality and morbidity attributable to malaria were now at levels not more than a third of those twelve years ago when the attack with residual insecticides was begun Prof G Macdonald, director of the institute, recalled that it was Dr Candau's powerful advocacy which led the World Health Assembly in 1955 to decide on a policy of eradication Turning to the work of the institute, he said that this comprised advisory and consultative services, teaching, and research Research was being directed towards the reasons for the prevalence of malaria, and the resistance of anopheles to insecticides

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On June 10 Prof J H Burn F R S, received the honorary D SC of Yale University

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CORRIGENDUM *Harvey Tercentenary*—In our report last week (p 1237) of the Harvey Tercentenary Conference we misrepresented Prof K. J Franklin's remarks Fabricius of Padua first noticed that valves are a feature of many (not *all*, as we stated) veins of the body in 1574, his book, however, was not published until 1603 Harvey *was* a fellow of the College of Physicians of London The epithet "Royal" was not added until towards the end of the 17th century, and then far from invariably

HÆMOLYTIC DISEASE OF THE NEWBORN

DEATHS IN ENGLAND AND WALES DURING 1953 AND 1955

W. WALKER *
M.D. Durh.
LECTURER IN CHILD HEALTH IN THE UNIVERSITY OF DURHAM

P. L. MOLLISON
B.A., M.D. Camb., F.R.C.P.
DIRECTOR, BLOOD TRANSFUSION RESEARCH UNIT, MEDICAL RESEARCH COUNCIL

From the Children's Department, Royal Victoria Infirmary, Newcastle upon Tyne, and the M.R.C. Blood Transfusion Research Unit, Postgraduate Medical School of London

THE increasing use of exchange transfusion has reduced the number of deaths from hæmolytic disease, but over the country as a whole the reduction has been less than was expected.

The correct use of exchange transfusion enables more than 95% of infants with hæmolytic disease to survive if born alive (Allen et al. 1950, Walker and Neligan 1955), whereas with simple transfusion only about 80% are likely to do so.†

Assuming that 1 in every 200 infants will have hæmolytic disease, and that 15% of affected infants will be stillborn, one can calculate the expected mortality under different régimes of treatment among those born alive: it is 0.85 per 1000 live births when simple transfusion is used but less than 0.2 when exchange transfusion is used exclusively.

Fig. 1 shows the changing mortality from hæmolytic disease over the past twenty-one years as recorded in the Registrar-General's Statistical Review.

In 1935–41 serological tests for hæmolytic disease were not available: this explains why the number of deaths ascribed to hæmolytic disease of the newborn is about half the number expected. From 1942 onwards the number of deaths registered as due to hæmolytic disease of the newborn rises steadily to almost 0.8 per 1000 live births in 1945–51, a level approaching that expected if simple transfusion alone was being used. A small part of this rise may be due to the greater number of women immunised by transfusion, after blood became more readily available from 1940 onwards.

The first year in which a definite decrease in mortality can be discerned is 1952. Although Diamond first described his method of exchange transfusion in 1947 and this method was used in some hospitals in England from then onwards (Mollison and Cutbush 1948, 1949), many hospitals were still using simple transfusion as late as 1952. In that year the results of a controlled trial comparing simple and exchange transfusion in many different centres in England, Wales, and Ireland were published (Mollison and Walker 1952) and this was followed by a more widespread use of exchange transfusion in England. Nevertheless in 1953 the reported mortality from hæmolytic disease of the newborn was 0.6 per 1000 live births—i.e., three times what would be expected if all severely affected infants were being satisfactorily treated by exchange transfusion.

In the face of this it was clearly desirable to study the circumstances of every death certified as due to hæmolytic disease to try to discover why the death-rate remained disappointingly high.

Method of Inquiry

Copies of the death certificates for all infants certified as dying from hæmolytic disease of the newborn in 1953 and 1955 were made available through the Registrar-General's Office, London.

TABLE I—CAUSES OF DEATH IN INFANTS REGISTERED AS DYING FROM HÆMOLYTIC DISEASE OF THE NEWBORN

—	1953		1955	
Due to H.D.N.		312		315
Not due to H.D.N.				
Kernicterus of prematurity	53	97	41	85
Non-hæmolytic hydrops	11		11	
Miscellaneous	33		33	
Not traced		2		0
Total registered as due to H.D.N.		411		400

A circular letter was sent to the doctor who had signed each certificate to explain the purpose of the inquiry, and a form was enclosed asking for the following data:

(1) The sex and birth weight of the infant.
(2) Its age on admission to hospital (if not born in hospital).
(3) The serological findings in mother and infant, including the result of antenatal tests.
(4) The cord-blood hæmoglobin and bilirubin levels.
(5) The time of onset and degree of jaundice.
(6) Details about any transfusions given.
(7) The clinical course of the disease and mode of death.
(8) The age at death.
(9) The necropsy findings.

In many cases the hospital notes were borrowed and, if necessary, letters were written to the pediatrician, pathologist, or family doctor, asking for more detailed information.

Data were obtained for 409 of 411 deaths registered in 1953 and for all 400 registered in 1955. (The number of liveborn infants was 684,000 in 1953 and 668,000 in 1955.)

Results

DEATHS NOT DUE TO HÆMOLYTIC DISEASE OF NEWBORN

At an early stage of the inquiry it became clear that many infants were certified as having died from hæmolytic disease of the newborn whereas in fact they had died from other causes (table I).

The commonest "other cause" was kernicterus of prematurity—i.e., kernicterus in a premature infant without any hæmatological or serological evidence of hæmolytic disease of the newborn. This condition was

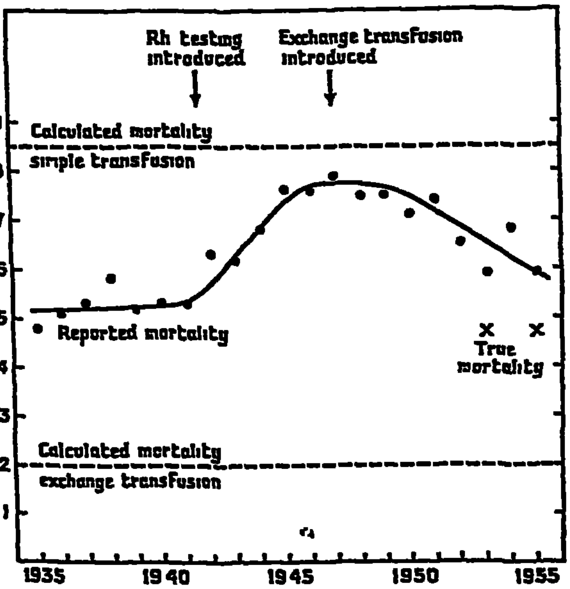

Fig. 1—Mortality from hæmolytic disease of newborn from 1935 to 1955. 'Reported mortality' is as reported to Registrar-General. Corrected figures for 1953 and 1955, based on the present investigation, are marked 'True mortality'.

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* Aided by a grant for secretarial help from the Scientific Research Committee of the Newcastle Regional Hospital Board.

† This figure is calculated from the data of Armitage and Mollison (1953) applied to the series of Mollison (1956, p. 464, table XXXV). According to these figures the calculated mortality with simple transfusion alone is 17%.

TABLE II—DEATHS DUE TO HÆMOLYTIC DISEASE OF THE NEWBORN

Cause of death	1953		1955	
Solely H D N				
Hydrops fœtalis		40		29
Heart failure	58		55	
Kernicterus	105		82	
Exchange transfusion	28	239	60	242
Late anæmia	4		1	
Other causes	44		44	
Important contributory factors		33		44
Total		312		315

recognised only after the publications of Aidin et al (1950) and Zuelzer and Mudgett (1950) Probably its increasing recognition in recent years has masked a slight fall in the number of deaths from hæmolytic disease of the newborn because, up to the end of 1955, deaths from kernicterus, from whatever cause, were recorded as due to hæmolytic disease of the newborn Similarly, all cases of hydrops fœtalis were recorded as due to hæmolytic disease of the newborn, whereas each year a number occurred where a diagnosis of hæmolytic disease was not supported on pathological grounds or had been excluded serologically In others—e g , some infants who had died from hæmorrhagic disease of the newborn—there was no evidence to justify the recorded diagnosis of hæmolytic disease , indeed in many this diagnosis had been excluded by serological tests

The 182 deaths not due to hæmolytic disease of the newborn will not be considered further here

CAUSES OF DEATH IN INFANTS WITH HÆMOLYTIC DISEASE

In 87% of the 627 cases in which death was attributed to hæmolytic disease of the newborn, full serological confirmation of the diagnosis was obtained 69% of the 627 cases were predicted antenatally, 3% were first recognised because of tests on cord blood, and in 15% serological confirmation was obtained postnatally after hæmolytic disease had been diagnosed clinically In the remaining 13% diagnosis rested mainly on clear-cut clinical and pathological evidence, although in some cases the Coombs test had been found to be positive at some time

In table II the 627 deaths have been subdivided into those due solely to hæmolytic disease of the newborn and those in which there were other important contributory factors An attempt was made to answer the question "Would the child have died if there had been no hæmolytic disease ?" If the answer was "Probably not," hæmolytic disease of the newborn was regarded as the sole cause of death These cases were then further subdivided into the categories shown in table II

Apart from the cases of hydrops fœtalis, among the deaths due solely to hæmolytic disease of the newborn, heart failure, kernicterus, and exchange transfusion accounted for 388 of the 481 deaths

Hydrops Fœtalis

69 deaths were stated to have occurred in hydropic infants born alive , 49 of these were in extremis at birth and died within an hour , 18 more died in the first nine hours , and 2 survived until the second day None who survived more than an hour were grossly œdematous, but all were very anæmic and should probably have been classified as having very severe hæmolytic disease rather than hydrops Only 3 were treated by exchange transfusion, and all died during the transfusion

Heart-failure

In many cases the diagnosis of heart failure was made by the clinician in charge of the case , in others it was deduced from the recorded observation of severe anæmia leading to death on the first day of life , occasionally it was based on necropsy findings Some infants who died during exchange transfusion were considered to have died from heart failure, present before transfusion, and these deaths have been included in the heart failure group and not among the deaths due to exchange transfusion

Only 75 of the 113 infants who died from heart-failure were treated by exchange transfusion, and only 66 of these within the first nine hours of life

Of the 75 in whom exchange transfusion was attempted, 57 died during the transfusion, and in many of these it seemed probable that the immediate cause of death was failure to remove more blood than was injected In fact, in 30 cases more blood was injected than withdrawn, and in 18 cases equal volumes were exchanged

The severe nature of hæmolytic disease in this group is shown by the observation that in two thirds of the cases in which the cord hæmoglobin was recorded it was less than 9 g per 100 ml Hæmolytic disease was predicted antenatally in only 88 of the 113 cases in this group, and 22 were recognised because of clinical evidence of very severe disease 26 of these infants were admitted to hospital only after birth

Kernicterus

Kernicterus accounted for 105 deaths in 1953 but for only 82 in 1955—a fall possibly associated with an increased use of exchange transfusion However, this fall was offset by the greater number of deaths during or soon after exchange transfusion in 1955, compared with 1953 In 151 cases, the diagnosis of kernicterus was based on post mortem findings, but in a few it was deduced from the clinical picture of cerebral damage during the first week of life in a deeply jaundiced infant without other apparent cause

Of the 187 infants who died from kernicterus, only 60% were born in the hospital where they received treatment In this group, failure to predict hæmolytic disease or to recognise it soon after birth seems to have been the cause of at least 41 deaths , for, in 31 cases kernicterus was already present when treatment was first considered, and in 10 others the infant was so deeply jaundiced that transfusion was not considered worth while

Cord-hæmoglobin levels were determined in 77 cases and were above 15 g per 100 ml in 30 of these , only 2 of these 30 infants had been treated by early adequate exchange transfusion (defined as more than 50 ml per lb body weight on the first day of life)

Cord bilirubin levels were determined in only 29 cases , in 3 the level was below 3 mg per 100 ml but in 19 it was above 5 mg

Of the 187 infants who died from kernicterus, exchange transfusion was attempted in only 64 , in 9 of these the operation failed completely , in 14 cases less than 40 ml , and in 13 cases between 40 ml and 60 ml of blood per lb body-weight was exchanged , in 4 other cases the volume was not recorded Thus in only 24 of the 187 cases was a relatively large exchange transfusion (more than 60 ml per lb) given

Exchange Transfusion

In table II deaths have been classed as "associated with exchange transfusion" only when they occurred during or within four hours of exchange transfusion, where the "immediate" cause was not clear but when it seemed, from the information available, that death would not otherwise have taken place at that time 50 other infants died during or shortly after exchange transfusion but have not been included because they might well have died without exchange transfusion 36 were already in heart failure , 3 others were moribund owing to kernicterus when transfusion was undertaken , and 11, when transfusion was begun, were already very ill because of severe hæmolytic disease or some complicating factor such as cerebral hæmorrhage

The number of deaths ascribed directly to exchange transfusion was 28 in 1953 and 60 in 1955 Among these 88 infants were 37 who were seriously ill at the time of transfusion (27 of them had cord-hæmoglobin levels below 9 g per 100 ml), but this leaves 51 infants whose condition was quite good (7 had cord-hæmoglobin levels above 14 8 g) Two-thirds of the deaths attributed to exchange transfusion took place before 60 ml per lb body-weight had been exchanged, but death was not related to the infant's age at the time of transfusion

Late Anæmia

In this series only 5 deaths were due to late anæmia—i e , anæmia recognised for the first time towards the end of the first week of life or later in an infant not seriously ill at birth All had hæmoglobin values below 5 g per 100 ml at the time of admission, and jaundice was never marked in any

Other Causes

The category "other" in table II refers to cases in which the available evidence suggested that death was due to hæmolytic disease or to the treatment given, but clinical and pathological records were incomplete or otherwise unsatisfactory.

"Important Contributory Factors"

Contributory factors were regarded as important when the degree of hæmolytic disease seemed insufficient to account for death In some instances it was easy to decide that a particular case fell into this category—e g , when an infant with mild or adequately treated hæmolytic disease had a severe congenital defect In others it was more difficult—e g , when an infant with moderately severe hæmolytic disease had a cerebral birth injury The 77 infants in this group included 11 with severe congenital defects , 18 with cerebral hæmorrhage , 11 with pneumonia, of whom 7 died in the first four days of life and the remainder at periods up to the age of two months , 23 premature infants, of whom 8 weighed less than 3 lb , and 7 weighed 3–4 lb , 8 whose death was due to maternal causes or associated with delivery , and 6 with miscellaneous conditions

MANAGEMENT OF HÆMOLYTIC DISEASE OF NEWBORN

Various analyses were made of the way in which the diagnosis was reached and the treatment was given The 69 cases of liveborn hydrops were excluded because this condition is rarely if ever compatible with survival On the other hand, cases in which there were thought to be "important contributory causes" of death were included because it was only in one or two isolated instances that the "contributory cause" modified the conduct of the case

Prediction and Recognition of Hæmolytic Disease

In table III the cases have been subdivided according to the manner in which the diagnosis was first made

Thus, of the 558 cases, 404 were diagnosed serologically, usually because antibodies had been detected antenatally but occasionally because cord blood taken routinely had given a positive Coombs test The remaining 154 were diagnosed clinically—149 because of deep jaundice or other evidence of severe disease, and 5 because of anæmia developing towards the end of the first week of life or later

TABLE III—AGE ON ADMISSION TO HOSPITAL IN RELATION TO METHOD OF DIAGNOSIS

Diagnosis	No of cases	Born in hospital	Age on admission to hospital			Never admitted
			First 12 hr	12–24 hr	After 1 day	
Serological	404(72%)	363	23	6	10	2
Clinical	154(28%)	27	29	11	71	16
Total *	558	390(70%)	52(9%)	17(3%)	81(15%)	18(3%)

* 69 cases of hydrops in babies born alive are excluded from this analysis

Of the 404 infants whose disease was diagnosed serologically, 363 were delivered in hospital and 29 were admitted within the first day of life Only 12 were admitted after the first day or not at all Of the 154 whose disease was diagnosed on clinical grounds only 67 were born in hospital or admitted within twenty-four hours

The clinically diagnosed cases can be subdivided into four approximately equal groups depending on the features that led to the recognition of hæmolytic disease those with signs of severe disease—e g , anæmia, jaundice, bruising, and œdema—within eight hours of birth , those in which jaundice appeared between eight and twenty-four hours of birth , those in which the diagnosis was made only because of intense jaundice during the first week of life , and those recognised only when signs of brain damage called attention to the diagnosis

Of the 558 infants under discussion, 289 were jaundiced within eight hours of birth and a further 95 within twenty-four hours Of the 174 who did not develop jaundice in the first twenty-four hours, 78 died within eight and 35 others within twenty-four hours of birth Thus only 61 infants (11%) survived more than a day without becoming jaundiced, and even then a quarter of those died from causes other than hæmolytic disease

In our opinion, 108 deaths could be partly attributed to failure to predict disease and 58 others to failure to recognise clinical evidence early

Failure to predict hæmolytic disease was very seldom due to the fact that the blood-group factor concerned was not Rh (D) In only 11 cases was disease due to some other incompatibility 8 were examples of incompatibility within the ABO blood group system, 2 were due to anti-c, and 1 to anti-E

TABLE IV—TREATMENT IN RELATION TO METHOD OF DIAGNOSIS

Diagnosis	No of cases	Exchange transfusion		Simple transfusion		No transfusion
		First day	Later	First day	Later	
Serological	404(72%)	268	7	33	16	80
Clinical	154(28%)	30	16	6	18	84
Total	558	298(54%)	23(4%)	39(7%)	34(6%)	164(29%)

Of the cases in which Rh (D) was concerned, only 2% of the failures to predict the disease were due to technical errors In the rest, failure to predict hæmolytic disease was due to the fact that adequate antenatal tests had not been made One surprising finding was that, in half the cases diagnosed only on clinical grounds, full serological tests were never carried out, even after delivery , hence the diagnosis was not proved, nor could any reliable prognosis have been given

It is evident from these various observations that failure to predict the disease was due chiefly to omission of antenatal serological tests rather than to any failure in the tests themselves

Treatment in Relation to Timely Diagnosis

Table III shows that 390 (70%) of the infants who died were born in hospital, and 52 (9%) were admitted within twelve hours of birth It is therefore evident that failure to recognise the disease early, although contributory in some cases, was not responsible for the majority of deaths

In table IV the cases have been divided in the same way as in table III but in relation to treatment

Of the infants whose disease was diagnosed serologically 66% were treated by exchange transfusion on the first day of life , but 20% received no treatment whatever, although almost all were born in, or admitted to, hospital within twelve hours of birth

Of those whose disease was diagnosed because of the development of clinical signs of the disease, only 31%

were treated by exchange transfusion and 54% received no treatment

In 1955, 202 infants had been treated by exchange transfusion, compared with 119 in 1953 Even so, 84 infants who died in 1955 and 153 who died in 1953 had not received exchange transfusion indeed, in the two years 164 infants had received no treatment at all

The fact that 321 died despite exchange transfusion calls for separate comment

Details of Exchange Transfusion

Of the 321 exchange transfusions, 258 were given within the first nine hours and 63 later Analyses of the amounts of blood exchanged showed no difference between these two groups or between the two years All the cases have therefore been considered together, and the amounts exchanged are shown in fig 2 In the cases in which exchange transfusion had been given or attempted only 34% of the babies received more than 60 ml per lb body-weight, 21% received 40–60 ml per lb, 22% received 20–40 ml per lb, and 11% less than 20 ml per lb In 12% the precise amount exchanged was not recorded, in half of these the amount was probably trivial

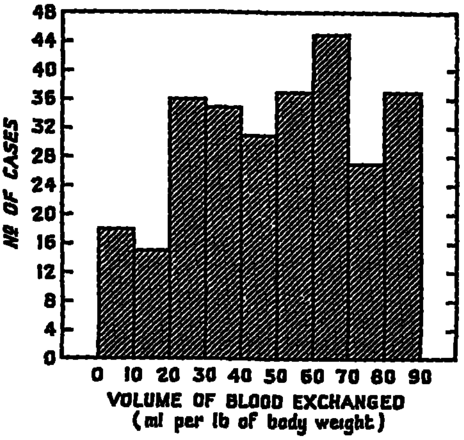

Fig 2—Volume of blood used in 281 of 321 cases in which exchange transfusion was attempted (volume used in remaining 40 cases was not recorded)

The amounts of blood injected and withdrawn were about equal in most cases In 56 infants with cord-hæmoglobin levels below 9 g per 100 ml it seems possible that failure to withdraw considerably more blood than was injected contributed to the infant's death Thus, in 37 of the 56 cases the amount injected was equal to, or greater than, the amount withdrawn, in the remaining cases the amount withdrawn was only slightly (10–20 ml) greater than the amount injected Many of these infants died during the transfusion but have been included among the deaths due to heart-failure rather than in those "associated with exchange transfusion"

In a few cases in which there did not seem to be any clear indication for removing more blood than was injected it appeared that this had contributed to the infant's death Thus in a case where the infant had a cord-hæmoglobin level about 15 g per 100 ml, 70 ml more blood was removed than was injected, and this seemed to precipitate collapse and death during transfusion

The time after birth at which exchange transfusion was performed varied from an hour to six days, but in 80% of cases it was less than nine hours In 33 cases failure of exchange transfusion was probably due to its being undertaken too late Among these were 4 very anæmic infants who were treated within the first nine hours of life but whose condition had much deteriorated between birth and transfusion

The technique of exchange transfusion seemed to have contributed to 28 of the deaths For example, in 5 the umbilical vein was perforated and a large amount of blood was found free in the peritoneal cavity at necropsy, and in 2 others umbilical thrombophlebitis, associated with a staphylococcal septicæmia and lung abscesses, was found at necropsy The time taken for exchange transfusion varied from nineteen minutes in one case to nine hours in another, and in 9 cases the rate at which the transfusion was given apparently contributed to death

Repeated exchange transfusion had been attempted in only 22 infants, all of whom had been born in hospital (6 in 1953 and 16 in 1955)

Tests on Cord Blood

A Coombs test on cord blood was performed in 67% of the cases in 1953 and 78% in 1955, these percentages are very similar to the proportion of cases in which the disease was predicted antenatally in those years Only 5 false negative results were recorded in the two years

Cord hæmoglobin levels were recorded in 50% of the cases in 1953 and 65% in 1955, the plasma bilirubin level of cord blood was recorded in 14% of cases in 1953 but in 40% in 1955

40% of all cord-hæmoglobin levels were below 9 g per 100 ml, 44% were 9 0–14 8 g, and 16% were above 14 8 g

Influence of Previous Obstetric History on Method of Treatment

Exchange transfusion was used in 70% of cases in which a previous infant in the family had been affected, compared with 54% where no previous infant had had hæmolytic disease Even so, 24% of infants preceded by affected siblings were allowed to die untreated There was no obvious relation between the use of exchange transfusion and the number of affected siblings or the severity of disease in these It was surprising that 8 of the 14 infants preceded by stillbirth due to hæmolytic disease did not receive exchange transfusion, in fact 5 received no treatment at all

ANALYSIS ON BASIS OF AGE AT DEATH, BIRTH-WEIGHT, AND SEX

Of the 558 infants, 275 died on the first day of life, mostly from heart-failure or during exchange transfusion, and 224 died between the second and fifth days, mainly from kernicterus 57 died later In 2 cases the time of death was not recorded

The birth-weight of 48 was not recorded but 104 (20%) of the remainder weighed $5^1/_2$ lb or less 63 had been born prematurely spontaneously and 41 by premature induction The birth-weight distribution in the two years was practically identical, and no correlation between birth-weight and cause of death was found except that in some cases prematurity was regarded as an important contributory factor

In both years there was a preponderance of males among the fatal cases, the ratio being 1 4/1 in 1953 and 1 1/1 in 1955 In table v the cases have been analysed by sex in relation to the main causes of death

TABLE V—SEX AND CAUSE OF DEATH

Cause of death	Male	Female	Sex not recorded	Ratio
Hydrops fœtalis	32	37	0	0 86
Heart failure	48	62	3	0 78
Exchange transfusion	41	45	2	0 91
Kernicterus	127	59	1	2 1
Miscellaneous	87	74	9	1 2
Total	335	277	16	1 2

The only difference between the sexes as regards the cause of death is that, among the infants dying with kernicterus, males were twice as common as females—a difference which is statistically significant (cf Diamond et al 1950 and Armitage and Mollison 1953) The preponderance of males developing kernicterus was greater in 1953 (75/29) than in 1955 (52/30) A possible explanation is that exchange transfusion was being used less in 1953, and that therefore more deaths from kernicterus took place in that year

There is a slight preponderance of females in the other groups of cases, but this is not significant

Discussion

One of the first findings in this inquiry was that many infants dying from other conditions were being registered as having died from hæmolytic disease of the newborn, which disease in fact accounted for only about 75% of the number certified Most of the deaths wrongly included were due to "kernicterus of prematurity" When this became apparent, the Registrar-General was informed, and he agreed that in future this condition should be certified separately from hæmolytic disease of the newborn

It is, of course, possible that some infants dying of hæmolytic disease of the newborn were being certified as dying from other causes The finding that so few infants were recorded as dying from anæmia after the first few days of life suggests that in some cases of this kind hæmolytic disease of the newborn may have been overlooked

Even when deaths not due to hæmolytic disease are excluded, the deaths are at least three times as numerous as would be expected with modern treatment There appear to be two main causes for this (1) failure to predict the disease before birth or to diagnose it sufficiently soon after birth, and (2) failure to attempt an exchange transfusion or to perform it satisfactorily

If early diagnosis is essential to the correct management of hæmolytic disease, antenatal prediction gives the infant its best chance This chance was denied to 168 of the 558 non-hydropic infants who died of hæmolytic disease Failure to predict disease was due to the presence of antibodies other than anti-Rh (D) in only 11 instances and to technical error in only 5 It is therefore clear that failure to predict hæmolytic disease almost always resulted from failure to carry out the necessary tests

The significance of early clinical features was not always appreciated Thus 87 infants, although clinically affected within the first twenty-four hours, were not admitted until after this time indeed 31 were not diagnosed until kernicterus had developed Early jaundice, present in more than 90% of the fatal cases, often failed to suggest the true diagnosis and the possible need for immediate exchange transfusion

There is little doubt that exchange transfusion should be given to all severely affected infants, for this is the only method of treatment which will overcome heart-failure in the very anæmic infants and prevent deep jaundice and kernicterus in the others Since the present inquiry deals only with fatal cases, it can be assumed that most of the infants should have received exchange transfusion, yet 80 of the 404 in whom the diagnosis was made serologically died untreated, and 49 received only simple transfusion 164 (29%) of the infants who died had not been transfused, and 73 (13%) had received simple transfusion Simple transfusion was used on the first day of life in 39 cases although only a third as much in 1955 as in 1953, but it is very doubtful whether simple transfusion is ever justified where treatment on the first day is needed In 52 cases premature labour had been induced in an effort to mitigate the severity of the disease, yet 17 of 45 non hydropic infants were not treated by exchange transfusion Similarly, 21 of 74 infants received no treatment even though a previous infant in the family had died from hæmolytic disease of the newborn or had been stillborn from this cause

321 infants (58%) were treated by exchange transfusion, among the infants admitted after the first day of life the proportion treated by exchange transfusion was lower (23 out of 81) There is little doubt that exchange transfusion should have been given to more of the infants who were deeply jaundiced on admission, for the transfusion can usually be performed by the umbilical route without difficulty up to the age of five or six days It could similarly be claimed that repeated exchange transfusion was not given as often as was indicated Of the 187 cases of kernicterus, 124 were not treated by exchange transfusion, and of the 63 where this was attempted, it failed completely in 8, while in 31 the amount of blood exchanged was less than 60 ml per lb body-weight

Although the majority of the cases had been treated by exchange transfusion, the amount of blood exchanged was too small in many cases, for in 121 the operation either failed completely or exchanged less than 40 ml per lb body-weight This, together with the finding that many infants died during the transfusion, suggests that the operation may not always have been carried out as well as it might have been In a third of the cases the balance between the volume of blood injected and withdrawn was incorrect, for some very anæmic infants received more blood than was withdrawn, and in others the amount withdrawn was no greater than the amount injected It is possible that citrate toxicity may have played a part in other deaths, but no information on this point was available

It seems that there is an increasing awareness of the value of estimating the hæmoglobin and bilirubin levels in cord blood certainly these estimates were made more often in 1955 than in 1953

The inadvisability of using the cord-hæmoglobin level as the sole criterion of severity is shown by the observation that 16% of all the cord-hæmoglobin levels were above 14·8 g per 100 ml, and that, among the cases of kernicterus, as many as 30 out of 77 (40%) of the recorded levels were over 15 g Of these 30, only 2 were treated by early adequate exchange transfusion

The incidence of kernicterus in mature infants with hæmolytic disease of the newborn with a cord-hæmoglobin level above 15 8 g per 100 ml is low (5%) without exchange transfusion (Armitage and Mollison 1953) Because of this known relationship, treatment is often withheld from mature infants when the cord-hæmoglobin level is found to be over about 15 g It has long been clear that, although a high cord-hæmoglobin level is a very favourable prognostic sign, exchange transfusion should still be given if more than a trace of jaundice develops within the first twenty-four hours of life

Although exchange transfusion is not a difficult operation, the best results are to be expected in hospitals where the staff treat a large number of cases and gain considerable experience The deaths investigated were distributed among 244 hospitals (172 in 1953 and 165 in 1955) Even if all cases of hæmolytic disease of the newborn were treated in these hospitals alone, the average yearly number in each would have been about 12, of which only about 8 would have needed exchange transfusion Since it is known that some hospitals have far more than others it is evident that in some the number of cases of hæmolytic disease treated must be very small indeed

Summary

The clinical records of all infants certified as dying from hæmolytic disease of the newborn in England and Wales during 1953 and 1955 have been examined

In each of the two years about 400 infants were certified as dying from hæmolytic disease of the newborn However, owing to the definition of hæmolytic disease of the newborn for the purpose of certification, the label was often attached to infants dying from other conditions such as "kernicterus of prematurity," and the true number of deaths from hæmolytic disease of the newborn was about 310 in each of the two years

Factors contributing to the deaths from hæmolytic disease were failure to predict the disease antenatally,

failure to recognise early clinical evidence of the disease, and failure to give adequate exchange transfusion

Attention is called to the fact that the treatment of hæmolytic disease of the newborn is undertaken at a very large number of hospitals In many of these the number of cases seen is very small, and it is therefore impossible for the staff to gain the necessary experience and familiarity with this condition

It is suggested that, if all cases of hæmolytic disease of the newborn (due to anti-Rh (D)) were predicted antenatally and were treated when necessary by early adequate exchange transfusion, the present death-rate could be greatly reduced Each year, in England and Wales, more than 150 infants would be saved

We are most grateful to Dr G E Godber, of the Ministry of Health, and to Dr W D P Logan, of the Registrar-General's department, for making this study possible We are also greatly indebted to the numerous doctors throughout the country who so readily put their clinical records at our disposal

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MONGOLISM AND OTHER CONGENITAL ABNORMALITIES

AN EPIDEMIOLOGICAL STUDY IN NORTHAMPTONSHIRE

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THIS investigation was undertaken because I noticed that in Northamptonshire mongol children seemed to be born in groups in different areas at different times The findings suggest that mongolism and other congenital abnormalities may be more closely related to maternal infection than has hitherto been supposed

Sources of Information

The information regarding the births of children with congenital abnormalities was obtained as follows

(1) A search was made of the mental deficiency records of the mental health department and the handicapped pupils register of the school health service department of the local health authority

(2) With the coöperation of the consultant pædiatricians, a search was made of their records *of the congenital abnormalities* referred to them

(3) All the health visitors and midwives of the local health authority were asked about births of children with congenital abnormalities in their areas, and where the mothers were living throughout the pregnancies

(4) A search was made of the hospital birth registers and the infant mortality records

(5) Further information about cases of hare lip and cleft palate was found in the records of the consultant surgeons serving the area, the school dental department, the hospital consultant dental officer, and the speech therapists of the local health authority

Where there was more than one abnormality the case was classified under the more serious defect Thus mongols with congenital heart disease or cleft palate were classed as mongols Cases of anencephaly with spina bifida were classed under anencephaly Cases of spina bifida and hydrocephalus were classed under spina bifida

TABLE I—BIRTHS OF INFANTS WITH CONGENITAL ABNORMALITIES IN NORTHAMPTONSHIRE, 1944–55

Year	No of live and still births	No of cases of					
		Mongolism	Congenital heart disease	Hare lip cleft palate	Anencephaly	Spina bifida	Hydrocephaly
1944	4798	6	16	10	3	10	1
1945	4443	7	10	4	2	7	3
1946	4639	4	10	7	4	8	1
1947	5011	8	18	2	6	10	3
1948	4423	5	13	10	1	5	2
1949	4127	7	17	5	2	5	
1950	4078	6	15	12	6	6	1
1951	4096	9	11	5	2	7	3
1952	4090	6	12	5	6	16	
1953	4342	12	11	4	6	5	1
1954	4396	9	13	8	5	8	4
1955	4286	7	10	11	3	11	5
Total	52,729	86	156	83	46	98	24
Incidence per 1000 live and still births		1 63	2 96	1 57	0 87	1 86	0 45

Mongolism

Incidence

84 mongols are known to have been conceived and born alive in the county during the twelve years 1944–55 2 mongols were stillborn Each case was confirmed by medical opinion Doubtful cases with "mongoloid" characteristics, and mongols who were conceived elsewhere but whose mothers moved into the county during pregnancy, were excluded from the survey No information was available in respect of mongols conceived in the county but born elsewhere

These data give an incidence of 1 mongol birth in every 613 live and still births (table I) Carter and MacCarthy (1951) found an incidence of 1 in 666 It will be seen from the table that more mongol births were recorded in the second six years of the period under review Though the incidence may have increased, it is probable that the records during the latter period are more complete and give a more accurate assessment, i e , 1 mongol birth for every 516 live and still births (In 1956 9 mongols are known to have been born, out of 4511 live and still births)

The incidence varied considerably from one year to another The lowest, in 1946, was 1 mongol birth for every 1160 live and still births , the highest, in 1953, was 1 in 362

The monthly distribution of mongol births was far from uniform Thus there is no record of a mongol birth during the eleven months beginning September, 1949, but 5 full-term mongols were born between June 8 and July 3, 1947—i e , more than 1% of the live births during this period

Grouping of Mongol Births

When the distribution of mongol births is considered in more detail it appears that about two thirds of them have occurred in small groups the remaining third were apparently isolated cases The following examples of groups are presented for illustration

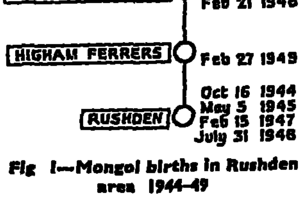

Fig 1—Mongol births in Rushden area 1944–49

Rushden Area

Rushden (population 15,210 in 1946), Higham Ferrers (population 3400), Irthlingborough (population 4700), and Finedon (population 3000) are linked by the road A6 In 1944–49, 10 mongols were born in this area (fig 1)

In the two years 1947–48 when there were 13 mongol births in the county, no fewer than 5 of these were in Rushden, Higham Ferrers, and Irthlingborough, whose populations and births are less than a tenth of those of the county. A mongol and an imbecile with some mongolian stigmata were born on the same day in Higham Ferrers and Irthlingborough, which are two miles apart

In Irthlingborough only 3 mongols are known to have been born in the twelve years but these 3 were born within a period of nine months 85 babies were born in Irthlingborough in 1947, so about 1 in every 21 babies born at this time was a mongol Also in 1945–47 there were born in this area 4 imbeciles for whose condition no cause could be found Their dates of birth were, in Rushden, Jan 27, 1945, and May 18, 1946, in Higham Ferrers, June 1 and June 8, 1947

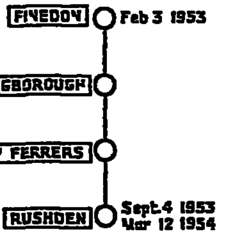

Fig 2—Mongol births in Rushden area, 1950–55

In 1950–55 only 3 mongol births were recorded in the same area, and all 3 births occurred within thirteen months (fig 2)

Oundle Area

In August, 1945, a mongol was born in Glapthorne (fig 3), where about 5 babies are born each year In December, 1946, a mongol was born in the hamlet of Stoke Doyle where about 2 babies are born annually On June 20, 1947, a full-term mongol was born at a farmhouse near Cotterstock. The next day another full-term mongol was born at Southwick Finally, a week later, a full-term mongol was born at Weldon In the nine years since then only 1 mongol has been born in this area

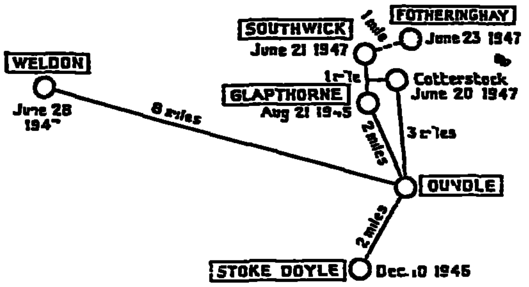

Fig 3—Mongol and imbecile births in Oundle area.

Only 2–3 babies are born each year in the neighbouring hamlets of Cotterstock and Southwick It seems a remarkable coincidence that, over a period of twelve years, 2 mongols were born on successive days in these two hamlets In Weldon, on a proportionate basis, 32 babies would have been born in 1947, and again it seems remarkable that the only mongol born in this village over the past twelve years was born a week after the 2 at Cotterstock and Southwick.

It is worth noting that on June 23, 1947, an imbecile, for whose condition no cause could be ascertained, was born at full term to a mother aged 26 about a mile from Southwick in the hamlet of Fotheringhay, where 3–4 babies are born each year

Wellingborough Area

9 mongols are known to have been born in the county in 1951 Of these, 5 were born in or near Wellingborough, 3 of them within seven weeks (fig 4)

On March 18 a mongol was stillborn at Wilby (population 523 in 1951 about 8 births a year) On May 20, a mongol was born at Holcot (population 350, about 5 births a year) On August 6 a mongol was born in Great Doddington (population 671, about 10 births a year) Three weeks later, a mongol was born at Little Harrowden, a village of about the same size A month later a 5th mongol was born in Wellingborough itself

Fig 4—Mo

Daventry Rural Di

5 of the 9 mong n described 2 other mo ural district about three mi weeks of each other

One birth was at Watfor , about 4 births a year), and the other in uses at Buckby Wharf, three miles away

An 8th mongol was born in Ke ring, and the 9th at Woodford

Corby Area

In the eight years 1944–51 there is no record of a mongol birth in this rapidly growing industrial town In 1952, however, 4 of the 6 mongol births recorded in the county took place in or near Corby (fig 5)

In February a mongol was born in Corby itself (population 18,050, with 449 births in 1952) Two months later a mongol was born in Great Oakley (population 272, with about 5 births a year) In November a full-term mongol was stillborn at Brigstock. Seven weeks later another full-term mongol was born in the same village (population 1098, with about 17 births a year) The only 2 mongol births recorded in Brigstock during the twelve years 1944–55 were within seven weeks of each other In July, 1953, a second mongol was born in Corby

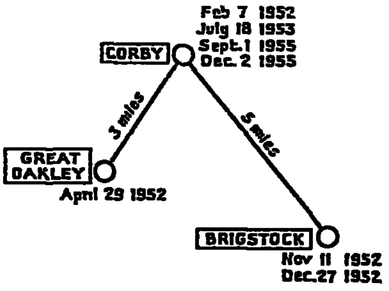

Fig 5—Mongol births in Corby area

In 1955 7 mongols are known to have been born in the county 2 were born in Corby within three months of each other

Urban and Rural Areas

The incidence of mongol births during the twelve years was not greater in towns than in the countryside, but the grouping is seen chiefly in the rural areas, where epidemiological patterns are always more distinct

Congenital Disease of the Heart

Incidence

From the sources already set out, the incidence of congenital heart-disease was assessed (table I) Of the 156 cases ascertained, 81 were obtained from the consultant pædiatricians, 5 from the school medical officers, and 70 from death certificates

The latter source is open to the criticism that, where necropsy was not performed, some cases of asphyxia livida and asphyxia pallida may have been diagnosed as congenital disease of the heart Nevertheless it is worth recording that the information thus obtained indicates the incidence of heart defect to vary from 1 per 243 live and still births in 1949, to 1 per 464 in 1946, the incidence over the twelve years under review being 1 per 338 live and still births (0 29%) This compares with an incidence of 0 24% in the obstetric units of University College Hospital and Queen Charlotte s Hospital, 1947–51 (Penrose 1955) failure to recognise early clinical evidence [illegible]ns of pregnancy and failure to give adequate exchange [illegible] the remaining 11

Attention is called to the fact [illegible]ere was no unusual con[illegible] hæmolytic disease of the new[illegible] areas As in mongolism, the large number of hospital[illegible]ion of the births suggests in some of cases seen is ver[illegible] for the staff [illegible] familiarit[illegible] It[illegible]

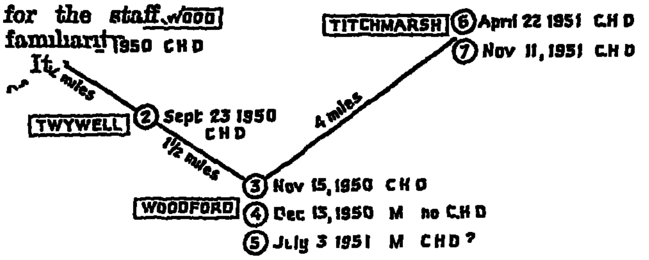

Fig 6—Births in Woodford area C H D = congenital heart-disease, M = mongol

places an infectious process Thus, of the 26 patients known to have been born in 1950–51, 5 were born in the Woodford area (fig 6) No others were born in these villages during the twelve years under review There was no known relationship between these cases

In 1951 (Census 1954) the populations (and annual births) were Grafton Underwood, 340 (about 5), Twywell, 339 (about 5), Woodford, 1435 (about 22), Titchmarsh, 538 (about 8)

Association Between Mongolism and Congenital Heart-disease

The geographical distribution of births of babies with mongolism and of babies with congenital heart disease sometimes suggests a common ætiological factor, since on occasions both conditions arise in the same area at about the same time (figs 6 and 8) Moreover, the incidence of congenital disease of the heart is high in mongols, and the pedigree of one family suggests a hereditary predisposition to both abnormalities in the same family

Hare-lip and Cleft Palate

Incidence

With these abnormalities, the incidence can be assessed with perhaps greater accuracy, for the diagnosis is obvious In the present survey, the cases ascertained give an incidence of 1 in 635 live and still births (table I) which is comparable with previous assessments cited in the literature The highest incidence was in 1950 (1 in 340 live and still births), and the lowest in 1947 (1 in 2506) Thus it varied considerably from year to year There was no unusual concentration of cases in urban areas

Geographical Distribution of Births

In 73 out of 83 cases it was possible to ascertain that the mother had lived in the area from the time of conception throughout her pregnancy The distribution of the births at times suggests an infectious process (fig 7), though this tendency seems less than with the other abnormalities There was no known relationship between any of the families affected in the Woodford Halse and Brackley areas

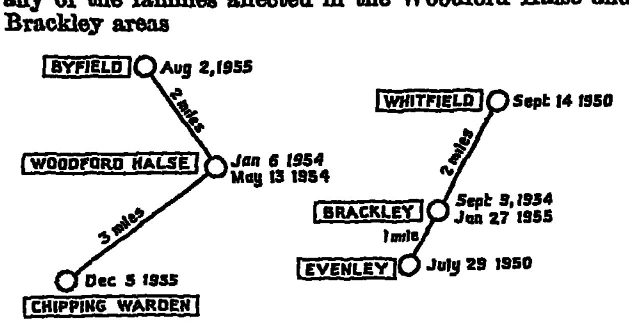

Fig 7—Births of children with hare-lip and cleft palate in two areas

In 1951 (Census 1954) the populations (and annual births) were Byfield, 796 (about 12), Woodford Halse, 1764 (about 27), Chipping Warden, 701 (about 11), Whitfield, 133 (about 2), Brackley, 2531 (about 38), Evenley, 382 (about 6)

No other cases of hare lip and cleft palate are known to have been conceived and born in these villages in 1944–55 In Brackley the years of births of infants with hare lip and cleft palate are the same as the years of births of mongols (figs 7 and 8)

Although this survey is restricted to 1944–55, it is worth recording that in Corby in 1955 and 1956, 8 babies were born with hare lip and cleft palate (i e, 1 per 170 live and still births), whereas in 1944–54 only 6 cases were ascertained (i e, 1 per 689) The months of birth in 1955 were May, July, and August, in 1956 4 of the 5 patients were born in the last six weeks of the year In November and December, 1956, 1 baby out of every 30 born in Corby had a hare-lip and cleft palate

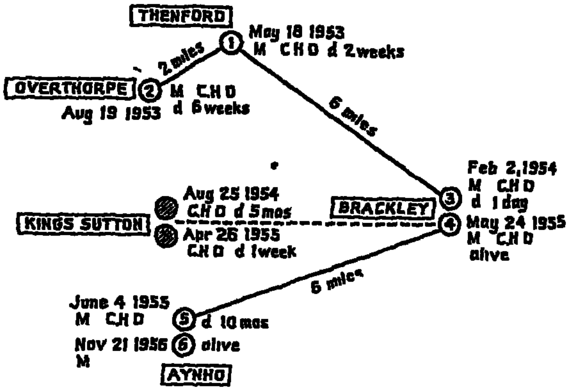

Fig 8—Births in Brackley area of infants with mongolism (M), congenital heart-disease (C H D), or both, showing age at death d = died.

Congenital Abnormalities of the Central Nervous System

Incidence

My figures for these abnormalities may well be incomplete since an analysis of all the causes of stillbirths could not be made It appears, however, that the geographical incidence varies considerably, and that anencephaly and spina bifida are subject to secular changes (Record and McKeown 1949) The incidence of central nervous system abnormalities (0 32%), compares with an incidence of 0 36% in University College Hospital and Queen Charlotte's Hospital, 1947–51 (Penrose 1955)

Geographical Distribution of Births

Only 46 anencephalic births were recorded, and it would be unwise to draw conclusions from so small a number Nevertheless it is worth reporting that the cases seem to be related to the density of population Thus the incidence in the urban areas is about double that in the rural areas, the incidence in the industrial belt is three times that in the rest of the county Most cases in rural areas arise not far distant from towns A similar distribution of hydrocephalic births is noted also, though the numbers are even more limited the urban incidence is nearly three times the rural incidence In contrast to the distribution of anencephalic and hydrocephalic births, there is no concentration in urban areas of babies born with spina bifida

When the anencephalic births are considered in more detail they are seen to occur in groups, as noted by P Del-Vesco as long ago as 1859 This grouping is less evident in cases of spina bifida and hydrocephalus, though in places the abnormalities seem to be associated

In 1954 there were 5 anencephalic births recorded in the county all of them were in Kettering—an incidence of about 1% of the live and still births in that borough

The dates of these births were April 16, May 16, Sept. 3, Sept. 5, Dec. 25. Of the other years in the period 1944–55, there were 2 anencephalic births in 1944, 2 in 1947, 1 in 1952, and none in any other year.

Loddington (population 315, with about 5 births a year). —The only congenital abnormalities recorded in this village over the past thirteen years are 2 cases of anencephaly. The infants were born in April and September, 1950; there was no known relationship between the families. (In 1950 6 cases of anencephaly were recorded in the county.)

Bozeat (population 1088, with about 17 births a year). —The only congenital abnormalities recorded are 1 case of spina bifida and 1 of anencephaly. Both were born at full term on the same day—Feb. 23, 1947. There is no known relationship between the families. (In 1947 6 cases of anencephaly and 10 of spina bifida were recorded in the county.)

Cransley (population 314, with 10 births in 1952 and 1953).—Only 2 cases of congenital abnormality are recorded in this village, but a mother who lived there until three weeks before her confinement gave birth to a baby with hare-lip and cleft palate. There is no known relationship between the families. The dates of birth were May 14, 1952 (anencephaly), June 29, 1952 (hare-lip and cleft palate), and Sept. 24, 1953 (anencephaly). Thus 3 of the 11 mothers living in Cransley during their pregnancies in 1952 and 1953 gave birth to abnormal babies. (In both 1952 and 1953 6 cases of anencephaly were recorded in the county.)

Wootton (population 1115, with about 18 births a year).—The only recorded cases of congenital abnormalities of the central nervous system in this parish are anencephaly on March 6, 1953 (this mother moved in at the seventh to eighth week of pregnancy); of spina bifida and hydrocephalus on Nov. 14, 1953; and of spina bifida and hydrocephalus on Feb. 3, 1954. (In 1953 6 cases of anencephaly and 5 of spina bifida were recorded in the county. In 1954 8 cases of spina bifida were recorded.)

Orthopædic Congenital Abnormalities

A complete survey was not undertaken of the incidence and distribution of talipes and congenital dislocation of the hip. The data obtained, however, in the present inquiry suggest an unusual distribution of births in these abnormalities also.

Association of Abnormal Births with Infections

The events recorded here could be due to chance; but on the face of it they suggest that some environmental factor induces congenital abnormalities—a factor which does not remain constant in any locality but is subject to variation. This environmental factor might be infection.

From a study of the epidemiological patterns of the notifiable infectious diseases in 1944–55, it seems that the distribution of mongol births has a closer association with scarlet fever than with any other infection. Most of the virus infections, however, are not notifiable, and the only epidemiological records relating to them are those provided in reports from head teachers of local-authority schools, who are asked to notify all such illnesses. These records are available only since 1951 and, though of very limited value, they too suggest that mongol births are more closely associated with scarlet fever than with other infectious diseases. In the first six year period both conditions were commoner in the north of the county than in the south, whereas in the second six years both were commoner in the south.

Seasonal Incidence

The seasonal incidence of births of babies with congenital heart disease has been described by Polani and Campbell (1954–55). McKeown and Record (1951) noted a seasonal variation of anencephalic births. My survey does not show any unusual seasonal distribution of conceptions or births of babies with hare lip and cleft palate. Classification of mongol births in individual months of the year is unsatisfactory since a considerable proportion are born prematurely; thus of the present series of 86 mongol births, judging by the information given by the mothers and by the records, 24 were premature, while 6 were overdue. From these data the *expected* dates of confinement were calculated and compared with the incidence of live births both in Northamptonshire and in England and Wales.

TABLE II—MONGOL DEVELOPMENT RELATED TO INCIDENCE OF SCARLET FEVER

—	Quarter			
	1st	2nd	3rd	4th
No. of mongol babies conceived (Northamptonshire, 1944–55)	22 (*26%*)	14 (*16%*)	23 (*27%*)	27 (*31%*)
No. of mongols 1 month after conception	22 (*26%*)	18 (*21%*)	16 (*19%*)	30 (*35%*)
No. of mongols 2 months after conception	31 (*36%*)	18 (*21%*)	14 (*16%*)	23 (*27%*)
No. of cases of scarlet fever (Northamptonshire, 1944–55)	384 (*28%*)	275 (*20%*)	271 (*19%*)	461 (*33%*)

Although the monthly figures of expected mongol confinements are small and subject to wide variation, it is noteworthy that the maximum incidence (approximately 40% of the total) was in the three months August, September, and October, when the national and county incidence of live and still births is steadily falling.

The ætiological factor responsible for mongolism is thought to operate within two months of conception. From the available data we can calculate the monthly and quarterly incidence of conceptions of mongol babies in Northamptonshire during the years under review. Unfortunately there is no information about the monthly incidence of notifiable diseases, but the figures for each quarter during the same period are known (returns to Registrar-General 1947–55). To compare the two sets of data, therefore, the conceptions were estimated on a quarterly basis. A comparison of the quarterly incidence of conceptions of mongols with that of notifiable infections shows a closer association with scarlet fever than with the other infections (table II).

Infant Mortality in Mongols

Of the 84 mongols born alive in 1944–55, 21 died in the first year of life—an infant-mortality rate of about 25%. It may be that the present survey is incomplete, particularly in the earlier years, in respect of mongols who died or moved out of the county in the first few months of life, and that the true incidence of mongol births and infant deaths is higher than the figures quoted. Nevertheless it is worth noting that in the first nine years of the survey (1944–52), 58 mongols were born, of whom 10 died in infancy including 1 in the neonatal period; whereas in the two years 1953 and 1954, 21 mongols were born, with 9 infant deaths including 4 neonatal deaths. In the last year, 1955, 2 of the 7 mongols born died in infancy.

If mongol births were not associated with an infectious process, one would expect an even distribution of such births in time and space and a progressive decrease in the number of infant deaths among mongols because of medical advances and economic improvement. If, however, mongol births were associated with an infectious process, one would expect variations in the incidence of the births, and fluctuations in the infant-mortality rate in relation to the severity of the infection. The incidence and distribution of mongol births and deaths in Northamptonshire support the hypothesis of infection.

The distribution of mongol deaths in the Brackley area deserves special mention (fig. 8). Of the 5 mongols born in this area in 1944–55, the 1st (born in May, 1953, in

Thenford) died after two weeks, from peripheral gangrene and coarctation of the aorta. The 2nd, born three months later only two miles away, died after six weeks from heart-failure due to congenital heart-disease. The 3rd, born in Brackley in February, 1954, died after one day and was found to have a patent interventricular septum. The 4th, born in May, 1955, in Brackley, was the only one to survive, and she is also thought to have a patent interventricular septum. The 5th, born two weeks after the 4th in Aynho, died after ten months from heart-failure due to a patent interventricular septum. The causes of death were verified at necropsy in all cases. It is also worth noting that 2 babies with congenital heart-disease who were not mongols were born in this area (at King's Sutton) in 1954–55. Both died, one after five months, the other after one week. In both cases the diagnosis was confirmed by autopsy.

In the present survey, records indicated that 14 out of 38 mongols appeared to have a heart defect—an incidence of more than 1 in 3. In the Brackley area however, all 5 mongols had cardiac defects—in 3 of such severity that they died in a few weeks; the 4th died within a year, and the 5th has a severe cardiac defect. (Clinical examination indicates that a mongol born in November, 1956, in this area has no heart defect.) It can be argued that such a concentration of gross heart defects in mongols in one area in a short period can occur by chance; but it is more easily explained by an infection, which was presumably of greater severity than elsewhere, since in no other part of the county is there a similar picture during the years under review. For example, no cardiac defect has been detected in the 6 mongols born in the Oundle area, 5 of whom are known to be alive (the sixth has moved out of the county).

Streptococcal Infections in Pregnancy

If mongolism is associated with a streptococcal infection in pregnancy, either one would expect a history of illness in the mother, or one must postulate that the mode of streptococcal infection is so selective that the fœtus is attacked without any maternal constitutional disturbance.

Attempts to associate a history of maternal illness in pregnancy with the subsequent birth of a mongol have not been convincing. In the present survey, of 35 mothers questioned, 12 gave a history suggestive of streptococcal infection in early pregnancy, but similar findings might well be obtained from a control group.

Lundstrom (1952) showed that the incidence of congenital heart disease was significantly higher in infants whose mothers had been exposed to rubella in the first four months of pregnancy, even when the mothers had previously suffered from rubella and gave no history of illness in pregnancy. Evidently, the fœtus is highly vulnerable during early pregnancy and can be attacked by an infectious organism when there is no sign of ill-health in the mother. There is reason to think that this may also happen with transplacental spread of streptococcal infections (De Lee 1916, Curtis 1916, Rosenow 1920, Nickel and Mussey 1927). The affinity of streptococcal toxin for rapidly dividing cells is well known.

Factors Known to be Related to Mongolism

Maternal age.—The fact that the incidence of mongolism is associated with maternal age does not exclude an infectious process. Acute rheumatism, and subacute bacterial endocarditis (Hobson and Juel-Jensen 1956), both of which are thought to be associated with streptococcal infections, have a higher incidence in certain age groups. A mother who is beginning or approaching the end of her childbearing period may be more subject to viral or bacterial attack than a young healthy woman. Moreover, dental sepsis is probably more common among mothers in the older age-groups.

Familial incidence.—The familial diathesis or predisposition of certain mothers to give birth to mongols or to babies with other abnormalities is compatible with an infectious process (cf. acute rheumatism). Turpin and Lejeune (1953) have reported the case of a girl who had acute rheumatism in adolescence and later gave birth to 5 mongols.

Social class.—The incidence of mongol births in the present survey appears to be higher among poorer persons. The incidence of infections is known to be higher among the poorer classes.

Discussion

Although it has been established that rubella plays an important part in the ætiology of congenital abnormalities, attempts to associate congenital abnormalities with other infections have been disappointing. The survey by Lundstrom (1952), however, indicated that the degree of immunity which will protect an expectant mother from overt illness is not necessarily sufficient to protect the fœtus. The epidemiological evidence in the present survey suggests that some abnormalities are the result of an infectious process; indeed sometimes its path can almost be traced in retrospect, through the community.

A survey of this kind can produce circumstantial evidence of the causal rôle of infections where clinical inquiry fails to elicit a history of illness or contact with illness. I cannot claim statistical significance for my data; but this is hardly surprising when one considers that not only can one infection, rubella, produce a number of different abnormalities, but also that one abnormality can probably be produced by a number of different factors. In addition, sex, heredity, and the critical time of attack are known to play their parts in determining the nature of the abnormality; their effects overlap the effects of infection, and the picture will often be confused and destroyed. Nevertheless it seems desirable that inquiries and surveys in other areas should be made.

It would be unwise on epidemiological evidence alone to try to establish which infection or infections are responsible for individual abnormalities. In the past attention has been concentrated on the virus infections, but there appears to be no reason to exclude bacterial agents. Congenital toxoplasmosis and congenital syphilis indicate that the placenta is no barrier to organisms; and some of them may act on the fœtus through exotoxins rather than by direct bacterial attack. The selective and toxic action of certain strains of streptococci on the fœtus, and the rôle of these bacteria in producing congenital abnormalities, may be greater than has been supposed.

The importance of establishing the association between infections and congenital abnormalities lies in the possibility of prevention. At present public health measures can be taken to try to prevent expectant mothers from coming into contact with rubella. Moreover, mothers who are exposed to rubella in early pregnancy can be partially protected with gamma globulin. If the Northamptonshire findings were corroborated, these preventive measures might have to be extended to expectant mothers exposed to other infections, to mothers in the vulnerable age groups, and to mothers who seem to have a hereditary predisposition to congenital abnormalities. Immunisation or chemotherapy as soon as pregnancy is diagnosed might tide both mother and fœtus over the early months of gestation. Perhaps in the future the protection of the individual against infection will start before or soon after conception rather than shortly after birth.

Summary

A survey has been made in Northamptonshire to ascertain the incidence and distribution of births of mongols and babies with certain other congenital abnormalities during the twelve years 1944–55.

Many of these births were geographically aggregated in a way that suggests that they resulted from infection

The known facts relating to mongolism and some other congenital abnormalities are compatible with an infectious ætiological factor In the present survey the seasonal incidence of mongol births, the severity of defect, and the distribution of deaths of mongol infants suggest that this abnormality is associated with infection of the mother—possibly streptococcal

If the Northamptonshire findings are corroborated, the public-health measures which are now undertaken to try to prevent fœtal abnormalities resulting from rubella infections might usefully be extended to protect the mother and fœtus from other infections

I should like to express my thanks to Dr C M Smith, county medical officer of health, Northamptonshire, for his encouragement in undertaking this survey to Prof L S Penrose for his advice, and to the consultant pædiatricians, surgeons, and obstetricians who let me see their records It also gives me pleasure to express my debt to the doctors who provided me with information in many cases, to the health visitors and district-nurse midwives for their conscientious inquiries on my behalf, and to the staff of the health department and the hospitals for the help they gave me

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TRICUSPID STENOSIS

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TRICUSPID stenosis is not infrequently found at necropsy in cases of rheumatic heart disease (Cooke and White 1941) It is almost always associated with mitral stenosis and often also with aortic valve lesions The presence of mitral stenosis tends to mask some of the signs and symptoms of the tricuspid valve lesions, and the diagnosis may thus be overlooked Bailey and Bolton (1956) explored the tricuspid valve at mitral valvotomy in 98 patients and found significant stenosis in 15, in only 3 of these had the diagnosis been established before operation

Until lately the diagnosis of tricuspid stenosis was of only academic interest Since 1953, however, occasional reports of tricuspid valvotomy have been published Hollman (1956) found details of 18 published cases and added another More recently 4 cases have been reported by Yu et al (1956) and 3 by Doglıotti et al (1956) It is clear that in suitably selected cases the operation is rewarding Tight tricuspid stenosis is extremely disabling, and we must hope that increasing awareness of its existence and its importance will lead to more cases being submitted for surgical correction

Of 400 patients selected for mitral valvotomy in the Royal Victoria Hospital, Belfast, 2 have also had tricuspid valvotomy, a 3rd patient has moderately severe tricuspid stenosis, but operation is not yet indicated In this paper we report these 3 cases and discuss the clinical, hæmodynamic, and surgical aspects of the condition

Case-reports

FIRST CASE

A girl, aged 19, was first seen in October, 1953, complaining of moderate dyspnœa on exertion and palpitation for the previous year She had no orthopnœa or hæmoptysis The jugular venous pressure was raised and there were prominent *a* waves The first sound in the mitral area was slapping in quality, a rumbling diastolic murmur with presystolic accentuation was maximal in the fourth left intercostal space just to the left of the sternum, and there was a blowing early diastolic murmur at Erb's point No murmurs were audible in the aortic area Fluoroscopy showed slight enlargement of the right atrium, there was no increase in pulmonary vascular markings Electrocardiography showed peaked P waves 2–4 mm high in the standard and precordial leads The diagnosis was mitral and tricuspid stenosis

Investigations

Cardiac catheterisation on Nov 17, 1954, showed the following pressures

Site	*Mean pressure (mm Hg)*
Right " pulmonary capillary "	1
Main pulmonary artery (rest)	5
Main pulmonary artery (exercise)	9
Right atrium	$4^1/_2$

The mean pressure in the right atrium equalled that in the pulmonary artery, in the absence of pulmonary stenosis this could be explained only by gross obstruction at the tricuspid valve

A year later (October, 1955) her condition had further deteriorated, she had dyspnœa and anginal pain after walking for a few yards and had frequent palpitation but no orthopnœa or hæmoptysis She felt weak and tired, and menstrual function had ceased The physical signs were unchanged Fluoroscopy showed considerable enlargement of the right atrium, the electrocardiogram (fig 1) was unchanged Femoral arterial blood was slightly desaturated (92%), and the hæmoglobin was 17 5 g per 100 ml

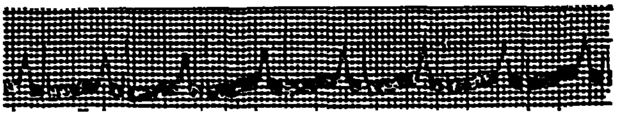

Fig 1—Electrocardiogram (case 1) showing tall peaked P waves in lead II

At cardiac catheterisation the right atrium was found to be grossly enlarged, the catheter repeatedly coiled up, and great difficulty was experienced in passing it through the tricuspid valve Pressures taken with a capacitance manometer and recorded on an Elmqvist four channel recorder (fig 2) provided conclusive evidence of tight tricuspid stenosis, right atrium 17/8 mm Hg (mean 10 mm Hg), right ventricle 15/0 mm Hg (mean 5 mm Hg)

Tricuspid Valvotomy

Mr T B Smiley operated on Feb 7, 1956, using a transverse sternum splitting approach The left atrium was entered through its auricle, and the mitral valve was found to be tightly stenosed, just admitting a finger tip A satisfactory valvotomy was achieved with the knife The right atrium was seen to be enormously enlarged and it too was entered through its auricle An extreme degree of tricuspid stenosis was found, the orifice was only a few millimetres in diameter A very satisfactory split was obtained with the finger No incompetence was noted at either valve before or after operation.

Progress

On return to the ward the patient was deeply cyanosed and cold, her peripheral pulses were impalpable, her blood-pressure was unrecordable, and her respirations were rapid and shallow Her pulse was irregular, with periods of asystole lasting up

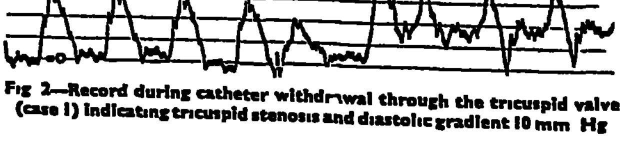

Fig 2—Record during catheter withdrawal through the tricuspid valve (case 1) indicating tricuspid stenosis and diastolic gradient 10 mm Hg

to five seconds Attempts to restore the blood-pressure by intravenous infusion of blood and of *l* noradrenaline were unsuccessful

Two days later she remained drowsy and cyanosed, with respirations rapid and shallow, pulse rapid though regular, blood pressure still unobtainable Triple rhythm was present Further attempts to restore the blood-pressure with *l* noradrenaline and hydrocortisone failed On Feb 11, four days after operation, she became conscious for the first time, with respirations improved, and systolic blood-pressure 90 mm Hg There was slight icterus, and the blood-urea level was 136 mg per 100 ml During the next week she rapidly improved, although the jaundice temporarily deepened The serum-bilirubin reached a peak of 5 9 mg per 100 ml, but other liver-function tests gave normal results The patient was fully ambulant on Feb 18, and was discharged home six days later with no evidence of hepatic or renal damage

Seen again in July, 1956, she was fit for all housework, walked several miles daily, and wanted to resume factory work Her jugular venous pressure was normal The mitral diastolic murmur was faint and no murmur was audible in the tricuspid area, but there were systolic and diastolic aortic murmurs The blood-pressure was 115/80 mm Hg

SECOND CASE

A housewife, aged 35, had uneventful pregnancies in 1946 and 1949 In 1954 she first noted moderate dyspnœa on hills and stairs Two years later she again became pregnant, the exertional dyspnœa steadily increased, and she had attacks of paroxysmal dyspnœa and orthopnœa

When she was admitted on Aug 15, 1956, the cardiac rhythm was regular, the mitral first sound was accentuated, there was a mitral diastolic murmur, and an early diastolic murmur was audible at Erb's point The uterus corresponded in size to a 28 week pregnancy Fluoroscopy showed gross pulmonary congestion, considerable enlargement of the right ventricle and the left atrium, and moderate prominence of the pulmonary trunk Electrocardiography showed evidence of right ventricular hypertrophy

Mitral Valvotomy

She was treated for a fortnight with complete rest in bed, a strictly salt free diet and mersalyl Since little improvement resulted from these measures, mitral valvotomy was performed on Aug 31, by Mr J A W Bingham The lateral commissure was satisfactorily split, and convalescence was uneventful apart from the onset of atrial fibrillation, which was controlled with digitalis

Six weeks after operation the patient was readmitted to hospital and was delivered of a child which was premature but survived During the puerperium the jugular venous pressure was high, the liver edge was palpable 15 cm below the costal margin, and the liver exhibited expansile pulsation A diastolic murmur was heard in the mitral and tricuspid areas and a systolic murmur at the lower end of the sternum

Cardiac catheterisation showed the following pressures

Site	*Mean pressure (mm Hg)*
Right ' pulmonary capillary	20
Main pulmonary artery	24
Right ventricle	14
Right atrium	14

An end diastolic pressure gradient was demonstrated across the tricuspid valve indicating the presence of tricuspid stenosis, and in addition a rise in intra atrial pressure at the time of ventricular systole indicated tricuspid incompetence (fig 3)

Tricuspid Valvotomy

At operation (Mr Bingham) on Nov 19, access to the tricuspid valve was through the wall of the right atrium Moderate stenosis with some incompetence was found The valve was split with the finger so as to make the orifice two or three times as large The amount of incompetence was unaffected

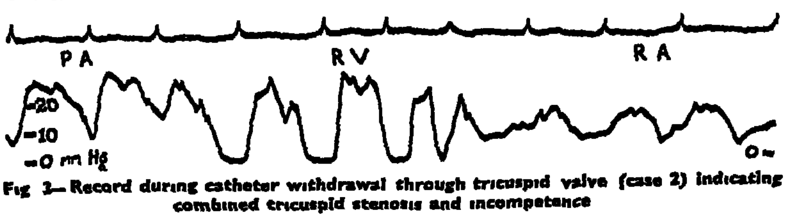

Fig 3—Record during catheter withdrawal through tricuspid valve (case 2) indicating combined tricuspid stenosis and incompetence

Convalescence was uneventful, and at the time of discharge the liver was smaller At review on May 15, 1957, improvement was maintained

THIRD CASE

A woman, aged 27, noted increasing dyspnœa on exertion since a pregnancy in 1949 When first seen in April, 1956, she was very breathless on hills and stairs and unfit for full housework

Her jugular venous pressure was slightly raised, and large *a* waves were seen A slapping first sound and a rumbling diastolic murmur in the mitral area were heard, and an opening snap was audible over the entire precordium The cardiac rhythm was regular Fluoroscopy showed slight increase in vascular markings, considerable enlargement of the right ventricle, and moderate enlargement of both atria Tall peaked P waves were present in the electrocardiogram, there was no evidence of right ventricular hypertrophy Cardiac catheterisation showed the following pressures

Site	*Pressure (mm Hg)*
Pulmonary " capillary " (resting)	(20)
Pulmonary " capillary " (after exercise)	(35)
Pulmonary artery	60/30 (40)
Right ventricle	60/0 (20)
Right atrium	10/5 (6)

(Mean pressures in parentheses)

The degree of pulmonary hypertension was consistent with severe mitral stenosis An end diastolic pressure gradient of 5 mm Hg across the tricuspid valve indicated tricuspid stenosis

Mitral Valvotomy

The mitral orifice was only a few millimetres in diameter A satisfactory split was achieved

Nine months after operation the jugular venous pressure was still raised and large *a* waves were seen A diastolic murmur in the mitral area was less conspicuous, but a diastolic murmur was easily audible over the lower end of the sternum, the opening snap was maximal in intensity in the tricuspid area Repeat cardiac catheterisation showed that the right ventricular systolic pressure was normal and the right atrial pressure was unaltered from that recorded before mitral valvotomy

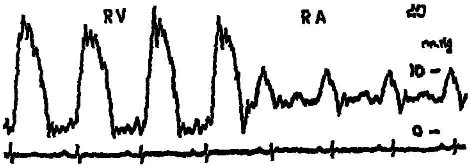

Fig 4—Withdrawal tracing (case 3) showing diastolic gradient of 5 mm Hg and large *a* waves on atrial tracing

Site	*Pressure (mm Hg)*
Right ventricle	17/0 (7)
Right atrium	10/5 (6)

(Mean pressures in parentheses)

Prominent *a* waves were still seen in the atrial pressure tracing, and the end diastolic pressure gradient was unaltered at 5 mm Hg (fig 4)

In view of the absence of symptoms tricuspid valvotomy has been postponed, it may well be required in the near future

Discussion

Symptoms and Signs

Thompson and Levine (1937) have pointed out that tricuspid stenosis resembles constrictive pericarditis in that cardiac filling is seriously impaired There is consequently a raised venous pressure and diminution of cardiac output, the latter causing fatigue and effort intolerance When, as in case 1, the tricuspid stenosis is critically tight, symptoms from the associated mitral lesion—e g, orthopnœa and hæmoptysis—are mild or absent, since the lungs are protected against congestion by the low fixed output from the right ventricle Conversely, when the tricuspid lesion is only moderate (cases 2 and 3), symptoms due to the mitral-valve lesion dominate the clinical picture, and the presence of a significant tricuspid lesion may become obvious only after a successful mitral valvotomy (case 2) Thus in any case of combined mitral and tricuspid stenosis the presenting symptoms depend on the relative severity of the lesions

Tricuspid stenosis raises venous pressure and in cases with sinus rhythm large presystolic *a* waves appear in the jugular venous pulse, these are similar to the giant *a* waves of pulmonary stenosis and pulmonary hypertension and indicate right atrial hypertrophy Presystolic hepatic pulsation may be found and must be distinguished from the systolic hepatic pulsation of predominant tricuspid incompetence In advanced cases the liver may be the seat of cardiac cirrhosis and a bronzed coloration of the head and neck (Altschule and Budnitz 1940) or frank icterus may be noted Characteristically, a rumbling diastolic murmur is heard at the left border of the sternum, but there may be difficulty in distinguishing it from the concomitant mitral diastolic murmur, it is said to be accentuated during inspiration and by turning the patient to the right (Chesterman and Whitaker 1955) The opening snap of the tricuspid valve may be heard (Kossmann 1955) According to Wood (1950) the most striking feature of tricuspid disease is that there may be gross physical signs suggesting right ventricular failure in patients who are practically free from symptoms A successful combined mitral and tricuspid valvotomy may unmask an aortic valvular lesion In case 1 no murmur was audible before operation in the aortic area, although a faint early diastolic murmur was audible at Erb's point After operation systolic and diastolic murmurs were heard in the aortic area although there was no alteration in the pulse pressure The postoperative appearance of these murmurs was clearly due to improvement in the hæmodynamic state, and in particular to augmentation of the left ventricular stroke volume

When tricuspid stenosis is suspected on clinical examination, confirmatory evidence may be obtained from fluoroscopy, electrocardiography, and cardiac catheterisation Fluoroscopy reveals enlargement of the right atrium Enlargement of the left atrium and of the right ventricle is due to the associated mitral lesion, and when the tricuspid stenosis is extreme (case 1) these changes may be disproportionately slight for the degree of mitral obstruction present In patients with sinus rhythm the electrocardiogram shows the peaked P waves of right atrial enlargement (fig 1), evidence of right ventricular hypertrophy is slight or absent

Cardiac Catheterisation

That protection from the hæmodynamic disturbances of mitral stenosis results from concomitant tight tricuspid stenosis is shown by the catheter findings in case 1 Although the mitral stenosis was undoubtedly severe at the initial examination in 1954, the pulmonary vascular pressures were subnormal (pulmonary "capillary" 1 mm Hg, pulmonary artery at rest 5 mm Hg, pulmonary artery during exercise 9 mm Hg) On the second occasion, when there was tight mitral stenosis, the catheter could not be manœuvred into the pulmonary artery, because it was impeded by the tricuspid stenosis however, the right ventricular systolic pressure was only 15 mm Hg (fig 2), and the mean pulmonary artery pressure could therefore not have exceeded 10–12 mm Hg

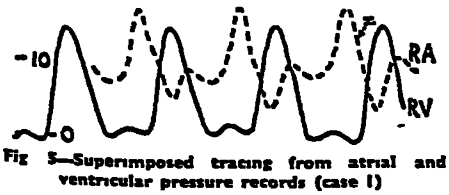

Fig 5—Superimposed tracing from atrial and ventricular pressure records (case 1)

Hæmodynamic changes on both sides of the tricuspid valve can best be studied according to the method of Ferrer et al (1953) by redrawing and superimposing pressure tracings from the atrium and ventricle (fig 5) This method is valid, since in case 1, the cardiac cycle was of constant duration (1 22 sec) in each tracing and there was very little respiratory fluctuation

In the normal heart the right atrial pressure equals the right ventricular end-diastolic pressure However, in case 1 the mean right atrial pressure is 10 mm Hg higher than the ventricular end-diastolic pressure and 5 mm Hg higher than the ventricular mean pressure The composite diagram shows that throughout ventricular diastole there is a constant atrioventricular pressure-gradient of not less than 8 mm Hg At the end of ventricular diastole, when the pressure is 0 mm Hg the corresponding right atrial pressure (Z point) is 12 mm Hg There is delay in the closure of the tricuspid valve with corresponding lengthening of the period of isometric contraction of the right ventricle The giant *a* wave 17 mm in height is caused by powerful contraction of the hypertrophied right atrium There is a rapid transient fall in intra-atrial pressure at the end of atrial systole, this is regarded by Yu et al (1956) among others, as an exaggeration of the X descent following vigorous systole in a distended right atrium No fall occurs in intra-atrial pressure at the opening of the tricuspid valve This provides confirmatory evidence of extreme tricuspid stenosis which prevents sudden discharge of blood into the right ventricle in early diastole

The pressure changes during the cardiac cycle in case 3 are similar but less (fig 4) The *a* wave measured 10 mm Hg and the pressure during atrial diastole is 5 mm Hg Since the ventricular end-diastolic pressure is 0 mm Hg, there is a 5 mm Hg pressure gradient across the valve The absence of any rise in intra-atrial pressure during ventricular systole indicates that there is no significant tricuspid incompetence

In case 2 successive cardiac cycles vary in length, and it is therefore impossible to superimpose tracings from atrium and ventricle The right ventricular pressure (fig 3) is 27/0 mm. Hg (mean 14 mm Hg) Since the atrium is fibrillating, there is no *a* wave However, there is a sustained rise in intra atrial pressure coinciding with ventricular systole, which indicates significant incompetence This is followed by a sudden drop in pressure to 5 mm Hg, corresponding to the opening of the tricuspid valve, and then a gradual rise until the end-diastolic pressure of 8–10 mm Hg is attained The record thus demonstrates combined stenosis and incompetence

Tricuspid Valvotomy

Hollman (1956) points out that incompetence complicates tricuspid stenosis more commonly than mitral stenosis, incompetence was absent in only 2 of the 9 published cases including his own for which information on this point was available Further, the danger of producing incompetence at operation is probably greater than in the case of the mitral valve Bailey (1955) and Chesterman and Whitaker (1955) advise that the anteroseptal commissure should not be divided because it renders the valve mechanically inefficient and may lead to incompetence It may therefore be advisable not to attempt complete relief of the stenosis, an orifice of 4 sq cm or more is probably adequate (Yu et al 1956) Instrumental splitting of the tricuspid valve is usually necessary since it is more leathery in texture than the mitral valve and is rarely calcified

The history of case 1, in which the manifestations of severe mitral stenosis were obscured by tight tricuspid stenosis indicates that mitral obstruction should always be sought and dealt with before tricuspid valvotomy When this is done the chances of pulmonary congestion and œdema due to loss of the 'protective' effect of the tricuspid stenosis will be avoided

The postoperative course of case 1 was complicated by extreme hypotension and hepatorenal failure The cause of the hypotension remains obscure , there had been no technical difficulty, excessive loss of blood, or hypotension during the operation There was no hæmoglobinuria or other evidence of incompatible blood-transfusion The long-continued postoperative hypotension was refractory to blood-transfusion and to intravenous infusion of *l* noradrenaline and hydrocortisone After recovery from the hypotensive state, hepatic and renal function rapidly returned to normal It might be postulated that, because of the preoperative hepatic congestion, unusual hepatic anoxia developed at operation or in the immediate post operative period with resultant excessive production of vasodepressor material

Summary

Tricuspid stenosis is a not infrequent complication of mitral stenosis The clinical features of combined stenosis of the mitral and tricuspid valves depend on the relative severity of the lesions

Three cases of tricuspid stenosis are reported In one the condition became apparent after successful mitral valvotomy In another, tight tricuspid stenosis completely obscured the changes in the lesser circulation expected from the presence of tight mitral stenosis

The clinical and hæmodynamic features of stenosis of the tricuspid valve are discussed

An unusual hypotensive state following combined mitral and tricuspid valvotomy is reported

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RENAL FUNCTION IN PROSTATISM

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OBSTRUCTION to the flow of urine has often been studied in experimental animals, but little is known about its effects on renal function in man The increasing incidence of prostatism in an ageing population provides a convenient opportunity to study this subject, and the development of reliable single-injection methods for the measurement of glomerular filtration-rate (G F R), renal plasma-flow (R P F), and maximal tubular excretory capacity (Tm) has simplified the technical problems involved (Robson et al 1949a and b, Ferguson et al 1950, Olbrich et al 1950a)

Using these methods, Olbrich et al (1950b) studied the effect of age on renal function, and showed that with advancing years G F R , R P F , and Tm were all decreased

We record here some observations of renal function in elderly patients with prostatism in an attempt to assess the effect on the kidney of obstruction to the flow of urine In addition to obstruction a further factor—infection—has had to be taken into account in many of the patients In a few observations have been made before and after prostatectomy

To exclude the effect of hypertension, which itself interferes with renal function in the elderly (Olbrich et al 1950b), we have confined our attention to patients with normal blood-pressures.

Methods

60 men with chronic urinary obstruction due to prostatic enlargement were investigated The average age was 72 (range 58–86) The main symptoms were frequency and difficulty in micturition, and all patients had some prostatic enlargement This was due to benign hyperplasia in 51 and to carcinoma in 9 The diagnosis was confirmed at operation in 34, at cystoscopy in 31, and at necropsy in 3

Three renal functions were studied (1) glomerular filtration-rate, which was measured by the method of inulin clearance (C_{in}) , (2) renal plasma flow, which was estimated by the method of diodone clearance at low concentrations (C_d) , and (3) maximal tubular excretory capacity, which was estimated by the use of diodone in high plasma concentration (Tm_d)

The methods, analytical technique, formulæ, and calculations have been described previously (Olbrich et al 1950c) The urine was collected by catheter to avoid inaccuracies caused by residual urine and incomplete emptying of the bladder All values were reduced to the standard of 1 73 sq m surface area

The renal-function tests were carried out in the early morning after an overnight fast No breakfast was allowed, but the patient was given about half a litre of weak tea before the test, followed by 150 ml of water every half to one hour during the investigation In this way hydration was achieved and the patients were able to maintain a good flow of urine, averaging 3–5 ml a minute

Routine observations in all cases included a bacteriological examination of the urine and a record of the body temperature, blood-pressure, and hæmoglobin, hæmatocrit, plasma protein, and blood-urea levels

Results

The G.F R was successfully estimated in all 60 patients The tests involving diodone, especially in high concentration, were in general well tolerated by the patients, but occasionally they led to considerable falls in blood pressure In spite of this reliable estimates of the R P F was achieved in 55 patients, and of Tm in 44

The urine was not infected in 32 patients and infected in 28 The average age of the uninfected group was 70 (58–81), and of the infected 74 (65–86) The range and average of the hæmoglobin, blood-pressure, plasma-proteins, and blood urea of the patients in these two groups are shown in table I

In normal elderly men G F R , R P F , and Tm were all reduced to about three quarters of the values in normal young adults (table II)

TABLE I—MEN WITH PROSTATIC ENLARGEMENT AVERAGE AND RANGE OF HÆMOGLOBIN, BLOOD-PRESSURE, PLASMA PROTEINS, AND BLOOD UREA

—	No	Hæmoglobin (g per 100 ml)	Blood pressure (mm Hg)	Plasma proteins (g per 100 ml)	Blood urea (mg per 100 ml)
Uninfected	32	11 3 (9 7–14 8)	153/84 (110/80–180/90)	6 9 (6 4–7 7)	50 (21–103)
Infected	28	10 5 (5 2–14 7)	152/87 (120/80–190/100)	6 7 (5 2–8 1)	47 (17–184)

TABLE II—RENAL FUNCTION IN MEN WITH PROSTATIC ENLARGEMENT WITH AND WITHOUT INFECTED URINE, COMPARED WITH NORMAL YOUNG AND AGED MEN

—	Age	G.F.R (ml per min.)				R.P.F (ml per min)				Tm_d (mg I per min.)			
		No	Mean	S D	% normal	No	Mean	S D	% normal	No	Mean	S.D	% normal
Normal young men *	20–39	9	126	16 7	100%	9	535	78	100%	8	41	7 4	100%
Normal aged men *	65–83	9	94	23 6	74%	8	419	133	78%	8	31	5 5	76%
Men with prostatic enlargement (uninfected)	58–81	32	64	23 0	51%	32	275	84	52%	22	32	11 6	78%
Men with prostatic enlargement (infected)	65–86	28	49	20 9	39%	23	219	82	41%	20	18	5 4	44%

* Figures from Olbrich et al (1950b)

In the uninfected prostatic group there was a striking contrast between the tubular function, which was well maintained at levels normal for the aged, and the G.F.R and R.P.F which were reduced to about two-thirds of the levels normal for the aged and to about half those of normal young adults

In the prostatic patients with infected urine, on the other hand, all three functions were diminished to about half of the normal for the aged and to about 40% of the normal for young adults

The differences for all three functions between the infected and the uninfected are statistically significant, especially that for tubular function, which exceeds the 0 1% level of significance

Derived Ratios

C_{in}/C_d—The G.F.R divided by the R.P.F is termed the filtration fraction and indicates the proportion of glomerular filtrate formed from each 100 ml of plasma flowing through the kidney This fraction remained relatively constant at about 25% in the normal subjects, whether young or old, as well as in the patients with prostatism (table III) The slight difference between the infected and the uninfected patients with prostatic enlargement was not statistically significant

C_d/Tm_d—The ratio between the R.P.F and the maximal tubular excretory-capacity for diodone gives a measure of the amount of plasma cleared of diodone per unit of functioning tubular tissue The ratio was slightly smaller in the prostatic patients, especially in the infected group, but none of the differences were statistically significant

C_{in}/Tm_d—The ratio between the G.F.R and the maximal tubular excretory-capacity for diodone gives a measure of the amount of glomerular filtrate per unit of functioning tubular tissue and provides an estimate of tubular efficiency in relation to glomerular activity The ratio was slightly less in the prostatic patients, especially the uninfected ones, but the difference was not statistically significant

Effect of Operation

12 of the patients who were submitted to prostatectomy were re-examined ten to ninety days after operation 10 were uninfected and 2 were infected

The G.F.R. increased in 6, decreased in 5, and was unchanged in 1 patient (table IV) The mean change was an increase of 13% (not statistically significant) The R.P.F, on the other hand, increased in every case save 1 by a highly significant average of 29%

As a result of the increase in R.P.F relative to the G.F.R, the filtration fraction fell after operation from a mean of 30% to 26%

Estimation of the Tm before and after operation was technically satisfactory in only 3 patients In these the excretion of diodone rose from an average of 29 (25, 43, 18) mg iodine per minute to an average of 36 (35, 52, 22) mg iodine per minute—an average increase of 28% (40%, 22%, 22%)

TABLE IV—EFFECT OF PROSTATECTOMY ON GLOMERULAR FILTRATION-RATE AND RENAL PLASMA-FLOW

Case	G.F.R. (ml per min)			R.P.F (ml per min)		
	Before	After *	Change %	Before	After *	Change %
1	126	126	= 0%	240	300	− 30%
2	30	60	−100%	157	274	− 75%
3	24	27	− 12%	50	100	−100%
4	69	67	− 3%	285	300	+ 5%
5	35	45	− 28%	140	160	− 12%
6	88	84	− 4%	314	331	− 5%
7	60	76	− 27%	224	235	− 5%
8	76	65	− 14%	200	251	−125%
9	89	122	− 37%	375	575	+ 54%
10	60	47	− 21%	243	309	− 32%
11	60	54	− 10%	155	135	− 13%
12	68	70	− 3%	223	268	− 22%
Mean	66	70	− 13%	218	270	− 29%

* Time 13–90 days after operation (mean 57 days) Cases 1–10 uninfected, 11 and 12 infected

Discussion

Our results show that in the elderly prostatic patient, chronic obstruction to the flow of urine leads to a reduction in R.P.F and G.F.R which is much greater than that caused by age alone. Tubular function, on the other hand, is unaffected unless the urinary tract becomes infected

These findings are contrary to those of Lich (1942), who has conducted the only previous comparable study of renal function in prostatism In a small series of 6

TABLE III—DERIVED RATIOS IN NORMAL YOUNG AND AGED MEN, AND IN AGED MEN WITH PROSTATIC ENLARGEMENT

—	Age	G.F.R./R.P.F (filtration fraction)			R.P.F /Tm_d			G.F.R /Tm_d		
		No	Mean	S D	No	Mean	S.D	No	Mean	S D
Normal young men *	20–39	9	23 8	2 8	8	13 3	2 4	8	3 2	0 7
Normal aged men *	65–83	8	24 3*	5 4	8	13 3	2 8	8	3 2	0 7
Men with prostatic enlargement (uninfected)	58–81	32	24 5	8 4	22	11 2	4 2	22	2 24	0 66
Men with prostatic enlargement (infected)	65–86	23	26 8	9 0	15	10 4	7 5	20	2 65	0 72

* Figures from Olbrich et al (1950b) S.D = standard deviation.

patients he found that the glomerular function, as judged by inulin clearance, was only slightly reduced, whereas tubular function was much reduced but improved following surgical relief of the obstruction The reason for these differences may lie in the factor of infection, which Lich does not mention, or in the method by which tubular function was estimated, for he used phenol red and we used diodone The reduction of tubular function in the presence of infection is almost certainly due to pyelonephritis This is known to affect the function of the tubules more than any other part of the kidney (Bradley et al 1950, Bodansky and Bodansky 1952, Brod 1956)

In 12 patients, prostatectomy led to a decisive improvement in R P F but had no significant effect on the G F R The filtration fraction was accordingly reduced Successful estimations of tubular function before and after operation were achieved in only 3 of our patients, but in each there was a striking improvement (averaging 28%) This is in line with Lich's results

Our findings have some interesting affinities with experimental results of obstruction to the ureter Selkurt et al (1952) showed that a moderate increase in ureteral pressure to 52 cm of water caused a slight fall in R P F and G F R, but did not affect tubular function, a pattern similar to the findings in our uninfected patients Similarly, Share (1952) found that, in dogs, increasing the pressure in the ureter to 20–30 mm Hg caused a reduction in R P F and G F R The G F R was more affected than the R P F, with a consequent reduction in the filtration fraction In our patients both these functions were affected equally, and the filtration fraction was not significantly changed Unfortunately, Share made no observations on the function of the tubules

The mechanism by which R P F and G F R are reduced in prostatism is a matter for speculation It may be due to a nervous reflex relating urinary output to the pressure in the bladder, for it has been shown experimentally that distension of the bladder leads to a reduced output of urine, even after the ureters have been divided so as to exclude any hydrostatic connection between the bladder and the kidney (Tolls and Dille 1955) It may be due to a decrease in effective filtration-pressure within the lumen of the nephron, a view which looks back to the 19th century and the days of Ludwig and Heidenhain (Winton 1937), or it may be mediated by an effect on the venous system of the kidney An increase in pressure in the ureter is known to increase the intrarenal interstitial pressure (Gottschalk 1950), and this might be expected to compress the venules which lie within the substance of the kidney *It is also known that experimental obstruction of the venous outflow from the kidney leads to a decrease in renal blood flow and glomerular filtration, but has no effect on the function of the tubules (Winton 1931)* Changes of this kind were seen in our patients with chronic obstruction for as long as the urine remained uninfected, and the possibility is also supported by the effect of prostatectomy for an increase in the R P F was the principal postoperative change and there was no significant alteration in the G F R such as might have been expected from a simple fall in effective filtration-pressure

Whether any of these mechanisms in fact operate in the human kidney has not been definitely established and must remain a matter for future research Our findings show only that there is some general correspondence between the effects of experimental obstruction to the flow of urine in laboratory animals and the natural event in man They also go some way to suggest that compression of the renal venules by increased interstitial pressure may be the primary mechanism by which kidney function is diminished in prostatism

Summary

Single-injection methods with inulin and diodone were used to investigate the glomerular filtration-rate, renal plasma flow, and maximal tubular excretory-capacity in 60 elderly men with chronic urinary obstruction due to prostatic enlargement

The glomerular filtration-rate and renal plasma flow were reduced to about half the levels found in normal young adults and to about two-thirds of the levels found in healthy aged men Where the urine was infected these levels were reduced still further

In the absence of infection, tubular function was well maintained at levels normal for healthy aged men, but when the urinary tract became infected tubular function was affected to the same degree as the glomerular filtration-rate and the renal plasma-flow

In 12 patients examined before and after prostatectomy, there was a highly significant increase in the renal plasma flow after operation, but there was no significant change in the glomerular filtration-rate Tubular function was much improved in the only 3 patients for whom technically satisfactory estimations were obtained

These findings are discussed in relation to experimental urinary obstruction in animals Compression of the renal venules by increased interstitial pressure within the kidney with consequent obstruction to the renal plasma flow may be the primary mechanism

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We are grateful for the cooperation of Mr J H Ross and Mr D A Sanford, who performed the operations, and to Mr D J. Newell for statistical advice

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SOME MODIFICATIONS IN PLASTER-OF-PARIS TECHNIQUE

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DURING the years of war, plaster of-paris played a significant part in the management of battle casualties, and lent itself readily to many of the modifications in treatment which were introduced The modifications described below were first developed during the Middle East campaign in response to some of the problems which beset the treatment of fractures at that time They constitute no major departure from normal routine, and were at first regarded as improvisations only In civilian practice, however, they have proved to be of more permanent worth, and publication is now undertaken in the hope that they may continue to be of occasional value

Application

Plaster of-paris casts are normally applied by unrolling wet individual bandages around body or limb, and there is probably no better way of securing a smooth, strong, and snugly fitting cast The method is time consuming, however, and there are occasions when this becomes of more than casual importance. At the end of a long operation the additional twenty minutes' anæsthesia while a thoracobrachial or a hip spica plaster is applied and allowed to set may indeed be vital. This was particularly true in field surgery, where it was imperative to avoid all factors likely to increase the degree of "shock." If, as has been shown, the mere transfer of a gravely wounded man from operating-table to stretcher may cause an immediate fall in blood-pressure, how much more disturbance must follow when such a patient is suddenly seated upright to facilitate the application of a shoulder spica? This upright position dare not be long maintained in a patient whose blood pressure is dangerously low following operation for a severe upper-limb injury, and, it may be, for a penetrating wound of the chest as well.

Of the various methods intended to hasten the application of this type of plaster cast, the "slab" technique is most widely used. In actual practice, however, this technique saves but little time and is difficult to manage single handed. Moreover it offends against the architectural preference for the strong tubular cast of uniform thickness as compared with one of unequal consistency. For the same reasons the "pattern" technique—so well described by Trueta (1944)—is not wholly satisfactory. Tailoring of the individual patterns is in itself a specialised task, and preparation of the patterns beforehand is seldom practicable if an accurate fit for every patient is to be obtained—and an accurate fit is essential in patients who may embark on a lengthy journey, without skilled supervision, within a few hours of injury.

The following technique has proved satisfactory in a considerable number of cases, and it is felt to be a safe and simple method of rapidly completing a plaster cast. By its means a shoulder or hip spica may be applied in a matter of minutes.

Three plaster bandages of the proprietary type are loosely rolled into one (fig. 1), and a stock of both 4-inch and 6-inch sizes is prepared and stored in airtight tins. When required, these composite bandages are well soaked in water and applied in the usual way. Care is taken to smooth each three-layer turn, as it is unrolled, to avoid "onion peeling," and each turn of the bandage is made to overlap the adjacent half of the preceding one. This produces a cast uniformly six layers thick, and any additional thickness which may be desired at points of stress is obtained by overlapping the turns at still closer intervals. In practice, this type of plaster dries rapidly, and cracking of the cast by inadvertent movement is minimised.

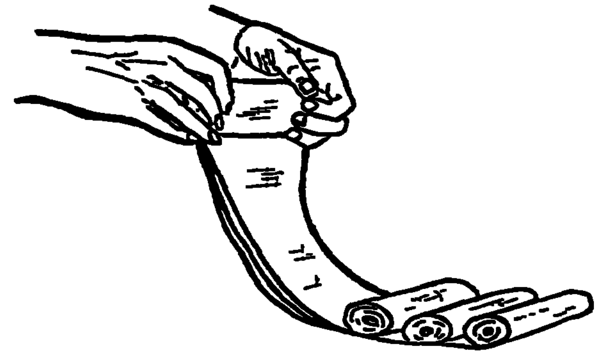

Fig. 1—Three-layer bandaging.

Although the urgency of the field surgical unit no longer obtains, these composite bandages may still be used for the larger types of plaster where speed of application is of advantage. The smoothness of the inner surface of the cast cannot, obviously, be so well controlled as when single bandages are used, and the use of composite bandages for skin-fitting plasters is therefore inadvisable. This need prove no real disadvantage, however, for it is clearly undesirable, in any event, to enclose a recently injured part of the body in a rigid and unyielding case.

Tibial Weight-bearing Plaster

This modification differs from the ordinary type of walking-plaster in so far as the body-weight is borne by the tibial tuberosities—much as in the case of a below-knee amputation—whilst the foot and ankle remain completely free. It was originally devised to relieve the tedium of prolonged recumbency in soldiers who had sustained bilateral fracture of the os calcis after a land-mine explosion and were being treated by non-weight-bearing exercises in bed. Since then it has proved equally effective in the treatment of other injuries of the foot and ankle where direct weight-bearing is contra-indicated.

The value of non-weight-bearing exercises is enhanced by this plaster, and the patient becomes ambulant without danger of direct weight-bearing on the fracture site. Active movements are encouraged as the patient walks, and, since a sock and soft shoe may be worn, the resulting gait often looks surprisingly normal.

Application of the plaster requires more than ordinary care.

A strip of thick adhesive felt, 3 inches wide, is first applied round the limb at the level of the tibial tuberosities, and a similar strip is placed in position just above the malleoli. The area which remains exposed between these two felt strips is protected by a layer of cotton-wool, and a light plaster is then applied. Half an inch of felt is left uncovered at either end, and the plaster is firmly moulded in the region of the tibial tuberosities and over the supramalleolar area. An ordinary Böhler walking-iron is then fixed in position, a clearance of at least 2 inches being left between the patient's heel and the bend of the iron (fig. 2).

In this way a cast is fashioned which is prevented from riding upwards by the cone-shaped tibial tuberosities and from slipping downwards by the flare of the malleoli. When the patient begins to walk, he soon discovers that dorsiflexion of the foot tightens the calf muscles and thus tends to fix the limb more firmly in the cast. Any tendency to foot-drop is thus corrected.

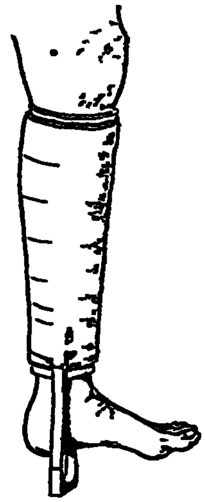

Fig. 2—Tibial weight-bearing plaster.

Some "pistoning" of the limb within the cast is inevitable, but this will be slight if the cast has been carefully moulded. Undue up-and-down movement will produce friction sores, but these may be largely prevented by the use of an aluminium walking-iron in conjunction with as light a cast as possible.

Swelling as a result of dependency has not proved troublesome when this plaster has been used, but gross swelling which has been present before its application has almost always been aggravated. Such swelling should be allowed to subside, therefore, before the plaster is applied. Too much walking is best discouraged at first, since the skin over the head of the tibia requires a little time in which to accustom itself to this unusual means of progression.

Wedging

The expedient of wedging a plaster cast to correct faulty alignment of a fracture has long been practised and is of accepted value. Where the adjustment required is small, wedging provides a means of correction without resort to removal and reapplication of the whole cast with, as often happens, failure to effect improvement in position. When wedging is done by guesswork, the same-

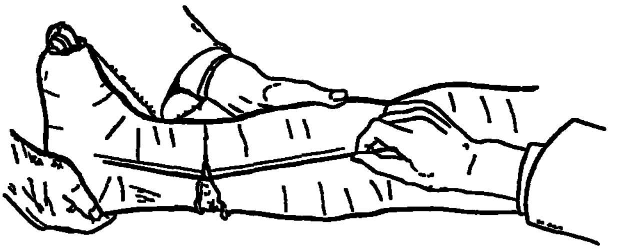

Fig. 3—Wedging.

failure to achieve correction at the first attempt is not unusual. Fluoroscopy provides an accurate means of control in gauging the amount of wedging required, but, apart from the image intensifier, its use is precluded by the danger which exists both to the patient and to the surgeon's hands.

Adjustment of alignment may be found possible at the first attempt in the following way:

A straight line is first pencilled on the appropriate surface of the plaster, and, by reference to the X-ray film, the site of fracture is carefully determined, and its position is marked on the cast. A Kirschner wire is then angulated to conform precisely with the deformity as shown on the X-ray film. The cast is divided transversely at the fracture site for at least half its circumference on the side opposite the angulation. Correction by manipulation is then made in the usual way. While this is being done, the Kirschner wire is held over the cast and manipulation is continued until the straight line previously drawn on the plaster angulates to correspond with the bend of the wire (fig. 3). Full correction should then have been obtained. The wedge is filled with cotton wool, and a plaster bandage is applied to restore the integrity of the cast.

Alternatively the angle of deformity may be drawn on the cast and correction continued until the angle is completely reduced.

When both lateral and anteroposterior angulation are present, the above procedure may be duplicated. It is preferable to cut the plaster transversely and to open the cut into a wedge, which increases the capacity of the cast, rather than to remove and then close a wedge, which reduces the capacity of the cast.

Gross faults in alignment are, of course, unsuitable for correction by wedging, and anæsthesia is best avoided. The manipulation need not be painful, and the conscious patient can give adequate warning if undue pressure is exerted.

Plaster-of-paris and the Thomas Splint

The combination of plaster-of-paris with the Thomas splint has already been well exemplified in the "Tobruk" plaster (Jack 1944), which did so much to ease the evacuation of severely wounded Service personnel. Complete comfort for these patients was not always possible, however, because the rings fitted to the Thomas splints were too big. In the field it was customary to fill the interval between the outer half of the ring and the patient's thigh with shell dressings, which were retained in position by the encircling plaster. When, however, the Thomas splint was used with fixed traction for the definitive treatment of the fractured femur, some more stable form of adjustment became necessary. The efficiency of the Thomas splint depends almost entirely on a well-fitting ring which allows counter-pressure to be maintained against the tuber ischii. Much has been done to discredit this splint by the use of unduly large rings which slip upwards to press in the groin and perineum almost as soon as they are applied. This gives rise to intense discomfort, and the patient's inability to tolerate such splintage can readily be understood.

In the case of the walking calliper, the problem of ring size was solved early in the war by the introduction of the Charnley adjustable splint (Charnley 1947)—an appliance still very much in active service. The same adaptability in the Thomas splint, however, was not at that time available, and as a substitute for a properly fitting ring the following manœuvre was then employed:

A strip of adhesive felt, about 8 × 3 in., is placed on the skin over the anterolateral aspect of the upper thigh, and the ring of the splint is then pulled forwards and outwards until it abuts comfortably against the tuber ischii. While the ring is maintained in this position, and before the extensions have been tightened, the interval between the felt and the ring is filled with wet unrolled plaster-of-paris bandages. These are moulded by lateral pressure until they conform to the outer aspect of the thigh and to the inner surface of the ring. A thin plaster slab is then applied over both ring and bandages to hold the latter in place (fig. 4).

In this way the splint is made to fit the particular limb to which it has been applied, and the patient's comfort is assured.

Subtrochanteric Fracture of Femur

In the management of fractures of the upper femoral shaft, where persistent abduction of the proximal fragment is so often troublesome, the use of a well-fitting ring is essential. Control of this abducted upper fragment is not easy to obtain without operation, but the lower fragment remains under control and can readily be abducted to bring it into line with the upper fragment.

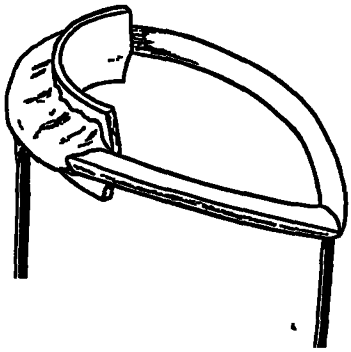

Fig. 4—Modification of Thomas splint.

A well-fitting ring which presses firmly against the tuber ischii and conforms to the contour of the thigh over the rest of its circumference cannot be made to tilt except by a corresponding tilt of the pelvis. If, therefore, the angle between the side-bars of the splint and the ring is decreased, the limb will be abducted accordingly. This alteration of angle can best be achieved by dividing the outer bar of the splint at the level of the fracture and bending the inner bar outwards until the required degree of abduction has been obtained. The splint is then reconstituted by the application of a plaster-of-paris bandage over the cut ends of the outer bar, where they overlap as a result of the altered angle (fig. 5). This procedure virtually amounts to wedging of the Thomas splint and is a less clumsy means of correcting alignment than by widely abducting both splint and limb beyond the edge of the bed. It has the additional advantage of allowing the patient to be transferred without disturbance of the fracture.

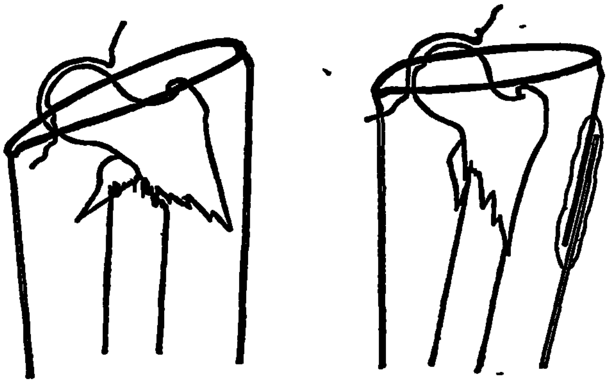

Fig. 5—Subtrochanteric fracture of femur.

Toe Protection

This simple expedient was introduced to counteract the ill effects of badly applied plaster-of-paris platforms which maintained the toes in forced dorsiflexion and thus led to stiffness and, on occasion, to permanent limitation of movement.

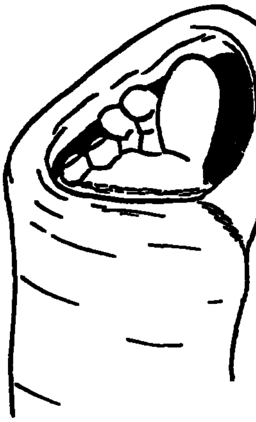

Fig 6—Toe protection

It consists of a loop of plaster (fig 6) which bridges the toes and protects them from the weight of bedclothes and accidental injury. Bed-cradles are seldom practicable when a patient is evacuated by ambulance, nor, in civilian practice, are they always available in the home. The weight of blankets can force the toes into plantar flexion and initiate deformity very easily. With this loop, the toes remain free, and flexion contracture or other deformity has not been noted as a result of its use. The plaster platform, never fully justified, is best reserved for sciatic or peroneal paralysis when active support is really required.

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CAPILLARY THINNING AND HIGH CAPILLARY BLOOD-PRESSURE IN HYPERTENSION

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THE nail bed capillaries have been studied in hypertension by Boas and Mufson (1923) and Brown and Roth (1927). Recently emphasis has shifted to the investigation of conjunctival capillaries. In hypertension Lack et al (1949) described severe thinning of the conjunctival capillaries, and Lee and Holze (1951) published photographs of narrowed conjunctival capillaries.

We have examined the morphology of both conjunctival and nail bed capillaries and capillary pressure in the nail-bed in hypertensive and control patients. The relation of the capillary findings to the cardinal clinical features of hypertension was studied.

Material and Methods

100 outpatients with established diastolic hypertension were studied and followed up for periods varying from one to five years. Excluded from the study were patients in whom the fundus could not be seen because of cataract and corneal opacities. Also excluded from the present report were patients with high systolic pressure but normal diastolic pressure, patients with nephritis, and patients with hypertension complicating diabetes mellitus.

In all the patients attention was paid to presence of proteinuria, changes in the fundus, classified by the method of Keith et al (1939), and symptoms and signs and tests of cardiac and cerebral complications. All the patients with proteinuria underwent microscopy of the urine and relevant blood tests, and also radiography of the kidneys where clinically indicated.

Heart disease was termed severe in the presence of congestive cardiac failure or auricular fibrillation or severe coronary disease or if there was severe cardiac enlargement radiologically or if the electrocardiogram was decidedly pathological. There were 37 such patients.

The cerebral complications noted were gross intellectual deterioration with hypertensive encephalopathy in 2 patients and hemiparesis or hemiparalysis in 5 others.

The nail-bed capillaries were examined at magnifications of 50–150. The bulbar conjunctiva was examined with a slit-lamp at magnifications of 12, 24, and 48. In many patients the nail-bed and conjunctival capillaries were photographed. The diameter of the lumen of the capillaries was measured by using clear photographs incorporating an ocular scale in which the actual distance represented between divisions and the actual width represented by a line between the divisions had been measured.

Thus in the nail bed the width of a line in the ocular scale at 60 × was 4 5 μ, and the distance between the beginning of one line and the beginning of the next was 17 μ.

The corresponding figures for the conjunctiva at 24 × were 6 7 μ and 25 μ. Photographs were enlarged and the capillaries measured against line and division. In the nail bed the "arteriolar" limb of the capillary was measured.

With practice a close estimate of capillary width could be made at the time of examination in terms of width of line and space of ocular scales.

Capillaries were put in two groups according to diameter: one group included normal capillaries with a range of diameter 5–12 μ (fig 1) and moderately thin capillaries with a range of diameter 3 5–5 μ (fig 2), and the second group comprised very thin capillaries with diameters of 2–3 5 μ (fig 3).

Although the methods of measurement are subject to appreciable error, the inaccuracies were not such as to invalidate the range of values given. In view of the natural variation in width of the capillaries the classification was only applied to the conjunctiva and nail-bed as a whole if the findings were characteristic of most of the capillaries seen.

The capillary blood-pressure was taken by the method of Davis (1953), and with practice the method became a routine procedure.

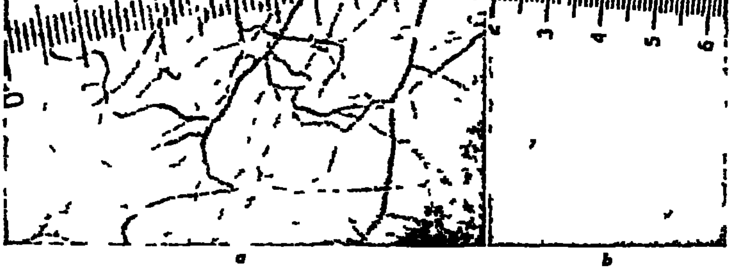

Fig 1—Normal capillaries: *a* conjunctival (smallest vessels in spaces framed by darker venules) (× 12); *b* nail bed (× 40).

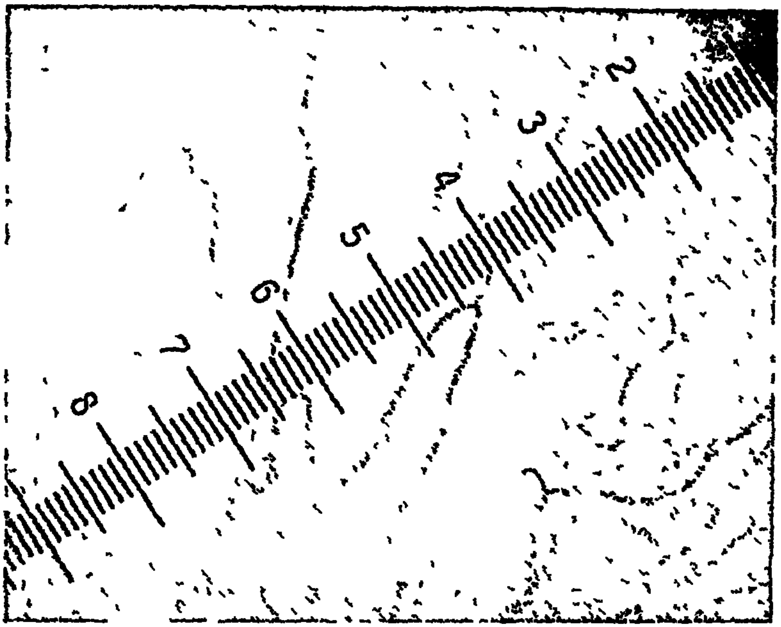

Fig 2—Moderate thinning of conjunctival capillaries in hypertension (× 54)

To estimate capillary pressure the principle of ordinary clinical sphygmomanometry was adapted for the nail bed A manometer cuff made for the newborn infant's arm was attached to an ordinary sphygmomanometer and fastened round the second phalanx and distal interphalangeal joint of the finger The nail bed capillaries were observed under the microscope The pressure in the cuff was quickly raised until all visible capillary blood flow stopped The pressure was then reduced until normal flow reappeared in several capillaries This pressure was taken as the capillary pressure

Capillary pressure less than 45 mm Hg was considered normal (45 cases), pressure 45 mm Hg or more was considered high (55 cases)

Of the 100 patients 28 were males and 72 females There were 65 patients aged less than 60, and 35 aged 60 or more

Results

The capillary blood pressure and the diameter of the lumen of the capillaries were not related to the sex or age of our patients The findings are set out in tables I–III, and the main statistical assessments in table IV

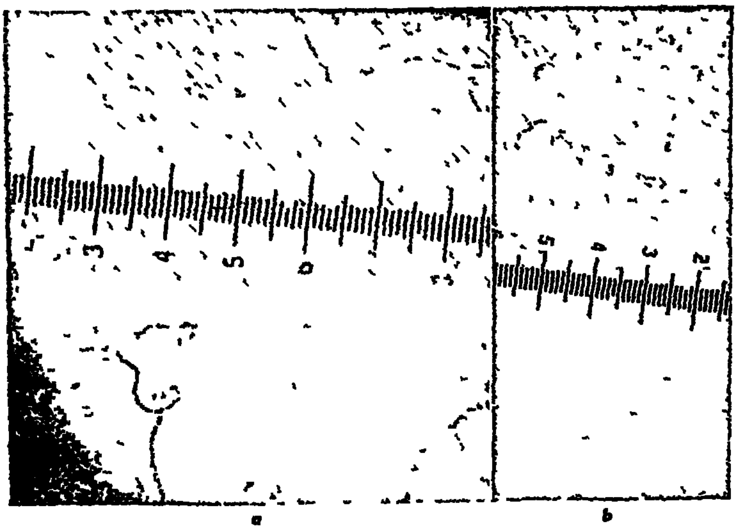

Fig 3—Severe hypertension *a* conjunctival capillaries are less than 3 μ in diameter and invisible in photograph, smaller visible vessels being venules and arterioles, also very thin (× 37) *b*, nail-bed capillaries are very thin (× 40)

Fundus (table II)

A normal fundus was not found where the conjunctival capillaries were very thin Grade 4 fundus was not found where the conjunctival capillaries were normal or moderately thin Of the 10 patients with grade 3 or grade-4 fundus 8 had very thin conjunctival capillaries Proteinuria was significantly associated with fundus grades 2, 3, and 4 (coefficient of association 0 58, χ^2++)

Capillary Thinning (table II)

This correlation between severe conjunctival capillary thinning and proteinuria was 0 45, which, though it just failed to be statistically significant, suggests a trend, and possibly in a larger series a significant correlation may be revealed

Severe conjunctival capillary thinning showed a trend of correlation with fundus changes and a positive correlation with high capillary pressure

Severe nail bed capillary thinning had a negative correlation with proteinuria and no correlation with fundus changes but was significantly correlated with severe heart disease (correlation 0 61, χ^2++), high capillary pressure, and severe conjunctival capillary thinning The nail-bed capillaries were very thin in only 16 of 48 patients with very thin conjunctival capillaries

TABLE I—RELATION OF FINDINGS IN HYPERTENSION TO PROTEINURIA

Finding	*No proteinuria or traces only (69 cases)*	Proteinuria (31 cases)
Diastolic pressure (mm Hg)		
Less than 120	50	18
120 or higher	19	13
Fundus		
Normal, stage 1	39	8
Stage 2 3, 4	30	23
Nail bed capillaries		
No or moderate thinning	52	26
Very thin	17	5
Conjunctival capillaries		
No or moderate thinning	41	11
Very thin	28	20
Capillary pressure		
Normal	38	7
High	31	24

However, when severe thinning in the nail bed was found it was mostly associated with severe thinning in the conjunctival capillaries

The lumen of the capillary was assessed in 100 control medical outpatients with conditions unconnected with hypertension Severe capillary thinning was seen in the conjuntiva in 3 and in the nail-bed in 8

Capillary Pressure (table III)

The correlation between high capillary pressure and high diastolic pressure of 120 mm Hg or more was 0 40, which although not statistically significant suggests a trend The incidence of fundus stage 2, 3, 4 was significantly increased in the presence of high capillary pressure As regards fundus 3 and 4, nine out of ten occurred in the presence of high capillary pressure

High capillary pressure was found in 55 of the 100 hypertensives In 69 patients with normal blood-pressure Davis (1953) found 8 with high capillary pressure

High capillary pressure had a significant correlation with proteinuria (0 62, χ^2++), changes in the fundus (stage 2, 3, 4), severe

TABLE II—CAPILLARY THINNING IN CONJUNCTIVA

—	None or moderate (52 cases)	Very thin (48 cases)
Diastolic pressure (mm. Hg)		
Less than 120	38	30
120 or higher	14	18
Fundus		
Normal	6	0
1	23	18
2	21	22
3	2	5
4	0	3
Capillary thinning in nail bed		
None or moderate	46	32
Severe	6	16
Capillary pressure		
Normal	37	8
High	15	40
Heart-disease		
None or moderate	37	26
Severe	15	22
Cerebral arteriopathy	1	6

thinning of nail-bed capillaries, severe thinning of conjunctival capillaries, and severe heart-disease. With the last named the correlation was 0·47, χ^2+.

Severe heart disease complicating hypertension was positively associated with high capillary pressure and severe thinning of nail-bed capillaries. The correlation with the latter was 0·61, χ^2++.

Of the 7 patients with cerebral arteriopathy 6 had severe capillary thinning and high capillary pressure. These figures are too small for statistical significance, but the trend is suggestive.

Discussion

In hypertension Lack et al. (1949) described extensive narrowing of the conjunctival capillaries with tubular thickening of walls and loss of normal distensibility. They claimed that 98% of hypertensives showed significant capillary changes. The severity of the pattern was correlated with the rise in diastolic pressures. Control patients showed minimal changes in 28%, but none showed the hypertensive pattern.

In the conjunctiva of hypertensive patients Lee and Holze (1951) found vasoconstriction of the minute arterioles and metarterioles. They described elongation, looping, and tortuosity of the true capillaries, including the smaller collecting venules.

A guide to the microscopic study of the conjunctiva in health and disease is found in the comprehensive study of Bloch (1956).

In hypertension, particularly with increasing proteinuria, Sieker et al. (1955) found a decreased retinal reactivity to raised oxygen tension in the blood. In the present study proteinuria was significantly associated with high capillary pressure and pathological changes in the fundus and possibly with severe conjunctival capillary thinning. There was correlation between high capillary pressure in the nail-bed and severe thinning of the conjunctival and nail-bed capillaries. Although conjunctival capillaries were more often very thin than were nail-bed capillaries, there was correlation between severe conjunctival capillary thinning and severe nail-bed capillary thinning. Morphologically the conjunctival capillaries are those of a network in a membrane, whereas those of the nail-bed are individual loops seen in their whole length. In rheumatic fever Davis and Landau (1956) have shown that the conjunctival capillaries were a more sensitive index of systemic pathology than those in the nail-bed. Yet high capillary pressure in the nail-bed is closely related to both conjunctival and nail bed severe capillary thinning and to the complications of hypertension.

TABLE III—CAPILLARY PRESSURE

—	Normal (45 cases)	High (55 cases)
Diastolic pressure (mm. Hg)		
Less than 120	35	33
120 or higher	10	22
Fundus		
Normal	6	0
1	23	18
2	15	28
3	1	6
4	0	3
Capillary thinning in nail bed		
None or moderate	42	36
Severe	3	19
Heart-disease		
None or moderate	34	29
Severe	11	26
Cerebral arteriopathy	1	6

The method of measuring capillary pressure described by Davis (1953) has proved useful in this study. Perhaps this method really measures the arteriolar pressure, but the values so obtained in healthy controls were the same as those found by Landis (1930) using the direct method of a microcannula in the capillary. However, since in some of the present patients the capillary pressure was nearly as high as the diastolic pressure, it is possible that precapillary arteriolar pressure was really being measured. Alternatively in certain circumstances the capillary resistance may be so increased as to bring the capillary pressure close to arteriolar pressure. Boas and Mufson (1923), studying capillary pressure in the nail-bed, mentioned this possibility. Our finding that with high capillary pressure the conjunctival capillaries were nearly always very thin may support this view.

TABLE IV—COEFFICIENT OF ASSOCIATION *

—	Diastolic pressure 120 mm. Hg or higher	Fundus 2, 3, 4	Nail bed capillaries <3·5 μ	Conjunctival capillaries <3·5 μ	High capillary pressure
Diastolic pressure 120 mm. Hg or higher		0·85++	−0·005	0·24	0·40
Fundus 2, 3, 4	0·85++		0·04	0·36	0·58++
Nail bed capillaries <3·5 μ	−0·005	0·04		0·59+	0·76++
Conjunctival capillaries <3·5 μ	0·24	0·36	0·59+		0·85++
High capillary pressure	0·40	0·58++	0·76++	0·85++	

++ Significant on χ^2 test at level <P 0·01
+ " χ^2 " <P 0·05
* By Margaret P. Yekutiel.

Of the 7 patients with cerebral arteriopathy 6 had severe capillary thinning and high capillary pressure. Byrom (1954) investigated in rats the pathogenesis of hypertensive encephalopathy. His fig. 14 illustrating diffuse and focal spasm in the smaller arteries, with intense thinning of the terminal arteries, in severe hypertension resembles our findings in the precapillaries and capillaries in severely hypertensive patients.

The evidence submitted here shows that the capillaries are altered in hypertension. High capillary pressure measured in the nail bed is significantly associated with some of the chief complications of hypertension—proteinuria, fundus stage 2, 3, and 4, and severe heart disease—and possibly with cerebral arteriopathy. High capillary pressure is not closely associated with diastolic pressure of 120 mm. Hg or more, although there is evidence of such a trend. Perhaps, once the diastolic pressure has reached 95 mm. Hg and remains persistently high, a further rise in diastolic pressure is not the main factor influencing capillary pressure. High capillary pressure is closely associated with severe capillary thinning. There is evidence, although in the main not statistically significant, that severe conjunctival capillary thinning may be associated with the same complications of hypertension as high capillary pressure.

This study shows the importance of investigating both conjunctival and nail-bed capillaries

Summary

In 100 patients with hypertension and in control patients the capillaries of the nail-bed and conjunctiva were examined by capillary microscopy and with slit-lamp and often photographed

The diameter of the lumen of the capillaries was measured, and the blood pressure in the nail bed capillaries was taken

The range of diameter of normal capillaries was 5 0–12 0 μ, of moderately thin capillaries 3 5–5 0 μ, and of very thin capillaries 2 0–3 5 μ

Very thin nail-bed capillaries were found in 22 and very thin conjunctival capillaries in 48 of the 100 hypertensives In 100 control patients without hypertension very thin capillaries were found in the nail-bed in 3 patients and in the conjunctiva in 3 patients

Capillary blood-pressure less than 45 mm Hg was considered normal Capillary pressure 45 mm Hg or higher was considered high and was found in 55 hypertensives High capillary pressure was not closely correlated with diastolic pressure of 120 mm Hg or higher

High capillary pressure had a significant correlation with proteinuria, changes in the fundus (stages 2, 3, 4), severe nail-bed and conjunctival capillary thinning, and severe heart-disease There was a trend of association with cerebral arteriopathy In 69 patients with normal blood-pressure high capillary pressure was found in 8

Severe conjunctival capillary thinning had a trend of association with proteinuria, changes in the fundus, and cerebral arteriopathy

Severe nail-bed capillary thinning was significantly correlated with severe conjunctival capillary thinning and severe heart disease

Severe capillary thinning was significantly correlated with high capillary pressure

The combined study of both conjunctival and nail-bed capillaries was worth while

Thanks are due to Mr M Ivri for photographs and skilled observations

Note on Statistical Method

MARGARET P YEKUTIEL, D PHIL Oxfd

The coefficient of association, Q, first suggested by Yule (Yule and Kendall 1947), represents a method for measuring the association between two attributes For a fourfold table of the following form

Attribute	Attribute		Total
	B	b	
A	(AB)	(Ab)	(A)
a	(aB)	(ab)	(a)
Total	(B)	(b)	N

the formula for Q is $Q = \frac{(AB)\,(ab) - (Ab)\,(aB)}{(AB)\,(ab) - (Ab)\,(aB)}$

The value of Q ranges from −1 to +1

In the calculation of Q two values only were used for each variable, hence fundus was classified as (a) normal and stage 1, or (b) stage 2, 3, 4, and diastolic pressure as (a) below 120 mm Hg, or (b) 120 mm Hg or above

Q, while it measures the intensity of association between two attributes, does not measure the statistical significance of the association χ^2 tests were therefore made, and those associations which show a significance at the 0 05 and 0 01 levels are indicated in table IV

References at foot of next column

PENICILLIN-RESISTANT STAPHYLOCOCCAL PERICARDITIS

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UNTIL recently the prognosis of staphylococcal septicæmia was very poor, and pericarditis was a formidable complication In a review of suppurative pericarditis, Streider and Sandusky (1941) remarked that the mortality for unoperated patients must approach 100% Since antibiotics were introduced, most acute staphylococcal infections have been cured, but septic pericarditis is still a very serious complication, particularly if the organism is penicillin-resistant

This paper records a case of penicillin-resistant staphylococcal septicæmia with pyopericardium, and discusses the relationship between septic pericarditis and constrictive pericarditis

Results

A man of 49 had a carbuncle on his neck Three weeks later, on April 28, 1955, he was admitted to hospital with general malaise, cough, and hæmoptysis He was very ill with a temperature of 103°F, jaundice, and purpura of both legs There was a discharging carbuncle on his neck, a pustule on his nose, severe cellulitis of the left elbow, and a subcutaneous abscess over the right elbow There were bilateral axillary pleural rubs and coarse crepitations in the right axilla The liver was tender and enlarged three fingers below the costal margin the spleen was tender and palpable There were no cardiac murmurs

A diagnosis of fulminating staphylococcal septicæmia was made, and penicillin ($1^1/_2$ million units 4 hourly) and streptomycin (1 g b d) were given Next day there were many further embolic skin lesions, he complained of headache and blurring of vision and there was neck stiffness on examination

Investigations—Blood culture, sputum culture, and culture of pus from 2 separate subcutaneous abscesses all gave a pure growth of a coagulase positive *Staphylococcus aureus*, resistant to penicillin, but sensitive to erythromycin and oxytetracycline (terramycin) White cell count, 16,500 per c mm (80% polymorphs) Serum bilirubin 3 5 mg per 100 ml Chest radiograph, "patchy pneumonic consolidation both mid zones and in the right lower zone"

On April 30 penicillin and streptomycin were discontinued and erythromycin was begun by mouth (500 mg 6 hourly) Next day he was expectorating foul bloodstained sputum and there were râles in both axillæ A pericardial rub was audible at the cardiac apex and an electrocardiogram (E C G) (fig 1*a*) showed the typical T_2 pattern of pericarditis

On May 6 he was orthopnœic, with striking pulsus paradoxus, increase of cardiac dullness to 1 in to the right of the sternum, and poor quality, rapid heart sounds A radiograph showed a large pericardial effusion and lung *abscesses in the right* middle zone and in the left upper lobe (fig 2*a*)

Pericardial aspiration yielded 300 ml of turbid yellow fluid, on culture this produced a pure growth of *Staph aureus*, resistant to penicillin and sensitive to erythromycin, chlortetracycline (aureomycin), and oxytetracycline Altogether, pericardial aspiration was performed nine times during the succeeding four weeks and staphylococci were grown on each occasion except the last (May 31)

On three occasions 200 mg chlortetracycline was injected into the pericardial sac During this period the patient's

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DR LANDAU, DR DAVIS REFERENCES

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general condition gradually improved Early in June, however, when the heart size had become normal and aspiration impossible, he deteriorated again Sacral œdema and ascites developed and his liver enlarged again to the umbilicus The jugular venous pressure was not raised and there were no basal crepitations Hb 100% (16 g per 100 ml) and serum-proteins 7 g per 100 ml It was considered that constrictive pericarditis was developing at the orifice of the inferior vena cava and possibly also over the right ventricle As he was allergic to mersalyl, acetazolamide ('Diamox ') 250 mg daily was given with a salt-restricted diet He gradually improved again after a stormy three weeks, and improvement continued slowly until he became fit for discharge on Aug 12

Since then fluoroscopy has demonstrated repeatedly that there is virtually no pulsation of the right border of the heart and that pulsation over the left border of the heart is diminished On Sept 20, 1955, a radiograph (fig 2*b*) showed the heart to be of normal size Kymograms (fig 2*c*) confirmed the almost complete absence of visible pulsation over the right cardiac border E C G s (figs 1*b* and *c*) showed negative T_1, T , T_3, T_{AVF}, T_{V_4}, T_{V_6}

On Oct 10, the results of cardiac catheterisation were within normal limits

The patient has since remained well and is now at work as a clerk. He is having no treatment

Discussion

Staphylococcal septicæmia, with or without pericarditis, is usually acute and fulminating and before the advent of antibiotics it was invariably fatal Drainage of the pericardium offered the only hope Shipley and Winslow (1935) stated that " when the pericarditis is an expression of a generalised septic process the field for successful operative intervention seems to be small On the other hand, practically all patients not operated on or treated by aspiration die " With the introduction of antibiotics many cures were reported (Bathurst and Ainsworth 1945, Smith and McHugh 1945, Wise and Shaffer 1945), but since 1949 antibiotic resistance has made staphylococcal infections more difficult to eradicate

In this patient the infecting organism was penicillin-resistant, and erythromycin was used because it is the antibiotic of choice in severe penicillin-resistant infection with pyogenic staphylococci (Martin 1953)

The natural history of healing pyopericardium and its relation to chronic constrictive pericarditis is still uncertain It is widely held that septic pericarditis may give rise in healing to constrictive pericarditis, but the evidence is far from conclusive Paul Wood (1950) states that "it is generally believed that recovery may be followed by constriction but the point is still perhaps uncertain " Pickering (1948) has been unable to find any case report in which a proved septic pericarditis developed constrictive pericarditis in the healed or healing phase Burwell and Flickinger (1935) described a 17-year old negro, with a two-week history of fever and dyspnœa, who presented with tachycardia, venous congestion,

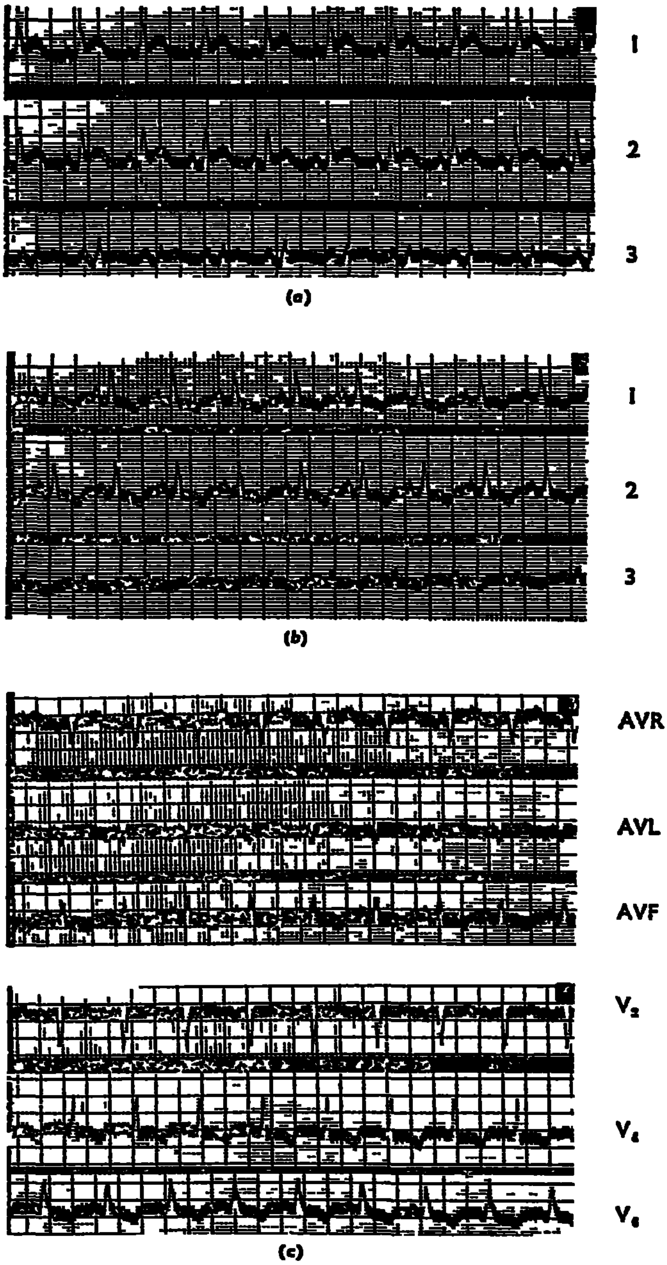

Fig 1—(*a*) Typical T. pattern of pericarditis during acute illness (b) and (c) E E G.s after recovery showing negative T_1, T , T_3, T_{AVF}, T_{V_4}, and T_{V_6}

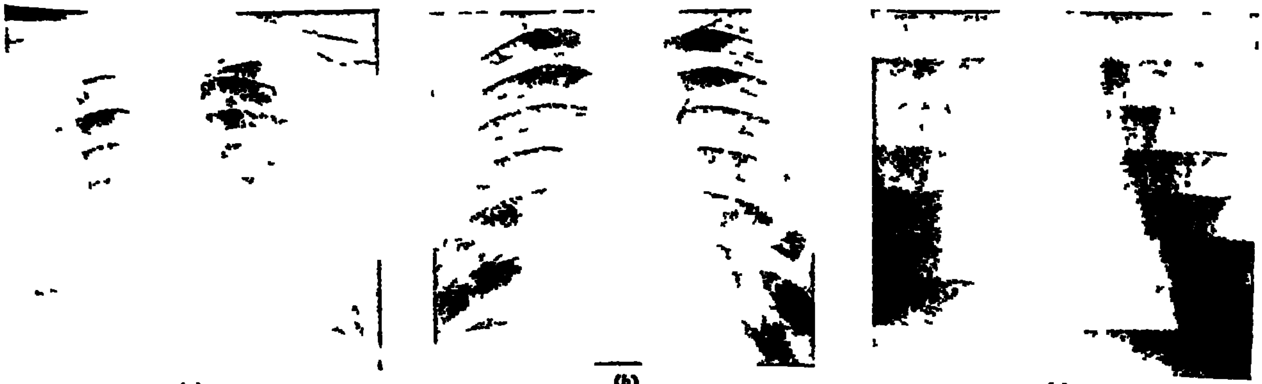

Fig 2—(*a*) Large pericardial effusion and lung abscesses in right middle zone and left upper lobe , (b) normal sized heart 4½ months later but with (c) hardly any pulsation of right cardiac border

dyspnœa, ascites, and bilateral effusions, and in whom fluoroscopy showed a poorly pulsating heart, operation disclosed a pericardium 7 mm thick containing pus from which *Staph aureus* was grown Pickering (1948) remarked that this was not strictly chronic constrictive pericarditis, but rather a septic pericarditis in the late acute or subacute phase The clinical picture and the thickness of the pericardium surely suggest, however, that chronic constrictive pericarditis might well ensue from such a case

More recently, Chambliss et al (1951) believed that out of 61 cases operated on for constrictive pericarditis, 2 had a septic origin, their evidence, however, is very slender. Evans and Jackson (1952) stated categorically that the condition was caused by tuberculosis only I have been unable to find a single case of constrictive pericarditis in the literature up to November, 1956, in which a septic origin was proved

Froment et al (1955) reported 5 cases of septic pericarditis and discussed the natural history Their most interesting case was a true chronic constrictive pericarditis observed for five years and relieved by operation The gross and histological appearances showed no evidence of tuberculosis Five years earlier the patient's symptoms had been preceded by a typical acute osteomyelitis The septic origin of the constrictive pericarditis seems likely, though unproven

In the case recorded here, there is unequivocal evidence of the staphylococcal origin of the pericarditis, of the reduced cardiac pulsation at a time when no fluid was obtainable or demonstrable, and of an episode of obstruction to venous return caused by pericardial constriction That constriction has not recurred means that this case cannot be classed as one of constrictive pericarditis, but further constriction may develop

Summary

Pericarditis developed in a patient with penicillin resistant staphylococcal septicæmia He was cured by oral erythromycin, pericardial aspiration, and intrapericardial chlortetracycline (aureomycin) A subsequent episode was attributed to temporary constrictive pericarditis following healing The relationship between septic pericarditis and constrictive pericarditis is still uncertain.

My thanks are due to Dr H Alstead, deputy physician superintendent of Walton Hospital, Liverpool, under whose care the patient was admitted, for permission to publish this case

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Preliminary Communications

EFFECT OF AN AMINE-OXIDASE INHIBITOR ON ARTERIAL AMMONIUM LEVELS IN LIVER DISEASE

THE main sources of the blood-ammonium are said to be the gut, where bacteria form ammonia from nitrogenous substances, and the kidney[1] It also seemed possible that some of the blood ammonium might be derived from amines through the activity of the widely distributed enzyme, amine oxidase If this were so, then administration of an amine oxidase inhibitor might be expected to lower the blood-ammonium, and this effect might be more easily recognised in subjects with a raised blood ammonium Patients with liver-disease, in whom the blood-ammonium is often increased,[2] [3] were therefore investigated The powerful amine-oxidase inhibitor, iproniazid[4] (isopropyl isonicotinic acid hydrazide, 'Marsilid'), was given intravenously in a dose of 5–10 mg per kg body-weight, to 17 patients with liver disease (see table) The fasting arterial ammonium level cited is the mean of two determinations taken thirty minutes apart, the differences being less than 0 2 μg per ml 8 patients had a raised fasting arterial ammonium level ($>$1 μg per ml) and in all there was a significant fall after the iproniazid sixty minutes ($p<0\ 02$) and ninety minutes ($p<0\ 01$) later 9 patients had a normal arterial-ammonium level ($<$1 μg per ml), in 5 administration of iproniazid was followed by a fall, and in 4 the arterial-ammonium level did not change more than 0 1 μg per ml The mean for the whole group showed no significant change

These observations suggest that some of the ammonium responsible for the increased arterial levels in liver-disease is derived from amine degradation The site of this action remains obscure Cardiac, hepatic vein, and renal-vein catheterisation studies have failed to incriminate the lungs, liver, or kidneys as the main site of this ammonia formation (these results will be published in detail elsewhere) This is not surprising, for amine oxidase is widely distributed in vessel walls,[5] and the inhibitory effect is probably general and not confined to any particular organ Amine oxidase is not present in blood, and the addition of iproniazid to blood in vitro did not alter the blood ammonium value

Some of the changes in hepatic coma have been attributed to ammonium toxicity When this investigation was planned, it was thought that iproniazid, by reducing the blood-ammonium level, might prove useful in treating

EFFECT OF IPRONIAZID (5–10 MG PER KG BODY-WEIGHT INTRAVENOUSLY) ON ARTERIAL AMMONIUM LEVELS IN LIVER DISEASE

Patient	Arterial ammonium (μg per ml)		
	Time after iproniazid (min)		
	0	60	90
1	3 8	3 3	2 7
2	2 3	1 8	2 1
3	2 0	2 0	0 8
4	1 7	1 0	1 0
5	1 2	0 5	0 5
6	1 2	0 8	0 6
7	1 2	0 6	0 1
8	1 0	0 5	0 4
Mean	1 8	1 3	1 1
9	0 9	0 6	0 6
10	0 9	0 8	0 8
11	0 8	0 7	0 7
12	0 8	0 6	0 4
13	0 8	0 1	0 5
14	0 7	0 4	0 6
15	0 7	0 7	0 7
16	0 6	0 4	0 4
17	0 1	0 5	0 4
Mean	0 7	0 6	0 6

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[1] White L P, Phear E A Summerskill, W H J Sherlock, S *J clin Invest* 1955 34, 158

[2] Traeger, H S Gabuzda G J jun, Ballou, A N, Davidson C S *Metabolism*, 1954, 3 99

[3] Phear E A, Sherlock, S Summerskill W H J *Lancet*, 1955, i 836

[4] Zeller E A, Barsky J *Proc Soc exp Biol, N Y* 1952, 81, 459

[5] Blaschko, H *Pharm Rev* 1952, 4, 415

hepatic coma But 1 patient deteriorated into coma on continuous iproniazid therapy In another patient, an electro encephalogram was recorded continuously after administration of iproniazid Initially, the tracing showed the features of impending hepatic coma,[6] and this was unaltered by the drug, though the arterial-ammonium level fell from 3 8 to 2 7 μg per ml At present iproniazid should not be used in the treatment of hepatic coma Circulatory amines may be more toxic to the brain than ammonium, or deterioration may be due to the other unknown metabolic effects of iproniazid

We wish to thank Roche Products Ltd for advice and generous supplies of 'Marsilid,' and the Medical Research Council for financial support

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[6] Foley, J M., Watson, C W, Adams, R D *Trans Amer neurol Ass* 1950, 75, 161

SOMATIC SEGREGATION OF "INAGGLUTINABLE" ERYTHROCYTES

WHEN human blood is treated with an appropriate antiserum (e g, group-A blood with anti-A antiserum) most of the red cells are agglutinated There remains, however, a small proportion of residual cells which do not agglutinate, even after repeated treatment with an avid antiserum The precise nature of these "inagglutinable" residual cells does not seem to have been investigated

I wish to report the results of three preliminary experiments which I have performed on "inagglutinable" human red cells

(1) In group AB blood, most of the cells which are inagglutinable after repeated treatment with a high-titre anti A antiserum can readily be agglutinated with anti B antiserum

(2) The A receptors on the cells do not seem to be blocked by incomplete antibody Neither Coombs anti globulin reagent nor albumin agglutinates these "inagglutinable" cells

(3) Manipulation of agglutinated red cells does not deprive them of their receptors A fivefold increase of mechanical agitation during the first stage of the Ashby technique does not increase the number of residual cells

These findings are compatible with the occurrence of somatic segregation[1 2] in heterozygous AB cells with the production of clones of B cells Further experiments, which I have so far been unable to perform, are needed to show to what extent, if any, somatic segregation is the explanation for "inagglutinable" erythrocytes

It must be shown that

(*a*) In group AB blood most of the cells inagglutinable after repeated treatment with high-titre anti-B antiserum are readily agglutinable with anti A antiserum

(*b*) Homozygous individuals (AA or BB) have far fewer residual cells than heterozygous (AO, AB, or BO) individuals

(*c*) The distribution of residual cell counts on a series of heterozygous individuals shows wild fluctuations from the mean as a result of the variation in the stage of embryonic development at which somatic segregation occurred

(*d*) In a series of group A_1B subjects there is a positive correlation between the residual cell counts after treating separate portions of each individual's blood with anti A and anti-B antisera With perfect antisera the expectation is that the two residual types should appear in equal proportion in any *one* individual

I submit these preliminary observations in the hope that they may be of interest to workers in the field of immunohæmatology who have at hand individuals of known genotype and adequate supplies of appropriate antisera

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1 Stern, C *Genetics* 1936 21, 625
2 Pontecorvo, G Kafer E *Heredity*, 1954, 8, 433

New Inventions

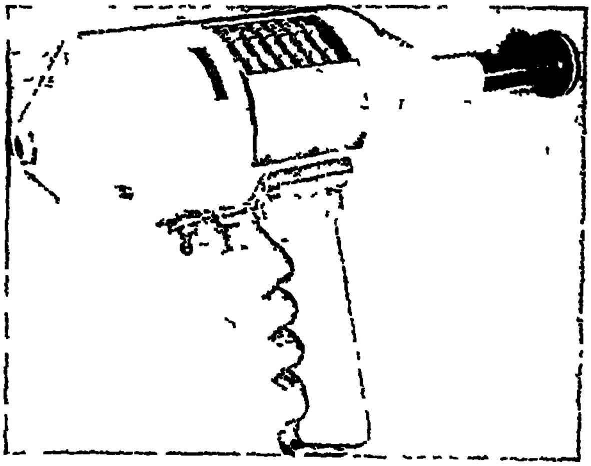
A HAND TINTOMETER FOR RADIOLOGICAL AND DERMATOLOGICAL WORK*

IN radiological work it is often desirable to measure and record radiation reactions of the skin In the past the lack of an exact method of measurement has greatly hindered investigations in this field In dermatology the need of quantitative evaluation of colour changes has long been felt Photometric methods have been tried but are unsatisfactory in that they do not record tone or hue but only intensity of light The instrument here illustrated was developed in collaboration with Messrs G J Chamberlin and F J Heath, Lovibond Tintometer Ltd, Salisbury, to whom we are indebted

In viewing, a circular split field is seen, one segment being the sample under examination and the other a standard white surface, both being illuminated equally with three electric bulbs inside the instrument By means of rotatable discs a graded series of 'Lovibond Glass Standards,' coloured red, yellow, and blue, can be interposed between the source of illumination and the white surface, the combination being adjusted until the two segments are matched in tone and intensity The values of the sample are defined in terms of the amount of each of the three filters required for colour match Provision is also made for insertion of neutral tints over the sample, if this is excessively bright

Practice is required to use the instrument to the best advantage, and it is advisable always to use it under the same conditions of room lighting As colour is a subjective sensation, the same person should make all the measurements in one series of experiments

The advantages of the method are as follows (1) the original tint can be reconstructed at any time, enabling comparison to be made with other samples or with the same sample at a later date, (2) it is possible to convert



the Lovibond values to international units, and (3) the *Lovibond units being known and accepted in most countries, the significance of the values recorded at any centre is not so restricted* as would be the case with other methods

The instrument has been in use in the department of radiotherapy in this hospital for more than three years and has proved very useful in radiobiological and dermatological work and as a research tool

In plastic surgery it has proved to be a boon as it dispenses with the need for repeated attendances for colour matching of patients for whom prostheses (artificial noses or ears) are prepared

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* The instrument was exhibited at the Eighth International Congress of Radiology in Mexico City (July 1956)

Medical Societies

BRITISH ORTHOPÆDIC ASSOCIATION

THE Robert Jones centenary meeting of the association was held at Shrewsbury and Oswestry on May 9–11, under the presidency of Mr PHILIP WILES.

Spinal Fusion for Scoliosis

Mr I W WINCHESTER (Oswestry) had reviewed the results in 66 cases considered suitable for fusion in the past twenty years at Oswestry—7% of the patients seen with scoliosis. Fusion was done to diminish final deformity or hold correction, to stabilise the spine, and to prevent pain. The Risser jacket had now been abandoned for the Abbott method. After fusion, patients spent three to six months lying and a further six months ambulatory in a jacket. 11 cases followed for less that two years were excluded, of the remainder, 33 were idiopathic, 11 congenital, and 11 paralytic. 80% had relapsed, including almost all those where some previous correction of the curve had been obtained. As a proportion of the original curve, the average original correction was 38%, the final maintained correction 14%. Mr Winchester accounted for this relapse rate under four headings: (1) inaccurate measurements, (2) failure to produce adequate compensatory curves (the danger of over compensation was probably theoretical only), (3) subsequent growth, associated with failure to extend the fusion into the compensatory curves, and (4) development of pseudarthroses, although none were detected in this series. He concluded that correction of rotation was a vital factor in preventing relapse, and that the object of plaster correction was to increase the compensatory curves rather than to correct the primary curve.

Posterior Dislocation of the Shoulder

Mr W GISSANE (Birmingham) said that Astley Cooper had described posterior dislocation as easily diagnosed, but in fact it was rare and the diagnosis often missed. Fractures of the humeral head (either a coronal split or a "pond" fracture), from contact with the posterior rim of the glenoid, were common and produced harsh crepitus. Dissection and operation had shown that the glenoid labrum remained intact, the capsule being torn close to it. The dislocation was due to an internal rotation force, the posterior glenoid margin might also be fractured. Subscapularis remained intact. The lesion had been explored through a posterior incision, splitting the posterior third of the deltoid and dividing infraspinatus. Fractures of the head had been wired, the wire lying under the articular cartilage, and the dislocation reduced by external rotation of the arm. The patient could return to work in three months, though full movement might take a further year to recover.

Sir REGINALD WATSON JONES said that the essential point of reduction was external rotation and that the arm must be splinted for three weeks in external rotation to prevent recurrence. Mr GISSANE denied that fixation in external rotation was necessary after open reduction and repair, the shoulder was perfectly stable in a sling.

Epiphyseal Stapling in Knock-knee

Mr A E PRITCHARD (Liverpool) spoke on stapling of the lower femoral epiphysis in idiopathic knock knee. He had studied 26 patients treated by Mr Robert Roaf at Liverpool and by the surgeons of the Robert Jones and Agnes Hunt Orthopædic Hospital. Conservative treatment had failed to benefit these children, who were all 8 years of age or more and almost all overweight. He maintained that surgery was occasionally indicated in this type of patient, and believed that epiphyseal stapling was superior to supracondylar osteotomy because (1) the cosmetic result was better, (2) the period in hospital was shorter, and (3) nursing was much easier. He described the technique and emphasised that no stripping of periosteum was necessary, and that it was probably unnecessary to staple the upper tibial epiphysis as well. Three staples must be used, and should be left in place until there was slight bow leg. It was impossible to predict the time required for correction in each individual: this varied from five to twenty-one months. The results were excellent in 24, 2 relapsed, 1 child was left with some loss of knee movement. After removal of staples there was a sudden growth spurt followed by normal epiphyseal growth. In no instance had this failed to follow. Tribute was paid to Dr Walter Blount, who had pioneered the procedure.

Sir REGINALD WATSON JONES said that in the past twenty years he had never found it necessary to operate for knock knee. Correction always took place within one to three years if Robert Jones's principle was followed, shoes with inner wedges on the crooked heel and sole must be worn constantly—even to the bathroom.

Mr W SAYLE CREER (Salford) denied that wedges always cured knock knee, and thought that the use of a night splint was essential. Stapling operations were liable to leave swollen knees with ugly scars, and he preferred a supracondylar osteotomy when necessary.

Mr ROBERT ROAF (Oswestry) said that all the cases discussed by Mr Pritchard had been deteriorating despite conservative treatment. There was no difficulty in removing the staples as long as they were not buried under the periosteum. He now rarely felt it necessary to staple the tibia also.

Mr H OSMOND CLARKE thought that splints were useless and inflicted psychological trauma on the child. His experience led him to use staples less and less in this condition.

Immunity Factors in Bone Homografts

Mr J CHALMERS reported experiments undertaken to see whether bone homografts participate in a tissue immunity reaction. Bone homografts to a muscle site in rats gave rise to an early phase of new bone formation which was arrested at ten days, the new bone later died. After several weeks, a second phase of new bone growth appeared in relation to the graft. If the rat had been immunised by a skin graft from the same donor, there was no early phase of new bone growth. If the homograft had been killed by freeze drying, the early phase did not occur, but the second phase did in a few instances. It was concluded that the early phase arose from osteogenic cells carried over with the graft, which became the victim of an immune response by the host. The second phase was due to metaplastic induction in the host connective tissue cells.

Further evidence was provided by experiments in which skin homografts were carried out in animals which had been previously grafted by fresh bone homografts from the same donors. The skin grafts were rejected early (at six days). When the bone homograft had previously been treated by freeze drying, subsequent skin homografts survived the normal span of eleven days. This showed that bone contained tissue antigens, and that both bone and skin had antigens in common. These antigens were inactivated by freeze drying.

Bone bank homograft was unlikely to prove inferior clinically to fresh homograft, for neither could contribute living cells. As dead graft did not stimulate immunity, some other process than a tissue immunity reaction must be responsible for the differences in behaviour between bank homograft and fresh autograft.

Dr PAUL CURTISS (Cleveland) held that, since no circulating antibody active against a homograft had been identified, immunisation was not yet proven.

Atlanto-axial Dislocation in Spondylitis

Mr D W PURSER and Dr J SHARP (Manchester) said that, although it was very rarely reported in the literature, they had seen 40 cases of spontaneous atlanto axial dislocation—17 in ankylosing spondylitis and 23 in rheumatoid arthritis. Tetraplegia might follow. The diagnosis depended on flexion extension radiographs, the lateral view revealing the forward shift as well as the angulation of the atlas on flexion which was associated with rupture of the transverse ligament. In ankylosing spondylitis it was usually seen in long standing (and often still active) cases, many with severe spinal flexion deformity and some with signs of cord involvement. The head was tilted forwards with flattening of the angle between neck and occiput. Pain made worse by coughing was a common symptom. Radiotherapy gave no relief. The onset of neurological symptoms might be very sudden, and the presence of lesions in the lower cervical spine might complicate the diagnostic problem. Reduction and fixation by bone grafting from occiput to axis usually led to almost complete recovery. Some patients stabilised spontaneously. In rheumatoid arthritis a painful click was often present on movement, but neurological involvement was much less common. Nerve lesions or severe pain were held to be an absolute indication for operation. Reduction was attained, and maintained during operation, by traction with skull callipers inserted further forwards than usual. Three weeks after operation, plaster was applied, embodying the skull callipers, and maintained until union was sound.

Mr. J. H. ANNAN (Huddersfield) demonstrated radiographs of a similar case with gross displacement when the patient was erect but which reduced spontaneously in dorsal decubitus.

Non-union of Humeral Condyle

Mr. C. C. JEFFERY (Exeter) said that of 13 cases of non-union of the lateral condyle of the humerus, 10 had resulted from minor displacements and 3 had followed open reduction and soft-tissue suture of major displacements. Some cases of initially slight displacement progressed to non-union with increasing deformity, grossly distorted elbows, and sometimes delayed ulnar palsy.

Open reductions should be stabilised by internal fixation with a *stainless-steel screw to maintain exact reposition*; imperfect closed reductions should be critically assessed with a bias towards open reduction and screwing; union must be established unequivocally by radiographs; and where union was delayed or where non-union was established without significant displacement, a hole should be drilled through the portion of diaphysis which had separated along with the displaced epiphysis and on into the humeral diaphysis. The resulting cavity was packed with iliac cancellous bone. This operation had resulted in bony union, minimising deformity, in the 3 cases of non-union which arose under supervision.

Poliomyelitis Vaccination

Prof. C. H. STUART-HARRIS (Sheffield) said that some people had argued against any preliminary clinical trial of poliomyelitis vaccine by analogy with the history of diphtheria immunisation, and on the *grounds that proof of the vaccine's* antigenicity in monkeys was sufficient evidence of its being beneficial, that large-scale experiment on children was morally unjustifiable, and that in any case the American trial would soon produce the evidence required. But after the disaster in the United States the British vaccine was modified and the American results were no longer applicable. Therefore the British vaccine was introduced in such a way that its effect could be measured. An appeal for volunteers yielded 30% of the 6,000,000 children aged 1–9 years. The fact that the vaccine was so scarce enabled controls, as far as possible free from bias, to be obtained from volunteers who could not be inoculated; the giving of an inert inoculation to this group—the ideal method—was not practicable.

All cases of poliomyelitis, both paralytic and non-paralytic, notified within the ages 1–9 were reported to the M.R.C. statistical unit, and for all registered children among them clinical reports were requested three weeks and three to five months later. These reports did not answer the question whether inoculation influenced infection by the virus (i.e., reduced its ability to infect the gut)—a matter to be settled only by laboratory tests. Type-I virus was found in more than 80% of cases, thus providing an adequate field test of the effectiveness of the type-I strain used in the British vaccine. The incidence of immediate local reaction was very low because of the small protein content, and sensitisation to antibiotics was very unlikely. Immunisation to monkey protein was possible, but tests for antibodies arising from the presence of Rh antigen and for nephritis from monkey-kidney material had all proved negative. The exclusion of live virus by stringent safety tests would prevent direct infection; the possibility that latent poliomyelitis in the child might be provoked by the injection was under consideration.

Dr. W. L. M. PERRY said that the virus was incubated in a medium containing a tissue-culture of monkey renal cortical cells; after filtration, the resulting suspension of living virus was treated with formalin for fourteen days.

In the United States disaster with the Cutter vaccine, virus was isolated from about half of the 200 cases of poliomyelitis, and of these isolations all but one were of the type I Mahoney strain. The presence of living virus in the offending batches of vaccine could be demonstrated easily only in tests on cortisone-treated monkeys, most of the tests in tissue-cultures of renal cells proving negative. The monkey tests demonstrated the presence in the vaccine of living virus of all three types. This discrepancy had never been explained, and was the main reason for the rejection of the Mahoney strain of type I for use in the British vaccine. In Britain tests were made both by the makers and by the M.R.C. In each laboratory nearly 2 litres from each batch was cultured and subcultured over a five-week period, and tests were also carried out by intracerebral, intraspinal, and intramuscular injection in both rhesus and cynomolgus monkeys, the latter being more sensitive than the former. Tests for antigenicity were made in monkeys after three injections at weekly intervals, the serum antibody content being estimated by its capacity to neutralise living virus added to tissue-cultures.

Prof. G. W. A. DICK (Belfast) emphasised that type I virus was responsible for most cases of paralysis. The antibodies produced by each type were specific. The object of work with live viruses had been to reproduce the immunity associated with natural infections, with the added advantage that the vaccine could be taken by mouth.

An attenuated type-II virus strain (originally used by Koprowski) was considered suitable because it never produced paralysis when inoculated intracerebrally in monkeys and was non-cytopathogenic. It was tried in 190 children and type-II antibodies developed in 77%. Unfortunately it was found that the virus was excreted by all subjects who developed antibody. Furthermore the excreted virus was cytopathogenic, and caused paralysis in inoculated monkeys. Because of the potential danger of this strain further study of it was abandoned. Experience with a type-I (SM) strain was similar.

There was at present no evidence that three injections of a good Salk-type vaccine produced an immunity inferior to that produced by attenuated strains, and one line of future research should be directed towards developing a purified dead-virus preparation of high antigenicity rather than towards the present types of live-virus vaccines.

Calcinosis Circumscripta

Dr. R. W. BAILEY (Los Angeles) divided calcinosis into two groups: (1) calcinosis circumscripta, usually seen in women and associated with scleroderma, sclerodactyly, and Raynaud's syndrome; and (2) calcinosis universalis, often an affection of children. Abnormal calcium and phosphorus metabolism, local failure of circulation, and some endocrine upset associated with the menopause had all been considered in the ætiology, but without clear-cut evidence. He reported a case in a woman of 63, whose hands and elbows were chiefly affected. She was in slightly positive calcium balance; phosphatase and other laboratory studies were normal. Biopsy showed that fascial planes and muscles were affected with intramuscular collagenous degeneration and thinning of the overlying skin. He had tried the effect of sodium edetate ('Versene') in this patient in the hope that it might bind with the calcium in the deposits and help disrupt them. Although calcium output in the urine was increased, there was no clinical change, nor reduction in the calcium percentage in the ashed deposits. The drug caused auricular fibrillation, which ceased on its withdrawal. He concluded that calcinosis was not a general metabolic disease but a local change. There was no evidence of preferential removal of calcium from the deposits. He postulated that in these cases something was lost from the cells which normally protected them from calcification and thought that future work should aim at further understanding of histochemistry and cell metabolism.

Mr. H. J. SEDDON commented that similar calcification was seen in Volkmann's ischæmic contracture.

Idiopathic Pes Cavus

Mr. J. N. ASTON had reviewed 755 cases of idiopathic pes cavus from hospital records. The information thus obtained was limited, and there was a bias in favour of the severer case, whatever aspect was considered.

Pes cavus did not often present under the age of 5 years, reached a peak between 9 and 13, and then fell off again. Males were affected more often, earlier, and (in the young) more severely, than *females*. This early male preponderance was not seen in the progressive cases, which did not seem to present any younger than the average.

Those with varus of the heel did badly; those with valgus did well. Clawing was the commonest individual feature, and those with either clawing or dropping of the 1st metatarsal head did not do as well as those in whom it was not severe. Forefoot varus and asymmetry between the feet seemed to make no difference to the outcome.

Some relationship seemed probable between pes cavus and spina bifida occulta. A laminar defect was found in 52 of 104 cases radiographed against about 18% in normal people; it did not seem to be associated with a bad prognosis.

Reviews of Books

Essentials of Fluid Balance

D A K BLACK, M D, F R C P, reader in medicine, University of Manchester Oxford Blackwell Scientific Publications 1957 Pp 127 18s 6d

IN less than 100 pages, Dr Black has summarised present knowledge of fluid balance, covering the metabolism of water, sodium, and potassium, and the acid-base balance In a short appendix he discusses some special problems This is concentrated fare, but it demonstrates well how knowledge gained from physiology, medicine, surgery, and therapeutics can be drawn together into an easily comprehensible story No amount of writing can encompass all the clinical problems, and attempts to do so have often been tedious and sometimes misleading This book provides the essential information on which to base decisions about particular problems It should prevent many misconceptions the serious student will enjoy it, and the clinician may well turn to it for help when some larger work has failed him

Dr Black brings out the limitations of treatment, where knowledge is still wanting He does not believe in rule-of-thumb methods, for here, perhaps even more than in other subjects, treatment is a matter of understanding and not of dogma, but in a final short chapter, aptly headed "an approach to treatment," he gives some guidance on how to apply what is known Some readers might have liked to see an example of a workable chart for the day-to-day records on which treatment should be based, but, as is his custom, Dr Black indicates where the information may easily be found, and many people may prefer to devise a chart of their own

The style is concise, forceful, and often witty An occasional ambiguity interrupts the reader's progress in the earlier parts of the book, on the other hand, when he comes to the chapter on potassium he is treated to a masterly presentation There is an up-to-date source of selected references, and the delay between writing and publication has been remarkably short Both students and teachers will be attracted and rewarded by Dr Black's skilful handling of his subject

Connaissance élémentaire du rhumatisme

S DE SEZE and M MAITRE Paris Expansion Scientifique Française 1957 Pp 273 2800 francs

THIS lively and attractive introduction to the rheumatic disorders has been written by Professor de Seze (with the aid of M Maurice Maitre's lucid diagrams) primarily to instruct nurses, physiotherapists, and occupational therapists There is, however, sufficient detail to make it a useful introduction for students and doctors, who would find the many excellently reproduced radiographs and clinical photographs particularly helpful In the section on treatment the emphasis is often different from that usual in this country Thus, sex hormones are given an important place in the treatment of degenerative joint disease, and in rheumatoid arthritis cortisone and its relations are dealt with first and at length, overshadowing the subsequent description of the basic regimen of rest, splinting, and exercises

Surgeon's Journey

J JOHNSTON ABRAHAM London Heinemann 1957 Pp 441 25s

IF any book called loudly for a sequel it was Mr Johnston Abraham's *The Surgeon's Log*, published in 1911, now in its 30th edition, and translated into several tongues This new book tells of his life before and since the casual voyage which gave him quite unexpected fame and our language one of the best of travel books

A boyhood in County Londonderry was followed by professional education at Trinity College, Dublin, in the palmy days of Mahaffy *et al* He reached consulting practice in London by the haphazard and strenuous route usually followed in those days Between 1914 and 1918 he served first in the Serbian army and then in our own in Egypt and Palestine Few accounts of th medical services in war are at once so readable and instructive In the years which followed the war it was his delight to write of his profession Though the laity favour the gripping works of "James Harpole," it is his life of Lettsom which has pleased the author most and given him his considerable repute as a medical historian As a publisher he has done his best to hel other medical authors But with all these distractio his life has centred on his surgical practice and hi hospitals, the Princess Beatrice and the Lock, whos obituary notice he writes with candour and charity

This is the urbane story of a man who has seen the best of life in London, social and professional, and enjoyed every minute of it In his native Coleraine they will be saying, no doubt, that Jamie Abraham is a great crack and a sound medical doctor forbye—and so he is

Left-handedness

Laterality Characteristics and their Educational Implications MARGARET M CLARK, M A, PH D, the Scottish Council for Research in Education. London University of London Press 1957 Pp 212 15s

THIS is an excellent account of a fundamental educational problem—the detection and training of left-handed children Dr Clark gives a brief, but just, review of the literature, a clear picture of the tests for dominant laterality, and a description of her own research Her book will be useful to teachers, educational psychologists, and school medical officers Any doctor who is in the habit of diagnosing "crossed-laterality" as a cause of clinical symptoms should read the book—and he will receive a salutary shock

The Bright Countenance

A Personal Biography of Walter Morley Fletcher MAISIE FLETCHER London Hodder & Stoughton 1957 Pp 351 25s

THIS biography began as a family record Written by Lady Fletcher, it was originally intended for Sir Walter's grandchildren, and, though it has now been made available to the public, the family intimacy of the writing has been retained The text includes long extracts from his letters and other writings on many subjects

The book begins with a delightful short biographical foreword by the late M R James and ends with a 40-page supplement in which Sir Arthur MacNalty describes Fletcher's contributions to physiology and his work for the Medical Research Committee and later for the Medical Research Council A great deal was achieved by these bodies under his wise guidance, but, as Sir Arthur points out, a whole volume would be needed to record the extraordinary progress of those eventful years

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Textbook of Orthopædic Medicine (3rd ed Vol I *Diagnosis of Soft Tissue Lesions* London Cassell 1957 Pp 711 45s)—Anyone who practises orthopædics soon discovers that many of his patients suffer from maladies which are not illustrated in any museum of pathology Their radiographs are normal, their laboratory investigations negative—and their treatment correspondingly difficult Dr *James* Cyriax has provided a guide to this dark hinterland in surgery From its pages the practitioner may learn to diagnose with confidence such conditions as "tennis elbow"—and even to distinguish between at least four distinct varieties of the disease Far from being nonplussed when confronted by a case of acute sciatica, he can now choose his treatment from more than forty thoughtful pages on its management Dr Cyriax is convincing and interesting on such debatable topics, but his excursions into the more familiar field of surgical orthopædics are less successful, and here clarity is sometimes sacrificed to brevity We are sorry to see that Georg Clemens Perthes is again poorly remembered in "Perthé's disease," though Dr Cyriax is by no means the first to add the accent and the apostrophe The volume is clearly based on long and careful thought, and all who undertake to relieve the painful and common conditions Dr Cyriax describes will be glad to have his advice to hand

THE LANCET

LONDON SATURDAY, JUNE 29, 1957

Cigarettes

> "We are constantly deluded by language We say a person dies of a cancer The truth must be that a person dies of the causes of cancer, and the cancer is not the cause, but the mode of dying'—WILLIAM LAMBE 1815[1]

THE evidence that heavy cigarette-smoking causes cancer and hence death has become increasingly difficult to ignore The Medical Research Council's statement set out on p 1345 summarises the facts clearly and concisely, and concludes with the important statement that ' In the opinion of the Council the most reasonable interpretation of this evidence is that the relationship is one of direct cause and effect " This conclusion accords with the view of most who are familiar with the mass of detailed evidence accumulated in the past seven years not least through the careful and convincing studies of Prof A BRADFORD HILL, F R S and Dr RICHARD DOLL The unhurried verdict of an impartial scientific body such as the M R C cannot but command respect and must make every thoughtful person reconsider the criticisms by the Tobacco Manufacturers' Standing Committee[2] This committee discounts the suggestion of cause and effect because it derives from observations rather than from strictly controlled human experimentation on randomly selected population groups and because, so far, no very convincing support has come from the laboratory The limitations of observational data have long been well known to epidemiologists, but should SNOW have waited for the discovery of the cholera vibrio before persuading Londoners not to drink their own sewage ? As the tobacco manufacturers have implied, atmospheric pollution may be a factor in the causation of cancer of the lung, but its incrimination, like the association of genotype and disease, rests equally on observed correlations In the urgent defence of the public health we should base action on the best evidence currently available

Whatever the reaction to the evidence we already have, all will agree that more would be welcome In 1954 the British Tobacco Manufacturers Association gave £250,000 to the Medical Research Council, of which £69,000 had been spent by the end of last October This may seem a comparatively small amount for such an important subject The work of the council is, however increasing, as its latest annual report, published this week, makes clear It has provided, with the help of the fund laboratory facilities and staff (in the University of Exeter) for a new carcinogenic-substances research group and has set up other research groups concerned with atmospheric pollution (at St Bartholomew's Hospital) and with epidemiological research in respiratory diseases (in the University of Sheffield) In addition grants have been made to individuals in universities, hospitals, and elsewhere

It would be unreasonable to expect the people or the Government to take kindly to the idea of reducing cigarette-smoking, for this is both a widespread pleasure and the source of immense State revenue and of an important element in international trade It may reasonably be argued that the citizen should be free to engage in the pleasures he chooses, provided he does not harm others, but all smokers and potential smokers should at least be aware of the extent of the risk in smoking cigarettes heavily, and this information can be conveyed best (and perhaps only) with the Government's help Measures aimed at direct control of smoking, even were this desirable, would have little chance of success No such measure could succeed without the approval of a large majority of the people, and it seems unlikely that approval on this scale would be forthcoming (Almost to a man, the large smoking public has more than once shrugged off indirect control applied through steep rises in the tax on tobacco) Yet the responsibility of Government and people, whether smokers or not, cannot end with subsidising research and publicising hazards it should extend to discouraging young people from taking up the habit of smoking cigarettes A middle-aged cigarette-smoker with a chronic cough may be moved by the fear of cancer to reduce his smoking or give it up, but we cannot expect a young person to be deterred by a risk that is apparently so remote and among adolescents smoking seems in fact to be lamentably common[3,4] Youngsters are unlikely to be influenced so much by lectures, pamphlets, and the advice of adults as by fashion among those to whom they look for an example Smoking is very much a matter of fashion, and if the large loss of life due to cigarettes is to be reduced the fashion, especially among young people, must be changed Such a change (as is clear from the article on p 1348 of this issue) does not necessarily require legislation, and closer study of the social history of tobacco might be rewarding In any event it is doubtful whether tobacco habits can be changed rapidly so long as the reformer's modest voice has to be pitted against the power of modern advertisements, but organisations, such as the British Broadcasting Corporation, that do not depend on advertising revenue could do much to counter commercial propaganda, and the cinema might shape tobacco habits just as it shapes hair styles In addition, fuller use should be made of existing legislation the law against selling tobacco to young people is often administered with the utmost laxity

It would be unrealistic as well as arrogant to suppose that cigarette-smoking can or should be forbidden the aim should rather be to influence the heavy smoker to modify his habit This modification might take two forms first, replacement of the cigarette by the less dangerous pipe or cigar, and, secondly, reduction in the amount of tobacco used The evidence suggests that the temperate cigarette-smoker, who confines himself to, say, one after each meal or to two or three in the evening, runs an appreciably lower risk Two hundred years ago "drunkenness was the acknowledged national vice of Englishmen of all classes"[5] Today, to drink whisky from a hip-flask in a suburban train on the way to work is socially unacceptable Maybe to smoke a cigarette at such a time will in due course also be deemed a social impropriety If so, the community will be the healthier

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[1] Lambe W Additional Reports on the Effects of a Peculiar Regimen in Cases of Cancer Scrofula Consumption, Asthma, and other Chronic Diseases London 1815

[2] Annual report by Tobacco Manufacturers Standing Committee See *Lancet*, June 22 1957, p 1306

[3] Jones A P *Ibid* March 23, 1957, p 631

[4] Raven R W *Ibid* June 1, 1957, p 1139, *Roy Soc Hlth J* 1957 77 250

The Newborn Infant's Oxygen-supply

The newborn infant, deprived of the placental circulation, will die unless by his own efforts he can produce and maintain a higher level of oxygenation than prevailed in the later phases of intra-uterine life The immediate adjustments of post-natal life are directed to this end and are primarily concerned with establishing adequate pulmonary ventilation and ensuring that the brain, rather than the liver, receives the best-oxygenated blood

The fundamental work of Barcroft[6] showed that in pre-natal life the fœtus elaborates the central nervous organisation required for breathing, which normally is inhibited until required for pulmonary respiration Release from inhibition occurs either because of the inflow of new sensory stimuli at birth or by hypoxic depression of the inhibitory centres Acheson et al[7] have extended this work using, like Barcroft, the sheep In a study of oxygen consumption in fœtal and newborn sheep they have shown that there exists a remarkable, but limited, capacity to adjust the oxygen need in relation to the supply In the latter half of pregnancy adequate oxygenation can be maintained only by great increases in umbilical blood-flow If the placenta is insufficient or the compensatory mechanisms in the fœtus fail, the survival of the fœtus depends entirely on its tolerance to anoxia That similar mechanisms operate in human pregnancy seems likely from the work of Walker[8] and Rachel MacKay,[9] who have shown a progressive fall in oxygen saturation of the umbilical-cord blood as pregnancy proceeds to term and, especially, beyond A similar fall is found when pregnancy is complicated by pre-eclamptic toxæmia Some of the clinical facets of placental insufficiency have been discussed by Randall[10]

Placental circulatory failure with decompensation of the fœtus will cause, in severe cases, intra-uterine death Lesser degrees of hypoxia may initiate intra-uterine gasping movements which, if associated with meconium-stained liquor amnii, produce asphyxia and meconium pneumonitis The anoxic infant is born with an inadequate oxygen reserve and a depressed nervous system—two factors which greatly decrease its ability to attain adequate pulmonary ventilation More acute lowering of fœtal oxygenation is found in cases of abnormal delivery, interruptions of placental blood-flow, as in placenta prævia and prolapsed cord, and interference with the oxygen-supply to the placenta by general or spinal anæsthesia Henderson et al[11] point out that, while all these factors produce a measurable lowering of umbilical-vein oxygen saturation, this is not necessarily a good guide to the clinical state of the infant Some infants at birth may survive with extremely low cord-oxygen saturations, whereas others with mildly reduced oxygen saturations are severely asphyxiated This is to be expected in view of the limited value of a single sampling of cord blood and the many traumatic and chemical factors which influence the first hours of a baby's life

After birth the majority of infants rapidly attain a near-adult arterial oxygen saturation[12] Shields and Taylor[13] have shown that infants born after complications of pregnancy, heavy maternal analgesia, or operative delivery are considerably slower in achieving a normal saturation, determined by a continuous recording ear oximeter Further studies on the lines of those reported by Cross et al[14] are needed in order to elucidate the special metabolism of the newborn and its powers of survival in low oxygen levels Possibly other factors are more important than oxygen saturation in determining the clinical condition of the newborn and the eventual prognosis One of the other factors is the circulatory status of the newborn The neonatal circulation plays an important part in producing lung expansion and also ensures preferential oxygenation of the brain Adams and Lind,[15] by cardiac catheterisation, have demonstrated directly the persistence of a patent ductus arteriosus with a predominantly left-to right shunt in the first few days of life Dr Gunther[16] has attempted to relate the complicated circulatory adjustments after birth with the changes in blood-volume consequent on occlusion of the cord and the later development of pulmonary syndrome Early clamping of the cord or elevation of the infant while the cord is still attached to an atonic uterus will deprive the infant of much of his blood-volume This will be of greatest importance in premature babies, who have a relatively larger proportion of blood in the placenta, and in babies delivered by cæsarean section It is just these two classes of infants that are susceptible to pulmonary syndrome or, as it is better known, hyaline membrane disease Brown[17] has already drawn attention to the possible connection between early clamping of the cord and the onset of hyaline membrane disease So far, the arguments for this association are largely theoretical Dr Bonham Carter,[18] summarising recent advances in this field, has ingeniously related the changes immediately after birth with the respiratory difficulties of early neonatal life It should not be difficult to devise a controlled study to demonstrate this relationship It is now generally, although not universally, accepted that hyaline membranes are formed from pulmonary exudate, probably as a result of pulmonary congestion or hypertension[19] Early clamping of the cord might well lead to pulmonary hypertension as the rise in systemic blood-pressure consequent on the increased peripheral resistance will be transmitted via the patent ductus arteriosus to the largely unopened pulmonary vessels It is more difficult to see how the reduced blood-volume consequent upon siphonage would operate Certainly, expansion of the lungs might be delayed, but the picture of hyaline membrane is one of obstructive dyspnœa, emphysema, and secondary collapse rather than of primary atelectasis Nor do infants born exsanguinated from acute blood-loss show clinical or pathological evidence of hyaline membrane

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[5] Trevelyan, G M English Social History London, 1942
[6] Barcroft J Researches on Pre natal Life Oxford, 1946
[7] Acheson, G H, Dawes G S, Mott, J C *J Physiol* 1957, 135 623
[8] Walker, J *J Obstet Gynæc Brit Emp* 1954, 61, 162
[9] MacKay, R B *Ibid*, 1957, 64, 185
[10] Randall, C L *Amer J Obstet Gynec* 1957, 73, 931
[11] Henderson, H, Mosher R, Bittrich N M *Ibid* p 664
[12] Smith C A Kaplan, E *Amer J Dis Child* 1942, 64, 843
[13] Shields L V, Taylor, E S *Amer J Obstet Gynec* 1957, 73, 1011
[14] Cross, K W, Tizard, J P M, Trythall D A H *Acta pædiat, Stockh* 1957 46 265
[15] Adams, F H Lind J *Pediatrics* 1957 19, 431
[16] Gunther M *Lancet* June 22 1957 p 1277
[17] Brown R J K *Ibid* Jan 19, 1957 p 163
[18] Bonham Carter, R E *Ibid*, June 22, 1957 p 1293
[19] Gitlin, D, Craig J M *Pediatrics*, 1956 17, 64

Whatever the truth concerning this hypothesis, it is salutary to review continually the management of the newborn in relation to newly discovered physiological facts The tragedies of retrolental fibroplasia and of kernicterus of prematurity due to excessive dosage with a vitamin-K analogue are stern reminders that we fail to do so at the infant's peril

Second Thoughts on Anticoagulant Treatment for Coronary Disease

JUST over a year ago we reviewed current views on the value of anticoagulant treatment in acute coronary disease [1] and drew attention to the conflict of opinion between those who, like GILCHRIST in Edinburgh and IRVING WRIGHT in New York, believed that every patient should be given the benefit of anticoagulant treatment, and those who, like RUSSEK and ZOHMAN, consider that such treatment should be reserved for the "poor risk" patient The choice between these two views is important because, if the first group are right, it would be logical to send to hospital every patient who is fit to be moved so that anticoagulant treatment can be begun without delay, whereas if the second group are correct it would be best for the "good risk" patients to be kept at home The burden of the anticoagulant treatment on hospital accommodation and laboratory facilities has already become considerable and coronary thrombosis is now one of the commoner causes for admission to hospital

The two papers from Oxford by Dr HONEY and Dr TRUELOVE which appeared in two of our recent issues [2] bear directly on this problem, since they have examined afresh the question whether anticoagulant treatment does in fact improve the prognosis of acute myocardial infarction, and how far the large expenditure of time, energy, and money on the admission to hospital and the laboratory control of treatment is justified by results They have made an elaborate analysis of the results of 543 admissions (involving 506 patients) to the Radcliffe Infirmary at Oxford in the years 1940–54 They took an arbitrary time of eight weeks from onset to represent the acute phase, and succeeded in tracing all but 1 of the 348 patients who had survived beyond this phase The period of the survey spans the introduction of anticoagulant treatment at the hospital in 1948, and since 1951 3 out of every 4 patients have received this treatment In their series of patients there were twice as many men as women, two-thirds of the men were aged 50–70, two-thirds of the women were aged 60–80 Women of equal age have a better chance of survival than men, but fatality increases with advancing years and these two opposed effects cancelled out, so it was not necessary to differentiate between the sexes Surprisingly, there was no appreciable difference in mortality-rate between those patients who were admitted in their first attack and those who had a clear-cut history of a previous infarction The fatality-rate was unaffected by a previous history of angina of effort, or hypertension It seems to make no difference whether the attack occurs during exertion or comes on at rest The really bad prognostic findings are, as so many physicians have emphasised, the presence of early shock and hypotension

HONEY and TRUELOVE have examined very critically the data about their patients treated or not treated with anticoagulants and conclude that their figures show that anticoagulants "have had only a small beneficial effect on the fatality of myocardial infarction" They calculate that in the period 1952–54, when anticoagulants were extensively used, out of 263 admissions only 11 lives were saved by this treatment—i e, the mortality was 11 lives less than would have been expected from previous experience with 263 cases of the same clinical characteristics Examination of post-mortem records showed very clearly that the reduction in deaths accompanying anticoagulant treatment was largely due to the elimination of pulmonary embolism as a cause of death Before anticoagulants were used, 6% of the patients who survived the first forty-eight hours after onset died from pulmonary embolism, in 1952–54 only 1% died HONEY and TRUELOVE consider that their figures show that "anticoagulants do not have any major influence upon the course of an established myocardial infarct per se, although they save some lives by removing almost completely the dangerous complication of pulmonary embolism" These conclusions are indeed in striking contrast to those of IRVING WRIGHT and the American Heart Association's survey, and to those of GILCHRIST and his associates in Edinburgh IRVING WRIGHT has restated his opinion,[3] supported by many others, that "if a patient suffers from a definite myocardial infarction, if there are no contraindications and if good facilities are available, he should receive anticoagulant therapy" HONEY and TRUELOVE's answer to these claims is that the figures on which they are based have not been adequately analysed and, in particular, insufficient attention has been paid to bias in the selection of patients which has the effect of exaggerating good results—by this they mean the tendency to allot relatively poor risk patients to the "control" untreated groups They point out that bias in selection of this type can be shown to account for previous good results reported from their own hospital with the same patients in the period 1948–51

In their second paper HONEY and TRUELOVE assembled facts about the long-term prognosis, derived from their well-observed group They found that 1 patient in every 10 admitted died within forty-eight hours, and one-third of the patients were dead by the end of the eighth week, after two years had elapsed half the original patients were dead Thereafter the risk of dying diminishes, another 10% died in the next three years, and by the end of five years 3 out of 5 patients were dead Of the patients who survived the acute attack, 10% died during the succeeding four months, and factors of bad prognosis in this group were evidence of cardiac distress in the early period of the acute attack—i e , cardiac failure or enlargement, or the occurrence of arrhythmias—and a history of previous myocardial infarction When patients are classified as " bad risks " or " good risks " according to the criteria of Russek and Zohman, the bad-risk patients are four times as liable to die in the first year as the good risks, and twice as liable in the second year , but after the second year there is no difference Good-risk patients over the age of 60 have a better prognosis than younger patients, because younger patients are more liable to recurrence (Oddly enough, according to Morris et al ,[4] this does not apply to medical practitioners) Honey and Truelove point out that it is therefore very important to find out whether long-term anticoagulant treatment will reduce the recurrence-rate in these good-risk patients under 60 years of age , and their figures will provide a standard for comparison since only a very few of their patients had this form of treatment So far no comparably large series of cases is available for analysis Keyes et al [5] treated a group of 121 cases for varying periods up to thirty-eight months and considered that the mortality from recurrence was much reduced, but their figures are not very closely analysed They do warn physicians that stopping long-term anticoagulant treatment is very liable to be followed by a further acute myocardial infarction Schlachman [6] recorded 3 patients whose anticoagulant treatment was begun as soon as premonitory symptoms occurred, but it did not arrest the progress of the myocardial infarct Such findings warn us that long-term anticoagulant therapy is not to be lightly undertaken

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[1] *Lancet* 1956 i, 599

[2] Honey G E Truelove S C *Ibid* June 8, 1957, p 1155 *Ibid*, June 15 1957 p 1209

[3] Wright I S *J Amer med Ass* 1957, 163, 918

Honey and Truelove's conclusions and criticism of previous workers' results are unlikely to pass unchallenged by the supporters of anticoagulant treatment for all But they are not alone in their views Russek and Zohman,[7] for example, have again expressed the opinion that " anticoagulant therapy, which has certain hazards, is neither necessary nor desirable for patients who have been classified as good risks " They give data about 511 good-risk patients who were not treated with anticoagulants , the patients were closely watched for thrombo embolic complications, which have occurred in only 19 (3 7%) of the cases and were always mild , only 18 (3 5%) deaths occurred in this group Russek and Zohman do, however, recommend anticoagulant treatment for poor-risk patients

The ordinary practitioner has therefore to come to a decision about individual cases in a field where experts continue to disagree He is likely to note that the opposing views are largely a matter of differing application of statistical methods of analysis to similar data But the arguments of Honey and Truelove and those who share their views will reinforce the physician's conviction, which must be communicated to anxious relatives, that not every patient with myocardial infarction needs admission to hospital , and Morgan Jones's [8] advice on the relative risks of transportation to hospital or no anticoagulants for the good-risk patient is still a good guide On the other hand, Honey and Truelove's statistics are unlikely, we think, to deflect hospital physicians from treating poor-risk patients with anticoagulants as soon as possible As Gilchrist and Tulloch [9] would doubtless remark, the saving of 11 lives in 263 patients is worth the effort

Annotations

AN EPIDEMIOLOGICAL STUDY OF MONGOLISM

In the past, the epidemiological approach to the causation of congenital malformations has been neglected It is probable that there are major variations in the incidence of malformations from country to country one instance is the high incidence of congenital dislocation of the hip in parts of Italy Some of these variations may depend on differences in gene frequencies, others on environmental differences , and these should be discoverable by epidemiological study

In an article on p 1314, Dr Pleydell (who has previously made a valuable study of Huntington's chorea in his county [10]) reports an epidemiological study in Northamptonshire of four types of malformation of unknown ætiology—mongolism, congenital malformations of the heart, hare-lip and cleft palate, and major malformations of the central nervous system He finds some apparently remarkable groupings in the births of children with these malformations, particularly mongolism, over the years 1944–55 Thus of 13 mongols born in the county of Northampton in 1947–48, no less than 5 were born in the Rushden area, whose population is less than a tenth of that of the county In evaluating apparent coincidences of this kind, it is important to discover whether they differ significantly from the random distribution Dr Pleydell does not give the details of his subdivision of the county, but two models will illustrate the possibilities of analysis

Let us suppose that the county is split into 100 regions, each with a population of about 3000 and about 50 births a year, and assume that the risk of any birth producing a mongol baby is 1 in 500 (Pleydell's figure of 1 in 613 agrees well with other surveys) Over a ten-year period of a total of 1000 region-years the number with no mongol births would be about 905, the number with 1 mongol birth about $90^1/_2$, with 2 about $4^1/_2$, and with 3 about $^1/_7$ That is to say, the odds would be only about 6 to 1 against any region having 3 mongol children born in a year Not less than 4 mongols born in one region, in one year of a ten year period, would be remarkable in populations grouped in this way In this light, that 3 mongols were born in nine months in Irthlingborough (population 4700) in 1947 is not by itself surprising Taking larger regions, with populations of about 30,000, and annual births about 500, the odds against 5 mongols being born in one year in such an area are only between 2 and 3 to 1, and only 7 or more in a year in a population of this size would be really noteworthy But these are exceptional individual events and an accumulation of discrepancies in different areas of the kind Dr Pleydell describes, each not significant in itself, might well be meaningful in combination

Now that Dr Pleydell has formulated the hypothesis that births of mongols are not random in time and space, we hope that it will be checked in one or two other counties There is no need for the population of the county to be subdivided into units of exactly equal size , but the subdivision should be fixed before the inquiry is made, and then the pattern of mongol births compared with what might be expected by chance

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[4] Morris, J N , Heady, J A , Barley R G *Brit Heart J* 1957, 19 227
[5] Keyes J W , Drake E H , Smith, F J *Circulation* 1956, 14, 254
[6] Schlachman M. *Ann intern Med* 1957, 46, 728
[7] Russek, H I , Zohman B L *J Amer med Ass* 1957, 163, 922
[8] Morgan Jones A *Brit med J* 1955, ii 1613
[9] Gilchrist, A. R , Tulloch, J A. *Scot med J* 1956, 1, 1
[10] Pleydell, M J *Brit med J* 1954, ii, 1121

A second suggestion of Dr Pleydell's is that there has been a seasonal incidence of the mongol births in his twelve year period of study, and that this may be related to the incidence of scarlet fever some seven or eight months previously This is an interesting hypothesis, but it needs confirmation since Pleydell's own findings as tabulated do not show a seasonal distribution greatly different from random expectation It is improbable that any short-lived infection in pregnancy could by itself be the cause of mongolism, even though the incidence of streptococcal infections varies with age For example, though (as Dr Pleydell notes) there are age specific differences in the incidence of streptococcal infection, it is difficult to explain in this way the fiftyfold increase in the incidence of mongolism from mothers aged 20 to mothers aged 45 But such environmental findings may play an important subsidiary rôle in mongolism, and even the main rôle in other malformations such as those of the heart

TESTOSTERONE THERAPY IN STUNTED CHILDREN

THOUGH testosterone is sometimes given to promote growth in stunted children, there are very few careful studies of its results The difficulty is largely one of knowing what growth would have taken place in the absence of the hormone, and, short of treating one of a pair of identical twins, no perfect control is possible The child's progress should be followed for six months to a year before any therapy is given, and thereafter with or without therapy for several years—if possible to full maturity A recent study by Sobel et al [1] goes a long way towards meeting this criterion, and considerably clarifies the main issue whether the immediate increase in height is ultimately outweighed by the earlier closure of the epiphyses also thought to be brought about by the hormone

Sobel et al studied 27 stunted children aged 5 to 10 years (thus avoiding the complications of the adolescent spurt in growth) They assessed their results by following on the one hand the increase in height, and on the other the increase in skeletal age—the latter being estimated in the usual way from radiographs of the hand and wrist. During six months before therapy, these children developed more slowly than was expected from the standards for Boston children, increasing by 4 7 months of average growth in height and by 4 3 months in skeletal age Testosterone was then given daily for six months, and there was a fairly sharp acceleration in height-growth and in skeletal maturation Height increased during these six months by the equivalent of 12 1 months of average growth, and reverted in the following year, without therapy, to the near average figure of 13 2 months of average growth Skeletal age increased 13 9 months during the six-month therapy period, and during the ensuing year continued to develop at above-average rate, advancing 17 0 months

Though it is usually believed that testosterone causes epiphyseal closure, the evidence for this is confused and contradictory, and indeed very little is known of the hormonal control of skeletal maturation—that is, of the "bone age"—in children [2] Under the abnormal stimulus of androgens in precocious puberty, the bone age is advanced, the epiphyses close early, and permanent stunting results Sobel et al now show that methyltestosterone 5 mg a day by mouth for six months accelerates bony development though without closing the epiphyses But in just over half the cases the acceleration in bony development was proportionally greater than the acceleration in height, and if therapy had been persisted in the effect would ultimately have been the reverse of what was desired Despite the immediate gain in height, the end-result would have been still greater stunting At present no effective preparation of growth-hormone is available, and while we wait for it, we should evidently avoid substitutes that do more harm than good

PROTECTION AGAINST RADIATION

ONE important way of minimising the dangers of ionising radiation is to ensure that everyone who works with machines or substances producing such radiation understands their power and adheres to rules known to be safe A new code of practice for the protection of radiation workers is published this week [1] Prepared by the standing advisory committee, under the chairmanship of Sir Charles Darwin, F R S, which was set up under the Radioactive Substances Act to advise Ministers, the code is intended primarily for the protection of persons exposed to ionising radiations in hospitals in the National Health Service

The code deals chiefly with technical data concerned in assessing the necessary safeguards to the users of X-ray and other radiological apparatus, such as cobalt therapy units, and radioactive isotopes It has been designed, as far as possible, as a set of purely technical rules The first part contains the rules applicable to the use of X rays in diagnosis and of X rays and γ rays in therapy, and the second part sets out rules for the diagnostic or therapeutic uses of radioactive isotopes, either sealed or unsealed A supplement records the relevant fundamental data and technical details about the design of diagnostic and therapy departments

Though the code makes no new scientific contribution, it incorporates much of the latest evidence, including the views of the Medical Research Council committee on the hazards of radiation, and it is a valuable working manual that will do much to fortify safety precautions The Minister of Health has sent copies to hospital authorities and has asked them to ensure that where necessary safety standards in radiological departments are brought into line with the code He emphasises that the clinical freedom of the individual consultant will not be restricted, but it has become essential, he adds, to secure a definite minimum standard of safety precautions and to place upon the head of the department the responsibility for maintaining that standard

POSTOPERATIVE SICKNESS

POSTOPERATIVE sickness is still one of the commonest complications of surgery and anæsthesia The principal predisposing factors are the use of opiates for premedication and postoperative analgesia, inhalational anæsthetic agents, and long major operations

The emetic effects of morphine are well known, but pethidine—though less troublesome in this respect—considerably increases postoperative sickness when given intravenously during an operation Burtles and Peckett [2] record an incidence of postoperative sickness of 18% after thiopentone, nitrous oxide, and oxygen, rising to 30% with the addition of intravenous pethidine, and an incidence of 26% with a similar anæsthetic sequence and trichlorethylene, rising to 46% with added pethidine All the potent inhalational anæsthetic agents are likely to produce some sickness, but ether remains the greatest offender amongst those commonly used

The site of surgery is probably of little importance (if operations on or near the labyrinth are excluded), and contrary to common belief intraperitoneal operations are no more likely than others to produce vomiting [3] But the incidence is high after protracted and major operations Women are more susceptible than men, and advancing years seem to lead to increasing resistance Other factors worth remembering are badly administered anæsthesia (which may result in severe anoxia or carbon-dioxide retention), idiosyncrasy (history of sickness after a previous operation or of travel sickness), and the emetic effect of anything more than occasional sips of fluid immediately after operation

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[1] Sobel E H Raymond, C S Quinn, K V, Talbot N B *J clin Endocrin* 1956, 16, 241

[2] Tanner J M Growth at Adolescence Oxford, 1955 pp 52, 129

[1] *Code of Practice for the Protection of Persons exposed to Ionising Radiations* H M Stationery Office Pp 83 8s

[2] Burtles R, Peckett, B W *Brit J Anæsth* 1957, 29, 114

[3] Knapp M R, Beecher H K *J Amer med Ass* 1956, 160, 376

Appreciating these and other ætiological features, the anæsthetist can vary his technique to suit the patient's requirements, but for general prevention and treatment the phenothiazine drugs offer the best prospect of success The value of these agents stems from their depressant effect on the region of the vomiting-centre, so that whatever the cause they are likely to work In susceptible patients they may not entirely prevent vomiting, but they usually reduce its severity Burtles and Peckett [3] found an overall sickness-rate of 30% in their control series, but this fell by half when a phenothiazine drug was given as part of the premedication They chose either promethazine or chlorpromazine, but ultimately they preferred the former, since with it such side effects as cerebral depression, dizziness, and postural hypotension were less troublesome Various workers have remarked on these side-effects of the phenothiazine drugs, and in certain circumstances it may be safer to accept the dis advantages of postoperative sickness than to add to the danger of the operation in this way In any event severe sickness is rare in Burtles and Peckett's series only 2 8% of patients vomited more than four times

BENIGN MYALGIC ENCEPHALOMYELITIS

LAST year we suggested the name " benign myalgic encephalomyelitis "[4] for an epidemic disease which is either new or has become very much more frequent than formerly It is a disease of rapid onset characterised by (1) symptoms and signs of damage to the brain or spinal cord (lower-motor-neurone palsies may lead to confusion with anterior poliomyelitis), (2) protracted muscle pain, (3) emotional disturbance, notably depression, extending into convalescence, (4) normal cerebrospinal fluid (C S F), although headache and stiff neck are common, (5) reticulo endothelial reaction in some cases, (6) a protracted course, often with relapses, and (7) a benign outcome in almost all cases

In London the Royal Free group of hospitals experienced a severe outbreak of a disease which apparently falls into this category, and its epidemiology has recently been described [5] The incubation period is usually 4–8 days, so an epidemic is likely to be explosive In this instance there were two fresh cases in the 3rd week of the epidemic, whereas in the 5th week there were fifty Although a few cases were found in which the disease was acquired from a single symptomless carrier, it was commonly transmitted by frequent personal contact, and in those circumstances the incidence of the disease was high Thus in the section of the hospital where the first case occurred 55% of the nurses contracted the disease within a month Since the largest number of cases was among nurses, the various types of worker in the hospital were roughly grouped according to the relative frequency with which each came into contact with members of the nursing staff, and the incidence of the disease in each group broadly corresponded with the frequency of contact The importance of frequent contact in the spread of the disease is also indicated by the low incidence of the disease outside the hospital when it was at its height among the hospital staff In contrast to the influence of frequent personal contact a search for a vehicle of infection—water, milk, food, laundry, insects—revealed no common links between cases There was no good evidence that age or sex affected liability to the disease, except in so far as these factors affected the probability of an individual being frequently exposed to infection Attempts were made to isolate the responsible virus at various stages of infection from nose, throat, blood, and bowel, but without success Serological tests were negative except that nearly 80% of those affected showed heterophil antibody in a titre of 1/40 or higher, but of these antibodies less than 4% were of infectious-mononucleosis type

This epidemiological study indicates that the risk of infection is greatest for anyone exposed to many infective persons, as in any form of community life, and that, on the contrary, in smaller units such as the home the risk of spread is slight At the Royal Free the epidemic was cut short by sending all the nurses home and keeping them under observation through their own family doctors, and no secondary case occurred as a result [6] Since the work of a large group of hospitals can be paralysed by an epidemic of benign myalgic encephalomyelitis, it is important to know of the success of this measure The management of an epidemic of benign encephalomyelitis is the reverse of that generally recommended for an epidemic of poliomyelitis in a closed community, such as a residential school, where sending all the children home is likely to disseminate the disease

SKIN GRAFTING BY THE EXPOSURE METHOD

SURGEONS often teach that skin is the best dressing, yet even with the high price of gauze and cotton wool today not all of them practise what they preach Sir John Bland-Sutton, it is said, thought that well-laundered sheets were the only cover needed by a healthy wound, and a return to this principle has lately been evident in the popularity of a pliable plastic film, sprayed on to the wound [7] The main value of the orthodox dressing is its absorbency, and the barrier to infection which it provides, and in freely draining wounds in which the risk of contamination is high because of their wetness there is still no better covering It is now recognised, on the other hand, that where the exudate is reasonably scanty, and contains (as it usually does) fluid protein, it will coagulate on the surface and provide an effective natural barrier Moreover this layer can easily be damaged by the pressure and movement of dressings, and fluid exudate, soaking into the gauze, may form an ideal medium for cross infecting organisms In the treatment of burns the exposure method is simple and often effective, and the progress of the burn can be observed and the moment chosen for surgical intervention in the doubtful case

In the more unfavourable situations split skin grafting is bedevilled by the risk of movement or pressure by the dressings displacing the newly adherent grafts, particularly where low grade infection (so difficult to eliminate from granulating surfaces) tends to cause the grafts to float off in their first few days Cannon [8] has found that with the exposure method split skin cover is feasible in many different circumstances—mobile areas such as the lower part of the abdominal wall, and the hand, moist wounds such as the granulating edges of a cerebrospinal fluid fistula, and lesions of the buttocks and thighs in paraplegic patients, and bony cavities once lined by granulation tissue This is just the kind of development which would have appealed to Ambroise Paré the replacement of an unsatisfactory ritual method by a simpler and apparently more effective one

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Lord COHEN of BIRKENHEAD has been elected chairman of the Central Health Services Council in succession to Sir FREDERICK MESSER Sir CECIL OAKES succeeds Lord Cohen as vice-chairman

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[4] *Lancet*, 1956 i 789
[5] Crowley, N, Nelson, M, Stovin, S *J Hyg*, *Camb* 1957, 55, 102
[6] Geffen D *Publ Hlth, Lond* 1957 71 13
[7] Rob, C G, Eastcott, H H G *Brit med J* 1954, ii, 117
[8] Cannon, B *New Engl J Med* 1957, 256 672

The Wider World

REFLECTIONS ON MEDICAL TRAVEL

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(concluded from p 1292)

One of the surprising things about the world is how little all the various modes of communication—talking, writing, photography, cinema, radio, and television—have prepared one for it Like psycho analysis, it must be experienced to be appreciated Who would have expected that one's auditory memory of San Francisco would have been the droning of fog-horns, of Bangkok the barking of dogs, and of Calcutta the cawing of crows ? Who would have supposed that Australian weather is even more unpredictable than British ? Who could have visualised, without seeing it, the squalor of the cities of the East, where the growth of population is exploding in an unpredictable chain reaction ? Who could have imagined the dinner of an Indian medical association, held in an enormous marquee like one of the tents of Genghis Khan, on a night so chilly after a summery day that the women all wore overcoats, and with the cold comfort of cocktails of lemonade and passion-fruit juice ? But, indeed, who could have imagined the miraculous beauty of India in the autumn, the light of the morning and the dust of the evening on the plains, the entrancing dress of the women, the colour that flames out of poverty ? Indian civilisation is as stable as the old red sandstone of its buildings, and out of it flowers an idealism like the airy cupolas and minarets that float above its forts and temples

* * *

Having known Australians and New Zealanders as a combative people, one of the surprises was to find them so amiable in their native land Indeed, Australians and New Zealanders differ from birds and dogs in being much more aggressive when they are abroad than when they are in their own territories They tell me we are the same At any rate, nothing can rival the friendliness and hospitality with which the Englishman is welcomed in Australia and New Zealand One is, of course, appalled by some aspects of the social scene in Australia—the evening swill of drink, the gambling, the lotteries, and the social strife One sometimes gets the impression that the aim of the Australian trades unions is to stop people working, and the aim of the Churches is to stop people enjoying themselves , but who are we to talk, with shipbuilders, engineers, railwaymen, and doctors behaving as they are ? With all its faults, however, Australian democracy is more real than any I have experienced elsewhere, and it is not overshadowed by plutocracy as it is in the United States of America The Australian taxi-driver is just as delightful and helpful as the Spanish, and that is saying a great deal You sit alongside him in the Holden cab and talk like two equals, and you learn a great deal about the country in the process He may, indeed, give you a good tip for the races you are just going to, and you may find that his brother owns a racehorse

Australian medicine is the apotheosis of private practice, extreme efficiency in the practical aspects of medicine being combined with a deficiency in that academic framework of the teaching hospitals which has made German medicine in the past and American medicine in our own time so great This is being remedied by the creation of new professional units, but the struggle will be an uphill one Australian thought at any rate in the professions, is intensely hostile to control by the State, and whole-time medicine is suspected of being a Trojan horse The various medical insurance schemes which have been introduced encourage the independence of the practitioner and the maintenance of private practice, but they probably do not promote the most efficient development and use of medical services, hospitals, and university clinical departments It is much more difficult to run a diabetic clinic or a hæmophilia reference centre in Australia than in this country, because the combined cost of transport to the hospital and treatment there is so much higher than the cost of treatment by the local practitioner

I am not persuaded that all Australian doctors should be trained in operative gynæcology, obstetrics and surgery A man in a group practice of 6000 cannot be a first-class surgeon, and so long as such a high proportion of the population lives in five of the State capitals where excellent hospital facilities are available, one would deprecate amateur surgery A great deal of the emphasis on the necessity for the general practitioner to be able to do surgery and major obstetrics seems to spring from the desire to give the practitioner an interesting and lucrative career rather than from the desire to give the cheapest and best service to the public Anyone who challenges a cherished national concept like that of the Australian doctor, located in the outback, hundreds of miles from help, self-sufficient and omnicompetent, is likely to provoke a violent reaction , but the gearing of the whole organisation of medicine to this uncommon person may not now be for the best A follow-up of the careers of a representative sample of Australian students qualified since the war would be of great value. Just as production changes—first subsistence agriculture, then a smaller and smaller proportion of the population as primary producers (in Australia not more than one in ten)—so medical practice changes , and in England now only 40% of those graduating go into general practice, the others being absorbed in diagnostic services, consultative work, preventive medicine, and similar specialised activities

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An aspect of Australian democracy that is surprising to the Englishman, who has perhaps forgotten how many Australian families were driven there by the harsh penal laws of Great Britain and how many were kept in virtual slavery to British administrators, merchants, and landowners when they arrived, is that her Asiatic neighbours are prepared to regard Australia as a liberated colony and an anti-colonial power In addition, they do not fear her economic and military might as they fear that of America, China, and Russia Hence, they turn to Australia for advice and technical assistance A Scotsman, now professor of medicine in an Australian university, spoke movingly of the chagrin he had felt on a mission to Indonesia, in which for the first time in his life he had had to conceal the fact that he was a Scotsman Australia is taking an active part in the Colombo Plan, and on visiting the classrooms and libraries in the universities one is surprised by the high proportion of Asiatics among the students and readers Indeed, Australia is putting us to shame by the contribution she is making to education and scientific developments in Asia and Melanesia, and is illustrating the new pattern of empire in which we should be taking a greater part

* * *

On passing from Australia to the Far East, one feels as if one had moved back in time to Edinburgh or Dublin of fifty years ago, except that the classes are much larger There is excessive emphasis on anatomy and pharmacognosy, because these subjects are easy to teach with primitive facilities There is a great shortage of modern apparatus for physiology, biochemistry and clinical pathology, and an equal shortage of teachers and technical staff The teachers themselves are well aware

help from wealthy Catholic relatives because he was an agnostic.

Two wars and conscription have blunted our appetite for the *Wanderjahre* and we have organised a national health service that makes no provision for the prodigal's return. We do not make experience in Africa or Asia a *sine qua non* for a consultant appointment, as the Belgians and the Dutch used to do. Instead, the senior medical registrar casts a lean and hungry look at the 20 openings a year for more than 200 of his kind, and fears with justification that if he gets off the local ladder of promotion, even for a year or two, he will never get on again. No longer can the man who has spent twenty or thirty years working in the tropical sun return home and buy a comfortable small practice with opportunities for hunting and fishing. In too much of our planning since the war we have been parochially minded.

Conclusion

The reward of travel is to see one's own country in perspective, and my main impression is of the central position we occupy in the thoughts of diverse peoples, and of our responsibility to continue to help in the control of disease and the training of doctors in our former dominions now that we have been divested of the material trappings of empire. More than once I have seen again in my own daydreams the man who appeared in a vision to St. Paul saying, "Come over into Macedonia, and help us."

A second impression is of the great and lasting effect that may be produced on visitors to this country by some brief encounter which we too quickly forget. Listening to votes of thanks ten thousand miles away from home, I have learnt for the first time how much it means to a man to come to this country, to find that there are people who are bubbling over with enthusiasm about some small field of specialisation or research over which he himself had hitherto felt a little self-conscious, or, unfortunately, to meet someone like Martha who is too busy with the daily chores to put work aside and talk to the stranger.

If one writes freely, as I have tried to do, it is hard to avoid saying things which may be misinterpreted or may unintentionally hurt, and I must therefore stress my final impression, which is of the open-hearted friendship and bountiful hospitality which the English visitor receives abroad and the sense of obligation with which he returns. Nor should I like to close without praising the British Council, whose merits are so much better appreciated abroad than at home and whose advice and hospitality are so generously offered to the traveller from this country.

Medicine and the Law

Insulin Coma in a Driver

A DIABETIC patient was found by a policeman in his invalid carriage at the entrance to his garage.[1] He had had hospital treatment. He told police that if he had felt a turn coming on he would have taken a lump of sugar which he always carried with him.

He was accused of being in charge of a motorised invalid-carriage while under the influence of a drug. The prosecution said that he had taken a dose of insulin that had made him go into coma. A physician, referring to the patient's lump of sugar, said: "It is in that way that most of our diabetics keep out of court."

The patient was found guilty, but given an absolute discharge. The defence considered it "a vital case from the point of view of diabetics who drive."

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MEDICAL RESEARCH COUNCIL'S STATEMENT ON TOBACCO SMOKING AND CANCER OF THE LUNG

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THE INCREASE IN LUNG CANCER

In their annual report for 1948–50 the Council drew attention to the very great increase that had taken place in the death-rate from lung cancer over the previous twenty-five years. Since that time the death-rate has continued to rise, and in 1955 it reached a level more than double that recorded only ten years earlier (388 deaths per million of the population in 1955 compared with 188 in 1945). Among males the disease is now responsible for approximately 1 in 18 of all deaths. Although the death-rate for females is still comparatively low, it also has shown a considerable increase in recent years and the disease is now responsible for 1 in 103 of all female deaths.

Three comments may be made on these figures. In the first place, the trend over the last few years indicates that the incidence has not yet reached its peak. Secondly, the figures are not to be explained as a mere reflection of the introduction and increasing use of improved methods of diagnosis but must be accepted as representing, in the main, a real rise in the incidence of the disease, to an extent which has occurred with no other form of cancer. Thirdly, only a small part of the rise can be attributed to the larger numbers of older persons now living in the population; in the last ten years the lung-cancer death-rates among both men and women have risen at all ages from early middle-life onwards.

POSSIBLE CAUSES OF THE INCREASE

The extent and rapidity of the increase in lung cancer point clearly to some potent environmental influence which has become prevalent in the past half century and to which different countries, and presumably also men as compared with women, have been unequally exposed. The pattern of incidence of the disease rules out any possibility that the increase can be due, in a substantial degree, to special conditions, such as occupational hazards, affecting only limited groups. It is necessary to seek some factor or factors distributed generally throughout the population, and in considering the possibilities it must be borne in mind that a very long period, 20 years or more, may elapse between exposure to a carcinogenic agent and the production of a tumour. From the nature of the disease attention has focused on two main environmental factors: (1) the smoking of tobacco, and (2) atmospheric pollution—whether from homes, factories, or the internal combustion engine.

SMOKING AS A CAUSE OF LUNG CANCER

Epidemiological Surveys

The evidence that heavy and prolonged smoking of tobacco, particularly in the form of cigarettes, is associated with an increased risk of lung cancer is not based on the observation that the substantial increase in the national mortality followed an increase in the national consumption of cigarettes. It is derived from two types of special inquiry. In the first, patients with lung cancer have been interviewed and their *previous* histories in relation to smoking and other factors that might be relevant have been compared with those similarly obtained from patients without lung cancer. The results of nineteen such inquiries (in this country, the U.S.A., Finland, Germany, Holland, Norway, and Switzerland) have been published. They agree in showing more of these defects. At the clinical level there are great deficiencies in social and preventive medicine, pædiatrics, and psychiatry.[2] By social medicine is meant not the detailed case taking—in many respects the modern equivalent of slumming—which is so dear to the hearts of British almoners and which has made the subject so distasteful to the average British medical student. It means public health, the medicine of communities, and in particular the medicine of communities in which the income per head and the proportion of doctors to patients are very small.

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[1] *Times*, June 21.

This is not to say that there are not institutes in the Far East and particularly in India which can compare with the best in Europe and America. New hospitals are being built and American aid is being poured in. The Americans are readier or better able than we to use the device of adoption of a school overseas by one in the United States and to arrange an interflow of staff—of trainees to the United States and of senior American staff and technicians to Asia. English is the key language to the world's scientific literature, and in view of the costs and delays of translation it is unlikely to be replaced by languages such as Hindi or Arabic as a medium of scientific instruction. So long as English remains the lingua franca of medical teaching, exchanges are essential, for there is a tendency for spoken English in India to diverge from the language spoken in England and America as spoken Latin diverged in Italy and Spain. The gain of these exchanges is not all on one side. There are great opportunities for research in Asia, whether in old fields such as the treatment of tuberculosis or in new ones such as the abnormal hæmoglobins.

It is all too easy to sneer at the efforts of the Asian and African students who come to this country to take a higher qualification in medicine or surgery, to lament that their previous training is defective and to assert that the Asian student may learn theory with the greatest of ease but is no good at getting to grips with the real world. Doubtless the social background in the East, with its enormous labour surplus, makes men and women used to being waited on hand and foot; but it does not prevent the development of doctors and nurses of great practical competence. Indeed, the Pakistani girl who has come direct from purdah to become a doctor or nurse has made a much greater step forward than the British student of medicine or nursing.

* * *

The desire for British or American higher qualifications is a good aspect of the nationalism which dominates world thought today. Just as every country must have air-lines, air hostesses, air fields, radio, and if possible television, of international standards, so too its medical teachers must be of international status. Moreover, only an external criterion of ability can prevent the nepotism which is still such a danger. It is for these reasons that in much of Asia today it is almost impossible for a man to get on the staff of a teaching hospital without having studied abroad and obtained a British or American higher degree.

This is almost certainly a temporary phase. When the peoples of Asia and Africa become more assured, they will probably no more think of coming here to take the M.R.C.P. or the F.R.C.S. than an American or European postgraduate student does today. While the phase lasts, however, we should bend every effort to help. Wherever one goes in medical circles in India and the Far East, the conversation soon turns to the difficulties which face their young men and women in getting house appointments in this country (even though they are sponsored by their universities), the difficulties of temporary registration, and the difficulties of satisfying the preliminary conditions for sitting examinations such as the membership of the College of Physicians. It is freely stated that we make much greater difficulties than the Americans. There is a desire for English external examiners, inspectors, and postgraduate lecturers who will make the preparation for higher degrees more efficient.

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I have said this is a temporary phase, because by and large Western medicine provides an unsuitable training for the problems of the East. They need an autochthonous form of medical education. Experiments on new lines have already been carried out at Vellore and Ludhiana, where medical education is oriented to public health and it is as important for the student to work at the rural health centre as to walk the wards of the hospital. The most important experiment is the All India Institute of Medical Sciences, which is being built at Delhi to be the Indian Johns Hopkins Hospital and train the teachers and researchers of the future. The number of students will be small and they will be selected from the whole of India. Faculties and staff will be provided on a relatively lavish scale.

It is doubtful whether at the start India will be able to staff this institute unaided and she will probably be anxious for help from England and America. Such help will have to be on a short-term basis, because India will naturally want the project to be firmly in Indian hands. The seconding of an English medical teacher to work for, say, two years in Delhi bristles with difficulties because heads of departments cannot easily be away so long and younger men fear the loss of promotion during an absence. In addition, living expenses may well be high. However, the compensations would be great. In the ordinary way I share Sir Robert Hutchison's view of "that most boring of subjects, the medical curriculum", but working out a medical curriculum for India could be exciting, for in India and the Far East people must sit down and think out from the beginning what they are training doctors for and the best way of doing it.

The visitor to India cannot but marvel at the outburst of creative energy liberated by independence, the enthusiasm for planning and the immensity of the tasks to be completed. At the top levels of their health service there has been a fusion of the best elements of the traditions of the Indian Medical Service, the Indian Civil Service, and the Congress Party into a precept of idealism and dedication to duty which fills the sympathetic visitor with respect. Like Wordsworth witnessing the French revolution, he murmurs, "Bliss was it in that dawn to be alive." Friendship to Britain is sincere, and it is surprising how tolerantly the relics of our domination have been preserved, for some of the manifestations of the Victoria cult were as inartistic as those of the Stalin cult. Pakistan is a smaller and poorer country than India, but friendship to Britain is as strong there or stronger and the desire for our cooperation in education and the advancement of science equally great.

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When I was a boy at the local grammar school, an old friend of my mother's used to say, "Put the lad in the Borough Treasurer's office and then he'll be right for life." The institution of the Welfare State has unfortunately set the seal of approval on the philosophy of being right for life and has weighted the odds against adventure. It is only necessary to read the autobiographical writings of Conan Doyle to realise how much harder were the conditions young doctors without means had to face two or three generations ago. Conan Doyle spent seven months on a whaling-ship in his final year to get the money to qualify. After qualification he had to go to sea again as ship's surgeon on the *Mayumba*, and on his return he complained of having had African fever, of having nearly been eaten by a shark, and of his ship catching fire in mid ocean. Despite his penury he refused help from wealthy Catholic relatives because he was an agnostic.

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[2] Taylor, C. E. *New Engl. J. Med.* 1956, 255, 397.

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Conclusion

The reward of travel is to see one's own country in perspective, and my main impression is of the central position we occupy in the thoughts of diverse peoples, and of our responsibility to continue to help in the control of disease and the training of doctors in our former dominions now that we have been divested of the material trappings of empire. More than once I have seen again in my own daydreams the man who appeared in a vision to St Paul saying, "Come over into Macedonia, and help us."

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Three comments may be made on these figures. In the first place, the trend over the last few years indicates that the incidence has not yet reached its peak. Secondly, the figures are not to be explained as a mere reflection of the introduction and increasing use of improved methods of diagnosis but must be accepted as representing, in the main, a real rise in the incidence of the disease, to an extent which has occurred with no other form of cancer. Thirdly, only a small part of the rise can be attributed to the larger numbers of older persons now living in the population; in the last ten years the lung-cancer death rates among both men and women have risen at all ages from early middle-life onwards.

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The extent and rapidity of the increase in lung cancer point clearly to some potent environmental influence which has become prevalent in the past half-century and to which different countries, and presumably also men as compared with women, have been unequally exposed. The pattern of incidence of the disease rules out any possibility that the increase can be due, in a substantial degree, to special conditions, such as occupational hazards, affecting only limited groups. It is necessary to seek some factor or factors distributed generally throughout the population, and in considering the possibilities it must be borne in mind that a very long period, 20 years or more, may elapse between exposure to a carcinogenic agent and the production of a tumour. From the nature of the disease attention has focused on two main environmental factors: (1) the smoking of tobacco, and (2) atmospheric pollution—whether from homes, factories, or the internal combustion engine.

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(1) A higher mortality in smokers than in non-smokers.

(2) A higher mortality in heavy smokers than in light smokers.

(3) A higher mortality in cigarette smokers than in pipe smokers.

(4) A higher mortality in those who continued to smoke than in those who gave it up.

It follows that the highest mortalities were found among men who were continuing to smoke cigarettes, heavy smokers in this group having a death-rate nearly 40 times the rate among non-smokers. Although no precise calculation can be made of the proportion of life-long heavy cigarette smokers who will die of lung cancer, the evidence suggests that, at current death-rates, it is likely to be of the order of 1 in 8, whereas the corresponding figure for non-smokers would be of the order of 1 in 300. The observation on the effect of giving up smoking is particularly important, since it indicates that men who cease to smoke, even in their early forties, may reduce their likelihood of developing the disease by at least one half.

It should be noted that the excess of deaths from lung cancer among smokers was not compensated for by any corresponding reduction in the number of deaths from cancer of other sites in the body; in other words, there was a total incidence of cancer in the smoking groups in excess of the incidence that would have prevailed in the absence of smoking.

It will be apparent from what has been said that the evidence from the many inquiries in the past eight years, both in this country and abroad, has been uniformly in one direction and is now very considerable. It has been further strengthened recently by the observation from several sources that the extent of the relationship with smoking differs for different types of lung tumour which can be distinguished only by microscopic examination.

Laboratory Evidence

From the physical and chemical point of view there is nothing inherently improbable in a connection between smoking and lung cancer. Tobacco smoke consists largely of microscopic oily droplets held in suspension in air, and these droplets are of a suitable size to be taken into the lungs and retained there. Over a hundred constituents have so far been identified and, among these, five substances have already been found which are known to be capable, in certain circumstances, of causing cancer in animals. Some workers have succeeded in producing tumours in animals by painting concentrated extracts of tobacco tar on the skin. Known carcinogens are present in tobacco smoke in very small amounts however, and there is no certainty that such low concentrations could be harmful to human beings. Nevertheless, the finding of carcinogenic agents in tobacco smoke is an important step forward, in that it provides a rational basis for the hypothesis of causation.

ATMOSPHERIC POLLUTION AS A CAUSE OF LUNG CANCER

It has been known for some years that mortality from lung cancer is greater in urban areas than in the countryside. This fact, together with the identification of carcinogenic substances in coal smoke and in motor-vehicle exhausts, has led to the supposition that exposure to atmospheric pollution may be concerned with the increase in lung cancer. The rôle of atmospheric pollution is particularly difficult to investigate however, and the evidence is neither so consistent nor so extensive as that relating to tobacco smoking. On the one hand, no excess mortality from lung cancer has been observed in persons who would be especially exposed by the nature of their work to atmospheric pollution—for example, transport workers, garage hands, and policemen. On the other hand, the results of a number of investigations have suggested that a relationship does exist between atmospheric pollution and lung cancer. Perhaps the best evidence for this relationship comes from studies of the small number of deaths from the disease among *non-smokers in different types of residential district*; in these studies higher death-rates have been observed among non-smokers in large towns than among those in rural areas. On balance it seems likely that atmospheric pollution plays some part in causing the disease, but a relatively minor one in comparison with cigarette smoking.

ASSESSMENT OF THE EVIDENCE RELATING TO SMOKING AND LUNG CANCER

Knowledge of the causation of lung cancer is still incomplete. Many factors other than tobacco smoking are undoubtedly capable of producing the disease; for example, at least five industrial causes have been recognised. Nevertheless, the evidence for an association between lung cancer and tobacco smoking has been steadily mounting throughout the past eight years and it is significant that, during the whole of this period, the most critical examination has failed to invalidate the main conclusions drawn from it. It has indeed been suggested that the fundamental cause may be some common factor underlying both the tendency to tobacco smoking and to the development of lung cancer some twenty-five to fifty years later, but no evidence has been produced in support of this hypothesis.

In scientific work, as in the practical affairs of everyday life, conclusions have often to be founded on the most reasonable and probable explanation of the observed facts and, so far, no adequate explanation for the large increase in the incidence of lung cancer has been advanced save that cigarette smoking is indeed the principal factor in the causation of the disease. The epidemiological evidence is now extensive and very detailed, and it follows a classical pattern upon which many advances in preventive medicine have been made in the past. It is clearly impossible to add to the evidence by means of an experiment in man. The council are, however, supporting a substantial amount of laboratory research which may throw more light on the mechanism by which tobacco smoke and other suspected causative factors exert their effect, and which may thus eventually add to the degree of proof already attained as a result of studies of human populations. It must be emphasised, however, that negative results from work with animals cannot invalidate conclusions drawn from observations on man.

CONCLUSIONS

1. A very great increase has occurred during the past twenty-five years in the death-rate from lung cancer in Great Britain and other countries.

2. A relatively small number of the total cases can be attributed to specific industrial hazards.

3. A proportion of cases, the exact extent of which cannot yet be defined, may be due to atmospheric pollution.

4. Evidence from many investigations in different countries indicates that a major part of the increase is

associated with tobacco smoking, particularly in the form of cigarettes In the opinion of the Council, the most reasonable interpretation of this evidence is that the relationship is one of direct cause and effect

5 The identification of several carcinogenic substances in tobacco smoke provides a rational basis for such a causal relationship

REPORT ON MEDICAL RESEARCH

LUNG cancer, radiation hazards, vaccination against poliomyelitis, and genetics are among the chief topics of the Medical Research Council's latest report[1]

The Council's activities complement those of hospitals and universities, and the Council provides for clinical research only when its scale, scope, or urgency dictates Besides setting up its own permanent units, whose staffs have careers in research, the Council makes whole-time or part time appointments to its external scientific staff, grants to independent workers, and awards for training in research Moreover, it organises cooperative studies At the national level, the Council allocates funds for the support of clinical research in both major schemes and individual projects Decentralised research may be supported by regional hospital boards and boards of governors of teaching hospitals, here the Clinical Research Board can often give advice

As before, the report includes an excellent succinct account of trends in selected fields of medical research The many publications of the Council and its staff are then listed They include the report on the *Hazards to Man of Nuclear and Allied Radiations*,[2] presented to Parliament as a white paper

Overseas liaison continues by means of units in Gambia, Jamaica, and Uganda Research groups have been set up to study ageing, atmospheric pollution, inherited disease, and other topics, and units are being established to study (among other things) metabolic disturbances in surgery, carcinogens, and the effects of radiation

Special attention is paid to *lung cancer* on account of its striking increase in late years, it is the cause of 1 in every 9 deaths in middle-aged men Retrospective and prospective investigations all indicate a relationship between heavy smoking, especially of cigarettes, and most forms of lung cancer, and no investigation suggests absence of such a relationship Carcinogens have been found in cigarette smoke, these induce hyperplasia in human fœtal lung grown in tissue culture Industrial hazards (e g, from chrome and asbestos) and atmospheric pollution probably account for a small proportion of the cases Statistical surveys and laboratory experiments are continuing

Poliomyelitis vaccination in North America is by killed viruses of the Mahoney strain For the British vaccine a less virulent (Brunenders) strain was chosen, but the rhesus monkey used for safety testing was found to be insensitive to this strain A cynomolgus monkey (treated with cortisone, or cortisone and irradiation) is used Antibody studies in children have shown that the British vaccine produces titres (against all three types of virus) which compare favourably with those found after use of the American vaccine Experiments in monkeys show that the vaccine confers a high degree of immunity to artificial infection with a virulent strain In children aged $1^1/_2$–$9^1/_2$, after vaccination the attack rate of paralytic poliomyelitis in the 1956–57 season was a fifth of that in unvaccinated children Live attenuated poliomyelitis vaccines are being tried so far they have been trouble-free, but the antibody response has not always been satisfactory

In experimental *filarial infections* it was found that microfilariæ remained in the lung capillaries during the day, and were more generally distributed in the circulating blood at night The antifilarial drug diethylcarbamazine ('Banocide') acts similarly to an opsonin, and is effective in the blood stream but less so in places inaccessible to the phagocytes The drug is most useful in the mass treatment of communities Species of wuchereria similar to the human type have been found in animals, and several species of mosquito are now known to be involved as vectors The response of onchocerciasis to chemotherapy is not satisfactory, but control of the simulium fly vector by dicophane (D D T) has been successful

The importance of the *kidney* in regulating the water and electrolyte content of the body is agreed, but attempts to compare the efficiency of the kidney in adults and in children have been frustrated by lack of an agreed basis for comparison—the body-weight, body-surface area, and body-water content give differing results But by most criteria the kidneys of infants (human and rat) are less efficient than those of adults Happily a balanced diet and the requirements of growth (which dictate that little protein be broken down) ensure that, normally, not too much material is presented for excretion

Investigation of the nature of the difference between *normal and sickle-cell hæmoglobins* has shown that the only chemical difference lies in one peptide, which bears a positive charge in sickle cell hæmoglobin at pH 6 4 but is unchanged in normal hæmoglobin, this difference is due to the presence of a valine molecule in the charged peptide and a glutamic acid molecule in the neutral peptide This is the first time that the effects of a single mutation on the chemical structure of a protein have been elucidated When the sickle-cell-hæmoglobin molecules lose oxygen they may form fibrillar aggregates which attract one another into a parallel orientation, distorting the cell In homozygotes the illness is severe, and four-fifths of them die before reaching reproductive age, the persistent high incidence of sickling in some African tribes is thought to be due to the high resistance of heterozygotes to malignant tertian malaria, which largely compensates for the lethality of sickling In malaria-free regions (e g, the United States) the prevalence of sickle cell trait has fallen, as would be expected Heterozygotes carrying a thalassæmic factor may be similarly resistant to malaria Mutations of the kind, where genes are beneficial in one situation and harmful in another, are important in evolution

Microbial genetics is briefly discussed There are 3 mechanisms for the transfer of bacterial genes from cell to cell

(1) Transformation operates in, e g, pneumococci If deoxyribonucleic acid (D N A) is extracted from one strain and added to another, the recipient strain takes on some characteristics of the donor

(2) Transduction operates in, e g, salmonella When virus multiplies in a donor cell, some chromosome fragments become incorporated in the virus, and may be integrated into the chromosomes of new infected cells which survive

(3) Conjugation operates in, e g, the colon bacillus During temporary fusion of two cells, chromosome material passes from one to the other

A bacterial virus acts by attaching itself to the bacterial cell and injecting its D N A, which then takes control of the host's synthesising mechanisms, causing them to produce more virus D N A and protein Often bacteria become permanently infected ("lysogenic") with a phage virus, and able to transmit it to their progeny Some bacterial properties (e g, toxin production by diphtheria bacilli) are impossible except by lysogenic organisms

Homografts are normally destroyed (except for blood, whose cells have no nuclei, and cornea, which has no blood-supply). This does not apply to grafts between identical twins or members of an inbred strain, and the power to destroy grafts may be lost after irradiation. Irradiated mice, which would have been expected to die after a week or two, recover when inoculated with marrow. It has been shown that the homologous marrow actually colonises the irradiated host. Even grafts from another species (rat) may survive. Leukæmic mice have been successfully treated by irradiation heavy enough to destroy all the blood-forming tissue, followed by a marrow graft from a normal animal. Another means of making homografting possible is to inject tissue from another animal before birth; after reaching maturity the recipient will tolerate further grafts from the donor.

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[1] Report of the Medical Research Council for the year 1955–56 H M Stationery Office Pp 247 9s

[2] See *Lancet* 1956 i 949

Other articles deal with the relationship between radiation and leukæmia, whooping-cough vaccines, protein turnover in tissues, the chemistry of proteins and peptides and of antibiotics, and mass spectrometry in gas analysis. The summary of work indicates the vast range of the council's activities—from hypogammaglobulinæmia to possible carcinogenic action of detergents. The list of publications is as long and impressive as ever.

Before Our Time

TOBACCO FASHIONS

WHEN the natives of North America discovered the Europeans in the 15th century they introduced them to the pleasures of tobacco—snuffed, chewed, and smoked. The form in which it was used in their society was probably governed to some extent by custom and fashion; and pipe smoking certainly had some religious and symbolic meanings. The history of tobacco-taking in Europe has also been strongly influenced by fashion, which, although partly shaped by authority, propaganda, and economics, owes much more to individual desires for novelty, distinction, emulation, and uniformity.

In England pipe smoking became the fashion of the rich in the late 16th century, and, as the price of tobacco fell, the habit spread to all classes, both sexes, and almost all ages; by the turn of the century it was a national pastime. On the Continent, on the other hand, the fashion was for snuffing. There was, of course, much opposition to all forms of tobacco using; and the first important book against it—the opinions of sundry learned physicians—was published as early as 1598. Two Papal Bulls proclaimed excommunication for being found guilty of using tobacco in the churches of Seville and within the walls of St Peter's in Rome. The Greek Church forbade its use entirely; and in Turkey, Persia, and India the death penalty was prescribed. A Russian tsar decreed that for the first offence the culprit should be whipped and for the second executed, while snuff-takers were to have their noses cut off; and Louis XIII of France prohibited its use unless ordered by a physician. In England, James I imposed a heavy import tax in 1604 and published his renowned Counterblaste with its bitter invective against the habit. But the fashion grew. Then, in the early years of the 18th century, it changed rapidly and there appears to have been no organised propaganda, legislation, or economic circumstance to account for this. In the time of the Stuarts, according to Sir William Besant, "the use of tobacco penetrated all ranks and classes of society. The grave divine, the soldier, the lawyer, the gallant about town, the merchant, the craftsman, the 'prentice, all used pipes. . . . People went to bed with tobacco box and pipe and candle on a table by the bedside . . . it is even stated that the very children in school took a pipe of tobacco instead of breakfast." But by the end of Queen Anne's reign the pipe had been deposed and the English were well set for a century of snuff taking.

Snuffing was already popular among all classes in France and in Scotland and Ireland. It seems probable that in England it grew up slowly among the "young bloods" as a protest against the excess to which smoking had been carried by the "lower orders." They imported the habit and the elegant ritual of snuff taking from the fashionable French with the fastidious attention to blend and perfume, the exquisite snuff-boxes, the tap on the lid and the delicate lifting of the pinch to the nose, the inaudible inhalation and elaborate gestures of the hands and dainty handkerchiefs. These affections, of course, were scorned by men such as Samuel Johnson who carried their snuff loose in their waistcoat pockets; but schools of etiquette gave instruction, as an advertisement of 1711 states, in "the exercise of the Snuff-box, according to the most fashionable Airs and Notions . . . with the best plain and scented snuff." An accident of war may have contributed to the rapid spread of the habit. In 1702 50 tons of fine Havana snuff captured in Spanish ships were distributed among the English seamen as perquisites. They sold it cheaply in England and flooded the market in the southern counties with excellent snuff at 3*d* or 4*d* a pound. By 1720 a contemporary writer was able to say: "The world has taken up a ridiculous fashion—the excessive use of snuff. All nations are snuffing. All classes snuff, from the highest to the lowest. . . . Both sexes snuff, for the fashion has spread to women; the ladies began it and it is now imitated by the washerwomen." Dr Johnson, fifty years later, remarked that "smoking has gone out. To be sure, it is a shocking thing, blowing smoke out of our mouths into other people's mouths, eyes and noses . . . yet I cannot account why a thing that requires so little exertion, and yet preserves the mind from total vacuity, should have gone out." According to Swift, the makers of snuff employed "by far the greatest number of hands of any manufacture of the kingdom." A snuff house was opened in the Haymarket in 1720 that has continued to blend and sell snuff without interruption to the present day. The ledgers and records provide an interesting history of fashions in the use of tobacco over more than 200 years. Queen Charlotte—nicknamed "snuffy Charlotte"—was a heavy snuff-taker and regular customer. Like many others she bought snuff by the pound, on Feb 20, 1804, ordering 12 lb of "Marrocca" at 8*s* 6*d* a pound with 4*s* for a "jar and bung" and another 6 lb on May 26. But by this time the craze of snuffing was waning. The mass of the people, among whom pipe smoking had never lost its appeal, were slowly discarding the snuff habit; and cigars were becoming more popular among the rich. Snuff remained highly fashionable in the foppish circles in which the craze had originated. Indeed, it reached a peak of fashionable excess in the time of the Prince Regent and Beau Brummell.

By the middle of the 19th century the famous Haymarket shop was supplying as many smokers as snuffers, and in 1859 a work on the habits of "grand society" recorded that the obsolete custom of snuffing was "retained only by a few old gentlemen." The birth of cigar smoking has been attributed to the Peninsular war, when the soldiers acquired a taste for Spanish cigars. The rise of cigarette smoking has been linked with the Crimean war and contact with the customs of the Turks and Russians. It may be significant that the snuff craze began about the time of the extended war of the Spanish succession on the Continent. But changes of fashion are not caused by single circumstances or events, though these may precipitate a change when the communal taste is ready for one. Both the sudden fashion of snuffing in the 18th century and the slower return to smoking in the 19th century followed periods when the habit had risen in quantity and quality to new heights of extravagance. It may be that the people were satiated with the monotony of one craze and ripe for the titillating novelty of another.

In the history of tobacco up to the appearance of cigarettes there is little evidence that the fashions were greatly influenced by the efforts of the tobacco trade. In the second half of the 19th century, however, tobacco advertising and intense competition for markets, together with increased production from the invention of the cigarette-making machine in 1880, undoubtedly influenced the fashion of smoking. In the past forty years the cigarette craze has blossomed as the pipe and the snuff crazes did before it. Changes of fashion can still happen without prompting: in the past ten years snuff sales in this country have been slowly but steadily rising without the aid of advertisement or preferential tax. The national fashion of ubiquitous cigarette-smoking may perhaps be reaching the limit of tolerable extravagance and be becoming ripe for decline.

Occasional Survey

SUBDURAL HÆMATOMA

THE first report on a traumatic subdural hæmatoma is probably that of Ambroise Paré[1]. He described the necropsy findings in King Henry II of France, who died in 1559 eleven days after being injured by a lance:

> "His skull being opened after his death there was a great deal of blood found between the dura and pia mater poured forth in the part opposite to the blow at the middle of the suture of the hind part of the head and there appeared signs by the native colour turned yellow that the substance of the brain was corrupted as much as one might cover with one's thumb."

Many reports of subdural accumulations of blood, or bloodstained fluid, were published in the following three centuries. In these a traumatic origin was usually assumed. But in 1857 Virchow[2] introduced the name "pachymeningitis hæmorrhagica interna." He emphasised the intradural origin of the chronic hæmatoma and its inflammatory character. Others (e.g., Huguenin[3]) postulated a traumatic origin for all hæmorrhagic effusions on the inner aspect of the dura mater. About the turn of the century Jores and his pupils[4–6] emphasised the need for examining membranes spread out flat, and sections of the dura cut in two directions at 90° and taken from various parts. They advocated that two conditions should be distinguished—i.e., traumatic subdural hæmatoma, and pachymeningitis hæmorrhagica interna (which might show either degenerative changes and vasoproliferation or fibrinous exudation and cellular infiltration). Aschoff[7] considered that the striking capillary proliferation, in the absence of fibrinous exudation, and cellular infiltration were not inflammatory in origin, and proposed the name "pachymeningosis hæmorrhagica interna." Changes in the collagenous fibres of the subdural membranes, the appearance of cystic spaces, the spread of fibroblastic proliferation, and vascular proliferation had been described by G. M. Robertson,[8] and by Ford Robertson,[9] who quoted Wilks and Sperling's finding of membrane formation after experimental injection of blood into the subdural space. Fahr[10] and Wohlwill[11] gave excellent accounts of the histological findings in pachymeningitis hæmorrhagica interna, and emphasised the capillary and endothelial proliferation in the absence of fibrinous exudate and without signs of organisation. The formation of wide engorged "giant capillaries" in the areolar layer of dura mater was generally recognised, particularly by Ostertag,[12] who studied the histology of pachymeningitis in whooping cough. Albertini[13] came to conclusions similar to those of Jores and Laurent.

In the United States, Putnam and Cushing[14] and Putnam and Putnam[15] claimed that the traumatic and the spontaneous forms showed histological differences. Baker[16] pointed out that the larger hæmorrhages took place in the inner capillary bed of the dura mater and dissected along the loose connective tissue of the submesothelial layer; he considered trauma an important cause but not the only one. But in general the unitarian traumatic theory was readily accepted, particularly when Gardner[17] and Putnam[18] put forward an attractive hypothesis to explain the symptomless interval and the gradual increase in size of a subdural hæmorrhagic cyst. Zollinger and Gross[19] supported the hypothesis by model-experiments. They assumed that the membrane enclosing a subdural hæmatoma is semipermeable and that the proteins which arise from the disintegrating erythrocytes exert a colloid osmotic pressure attracting fluids with low protein content, such as cerebrospinal fluid and possibly interstitial fluid of the dura mater. This is certainly a better explanation than repeated bleeding between laminated neomembranes, because, though the concentration of proteins in such a "blood cyst" is high, it is lower than that of blood, indicating a dilution with protein-free fluid[19]. The same pathogenesis was accepted for the pachymeningitis hæmorrhagica of infants, and the alternative name "chronic subdural hæmatoma" became popular[20–23]. Birth injury or insignificant, often overlooked, postnatal trauma were held to be the cause of the disorder.

Two thorough investigations on a very large material have lately been published. Link and Schleussing[24] studied the necropsy and histological findings from 941 patients aged over 16. They, like Gellerstedt,[25] separate sharply the traumatic subdural hæmatoma from true pachymeningitis hæmorrhagica. They believe that the fate of a post-traumatic hæmatoma depends on its size. Thus small hæmatomas are completely absorbed, leaving only hæmosiderotic pigmentation on the inner aspect of the dura mater; and larger ones result in rusty, brown, or brownish grey thin neomembranes or pseudomembranes (often erroneously called pachymeningitic membranes). The largest are organised like hæmatomas in any other part of the body, beginning with fibroblastic proliferation and capillary budding in the inner areolar layer of the dura mater, the end result is focal thickening of the dura mater—a dural scar In the intermediate stage, clefts sometimes appear, either naked or lined by fibroblasts which may resemble a mesothelial lining, but usually such clefts are the result of shrinkage or even post-mortem artefacts Wide spaces, when seen in spread-out membranes or sections parallel to the dural surface, communicate with each other, and cysts with one or many locules are exceptional Hæmosiderin-laden macrophages may be seen in any of the stages, and in the milder forms of subdural hæmatoma Extracellular hæmosiderin granules are rarer

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[1] Paré A. Cited by Buchanan D N. *In* Brennemann s Practice of Pediatrics. Hagerstown Md, 1946 vol IV chap 6 p 1
[2] Virchow, R. *Verh phys med Ges Würzb* 1857 7 134
[3] Huguenin, O. *In* Ziemssen s Cyclopedia. New York, 1877
[4] Jores, L. *Zbl Path Verh path Ges* 1898 9, 841
[5] Jores L., Laurent, H. *Beitr path Anat* 1901 29 486
[6] Laurent H. Zur Histogenese der Pachymeningitis hæmorrhagica interna. Dusseldorf 1898
[7] Aschoff L. *Med. Klinik* 1938, 34 569
[8] Robertson, G M. *J ment Sci* 1893 39 208 358
[9] Robertson W F. *J Path Bact* 1896 4 119
[10] Fahr T. *Zbl allg Path path Anat* 1912 23 977
[11] Wohlwill F. *Virchows Arch* 1913 214 388
[12] Ostertag B. *Ibid* 1925 255 129
[13] Albertini A v. *Schw Z allg Path* 1941 4 442
[14] Putnam T J, Cushing, H. *Arch Surg, Chicago* 1925 11 329
[15] Putnam T J, Putnam I K. *J nerv ment Dis* 1927, 65, 260
[16] Baker A B. *Arch Path (Lab Med)* 1938 26 535
[17] Gardner W J. *Arch Neurol Psychiat, Chicago* 1932 27, 847
[18] Putnam T J. *Ibid* p 856
[19] Zollinger R., Gross R E. *J Amer med Ass* 1934, 103 245
[20] Sherwood D. *Amer J Dis Child* 1930 39 980
[21] Ingraham F D, Matson, D D. *J Pediat* 1944, 24 1
[22] Ingraham F D, Matson D D. *In* Levine S Z, Butler, A M, Holt L E jun, Weech A A. Advances in Pediatrics. New York, 1949, vol IV, p 231
[23] Korwitz H L. *Virchows Arch* 1914 215, 233
[24] Link K, Schleussing H. *In* Lubarsch Henke and Rössle s Handbuch der pathologische, Anatomie und Histologie. Berlin 1955, vol 13/3
[25] Gellerstedt N. *Ibid*. Berlin 1956, vol 13/4

In true pachymeningitis hæmorrhagica the process starts as serous imbibition of the dura mater, swelling of collagenous fibres, and proliferation of vascular adventitia with accumulation of pigmented histiocytes This is followed by larger intradural hæmorrhages which spread in the plane of the dura, and lead to the formation of neomembranes, finally a dural blood sac is formed There is little or no evidence of organisation The capillary proliferation in the areolar layer of dura mater with the formation of giant capillaries is conspicuous though not absolutely characteristic In addition to the vasoproliferative form of pachymeningitis hæmorrhagica—for which Aschoff's designation "pachymeningosis hæmorrhagica" is probably more appropriate—there are (as Jores and Laurent pointed out) cases with primarily fibrinous or fibrino hæmorrhagic exudation and much cellular infiltration In a few cases only it seems that a primary intradural hæmorrhage associated with a subdural hæmatoma *leads to a chronic pachymeningitis hæmorrhagica* In the clinical history of patients with pachymeningitis hæmorrhagica, trauma is absent or insignificant

At first sight it seems surprising that the dispute could go on for a hundred years, but most of the workers had only one type of material Moreover, the difficulty in the interpretation of histological findings in dural or subdural lesions can be well understood from the account by Russel and Cairns [26] of their investigation of 4 cases of metastatic neoplastic infiltration of the veins in the dense layer of dura mater *This obstruction resulted in engorgement* and rupture of the blood vessels in the inner layer and bleeding not only into the areolar tissue but also into the subdural space Thus a pathological process primarily located in the dura mater gave rise to a subdural hæmatoma As Hamperl [27] says, subdural hæmorrhage and chronic pachymeningitis may lead to almost indistinguishable end-results, but *it would be a mistake to* consider them as identical disorders from the beginning

FINDINGS IN INFANTS

Unfortunately all the cases of Link and Schleussing, and nearly all Gellerstedt's, were in adults In many regards findings in infants are illuminating Acute subdural hæmorrhage as the result of birth injury has been described [28 29] It is seen mainly in full-term and post mature infants, either in forceps delivery or with a disproportion between *the size of the head and that of the* birth canal It is due to bitemporal compression with elongation of the falx cerebri and pull on the tentorium At the same time the parietal squamæ overlap, one usually being shifted anteriorly over the other This results in kinking and often rupture of the pial veins as they pass from the arachnoid through the subdural space into the superior *longitudinal* sinus [30] Possibly in some cases the "bridging veins" (which cross the subdural space into the dura outside the sinuses in about a third of *the population*) are the source of hæmorrhage From this description it is understandable that the subdural hæmatoma of the newborn is almost always associated with tears in the upper layer of the tentorium (usually near *to the margins of the incisura tentorii*) and with a layer of blood on the upper tentorial surface Blood may or may not leak into the infratentorial space By gravity, the blood accumulates in the *posterior (temporo parieto-occipital)* regions At necropsy the subdural hæmatoma may either cover the whole vertex or be localised in the posterior regions If the hæmatoma is not immediately fatal, the common outcome is complete absorption leaving only rusty, reddish-brown spots on the inner aspect of the dura mater in the temporo-parieto-occipital regions, on the upper aspect of the tentorium and usually also in the middle cranial fossa Contrary to some opinions, absorption does take place from the subdural space, and there is a rich network of lymphatics in the outer subperiosteal layer of the dura mater [31 32] Usually the residua of neonatal subdural hæmatoma are incidental findings or the infants are admitted to hospital with feeding difficulties When infants with moderate subdural hæmatoma die in the neonatal period from other causes, a few reddish-brown, thin, neomembranes like spiders' webs may be found in the same place

Subdural hæmorrhagic effusions in premature newborn infants are different in nature They arise from rupture of the distended arachnoid, enormous amounts of thin hæmorrhagic fluid, which have accumulated in the subarachnoid space, pour into the subdural space If not fatal immediately, such hæmorrhagic effusions are absorbed without residua

Another form of subdural hæmorrhagic effusion of which the mechanism can be clearly understood is that associated with diffuse atrophy of the brain In children this is usually Tay Sachs idiocy [33] or Alpers's disease (progressive diffuse degeneration of cerebral grey matter) [34] If the infant survives for some time, neomembranes are seen on the inner aspect of the dura mater over the whole vertex, and there is a patchy thickening of dura mater which may involve the walls of the dural sinuses (mainly the superior longitudinal) leading to stenosis and eventually thrombosis *Here the obvious explanation is the pressure difference and effusion e vacuo*

Entirely different in clinical aspects and localisation, and often difficult to interpret in histological findings, is the pachymeningitis hæmorrhagica interna of infants [35–38] The disease is seen mainly between the fourth and eighth months of life The infants are usually underweight, sometimes suffering from diarrhœa and occasionally from scurvy or a hæmorrhagic nasal discharge The illness is usually chronic, starting with a slow enlargement of the head The enlargement is usually uniform and globoid, unlike that seen in internal hydrocephalus The fontanelle is bulging Vomiting, crying, and somnolence are common The infants may develop a hydrocephalic facies with the eyes directed downwards Retinal hæmorrhages are the rule in these children, though rare in the pachymeningitis of adults Occasionally the onset is acute, or even fulminating with symptoms like those of acute purulent meningitis, in some of these cases the acute symptoms subside, and the illness takes the chronic form At necropsy the lesions are typically fronto parietal and almost always bilateral A subdural tap in the lateral angle of the fontanelle is therefore almost always successful, though it is not in the subdural hæmatoma of the newborn. Cysts are found with one or many locules filled with a hæmorrhagic and xanthochromic fluid, and thin reddish-brown membranes on either aspect of the sac. The dura is seen to be altered on histological examination. There are wide capillaries in the areolar layer, though "giant capillaries" are not as conspicuous as in pachymeningitis of the adult. Occasionally the condition is associated with internal hydrocephalus. Pigmentation of the dura in the temporo-occipital regions and on the upper aspect of the tentorium is rare, and pachymeningitic cysts are not seen on the upper lamina of the tentorium, where in birth injury tears are common. These findings, together with the clinical course and symptoms, exclude birth injury with subdural hæmatoma as the origin of this disease. It is very unlikely that it is caused by traumatic intradural hæmorrhage. Such hæmatomas are extremely common between the two dural layers of the tentorium, they are harmless and resorbed without any residual changes, but in sites where hæmorrhagic pachymeningitis is common they are practically never seen in infants dying from birth injury in the first few days of life. It is noteworthy that scurvy (in which an alteration of the ground substances of connective tissue is well known) is fairly commonly associated with pachymeningitis, but no association with hæmorrhagic disorders has been found. Walthard[39] has reported a capillary proliferation close to the inner aspect of the dura, similar to that seen in pachymeningitis hæmorrhagica, in laboratory animals on diets deficient in vitamin B_1. The high incidence of alcoholism in pachymeningitis hæmorrhagica of adults may be related to this. Various causes may lead to degenerative, vasoproliferative, and inflammatory changes in the areolar layer of the dura mater and thus to pachymeningitis hæmorrhagica interna.

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[26] Russel, D S Cairns, H *Brain* 1934, 57, 32
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TREATMENT

In treatment, the surgical approach described by Ingraham and Matson[21, 22] seems to be the method of choice when there are appreciable amounts of clotted blood in the subdural space. For pachymeningitis hæmorrhagica interna with cysts which grow slowly in size, conservative treatment will be preferred by most pædiatricians. Beneficial results, with absorption of fluid, were reported[40–42] after aspirations of subdural fluid in addition to administration of antibiotics or vitamins, or both. Freislederer and Schweier[43] have now reported encouraging results using hyaluronidase in infants with verified pachymeningitis hæmorrhagica. This enzyme, one of the spreading factors, is known to catalyse the depolymerisation of mucopolysaccharides of ground substances, to increase the permeability of capillaries[44] and fascial membranes,[45] and to facilitate the absorption of subcutaneous fluid.[46, 47] Accepting the theory of Gardner[17] and others, Freislederer and Schweier injected hyaluronidase into the dural sacs expecting to alter the physico-chemical properties of the semipermeable membranes and promote a rapid absorption of the encysted fluid. They treated in this way 9 infants aged $3^1/_2$–12 months. In all of them the pachymeningitic cysts disappeared, and all gained in weight.

H. S. B.

In England Now

A Running Commentary by Peripatetic Correspondents

NOT for me sightseeing in Europe, cruising in cargo boats, or even sampling Spanish food. For 14 carefree, phoneless days I forgot I was a G.P. and along with a dozen others became a budding artist. We assembled at Rock on the North Cornish coast and, from a comfortable hotel, sallied forth daily, our Irish tutor in tow, to paint the coast-line if not exactly red most other colours. Budding artists are a mixed bunch and we ranged in age from Arthur, aged 74, who painted exquisite water-colours during the day, at night regaling us with cups of tea, and Betsy, just starting in oils and the proud possessor of four grandchildren and a bubble-car, to George, Ruth, and Mary in their early 20s who came because they loved a painting holiday. We took our work seriously and our day began about 9.20 when the elder members of the party did their daily dozen by sprinting for the bus whose time of departure was as variable as an English summer. We painted till lunch with Paddy, our tutor, who swore he could teach anyone to paint, instructing, extolling, and encouraging all in turn. We painted till tea and if we wished we painted till dinner and the sun still shone. Almost before we knew we had started the holiday was over. Between us we had produced getting on for 150 pictures. We may not all reach exhibition standard, but by the end of that fortnight we discovered a new way of expressing ourselves which though by no means perfect gave infinite pleasure to the doer. And miraculously Paddy was right: WE COULD PAINT.

* * *

Hallo, Sarah. Take a seat. How can I help you?

Aren't you busy, doctor! I've been waitin' for an hour and your room is still full . . . but I won't keep you long, I said to Nelly "'e's got enough to do." But she said 'Get yourself along or I'll call 'im round.' So I come right over from work . . . you'll excuse my workin' clothes. Well it's this 'ere. For a long time when I've been walkin' I get a little . . .

A little mazy?

No. I wouldn't say mazy. It's all down this side, an' I get a . . .

A pain?

No, it's not a pain.

More of an ache?

You wouldn't rightly call it an ache. It strikes 'ere then it travels 'ere an' strikes through to the back an' up my neck an' leaves me feelin' cold an' 'ot.

Cold or hot?

Cold an' 'ot . . . if you know what I mean, an' then of course my bowels don't improve.

Still stubborn?

Just the other way!

Oh. Well I can give you something for that.

Are you writin' somethin' out for diarrhœa?

Well . . . yes.

But it's not the diarrhœa I've got . . . not really. I can be that way one day an' just the other the next. That's what I was tellin' our Nelly. I said 'It's not natural. There's somethin' sadly wrong." I said. So I come right over. Do you remember them pills you gave me?

Er . . . the white ones?

No, the red.

I don't seem to have written them down. When did I prescribe them?

I met you in the market one day an' you 'ad your scripts with you an' you wrote me down for a course of 'em an' said they was just what I needed.

Of course. Of course. You were run down.

That's it.

A bit anæmic . . . and a bit chesty?

Yes I was.

And your stomach was off?

That's right. I was tellin' Mr Hudson the butcher about my wind just before you came along.

Yes I remember, Sarah. And you were hot and cold and faint and sick. You can have some more with pleasure.

I was just goin' to say, doctor.

How many do you want, Sarah? 50? 100?

I was just goin' to say, doctor . . .

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I'll give you 100, it will keep you well stocked. No use making extra journeys to the surgery. You are busy enough I am sure.

I was just goin' to say, doctor

Yes, Sarah?

Are you givin' me a recipe for them tablets ... the same ones?

I am indeed ... exactly the same ... er ... that's what you want isn't it?

No please, doctor. They were very good but they made me sick an' they didn't really relieve the

The pain?

Well you wouldn't call it a pain

* * *

My friend has an inbred politeness which makes him unable to assert himself in small matters. His wife and he were at a London theatre and, just before the play started, his nose began to bleed. His technique, developed over the years, is not to fuss but hold his head over a basin and soon the bleeding stops. When he felt it coming on he accordingly left his seat and proceeded to a wash-basin. There the dripping went on as usual and was beginning to get less when a voice behind him said "Ah! a nose-bleed. I'm a doctor. I'll stop that for you." My friend protested, probably a little at a disadvantage with head forward and having to be careful where he aimed the blood, that he was quite all right, was used to it, and that it would soon stop. The energetic doctor quickly returned with cotton-wool and despite spluttering protests proceeded to pack each nostril with what could have been an excess of therapeutic zeal, for when he had finished the patient said, in retrospect, he felt that his head was full of cotton-wool, and he felt faint. He asked if he could have a glass of brandy, a traditional syncopal remedy in which he had much faith, but the doctor said certainly not and that orange juice was the thing for him. Orange juice is anathema to this particular epistaxian, but having been shaken and probably speaking even more indistinctly he was unable to make this plain and at the point of the stethoscope he ingested a large glass of orange juice. The doctor disappeared.

My friend saw the play without pleasure, being more concerned, he says, with his endogenous throbbings in the head than the emotional ones on the stage. When he returned home that night he couldn't remove the cotton-wool which had been well and truly packed and being a considerate person sat with his head in his hands all night because of his discomfort before calling his own doctor in the morning.

* * *

In the routine history I asked: "Do you ever get short of breath?"

"Only since I've been doing my present job."

"And what is that?"

"Carrying gas cookers."

"Oh. Well, how many stairs can you climb before you get breathless?"

"Oo, carrying a gas cooker, only about three flights."

* * *

My patient, an elderly lady with a broken hip, shares a room in hospital with a younger lady who has recently undergone pelvic surgery. Weaning the latter from her catheter has been difficult and two days ago her doctor tried hypnotic suggestion. She still has her catheter. But *my* patient complains that she should have been given ear-plugs—she has had frequency ever since.

* * *

I had some difficulty in making my American friend understand how to get to his destination.

"You take the left fork at the doss house," I explained.

"What is a doss house?"

"A doss house is a place where tramps put up for a night."

"What is a tramp?"

"A vagrant, a vagabond, wayfarer, loafer ..."

He looked at me blankly.

"A hoofer, a hobo, someone dressed in old clothes with a straggly beard who lives on the road," I continued desperately.

"Now I get you," he exclaimed at last. "You mean a bum."

* * *

Science Fiction Footnote.—He chemotaxied towards her and took her in his arms.

Letters to the Editor

CONSULTANT AND SPECIALIST

SIR,—Your article and leader of June 1 are well timed and should instil a sense of urgency into those responsible for our hospital services.

Stated simply, the problem is that our present hospital provision does not meet the needs of outpatient consultation and investigation or inpatient treatment. There are nearly 500,000 people on our waiting-lists, patients and practitioners weary of waiting for outpatient consultations, and senior registrars, trained to deal with this situation, are unable to find a satisfying outlet.

There is a great disparity of consultant distribution throughout the country—the facts are known, but not published. You, Sir, must have obtained some insight into these in your recent partial survey. The Ministry will not reveal the recommendations made by working parties of senior consultants in each region some five years ago and the Consultants and Specialists Committee does not appear to have been very insistent in demanding this information. In many areas there is known to be resistance by the profession to the appointment of more consultants. Our traumatic service cannot deal adequately with a rising accident-rate, but the resistance to proposals for remedying this is mainly medical.

The situation is urgent. Many in the profession feel unable to voice their opinions openly. Consultants, in part, because the system by which merit awards are made discourages outspokenness, while senior registrars and their juniors obviously cannot put themselves in a position which diminishes still further their meagre chance of promotion.

There is need for change and this can only come from outside the present administration. General-practitioner distribution is being ensured by statutory means. It is essential for Parliament to set up a committee forthwith to obtain the facts, so carefully guarded, and to make recommendations for immediate implementation.

This would ensure that "waiting" is not regarded as normal for our hospital population and that senior registrars get the consultant appointments for which they have been trained.

Central Middlesex Hospital,
London, N.W.10.

HORACE JOULES.

SIR,—Your leader (June 1) and the correspondence arising from it have been headed Consultant and Specialist. It may be that at least some of our present discontents are linked with the circumstances which have caused this distinction to be created.

In the days before the National Health Service, a patient looked in the first place, for medical advice and help, to his personal or family doctor, who gradually, as a consequence of the rise of specialism, came to be known as a general practitioner. When this personal medical attendant felt that he needed a second opinion, he called in a specialist of his choice, with whom he went into consultation. This was a conference between practitioners who were regarded as collaborators, and it was the personal attendant, and not the second opinion, who took the responsibility for the action which ensued from the meeting. If the patient could afford to pay for the specialist's opinion, he was expected to do so, but if he could not, it was usual for him to go to a hospital or clinic at which the specialist gave his services freely, and as a consequence became known as an honorary surgeon or physician as the case might be. In some hospitals, each specialty might have more than one honorary accredited to it, and in such cases the senior honorary was designated accordingly. His juniors were specialists as he was, and in due time would probably step into his position. In the meantime, private consulting practice was open to the junior

The point is that in that period a practitioner was called a specialist because he practised a specialty, and when the word consultant was applied to him, it carried no implication that other specialists were of lower rank or had need of his supervision, although it was open to them to consult with him in a particular case if they so wished.

With the advent of the health service, the word "honorary" was no longer appropriate, and since the specialists concerned saw only patients referred to them by general practitioners, they were given the title "consultant." At the same time it was realised that some hospitals, mostly of the long-stay type, were giving treatment which was appropriate to the needs of the patients but could not be considered the practice of a specialty, and in others the assistant medical officers were working under the immediate supervision of a medical superintendent; and as a purely temporary expedient the title "senior hospital medical officer" was coined for such officers. At that time the criterion was the nature of the work carried out by the holder of the post, not his personal qualities or academic attainments; in short, "the rate for the job," and it would be difficult to quarrel with this principle.

At that time the consultant appeared to be in line of succession to the pre-1948 honorary, and the S.H.M.O. was the successor of the hospital medical officer in the employ of local authorities and similar bodies, who provided treatment for patients who were in hospital for such long periods that they could no longer be regarded as being under the care of their own private or panel doctors.

In the Terms and Conditions of Service of Hospital Medical and Dental Staff, published on June 7, 1949, S.H.M.O.s were defined as "senior officers performing clinical duties who are not of consultant status but not registrars." At this point it became clear that the criterion which defined the S.H.M.O. was not the nature of the work but the assessment of the holder of the post. On Oct. 5, 1950, circular R.H.B. (50) 96 appeared, and it became clear that the S.H.M.O. was now to be regarded, not as a senior practitioner who worked in hospital, but as a grade of specialist beneath the rank of consultant and therefore suitable to be an assistant grade which would have the function of extending specialist treatment to fields which the existing consultants were not sufficiently numerous to cover, but which could be said to have consultant cover by reason of the supervision which the consultant was presumed to exercise over the S.H.M.O. At this point it became clear that the original understanding—that the S.H.M.O. grade was a temporary one which would tend to die out as the National Health Service developed—had been dropped.

There is a widespread impression that it is proposed to perpetuate a species of subconsultant specialists in grade III of the Strachan proposals, at a rate in which the maximum would be comparable with the starting remuneration of the most junior consultant. It is difficult to imagine that any practitioner would accept this subordinate role as the summit of his ambitions. At present S.H.M.O.s constitute more than a third of the total specialist body, and if the impression is well founded they might approach parity in numbers. The last paragraph of your editorial asserts that it is baseless to harbour a fear that the Ministry might ruthlessly seek to swell the ranks of specialists with the aim of securing cut-price consultants. Whether this is the Ministry's aim is irrelevant. It would be the logical outcome if this impression proves to be well founded.

Cambridge C. B. V. WALKER

SIR,—I should like to support Dr. Herford's views (June 15) which in many ways go to the rock bottom of our principal troubles in the National Health Service as it exists today.

If general practitioners had the time and the inclination to do for their patients *themselves* all the work for which they were trained—to accept continuous care for them under all circumstances and all conditions, whether of body or mind, from the time they come on their lists till they depart or die, if or when that becomes so, then *out*patient departments could become mere shadows of what they once were. Consultants and specialists could at long last have ample time to devote to those patients who were really in need of the services of a man of consultant rank, with consequent enormous saving in the administration.

With all due respect, Sir, I must entirely disagree with you when you suggest the appointment of assistant physicians and surgeons.

Having made a special study of the working of the National Health Service since its inception, I am convinced that you may have the finest hospital and specialist staff in the world; but if you have not got a first-class general-practitioner service as well you can no more wage a successful campaign against disease than can the general commanding an army in battle, who has been given a first-class team of experts to help him, but whose fighting troops are of poor quality.

Worthing HAROLD LEESON

SEX DIFFERENCE IN GENETIC RISKS OF RADIATION

SIR,—Many authorities on radiogenetics, among whom Muller is one of the most prominent,[1–5] believe that increased radioactivity of the external medium, as a result of nuclear tests and of the peaceful utilisation of "heavy" nuclear energy, will prove detrimental to the future of the human race by unbalancing the ratio between the rate of mutations and the rate of eliminations.

It is highly regrettable that humanity should waste enormous amounts of technical skill, money, and fissile material in merely destructive fields. Let us hope that in not too remote a day, common agreement of the great nuclear powers will stop this nonsensical bomb race.

Nevertheless, the industrial use of atomic power faces humanity with serious problems, among which radioprotection is not the least important. I think that the present maximum permissible dose of ionising radiation (0·3r per week, which amounts to about 300–350r for the entire reproductive period of the human individual) is too high and needs urgent revision.

But the possible genetic damage from irradiation may not be equal in both sexes. From a close scrutiny of the biology of reproductive cells of both sexes, it seems probable that male gametes are not so liable as the ova to transmit acquired radio-induced mutation.

If we accept that the spontaneous mutation-rate found in mice is applicable to man, then one gene mutation per 40,000 gametes is likely to have little effect on the descendants,[6] since millions of spermatozoa are produced, and only one (and we may suppose it the best qualified one) is accepted by the ovum. A monogenic mutation is likely to be transmitted only if the vast majority of male gametes bear it. Rare monogenic or oligogenic mutations of the kind produced by ionising radiations, are likely to affect the biology of the bearer in such a way as not to permit it to compete with its brother gametes.

On the other hand, the maturation-rate of spermatogonia and spermatocytes is so high that the accumulation of irradiation seems less perilous than for the female sex-cells. The production and elimination of the ova is a slow process, during which radiations have time to act. Only one ovum takes part in the act of reproduction.

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The rate of maturation is slow, therefore the damage due to accumulation could be greater, and the dimensions of the cell make it a bigger target for ionising particles

On the other hand, there is a well-known direct relationship between radiosensitivity and the metabolic state of the cell, and ovogenesis is a much slower process than spermogenesis, but the ages of the cells are equal, *and in the premeiotic stages their nuclei play similar* rôles

I think that women are more exposed to the genetic hazards of the increasing radioactivity of their surroundings and that there should be different standards for the maximum permissible dose of irradiation for each sex

Laboratory Division, Dobrita
Sanitarium Craiova, Rumania

EUGEN J ALTESCU

RADIATION AND INFLUENZA MUTATION

SIR,—Mr Pirie's suggestion (June 15) that the mutant strain of the influenza virus which is causing the present epidemic in the Far East may be the result of the nuclear-weapon tests in the Pacific is difficult to refute, if only because of the logical impossibility of proving a negative It would be equally difficult for him to disprove that the mutation is not the consequence of any other cosmic event—e g, the arrival of a particle of extremely high energy from outer space, such as has been recently reported from the Massachusetts Institute of Technology We are therefore left with probabilities, and as it is notorious that the influenza virus is more liable to spontaneous mutation than almost any other virus, it would seem unnecessary to invoke any special circumstance to account for the appearance of this particular mutant strain

The Eastern origin of the epidemic is by no means unique and cannot be attributed to any sinister effects of the weapon tests Every schoolboy must know that the Black Death came from the East, and most practitioners are aware that the majority of the pestilences which have ravaged Europe in the past have originated in the East There is much evidence which points to the East as the home of nearly all the infectious diseases which have afflicted and still afflict us

London, W 1

E J MOYNAHAN

THE CHILD'S RIGHT TO ADOPTION

SIR,—Miss Hunter's letter of June 15 raises some interesting points

I would agree with her that there are a large number of unwanted legitimate children, but wonder very much why she thinks that to have these children adopted would solve the situation

Psychologically the evidence would certainly not seem to support such a hypothesis The crux of the children's emotional disturbance as evidenced by their behaviour disorders or neurotic or psychosomatic symptoms lies in the fact that they are not wanted by the parents who have them and one repeatedly finds that adopted children vent the insecurity which is the result of this situation on the adoptive parents and become their problem This was clearly expressed by one such child who said "The fact they loved me made me feel worse—why was I not loved by my own mother and father?" It is often also true that the children vent the hate and aggression that really belongs to the rejecting natural parents against the adoptive ones, and try to force them to repeat the original situation

In thinking of this problem, I would like to comment on another point It seems to be assumed that all persons wanting to adopt children have "good" reasons for doing so and will make "good parents" Many of them, I would feel, in fact want them to appease their own sense of failure, and at once reject the child who does not fulfil their sometimes irrational demands for intellectual and social qualities that do them credit Such people make bad parents, but although great care is taken that adoptive parents shall be given "satisfactory children," less is taken that the children shall be given "satisfactory parents"

Department of Psychiatry,
University of Leeds

W MARY BURBURY

CARDIAC ARREST WITH FLUOTHANE

SIR,—Since I have in preparation a report of 25 selected cases of cardiopulmonary disease, which include conditions such as congestive heart failure and fulminating *thyrotoxicosis*, successfully anæsthetised with 'Fluothane' (halothane), I would like to comment on Dr Foster's letter of June 1

In my experience fluothane has proved entirely safe when used in concentrations of under 2% Safety is increased by the use of an inhaler giving precise vapour percentages The 'Fluotec' (Cyprane Ltd), a temperature-regulated inhaler, delivers a vapour of from 0 5 to 3% at gas flows of 4 to 10 litres a minute Concentrations of 0 5 to 0 8%, which do not materially affect blood pressure or pulse rate, are sufficient for all operations where muscular relaxation is not required, provided it is not intended deliberately to lower the blood-pressure For operations in the pelvis or lower abdomen 1 2 to 1 5% produces sufficient muscular relaxation This strength has not normally affected blood-pressure or pulse-rate to an extent necessitating intravenous atropine for bradycardia or methoxamine for hypotension, when hyperduric atropine has been used in premedication

The safety factor has been carefully studied by Raventos in animal experiments[1]

> *In dogs a vapour strength of 3 6% produced respiratory* arrest in 60 min, but cardiac arrest did not occur for a further 9–10 min In another experiment 4% vapour produced respiratory arrest in 9 min Artificial respiration was continued for a further 90 min at this concentration This produced a decrease in voltage of QRST complex, but the heart continued to beat regularly

Very precise control of vapour strength is essential in the use of fluothane I think that Dr Foster has probably been instrumental in preventing accidents with this drug and I should like to congratulate him on his frankness in reporting this case

Crewe and District Memorial Hospital
Crewe

E S POPE

SIR,—'Fluothane' (halothane) is a potent anæsthetic agent and in my opinion a valuable addition to our armamentarium Because it is so potent—2% or less of fluothane vapour sufficing for anæsthesia in the great majority of subjects, while 3% should not be exceeded —it is essential *that it should be administered* via an apparatus which enables one to control the strength of the mixture delicately and accurately There is at least one inhaler on the market which does this the ether bottle of the Boyle mark 2 circle absorber, which was designed to provide high concentrations *of ether* vapour, certainly does not

In an attempt to reproduce in the laboratory a mixture similar to that used by Dr Foster (June 1), I connected a sine curve respiratory pump to a Boyle mark-2 circle absorber and adjusted it to give a stroke of 500 ml sixteen times a minute Just under 2 oz of fluothane were placed *in the* ether bottle and the control turned to the sixth notch Samples were drawn by suction from the facepiece end of a corrugated tube through a Rayleigh gas interference refractometer In 60 sec the concentration of fluothane rose to 11%, in 90 sec to 13%, and in 2 min *to 15%*

When the experiment was repeated with 4 oz of fluothane in the bottle the concentration rose to 12 8% after 60 sec and to 15% after 90 sec In clinical use the warm expired gases would presumably result in even higher figures These figures are some four to five times the maximum permissible clinical strength of 3%

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[1] *Brit J Pharmacol* 1956, 11, 394

The Royal Infirmary
Manchester

H J **BRENNAN**

ORGANIC DISEASE AND SUICIDE

SIR,—To the layman, and to many doctors, suicide is a matter of mental rather than physical disturbance The customary verdict of the coroner's court is that the event took place "while the balance of the mind was disturbed," and this contributes to the exclusion of organic disease as a contributory factor

As the coroner is concerned only with the mode of death and with the state of mind of the deceased no report of organic disease present is made to the Registrar-General Consequently, the only source of information about them is the file of the individual pathologist My records over the past five years show 65 cases—a number which cannot be expected to provide accurate statistics, but will, perhaps, show that physical disease is important enough to warrant its inclusion in the coroner's certificate in many of the cases

In the series there are three groups

Group 1—No organic disease (21 cases) (32%)

Group 2—Organic disease which might initiate or enhance depression (19 cases) (29%)

(*a*) Arterial hypertension (12) In all there was massive hypertrophy of the left ventricle the heart weights ranging from 16 to 31 oz No valve defect was found In 1 case there was an adrenal cortical adenoma 5 cm in diameter

(*b*) Active peptic ulcer (4) The presence of such lesions in persons who have not sought medical advice may, apart from the stress induced by pain, foster the belief that there is a cancer

(*c*) Kümmell's disease (1) This man had had a severe crush fracture of the lower dorsal spine some years previously and progressive collapse of the vertebræ led to his being bedridden and in constant severe pain for many months

(*d*) Recurrence of uterine prolapse (1) This patient although in considerable discomfort, had declined to consider a further operation

(*e*) Cerebral thrombosis with hemiplegia, immediately following an abdominal operation (1)

Group 3—Organic disease possibly associated with depression (25 cases) (39%)

(*a*) Cholelithiasis (7) Of these 5 had large gall stones at necropsy, and 2 had recently had the gall bladder excised for stone

(*b*) Fatty infiltration of the heart (7) These showed a great excess of epicardial fat with penetration of the muscle of the right heart Only 1 was grossly obese and in the other 6 the condition appeared to be due to chronic bronchitis and emphysema In all there was certainly a severe restriction of physical activity

(*c*) Gross obesity (5) Advanced fatty degeneration of the liver was present in 1 case Here again there was a severe restriction of physical activity None of them could have walked upstairs without dyspnœa (In all, in the whole series, there were 11 examples of gross obesity)

(*d*) Thyroid disorders (nodular goitre 1, large adenomas 2) Apart from their toxic effects these may have been interpreted as cancers

(*e*) Enlarged prostate with hypertrophied bladder (1)

(*f*) Bilateral adrenal hypertrophy (1) The glands were about 3 times normal size

(*g*) Chronic hypertrophic gastritis (1) This may of course have been due to the misuse of alcohol

It may well be argued that there are large numbers of contented people with high blood-pressure that fat and jolly men can be found everywhere, and that a considerable proportion of the population goes to the grave with gall stones of which it has never been aware But the parade of pathology in these 65 persons indicates that organic disease in suicide is a matter of some importance, and deserving of further consideration

Victoria Hospital
Keighley Yorks

IAN **STEWART**

RELATIVES IN HOSPITAL

SIR —In your leading article of May 11 you referred to the necessity of providing for visitors Through the good offices of the former contributory scheme, it has been possible to provide, at this hospital, a hostel for patients relatives It is a modern bungalow and includes a double room two single rooms kitchenette, lounge, bathroom and two toilets Four people can stay overnight, and a larger number during the day in the spacious lounge No meals are provided in the hostel The relatives can obtain them either in the dining-rooms or in the staff canteen where they pay the normal charges

Occupants of the hostel are expected to look after their rooms, to make their own beds and generally to care for the place though the cleaning services are provided by the hospital Care is taken to ensure that the privileges are not abused, and when a ward sister is aware of a relative who genuinely needs accommodation the hostel is used It is not intended to provide lodging free of charge where people are able to pay hotel charges but in all deserving cases the services of the hostel are free

A second use to which the building is put is to accommodate nursing mothers whose infants are patients of the hospital Accommodation of these mothers has often in the past presented difficulty, even where, by arrangement, billets were available in the town Through the use of the hostel these difficulties no longer exist

Before the construction of the hostel records showed the potential demand for such accommodation, and the forecast has been entirely justified by the experience gained since it was opened It has been occupied constantly and within six weeks was in full occupation, though of course this will not be continuous

Lack of capital funds prohibit such provision from normal resources but a scheme like this should be well within the target of most Leagues of Friends

Royal Hampshire
County Hospital
Winchester

FRANK **REEVES**
Group Secretary and Superintendent

AN "OUTBREAK" OF CORONARY-ARTERY DISEASE

SIR,—Since the beginning of the year we, in the course of our work as general practitioners seem to have struck a very peculiar "epidemic" and we should be interested to learn whether any other doctor has had a similar experience

About the middle of March it occurred to us that we were seeing an unprecedented number of cases of angina and coronary occlusion The patients many of whom up to then had rarely complained of any serious illness had at some time in January suffered from an illness which we had labelled "influenza" They had complained of severe malaise ("feeling awful"), unusual tiredness, and occasionally sharp supra orbital pain They looked very ill but had none of the aches and pains of true influenza They had a brown furred tongue, a variable temperature and a basal bronchiolitis but nothing else Seven to ten days later the picture changed to that of a very resistant bronchitis and sometimes to a severe broncho pneumonia

When they appeared to be recuperating and even after apparent recovery, they began to complain either of retrosternal pain radiating to the throat or precordial pain, or pins and needles radiating to the left shoulder and to the little finger, relieved by rest, and associated with temporary but striking fall in blood-pressure In a few, a full coronary thrombosis developed At this stage through the kindness of the casualty officers of St Bartholomew's Hospital some electrocardiograms were done and the reports often read "The tracing is an unusual one of the S1, S2 S3 type" In some cases there was slight depression of the S T segments in leads 2 and V6 Six had definite evidence of small cardiac infarcts Three others died of coronary thrombosis

In all cases whether the patient developed cardiac symptoms or not he sooner or later had signs or symptoms which we attributed to liver insufficiency—muddy complexion, flatulence abdominal discomfort and much hepatic tenderness but no obvious jaundice, though the urine with colour varying from orange to dark brown gave positive froth and sulphur tests and the stools were often pale , but both changes were transitory

Still under the illusion that this was some obscure form of virus A influenza, we approached the director of the Central Public Health Laboratory, Colindale, who very kindly investigated the bloods of about a dozen of these patients for a virus infection, but was unable to arrive at any definite conclusion

Men and women were equally affected, sometimes more than one in a family Most were over the age of 40 Those with a tendency to cardiovascular disorders seemed to be more readily affected and were often left with a varying degree of permanent damage We have traced a few children whose bouts of peculiar malaise and unexplained pyrexia seem to us in retrospect to fit in with the same sequence of events

Treatment consisted of salicylates and antibiotics in the acute stages, with symptomatic treatment later on

In view of the seriousness of the sequelæ, we should like to know whether any other doctor has had a like experience, and whether anyone can offer an explanation of this "epidemic" of coronary-artery disease ?

We should like to point out that in this district coronary and general arterial disorders are very common, and that one of us (J Z) has, in fact, been following up a series of cases of cardiovascular and hypertensive disease for the past eight years, hence the sudden appearance of an unusual number of acute cardiac cases was all the more striking

London, E 8

J ZEITLIN
A MELINEK

CIRCUMCISION WITH BONE-CUTTERS

SIR,—I think it would be unfortunate if the advocacy by Mr Skegg (June 8) and Mr Crossling (June 22) of the bone forceps technique for circumcision was allowed to pass without reference to a serious objection to the method—namely, the removal of an inadequate amount of the lining mucous membrane of the prepuce The fusion of the residual mucous membrane, which is still able to cover the greater part of the glans penis, to the preputial skin is liable to be followed by a severe degree of postoperative phimosis and a revision of the circumcision may become necessary The fear of this unfortunate and avoidable complication no doubt accounts for much of the unpopularity of the method in this country

Leamington Spa,
Warwickshire

C R SAVAGE

TREATMENT OF MIGRAINE

SIR,—Without any desire to discuss the theories current about the cause of migraine, or indeed sufficient knowledge to enable me to do so, I nevertheless am led, after investigation of a sufferer in whom I take a deep interest, to mention one point for the benefit of those who, like most of us, have to treat patients in a symptomatic way—a point which does not seem to be sufficiently remembered

In this patient, at the beginning of an attack, the pylorus shuts completely, so making the swallowing of drugs entirely useless, since they simply stay in the stomach until the attack is over I should imagine that this condition is fairly common, judging from statements from other patients If this is so, drugs taken by mouth might as well be thrown at once into whatever receptacle the patient seizes when vomiting starts, as it usually does

For this patient nothing has been of any use in stopping an attack until he tried hypodermic injection of ergotamine tartrate or some of the barbiturates, which are useful sometimes as a change Recently, however, a chlorophenothiazinyl propyl - methyl - piperazine derivative ('Stemetil') has been advocated for the control of migraine My patient finds it of no use when taken alone, but it does control vomiting, apparently by keeping the pylorus open, and he finds that four 5 mg tablets with a 2-mg tablet of ergotamine tartrate, if taken as soon as the premonitory feeling comes on, will stop an attack If the attack has been allowed to develop further, as may sometimes happen when it starts during sleep, a second or third dose of both may be taken

I intend to try the effect of following the stemetil by some of the more ordinary sedatives, but meanwhile I hope that this letter may help to relieve those who have frequent attacks of migraine

I am very grateful to Dr C W Walker, of Hereford for bringing this drug to my notice

Holme Lacy Hospital
Hereford

D S SPENCE

CHRONIC LYMPHATIC LEUKÆMIA AND THE NEPHROTIC SYNDROME

SIR,—Dr Bodley Scott (June 8) reported for the first time the association of the nephrotic syndrome in two patients suffering from chronic lymphatic leukæmia Amyloidosis involving the kidneys was responsible for the syndrome in one of these patients He recalls that amyloidosis is seen occasionally with myelomatosis and suggests that this forms another link between myelomatosis and chronic lymphatic leukæmia

In the past twelve months I have seen two examples of the nephrotic syndrome due to amyloidosis—one occurring in association with chronic lymphatic leukæmia and the other with Hodgkin's disease

CASE 1 —Six months before his death, a man of 47 was found to have an early form of chronic lymphatic leukæmia Blood examination Hb 13 1 g per 100 ml , red cells 4,400,000 per c mm , white cells 23,100 per c mm (polymorphs 47 5%, lymphocytes 46 5%, monocytes 5 5%, eosinophils 0 [illegible]), platelets 271,000 per c mm The marrow showed a moderate increase in small mature lymphocytes Serum protein total 4 5, albumin 2 4, globulin 2 1 g per 100 ml Electrophoretic pattern of the proteins showed no characteristic abnormality No treatment was given for the leukæmia A few weeks before death considerable œdema of the extremities and gross proteinuria developed

Necropsy —Considerable amyloidosis of liver (2450 g) and spleen (510 g), and smaller amounts in marrow, lymph nodes, and suprarenals Congenital absence of right kidney Cystic disease and considerable amyloidosis of left kidney Moderate leukæmic infiltration of liver, spleen, marrow, and lymph nodes

CASE 2 —Two years before death, a man of 29 complained of night sweats, anorexia, and loss of weight There were no significant abnormal signs, and investigations failed to find a cause for the pyrexia Eighteen months later he complained of low abdominal pain and a pelvic mass was palpable Laparotomy revealed a mass of firm lymph nodes encircling the left common iliac vessels Histological examination of one of these nodes showed Hodgkin's disease The blood and marrow pictures were normal Serum protein total 8 9 albumin 3 9, globulin 5 0 g per 100 ml Electrophoresis showed no demonstrable abnormality of the globulin fraction

A total of 30 mg of nitrogen mustard ('Trillekamin') was given intravenously, in five divided doses Four months later severe anæmia, diarrhœa, and anorexia developed and there was further loss in weight Peripheral œdema was extensive and there was a heavy proteinuria (Esbach, 20 g per day) Serum protein total 3 3, albumin 1 0, globulin 2 3 g per 100 ml

Necropsy —Considerable amyloidosis of liver (3450 g), spleen (280 g), kidneys (340 g each), and suprarenals Hodgkin's disease of lymph nodes and spleen

Teilum [1] recorded the induction or enhancement of amyloidosis by nitrogen mustards, cortisone, and corticotrophin in mice treated with subcutaneous injections of sodium caseinate Teilum believes that a suppression of mesenchymal cells which are in a state of active proliferation is involved in the basic mechanism of the formation of amyloid This theory is further supported by reports of Hodgkin's disease in man treated by nitrogen mustard in which amyloidosis rapidly developed [1 2]

In case 2, nitrogen mustards were given for the Hodgkin's disease and this was followed by amyloidosis

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1 Teilum G *J Lab clin Med* 1954 43, 367
2 Spain D M *Amer* *clin Path* 1956, 26, 52

Purists may like to note that *homotope* would be more exact, Soddy, however, gratefully adopted the suggestion of isotope, and its use in its now accepted sense was first published by him in 1913

To commemorate the coming of the radiochemical word, the Glasgow and West of Scotland section of the Royal Institute of Chemistry is making arrangements to affix a plain lettered plaque bearing the names of Soddy and Dr Todd to the house concerned This house is now the property of the University of Glasgow, and the arrangements are being made with the consent and support of the University authorities No public appeal for funds is being made

HUGH NICOL

West of Scotland
Agricultural College,
Glasgow, C 2

Chairman, Glasgow and
West of Scotland section,
Royal Institute of Chemistry

Public Health

Influenza

INFLUENZA-A virus, provisionally identified as the Far Eastern type, has been isolated from several Pakistani seamen lately arrived in this country The seamen fell ill after they had been flown to this country to man a ship in London The virus has apparently established itself in North America The disease has appeared among men of the United States Atlantic destroyer force at Newport, Rhode Island, and it is reported [1] that none of the crews affected had been in contact with persons from the Far East The infection may have spread indirectly via Europe At Newport about 550 sailors aboard eight ships were said on June 21 to have been infected The disease lasted three or four days and the main features were severe headache, fever up to 104°F, and aching muscles Military transports docking at Californian ports have had influenza aboard

Speaking at a press conference in *London* [2] *on June 18*, Sir Macfarlane Burnet referred to the changes in the quality of the virus that took place every five to ten years The last sharp change had been in 1946–47 The new type of virus might also continue for five to ten years, but after the first wave it would settle down to become " just ordinary influenza " Sir Macfarlane added that Australian laboratories would be ready to begin commercial production of a vaccine last week Laboratories in other countries would also be preparing a similar vaccine (the Wright-Fleming Institute of Microbiology is doing so in London), but in Australia it had been an urgent matter because of the onset of winter Nothing more extensive was contemplated than the vaccination of hospital nursing staffs and those in regular contact with travellers Unless a country was prepared to take extreme measures, Sir Macfarlane said, it would not be possible to keep the infection completely at bay because of the new virus type

A report from Holland [3] suggests that the new virus *may be related to the one* which caused the pandemic of 1889, since antibodies against it have been found only in people over 70 years of age

Poliomyelitis

Uncorrected notifications of poliomyelitis in the week ended June 15 (24th week of the year) were as follows (previous week in parentheses) paralytic 41 (48), non-paralytic 12 (26), total 83 (74) The following figures compare this year's notifications with those in the preceding nine years

Year	*Total cases up to and including 24th week*	*Cases in 24th week*
1948	612	15
1949	421	38
1950	933	93
1951	641	50
1952	651	48
1953	831	65
1954	560	32
1955	448	29
1956	689	43
1957	1167	83

Prevention and Cure in Sweden

In a talk broadcast on April 11, Miss Joan Lamont described Sweden as an example and an inspiration to the public-health worker The infant death rate, she said, was half that in Scotland, and the expectation of life greater, tuberculosis, thanks partly to B C G vaccination, had " almost vanished "

She found that the differences were due to neither a better climate nor a higher standard of living, but rather to the emphasis on prevention in the training of nurses and doctors, and to the allocation of adequate money to preventive services, although expenditure on all health services was less than in Britain For equal numbers of people there were fewer consultants, general practitioners, and hospital nurses in Sweden than in Britain, but many more public-health doctors and nurses There were enough of these nurses (the equivalent of our health visitors) to do all the important jobs that needed them Student nurses were treated as students, and were not used for routine ward-work any more than were medical students in Britain The student spent a fair proportion of her nursing training with public-health nurses, and, even if she remained in hospital work, kept her interest in teaching health and preventing disease Ward-orderlies were employed to do the unskilled work, and the prestige of nursing was such that it got its fair share of recruits of high calibre

The Swedes, said Miss Lamont, had discovered that " prevention pays dividends not only in money but also in human happiness "

Diary of the Week

JUNE 30 TO JULY 6

Monday, 1st

INSTITUTE OF NEUROLOGY

5 30 P.M (National Hospital for Nervous Diseases, Queen Square W C 1) Prof J C Eccles, F R.S (Australian National University) Central Action of Afferent Impulses from Muscle Spindles

Tuesday, 2nd

ROYAL COLLEGE OF SURGEONS, Lincoln's Inn Fields W C 2

5 P.M. Dr Isaac Berenblum (Weizmann Institute of Science, Israel) Some Recent Advances in Skin Carcinogenesis (Imperial Cancer Research Fund lecture)

Wednesday, 3rd

INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330, Gray's Inn Road, W C 1

5 P M Dr N Rh Blegvad (Copenhagen) A Modern View of the Treatment of Sinusitis

6 P M. Dr B T Withers (Houston Texas) Combined Operation of Submucous Resection and Rhinoplasty

INSTITUTE OF DISEASES OF THE CHEST Brompton, S W 3

5 P M Mr O S Tubbs Surgery of the Pericardium

Thursday, 4th

ROYAL COLLEGE OF SURGEONS

5 30 P M Dr W H Kelleher The Modern Approach to the Treatment of Respiratory Defects in Poliomyelitis

Friday, 5th

MEDICAL RESEARCH COUNCIL

5 P M (National Institute for Medical Research Mill Hill, N W 7) Dr G W Corner (Rockefeller Institute for Medical Research) The Rockefeller Institute for Medical Research —its Founders and its Achievements

Appointments

HARRISON M H M CH M Leeds F R C S part time orthopædic casualty and traumatic surgeon, United Birmingham Hospitals and Birmingham Regional Hospital Board

ROPER HALL, M. J, CH M Birm F R.C.S D O M S part time ophthalmic surgeon United Birmingham Hospitals and Birmingham Regional Hospital Board.

THOMPSON P W M B Camb F F A R.C.S, D A consultant anæsthetist United Cardiff Hospitals

WATSON J A M B Glasg, D M R.D consultant radiologist, Cardiff Royal Infirmary

Colonial Appointments

BECKETT D W M D Dubl. D T.M & H senior M O (medical superintendent) Fiji Leprosy Hospital Makogai Fiji.

HOLLINS F R T M B Dubl D P H senior M O, Tanganyika

KELLETT F R S M B Calcutta D P H superintendent M O (specialist) Trinidad

LAMBO T A M D Birm D P M. specialist (alienist) Western Region, Nigeria

MILES P J L A H Dubl, D A M O (grade A) anæsthetist Colonial Hospital, Port of Spain, Trinidad available for the immediate relief of any undue rise in intracranial pressure

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[1] *New York Times*, June 22, 1957

[2] *Times* June 19 1957

[3] *Manchester Guardian*, June 22 1957

The tuberculin courses given by Smith and Vollum [1, 5] in meningitis and by Howells and Swithinbank [2] in pulmonary tuberculosis were designed specifically to provoke as many focal reactions as possible before the development of desensitisation For this reason injections of tuberculin were spaced at intervals of 5 or 7 days These series were not designed to study the significance of prolonged desensitisation and in neither instance was there any plan to continue tuberculin therapy as a long-term outpatient measure The detailed daily C S F examinations which are an essential part of Smith and Vollum's routine give a quantitative picture of the focal reaction in the tuberculous theca In pulmonary tuberculosis the focal reaction can only be presumed from the presence of a mild general reaction characterised by fever, malaise, and, in some cases, brief increase in local symptoms and signs These reactions, it is true, cause the patient some inconvenience Not one of my 78 patients has asked to discontinue the course on account of unpleasant reactions In one of the Oxford cases, tuberculin reactions provoked hæmoptysis from a giant cavity, and the treatment had to be stopped for this reason

The focal tuberculin reaction is, as you say, a hyperæmic phenomenon designed to carry the antimicrobial drugs to the place where they will do the most good It must be emphasised, however, that it is the inaccessible and not the resistant bacillus at which the reactions are aimed There is little, sense and there may be real danger, in provoking hyperæmia in tuberculous tissues if the bacilli are thereby exposed only to drugs to which they are resistant

The Churchill Hospital
Oxford

F RIDEHALGH

PRIMARY HEPATIC CARCINOMA

SIR,—Your annotation of April 6 draws certain conclusions which do not appear altogether justified While it is true that primary carcinoma of the liver is common in oriental countries and parts of Africa, there is insufficient evidence to justify the conclusion that the incidence is highest among the Bantu Negro The older reports from this Institute refer to highly selected groups of young adult males in whom liver cancer is the most common tumour While there is some evidence that the Bantu tribes in Portuguese East Africa may have a much higher incidence than those of the Union of South Africa,[6] comparison with the West African Negro is as yet impossible in the absence of incidence studies, which are only now being initiated Visits to Uganda, the Belgian Congo, and French West Africa, however, have given me the impression that carcinoma of the liver is at least as common if not more frequent in some of these areas than in South Africa and what statistics are available support this view [7]

In a series of necropsies from a general Bantu hospital in Johannesburg, primary carcinoma of the liver constituted slightly more than 2% of all necropsies In a rate study, we found, however, that the incidence of primary carcinoma was 22% of all carcinomas in males [8] While this relatively high frequency is mainly due to a high absolute incidence, it is accentuated by the composition of the population at risk which includes a high proportion of young adult males The reduced incidence of cancer of the skin and of the gastro intestinal tract in the local African also increases the relative frequency

It is difficult to compare the frequency of cirrhosis in different populations, since we are dependent chiefly on post mortem studies In the United States the frequency of cirrhosis usually varies between 2 and 5% of all necropsies,[9] whereas the frequency of cirrhosis at post mortem in Johannesburg in the Bantu is approximately 9 1% in males and 4 0% in females [10] On the other hand, for 1947–54, at the Boston City Hospital, in the series quoted by your editorial, the frequency was 13 93% [11] While this hospital may not be representative of the United States as a whole, it is probably similar to those hospitals serving the Bantu population of South Africa These observations should cast some doubt on the statement that the high incidence of primary liver cancer in Africa is mainly attributable to a higher frequency of cirrhosis There is evidence on the other hand, however, to suggest that the high incidence of liver cancer in the African Negro and in other countries with a high incidence, may be dependent on the high frequency with which cirrhosis undergoes malignant change [12] Approximately 54% of cirrhotic livers in males at post mortem in Johannesburg show malignant change

You also state that the relationship of dietary deficiency to cirrhosis in both man and laboratory animals is now well established While this may be true for animals, the rôle of nutrition in liver disease in man is far from clear The only relatively well documented, "nutritional" liver disease in man is the fatty liver of kwashiorkor, in which cirrhosis is a very rare sequel

In European practice the term "nutritional cirrhosis" is applied to the common "alcoholic" or Laennec's cirrhosis although the nutritional ætiology is by no means universally accepted Livers of this nature, although common among the white races of South Africa, are exceedingly rare in the indigenous and poorer Bantu population [10] In contrast the common cirrhosis in which carcinoma develops in South Africa is not of this type, but usually has the features of a post necrotic or post hepatitic cirrhosis The ætiology is definitely unknown, but according to French studies, this cirrhosis may be viral in origin [13] and our experience supports this view Nutrition as a direct factor in this type of cirrhosis has not been demonstrated

I would therefore like to suggest that (i) a high frequency of cirrhosis has not yet been shown to be the cause of the high incidence of liver cancer in under privileged communities, (ii) the relationship of diet to liver cancer and cirrhosis is by no means satisfactorily proven, and (iii) that the term "nutritional cirrhosis" in man be dropped until it can be used with greater knowledge of the ætiological background

South African Institute for
Medical Research,
Johannesburg

JOHN HIGGINSON

THE WORD "ISOTOPE"

SIR,—This word, now so familiar, was introduced in Glasgow about 1912 by a medical woman—Margaret Todd, who was also a novelist writing under the name Graham Travers—to fit the concept of elements occupying the same place in the periodic table The occasion was a social gathering at 11, University Gardens, then the home of Sir George Beilby (the father-in law of the late Frederick Soddy, who originated the concept of isotopes and other achievements in radiochemistry including the first approach to atomic numbers) Having been obliged to use awkward periphrases to express his "isotopic" ideas, Soddy said he needed a word for the concept, Dr Todd immediately suggested *isotope—iso*, the same, *topos*, place The word had indeed been published a few years before in a context of organic chemistry, but there is no reason to suppose that Dr Todd was aware of that

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11 MacDonald, R A *New Engl J Med* 1956, 255, 1179
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13 Charnot R Camain, R Guidicelli, P *Bull Soc Path exot* 1953 46 817

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Notes and News

NATIONAL ASSISTANCE BOARD

THE report[1] of the board for 1956, shows that the number of weekly allowances rose during the year by 44,000 to 1,656,000 (covering the needs of over 2¹/₄ million people) Payments of assistance in 1956 amounted to £105,160,000 More than two thirds of the allowances went to supplement national insurance benefits, including 117,000 to supplement sickness benefit or industrial injury payments

About 300,000 people were registered as unemployed in December of last year Of these, 73,000 were receiving assistance allowances (compared with 61,000 a year before) During 1956 the board collected information about people whose assistance was paid only on condition that they registered for employment The results show that the hard core of the unemployed maintained by national assistance consist mainly of disabled persons and unskilled men and women with physical or mental limitations which restrict their chances of getting and keeping a job During the year the number of reception centres for people without a settled way of living fell from 109 to 68 The average nightly number of people using the centres was about 1800, 130 more than in 1955

URINE TEST FOR PHENYLKETONURIA

A SIMPLE test, using ferric chloride, has been devised for the detection of phenylpyruvic oligophrenia, and it has been recommended that every child be tested at the age of 21 days If it is positive, dietary treatment can be started at once Cards describing and illustrating the test may be had from the Secretary, The Hospital for Sick Children, Great Ormond Street, London, W C 1, at 6*d*

University of Cambridge

Dr P J Randle has been elected to an official fellowship at Trinity Hall

On June 15 the following degrees were conferred

M.D —Gordon Scott
M B, *B Chir* —J M L Goddard (by proxy), R C M Kew
M.B —P J Lachmann

University of London

Sir John Charles has been appointed Heath Clark lecturer for 1959

Mr G H Bourne, D SC, is resigning the readership in histology at London Hospital Medical College on Sept 30, to take up the appointment of professor of anatomy and chairman of the anatomy department of Emory University, Georgia

University of Sheffield

Dr G R Hervey has been appointed lecturer in physiology

University of Glasgow

On June 19 the honorary degree of LL D was conferred on Sir James Paterson Ross and Brigadier J S K Boyd, F R S

Royal Society of Tropical Medicine and Hygiene

Brigadier J S K Boyd, F R S, has been elected president for the coming two years

Society of Medical Officers of Health

Dr H D Chalke has been elected president, and Dr C Metcalfe Brown chairman of council, of this society for 1957–58

World Federation of Societies of Anæsthesiologists

The World Congress of Anæsthesiologists is to be held in Toronto from Sept 4 to 10, 1960 All inquiries should be addressed to Dr R A Gordon, chairman of the organising committee, 516, Medical Arts Building, Toronto 5, Ontario

National Association for the Prevention of Tuberculosis

This association will commemorate the centenary of the birth of Sir Robert Philip by placing a tablet on the wall of 13, Bank Street, Edinburgh, where he founded the first tuberculosis dispensary in 1887 Mr Walter Elliot will unveil the plaque on Friday, July 26, after a short ceremony to be held at noon in court room no 4, Sheriff Court House, High Street, Edinburgh

World Congress of Gastroenterology

This congress will be held in Washington, D C, fr May 25 to 31, 1958 Further particulars may be had fr Dr H M Pollard, University Hospital, Ann Arbor, Michig U S A

Royal Medico-Psychological Association

The annual meeting of this association will be held Oxford from July 2 to 5 under the presidency of Dr R Armstrong Further particulars may be had from t secretary of the association, 11, Chandos Street, London, W

Christian Medical Fellowship

This fellowship will hold its annual breakfast on Tuesda July 16, at 8 15 A M, at the Royal Station Hotel, Newcas upon Tyne Mr Weldon Watts will be in the chair a Dr R G Cochrane will speak on Changing Standards Medical Practice Further particulars will be found in o advertisement columns

International Congress of Internal Medicine

The International Society of Internal Medicine is to hold fifth congress next year from April 24 to 26 in Philadelph under the presidency of Dr T Grier Miller This will be t first time that the society has met outside Europe T secretary general is Dr E R Loveland, 4200, Pine Stree Philadelphia, Pa

Psychiatric Congresses at Zurich

The International Congress of Group Psychiatry is to b held at Zurich from Aug 29 to 31 The following day, Sept the International Congress of Psychiatry will begin, and th will continue till Sept 7 Its main theme is the Presen Status of our Knowledge about the Group of Schizophrenia Further particulars about both congresses may be had fro the secretariat, Lengstrasse 28, Zurich 8, Switzerland

Harveian Society of London

The summer meeting of this society was held on Sunda June 23, when more than 60 members and guests attended service at Hempstead Parish Church, Essex, where Harve is buried Dr R Cove Smith gave an address and the servic ended with prayers of thanksgiving and re dedication by th Bishop of Colchester Afterwards Mr Dickson Wright wa presented with a gold medallion to mark his presidency of th society and of the Harvey tercentenary congress

Wellcome Trust

The Wellcome Trustees have made a grant of £5000 t McGill University, Montreal, for the purchase in the sterlin area of books related to the history of medicine which ar needed to fill gaps in the Osler Library The Trustees hav also agreed to provide £1200 annually for twenty five year to assist the further development of this library A ne extension and reading room for the library, to be known a the Wellcome Camera is to be provided by the university

The Brain and its Functions

An Anglo American symposium on the history and philo sophy of knowledge of the brain and its functions is to be hel in London from July 15 to 17 in connection with the first International Congress of Neurological Sciences, which is t take place in Brussels from July 21 to 28 The symposium i sponsored by the Wellcome Historical Medical Library with the cooperation of the National Hospital, Queen Square, and the Maudsley Hospital Further particulars may be had from Dr F N L Poynter at the library, Euston Road, N W 1

Reorganisation of Local Government

At a meeting of the Rural District Councils Association (*Times*, June 20) Mr Henry Brooke, Minister of Housing and Local Government, said that he hoped that a Bill on local government reorganisation would be ready in the autumn He realised that some of the smaller councils were disappointed because the white paper did not offer them much in the way of additional functions, but he thought that we must face realities Today some of the larger services, such as health and education, could not be operated over small units But the Government proposed that the larger urban authorities—those with a population of at least 60,000—should automatically be given charge of the local health and welfare services which at present were exclusively a county council responsibility He believed that this would be a big step in the right direction for a service in which "the personal element matters so much, and to which the local elected representative has a personal contribution to make"

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[1] Cmd 181 H M Stationery Office 3*s*

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